List of appendices

Appendix 6

Electrical activity of the septo-hippocampal system and behaviour

A6.1 Introduction

We now have a picture of the anatomy (Appendix 4) and the electrophysiology (Appendix 5) of the hippocampal formation. Together, they provide a preliminary circuit diagram. It is the business of this appendix to flesh out the bare bones of this diagram with a description of the functional correlates of hippocampal electrical activity.

However, stimulus–activity and activity–behaviour relationships are unlike anatomical, electrophysiological, or lesion data. The results are, to a certain extent, in the mind of the beholder. A cell can only react to those environmental features supplied by the experimenter and, if the appropriate feature is not there, the cell cannot display its normal capacities. Furthermore, where a stimulus produces a response, it will not be clear whether firing is stimulus or response related; and both environmental features (including stimuli deliberately presented in a phasic fashion by the experimenter) and the responses of the animal must be deliberately selected by the experimenter if they are to be analysed. We will also need to bear in mind that the firing of a cell or the production of synchronous activity in many cells: (a) does not mean that this activity is affecting behavioural output; (b) can be maximal in conditions which are not directly related to its function; (c) may give a very poor indication, in large neural networks, of the nature of the information processing of the network as a whole (see, for example, Sakuarai 1996 on population coding rather than single-unit coding of information); and (d), in the hippocampus, is so many synapses distant from sensory transduction and muscle activation that the activity of the cells is likely to correlate with a complex function of the properties of both. (For further methodological considerations, see Wiener 1996.)

Under these circumstances, correlating firing with stimuli or with responses might seem like looking for a very small needle in the wrong haystack. But, while single-cell activity correlates are not clear indicators of the function of neurons (and if treated as such can be grossly misleading), they provide information about moment to moment changes in a structure which cannot be obtained in other ways. Accounting for detailed patterns of firing under different circumstances will tax any specific theory of the operation of the network. This is particularly true when we compare (as we will try to do) firing at successive synaptic links in a chain under comparable conditions. Finally, when cell firing, lesion effects, and other data can be made to fit a single model, then we will have a reasonable theory. Where they cannot be made to fit a single model, any model based on only one of the types of data must be wrong.

With correlates of single-unit firing, we will see that people have often found what they were looking for—with each group finding something different. We will suggest that this is because hippocampal neurons respond, in a sense, to whatever stimuli or responses (or combinations thereof) the experimenter has rendered important to the subject—and particularly because experimenters are more likely to look to the stimuli under their control than to the animal's internal or external response for the correlates of cell firing. Our prime axiom, however, is that all these different correlates reflect the same underlying function of a cell. It will be our business to discover a perspective that allows us to assimilate all the data within a single rubric.

Our descriptions of cell firing, for methodological reasons, must be phrased in terms of 'stimulus' or 'response', these being unambiguous observables. But, for interpretation, we will make extensive use of the word 'goal' (Fig. 1.7 in the printed text). We will not use it in any exact sense except in Chapter 7; but its everyday meaning will be sufficient to resolve a number of problems.

First, 'stimulus' and 'response' are external observables. Yet, the hippocampus is deep in the brain where cellular activity should reflect more cognitive processing. 'Goal' captures the subject-oriented essence of cognition. It is the subject, not the experimenter, who defines a goal. Indeed, the experimenter can only manipulate the subject's behaviour by first discovering the subject's usual goals.

Second, we will find that the same class of cell in the hippocampus can have an apparently stimulus-related receptive field in one experiment and an apparently response-related receptive field in another. 'Goal' captures this ambiguity. A 'goal' is neither a stimulus as such, nor a response as such. A 'goal' is related to environmental stimuli (which define its location in space or time). However, alterations in those stimuli may not change the goal, whereas alterations in the animal's response tendencies will. A 'goal' is related to responses (which must be made if the goal is to be achieved), but many different responses can achieve the same goal.

Third, as a corollary of the above, there are some cases where we would wish to use stimulus-loaded terms and others where we would want to use response-loaded terms to describe hippocampal activity. 'Goal' encompasses both. For example, in an approach–avoidance conflict with an electrified water spout, it is usually easiest to describe the situation in terms of the responses to be made (approach–avoidance) than specific stimuli to be approached (since in the avoidance case there is only a single stimulus to avoid, but all of the apparatus, except the spout, is safe). But, it does no violence to normal usage to refer to approach and avoidance, respectively, as the subject's alternative goals. Likewise, in a discrimination task, it is usually easiest to describe the situation in terms of the stimuli to be responded to. But again, conventional usage allows us to refer to the left lever and the right lever as being the subject's alternative goals. This is an important point to which we will return at the end of this appendix.

There is one area which we will not cover in the present appendix. For convenience, we will leave correlations with sleep until the end of the next appendix, after we have dealt with the effects of theta-eliciting stimulation on behaviour.

A6.2 Single-unit studies

In the nearly two decades since the first edition, studies of single units in the hippocampal formation have made spectacular progress (see review by Wiener 1996), so that it is now technically possible to record from as many as 150 neurons simultaneously (e.g. Wilson and McNaughton 1993). Even now, however, it is seldom clear whether a record has been obtained from only one cell, and so the term 'single unit' is used to describe what are hoped, but not guaranteed, to be single cells (Wiener 1996). It is also a matter of controversy how far units can be separated into categorical types in relation to their firing patterns, and how far a single cell may demonstrate different types of firing at different times. For this reason, we will treat all the results as being from potentially multiunit records of potentially mixed types of cell. This will not generally cause a problem, as an increase in unit firing must represent either an increase in firing rate of a single cell or an increase in the average firing of a group of cells and, in both cases, at least one cell must have increased its rate.

We will divide our comments on single units into four main areas: habituation, simple conditioning, complex conditioning, and spatial mapping. We will take them in this order as the knowledge gained from the simpler paradigms helps to interpret the results in the more complex ones.

A6.2.1 Vinogradova's studies of habituation

The habituation studies we will describe are taken from Olga Vinogradova's laboratory at Puschino near Moscow. These have used a consistent paradigm across a very wide range of brain areas and so are worth considering as an isolated block. More recent studies, including those which have taken care to isolate pyramidal cells, are generally consistent with her findings. Where no reference is given for a fact, it is taken from her own reviews (Vinogradova 1975, 1995; Vinogradova and Brazhnik 1978). The experiments were done with rabbits, restrained by confinement in a box in which the presentation of stimuli was under rigorous experimental control. So, cell firing was assessed in terms of the modality of the stimuli, their rate of presentation, etc.; but we will argue that the responses elicited by the stimuli are likely to have been a critical factor in determining firing.

We will detail activity changes in terms of both experimental parameters and parts of the hippocampal formation, but there are three general points which will emerge from the present section. First, many units in the septo-hippocampal system are 'multimodal', responding to stimuli of several sensory modalities. Second, in some areas, unit responses are elicited by novel stimuli and are then subject to habituation with a time course which closely resembles the one described by Sokolov (1960) for the orienting reflex in the intact organism. The fact that novel sensory stimuli do not always elicit hippocampal responses suggests that the latter reflect orienting as much as they do stimulus processing per se.

A variety of specific firing patterns were observed to sensory stimuli. 'Phasic' responses were bound to the stimulus, occasionally involving an 'on' and 'off' response at the start and the end of the stimulus respectively. 'Tonic' responses continued after the termination of the stimulus. All of the above (including on–off)

could be initially excitatory or initially inhibitory. An advantage of the simple paradigm employed is that latency data as well as firing pattern were used in the analysis of the system. As Wiener (1996, pp. 350–1) notes, similar results have been obtained in restrained rats, cats, and monkeys, and also, apparently, in freely moving rats. In what follows, we will generally conflate the different types of response and concentrate on the relationship of the responses to stimulus presentation. However, it should be noted that the average firing rates reported by Vinogradova are often in the 10–40 spike/s range associated with 'theta' cells in the rat (see below). There is disagreement as to whether high rates and theta-related firing are a mode of cell activation or a type of cell (Vinogradova *et al*. 1993; Rivas *et al*. 1996). Whichever is the case, high-rate cells do not have the same receptive fields as low-rate cells (Jung *et al.* 1994). Thus, Vinogradova's results may apply to only a subpopulation of hippocampal cells; and, indeed, her conditions may have been such as to activate only that subpopulation, since many principal cells of the hippocampus (granule and pyramidal cells) may be silent except under quite limited conditions (see, for example, Jung and McNaughton 1993, p. 182).

A6.2.1.1 Entorhinal cortex

In the entorhinal cortex the spontaneous firing rates observed by Vinogradova's group were 20–30 spikes/s. The majority of responses were of the phasic and on–off varieties, mostly excitatory. Only 17 per cent of the responses were tonic. Both short-latency (12–20 ms) and long-latency (40–100 ms) responses were seen. Over 60 per cent of the cells showed multimodal convergence, but the responses to different modalities were usually of different kinds, as were responses to different stimuli within a modality (e.g. high and low tones). Habituation was virtually absent, and there was a tendency for reactions to increase after several (2–12) repetitions of the same stimulus.

These data are all consistent with the view that the entorhinal cortex encodes relatively specific multimodal sensory information (preprocessed and filtered by uni- and multimodal neocortical areas) which it then passes to the remaining levels of the hippocampal formation.

A6.2.1.2 Medial septal nucleus

Spontaneous activity was high (20–30 spikes/s) and often involved theta activity (see also Stumpf 1965; Apostol and Creutzfeldt 1974; Givens 1996). Reactions to stimuli were usually tonic and multimodal, with inhibitory responses (i.e. decreases in baseline activity on presentation of the sensory stimulus) slightly more numerous than excitatory ones. Both inhibitory and excitatory reactions tended to show theta activity. Signs of habituation were seen in only about one in three neurons and tended to be much more protracted and less complete than in CA3 or CA1. This habituation could reflect habituation of the cells providing the afferent input to the medial septum.

These data are all consistent with the view that the medial septum is a source of relatively non-specific multimodal sensory information (preprocessed by nuclei in the midbrain reticular formation) which it then passes to the remaining levels of the hippocampal formation. This information could also reflect the activation of

subcortical systems which direct responses to the stimuli, and we will argue that this is the better description.

Note that the principal effects of the septum on entorhinal activity may be through the presumed inhibitory (see Appendix 5), phasic component of theta activity. Our model of theta assumes that the medial septal nucleus also sends to the entorhinal cortex concurrent excitatory drive. But this clearly had little effect in Vinogradova's experiments, since entorhinal responses show much greater modality specificity than do medial septal responses. So it could be argued that the pacemaker (inhibitory) input from the septum to the entorhinal cortex (originating in the hypothalamus) represents an asymmetry which is not balanced by an equivalent entorhino-septal connection (although recent evidence suggests that such an entorhino-septal pathway does exist). On the other hand, the inputs from the medial septum to the hippocampal formation (originating in the reticular formation) and from the entorhinal cortex to the hippocampal formation both appear to target all levels. Both can therefore be viewed as primary input stages to the remainder of the system.

A6.2.1.3 Dentate gyrus

Spontaneous firing rates were either very low (1–2 spikes/s) or very high (30–40 spikes/s). The reactions fell into roughly three types: tonic inhibitory, phasic excitatory, and 'on' effects, i.e. short bursts of pulses at stimulus onset. The shortest latencies seen were about 3–4 ms longer than those seen in the entorhinal cortex, consistent with input from the perforant path. The majority of responses were multimodal. Habituation as such was absent. The duration of tonic inhibition sometimes reduced, but never disappeared, even after 200–300 trials. By contrast, nearly half the cells (42 per cent) gradually developed a response after about 15–20 trials. Some transformations from inhibitory to excitatory reaction or vice versa also occurred.

These data are consistent with the idea that the dentate gyrus responds to the familiarity of a stimulus. Analysis of sensory-evoked potentials in the molecular layer (essentially measuring the entorhinal input to these granule cells) suggests that the early firing (20 ms) cells in the entorhinal cortex produce EPSPs (excitatory post-synaptic potentials) which are progressively inhibited by (or as a result of) medial septal input as familiarity develops. Vinogradova's experiments suggest that, with simple habituation-type conditions, these EPSPs are insufficient to fire the granule cells (which may be receiving tonic inhibition). Likewise, the progressive increase in firing with training is the result of a progressive loss, during conditioning, of an inhibitory septal input (Deadwyler *et al.* 1981). Thus, the medial septum is gating the passage of information between the entorhinal cortex and the dentate.

A6.2.1.4 Field CA3 of the hippocampus

Spontaneous firing rates were typically 15–30 spikes/s. The majority of neurons responded to stimuli in all modalities tested with long-latency (50–200 ms) diffuse tonic changes of firing rate which outlasted the stimulus by several seconds. Both the latency and the multimodality of the responses were consistent with driving of the CA3 cells by septal rather than entorhinal input. Neurons with inhibitory reactions were somewhat more numerous than those with excitatory reactions. The adequate

stimulus for these neurons (in Vinogradova's experiments) was novelty, with a complete habituation of responses between 8 and 20 trials. This was true habituation, since the response could be reinstated by both increases and decreases in intensity, duration, or repetition rate of the stimulus. The reduction in response could also survive, without repetition of the stimulus and without apparent return to baseline, till at least the following day. This occurred despite the fact that the response of the same neuron to other, more novel, stimuli remained intact. Thus, while the initial response of the neuron was not stimulus-specific, and indeed was multimodal, the habituation of the response *was* stimulus-specific.

These data are consistent with the following hypothesis: non-specific stimulus information arrives from the medial septal area and induces a response in CA3 neurons; this response, however, is blocked if a stimulus-specific 'familiar–ignore' signal comes from the dentate gyrus. Note that, in this case, feedforward inhibition from the dentate to CA3 must be more important than feedforward excitation (consistent with the recent studies of mossy fibre anatomy discussed in Appendix 4). As we shall see, there are other experimental conditions where the reverse is the case. It is possible that the direct input from the entorhinal cortex to CA3 could be important here, as it could provide the basis for a comparison between the entorhinal signal and the dentate signal, determining the extent to which the stimulus had been successfully modelled. Essentially the same results are obtained in the septal and temporal portions of CA3.

A6.2.1.5 Field CA1 of the hippocampus

The spontaneous firing rates reported by Vinogradova's group in CA1 were typically lower than in CA3 (3–25 spikes/s). About half the cells responded to stimuli in only one sensory modality (as against 5 per cent in CA3), and some multimodal cells responded differently depending on modality. Many responses consisted of phasic changes, limited to the duration of the applied stimulus, rather than the tonic reactions typical of CA3. As with the entorhinal cortex, responses often incremented over the first 2–3 presentations. Given the responses observed in area CA3 and in the medial septum, at least some CA1 cells must receive their input from some other location, with the direct input from entorhinal cortex (Steward 1976) being the most likely. In this context it should be noted that, while perforant path stimulation produces only modest evoked potentials in area CA1, the ease with which it can fire CA1 pyramidal cells is equal to that seen in dentate granule cells (N. McNaughton, unpublished observations). In contrast to the predominantly excitatory reactions in the entorhinal cortex, about half the CA1 cells showed inhibitory responses. Habituation occurred as in CA3, but in fewer cases (74 per cent).

These data are consistent with input from the entorhinal cortex producing initial specific sensory responses in CA1 which, as a result, have the capacity to increment with familiarity. Unlike the entorhinal cortex and like CA3, the responses decrement with repetition. We can explain this if there is initially a diffuse subthreshold net activation of CA1 by CA3. There are at least two possible scenarios.

The first scenario involves excitation. On the first few trials, CA3 cells fire and depolarize large numbers of CA1 cells, without, however, taking them beyond their threshold. Those CA1 cells which receive additional input from the entorhinal cortex

then fire (and the firing over the first few trials increments because of the increments in entorhinal activity). As CA3 habituates, CA1 loses its modest background depolarization and cells cease to fire. (Those cells which do not habituate are ones which receive sufficient input from entorhinal cortex not to require CA3 input.) This scenario should please those who wish to put the monosynaptic excitatory Schaffer collateral input to work.

The second scenario involves disinhibition. The details are essentially as for the first scenario, except that the firing of CA3 cells is presumed to inhibit inhibitory interneurons which are normally tonically active. In terms of a system which controls stimulus-specific habituation, this latter is preferable to the first scenario, as it provides a cleaner 'gating' function. One might object that this arrangement does not make use of the major excitatory Schaffer collateral input in the way that this is usually assumed to work. However, we have already committed this same 'error' with the dentate input to CA3; and we will shortly describe conditions where the reverse is the case.

These two scenarios are not mutually exclusive, of course, but for the present paradigm, the second seems preferable. This will become more apparent when, at the end of this appendix, we consider the operation of the system as a whole and its rather different responses to simple stimuli (as in the experiments considered here) and complex ones (as in the spatial experiments considered later).

A6.2.1.6 Lateral septal nucleus

Most of the firing correlates of lateral septal neurons in these habituation experiments were the same as those observed in area CA3.

A6.2.1.7 Mammillary bodies

About half the neurons were 'pacemaker' neurons (not to be confused with the septal theta pacemakers) with regular firing which continues for long periods and which did not alter with sensory stimulation or repetition. The remainder had virtually no spontaneous activity and produced phasic excitatory responses locked to the stimuli. The responses were unimodal but not stimulus-specific and showed habituation. Of particular interest is the fact that the cells showed predictive or extrapolatory qualities: '(a) reaction prolongation up to the usual duration of a stimulus after the sudden shortening of a stimulus, (b) reaction cessation at the usual duration after the sudden prolongation of a stimulus, or (c) reproduction of the rhythmic reactions after switching off a stimulus series . . . [but] only when a stimulus is relatively novel (i.e. when reactions are not yet habituated in the hippocampus)' (Vinogradova 1975, pp. 17–19).

The mammillary bodies clearly get their input from areas outside the hippocampus which code complex, although largely unimodal, sensory information. These areas either carry out extrapolation themselves or may do so in interaction with the dorsal and ventral tegmental nuclei. In the same way that (as we have argued) CA3 sends a permissive signal which allows some CA1 cells to respond to entorhinal input, so it appears that the hippocampal formation can send a permissive signal which allows the mammillary bodies to receive the largely extrapolatory input from some other source.

This placement of extrapolation itself outside the hippocampal formation, coupled with the presumption that the extrapolatory function requires hippocampal input, is one of the many cases where we wish to attribute apparently complex information processing functions of the hippocampus to its interactions with its target structures rather than its own intrinsic capacities.

A6.2.1.8 The hippocampus and habituation

Before moving on we must draw the most obvious conclusions from the data summarized above.

First, even in this simplest of paradigms there was a large variety of different patterns of response, varying in whether the unit was initially activated or inhibited by a stimulus and the nature and time course of subsequent changes. However, when looking at the general pattern of changes across areas, some consistency emerged.

Second, CA3 appeared to be the focus of a *hippocampal* habituation process. Habituation was not seen extensively in the three structures which project to CA3 (the medial septal nucleus, entorhinal cortex, and dentate gyrus). It was, however, seen in the two structures which receive output from CA3 (the lateral septal nucleus and, less regularly, CA1). Thus, hippocampal habituation took place in CA3 and was then passed on to the latter two structures, as well as, potentially, the hypothalamus and other target areas. An active transfer of habituation, as opposed to a loss of previous excitation, was suggested by the fact that, if the connection between CA3 and the lateral septum was severed, habituation no longer occurred in the lateral septal area; on the contrary, unit responses tended to increase with stimulus repetition (Vinogradova 1975; Vinogradova and Brazhnik 1978).

Third, habituation in CA3 appeared to be based on detection of a match between medial septal and entorhinal inputs. If the septum was disconnected from the hippocampus *or* if the entorhinal cortex was disconnected from the hippocampus, the ultimate response of CA3 cells was a gradual increase rather than decrease in firing rate. Further, the initial stimulus-non-specific responses in CA3 must come largely from the septum, while the stimulus-specificity of the habituation must come from the entorhinal cortex. Note that a mismatch in either direction resulted in CA3 output, and that a stimulus-specific signal could cancel a multimodal signal.

Fourth, concurrent with habituation to a familiar stimulus in CA3 (8–15 presentations), there was a build-up in the response first in the entorhinal cortex (2–12 presentations of the stimulus) and then in the dentate gyrus (15–20 presentations). This augmentation of response is most simply explained as a spread of long-term potentiation (LTP), probably starting in cortical areas which build up a model of the stimulus, and progressing through the entorhinal cortex to the dentate gyrus. This potentiation could correspond to a build-up of ‘familiarity’ (Vinogradova and Brazhnik 1978).

Thus, according to Vinogradova, the same simple stimulus can affect the hippocampus through two routes. On first and subsequent presentations, it activates the reticular system and affects the hippocampus via input from the medial septum. Successive presentations allow a ‘cortical model’ of the stimulus to be built (which

could be done by Hebbian association, initially depending on LTP or related mechanisms). Once this cortical model is sufficiently complete, it affects the hippocampus through the second route, the entorhinal cortex. This second input cancels the effects of the first, resulting in the observed habituation in CA3.

There is an important practical reason for preferring this, essentially inhibitory, view of dentate gyrus LTP to the view that it reflects associational learning or map building (see discussion in Elliott and Whelan 1978, p. 407 et seq; and, for example, McNaughton and Morris 1987; O'Keefe and Nadel 1978, p. 230). Vinogradova (personal communication) has shown that, if LTP is artificially induced by perforant path stimulation, the hippocampus proper becomes totally unresponsive to natural stimuli which had previously elicited a response (see also Miller *et al*. 1995). If LTP represented storage of a stimulus, the opposite result would be expected—an increase in responses to natural stimuli.

The results presented by Vinogradova's group provide a satisfyingly coherent account of how the septo-hippocampal system performs at least one of the functions, processing of novel stimuli, which has been attributed to it. There is also evidence from PET (positron emission tomography) scans that the hippocampus (and other components of the limbic circuit) is activated by novelty of stimuli in human beings (Tulving *et al*. 1994). But Vinogradova herself has warned that 'it is curious how we find in the brain what we are looking for' (in Elliott and Whelan 1978, p. 197). There has, indeed, been some question as to how far Vinogradova's results can be replicated (Hirano *et al*. 1970; Lidsky *et al*. 1974*a*,*b*; Mays and Best 1975; but see also Segal 1974; Best and Best 1976). As we shall see below, this variability of results is likely to depend on the extent to which different stimuli result in orienting; and we will argue that the habituation experiments are better explained in terms of processing of goals (and hence, potentially, responses) than processing only of stimuli.

Thus, Wiener and co-workers obtained sensory correlates of hippocampal unit activity in freely moving rats of a similar type to Vinogradova's, and noted that 'these discharges had no location-selective or task-related correlates. . . . These were not simply novelty responses since the rats had experienced these stimuli in many training sessions. . . . [They appear] linked, perhaps in an indirect manner, with movements triggered by the sensory stimuli. . . . [For example,] visual stimuli could trigger orienting responses like eye movements; the latter have been shown to be correlated with hippocampal activity in the monkey' (Wiener 1996, pp. 351–2; Korshunov *et al*. 1996; see also Givens 1996 on the predominance of response-related correlates in the medial septum).

There are, in any event, results which suggest that, in other paradigms, quite different types of event can affect the hippocampus, and quite different changes in cell firing can be obtained. We will now consider, therefore, results obtained with simple conditioning experiments.

A6.2.2 Correlates of simple conditioning

The stimuli used in habituation experiments have little enduring significance for the animal. The same kinds of simple sensory stimuli can be given continuing

significance by the methods of classical or instrumental conditioning. This significance can preserve hippocampal unit responses from habituation.

An extensive research programme studying the conditioning of the rabbit's nictitating membrane response, initiated by Theodore Berger and Richard Thompson, is of particular interest, as essentially the whole neural circuit involved in this response is now known (and has also been confirmed in human beings; Logan and Grafton 1995; Blaxton *et al*. 1996). We will deal with the septo-hippocampal responses first.

Hippocampal and septal responses were recorded (Berger and Alger 1976; Berger and Thompson 1978*a*,*b*) during the course of nictitating membrane conditioning with a tone CS and an air-puff UCS in restrained rabbits. A control group received unpaired presentations of the CS and UCS. An important point to note is that this preparation is largely the same as Vinogradova's, differing only in the behavioural paradigm and in providing a less sensorily deprived environment. This similarity facilitates comparison. The bulk of Thompson's early data was obtained with *multiunit* recording; more complex results can be obtained with conventional single-unit separation techniques (e.g. Berger *et al*. 1983; Weiss *et al*. 1996).

Medial septal neurons showed an average increase in responding (the multiunit record must be treated as a form of average) to both the tone and the airpuff, and showed no change in responding over the course of training. Similarly, Segal (1973), using a lever press paradigm in rats, found only non-habituating, short latency (12–24 ms) unconditioned responses in the medial septal area when tones were used as CS+ and CS– for food; but see Yadin (1989). These multimodal, non-habituating responses are consistent with Vinogradova's results.

Dentate, CA3, and CA1 activity did not change on presentation of the stimulus or on repeated unpaired presentations, but increased with conditioning trials. The fact that the hippocampal response only occurred in relation to conditioned but not unconditioned nictitating membrane responses is of particular importance for interpretation of these results. The changes in the frequency of multiunit activity with time within a trial showed a strong relationship to the amplitude–time relationship of the nictitating membrane response (providing a 'temporal neuronal "model"'; Alger and Teyler 1976, but see also Weiss *et al*. 1996). These electrophysiological changes preceded the behavioural response both within a trial and in the sense that they showed conditioning before behavioural conditioning was evident (Berger *et al*. 1983). The same pattern has also been seen with classical conditioning of an appetitive jaw movement in the rabbit. As the occurrence of the eyeblink moved forward in time from trial to trial, so too did the hippocampal activity. This occurred in an apparently similar manner for all three hippocampal areas. A similar change occurred in lateral septal neurons. However, the development of conditioned lateral septal responses appeared slower than that of hippocampal responses during the early part of conditioning. Importantly, activity in the mammillary bodies was not changed by the stimuli and did not develop with conditioning.

An apparent major discrepancy between these results and those of Vinogradova is that there was no response to the CS or US on the first few trials. There are two possible reasons for this discrepancy.

First, Vinogradova's rabbits appear to have been in a more sensory-reduced environment, within a semi-dark, soundproof box as opposed to a plexiglass apparatus. This should have made her stimuli more startling or salient than the stimuli used by Berger and Thompson. We have already suggested that her single-unit responses could have some relation to the orienting reflex, and orienting would be more likely under her conditions. The intermittent short responses in CA3 during pseudoconditioning of CS-food by Segal and Olds (1972) suggest that fast habituation, as well as an initial lesser orienting response, could have led to the lack of CS-induced responses in Berger and Thompson's results. The detailed conformity of the firing to the occurrence of the response suggests a functional relationship with these responses, or with response-related stimulus processing, rather than simply with the stimulus itself. Similar results are obtained with auditory-evoked potentials in the hippocampus. These too model conditioned orienting (Ruusuvirta *et al*. 1995).

Second, Vinogradova reported approximately equal increases and decreases in responding in each of the areas of interest. The multiunit record would have averaged these to no apparent response. Such cancellation would occur with 'theta cells', since Berger *et al*. (1983) found both phasic theta-on and phasic theta-off cells. However, separate pyramidal cells were found to show no unconditioned responses and to model the nictitating membrane response, respectively (Berger *et al*. 1983).

A major similarity between the two sets of studies is the gradual development in the dentate gyrus of responses with repeated trials. In the case of the conditioning experiments, these responses have the temporal topology of the motor response. This is likely to have been the case also for the (unmeasured) responses in Vinogradova's experiments, given the results of Ruusuvirta *et al*. (1995).

A theoretically important difference between the results obtained in the habituation and conditioning experiments, respectively, appears in both CA3 and CA1. In the conditioning experiments responding increases, in both CA3 and CA1, in parallel with the increase in the dentate. This increase parallels the development of conditioned responding (but see below). In the habituation experiments, responding decreases in CA3 and CA1, apparently suppressed by the increase seen in the dentate. In both cases, therefore, the dentate 'model' (Berger and Alger 1976) is closer to the stimulus events, while the CA3 and CA1 'model' is closer to the response events (changing from non-response to response in the conditioning experiments, and changing from response to non-response in the habituation experiments).

Two additional points should be noted about the conditioning results (for most of the following see Berger *et al.* 1986*a*).

First, the circuit which is the basis for both the actual conditioning and for the conditioned response itself has been well worked out by Berger, Thompson, and their colleagues. It does *not* include any part of the septo-hippocampal system. Conditioning depends on a simple reflex system eliciting the unconditioned response. The unconditioned response is transformed into a conditioned response by plasticity in a circuit involving the deep cerebellar nucleus and the red nucleus. This circuit connects neurons which respond to the CS with neurons in the UR circuit, and so closely parallels the mechanism of simple avoidance conditioning in the amygdala (described in Chapter 6).

Second, lesion of the hippocampus (or indeed decerebration; Mauk and Thompson 1987) does not usually interfere with the conditioned nictitating membrane response; nor with its acquisition in the basic form of the paradigm; nor when a delay procedure is used (in which the CS overlaps the US in time). Here, we should remember that, while area CA1 showed conditioned responses, the mammillary bodies did not. The mammillary bodies receive their hippocampal information from the subiculum rather than CA1, and from the lateral septum rather than CA3. This suggests that the conditioned reactions in CA1 and CA3 are not transferred to the subiculum and lateral septum, respectively, unless additional criteria are met. (We have already seen such a lack of transfer within the hippocampus in that the dentate reaction is not matched in CA3 and CA1 if the stimuli prove unimportant.) What these other criteria may be we will consider in Chapter 10—but it is a pity that the subiculum, lateral septum, and mammillary bodies are not as popular places for recording as area CA1.

By contrast, eyeblink conditioning becomes sensitive to hippocampal lesions if more complex conditioning paradigms are used: trace conditioning (where there is no temporal overlap between the CS and the US); latent inhibition; blocking; and reversal but not acquisition of a variety of sensory discriminations (Appendix 8). These results, taken with the 'modelling' by the hippocampus of the simple conditioned response, are a reminder of a point we started with, that the most obvious correlate of an increase in a cell's response may not be a good indicator of function. Consistent with the inhibitory view of the hippocampus which we present in Appendix 8, reversal of the nictitating membrane response is impaired after hippocampal lesions due to failure to inhibit responses to the previously incorrect, but now correct, stimulus, rather than due to failure to acquire the newly correct response. The missing inhibition could, when the hippocampus is intact, be supplied via the CA3 output to the lateral septum, via the subicular output to the mammillary bodies, via the subicular output to posterior cingulate, or via more minor efferents (Berger *et al*. 1986*a*). Consistent with the idea of a posterior cingulate route, Berger *et al*. (1986*b*) showed that lesion of this region produced a similar loss of inhibition of incorrect responses.

As we have seen, there are a number of points at which these results with conditioning are in general agreement with Vinogradova's experiments on habituation. Medial septal responses are immediate and relatively unchanging. CA1 and CA3 pyramidal cell responses appear to depend on interactions between the septum and entorhinal cortex. Only the nature of the change in activity is diametrically opposite in the two paradigms. An initial response is lost in the habituation experiments. An initial lack of response is replaced by a large response in the conditioning experiments. There is a strong resemblance between lateral septal and hippocampal activity. This resemblance appears to be due to transfer of information from CA3 to the lateral septum.

Vinogradova's results are most easily described in terms of hippocampal activity coding for familiarity of stimuli, with the critical output from area CA3 permitting novel stimuli to activate the lateral septal area and the mammillary bodies. Given the hypothalamic targets of this output, we can then say that the output from area CA3 allows novel stimuli access to response mechanisms. However, novelty itself may not be critical, given the lack of response to simple stimuli observed in the conditioning experiments; and, as suggested by Wiener, the septal activity may reflect input from subcortical orienting-related mechanisms.

The results of the conditioning experiments are most easily described in terms of hippocampal activity coding for upcoming responses, rather than for the stimuli which elicit the responses. However, this coding is not necessary for production of the responses being coded; nor does it appear to produce significant output from the hippocampal formation; nor does it accompany the unconditioned responses.

What is needed, then, is a view of Vinogradova's results that is more response-oriented, coupled with a view of the conditioning experiments that is more stimulus-oriented. This can be achieved by rephrasing both sets of data in terms of goals.

We propose that, with a stimulus which is sufficiently intense or significant to elicit an orienting reflex, septal and hence hippocampal cells react. Here the hippocampus is detecting neither the stimulus nor its novelty, as such, but the requirement to produce a response directed to the source of the stimulus (possibly indicated by the priming, but not release, of subcortical response systems), that is it has detected a goal. After suitable long-term potentiation (or other plasticity) in a variety of structures, including finally the entorhinal cortex and dentate gyrus, a model of the goal arrives in the hippocampus and (if the stimulus is a neutral one) cancels the effect of the septal response. This model of the goal effectively codes familiarity. Since it is not accompanied by other inputs which would indicate preparation for action (see below), it also indicates unimportance. A significant feature of this circuit is that a subsequent failure of the septal input to match the model, that is omission of the expected stimulus, will result in hippocampal output. Thus, not only does the entorhinal input gain the capacity to block the effects of the septal input, but the septal input concurrently gains the capacity to block the effects of the entorhinal input.

This symmetry between the perforant path and septal inputs to the dentate may result from the fact that both are equally capable of long-term potentiation (McNaughton and Miller 1984).

Essentially the same processes occur in relation to conditioned responses. The septal input remains constant, and the perforant path finally provides a model of the goal. However, the presence of an additional input signifying response preparation results in augmentation rather than depression of responses in the trisynaptic circuit. This additional input almost certainly includes corollary discharge from the response system, as shown by the nictitating membrane response 'model', but in at least some cases (see below) will include less specific serotonergic input. However, the lesion data show that the absence of some further signal prevents CA3 and CA1 activity from being passed to output targets of the hippocampal formation. This gating could occur between CA1 and its outputs, particularly the subiculum, or between subiculum and mammillary bodies; or in the lateral septum, which is known to show long-term potentiation and so could pass altered output to its targets (Garcia *et al*. 1993; Garcia and Jaffard 1996).

We should also note that the multicellular records suggest that the increase in firing rate, at least in area CA3, is quite general. It occurs even when the classically conditioned stimulus is superimposed on quite different instrumentally conditioned baselines. Thus a CS for shock produces an increase in CA3 firing rate, and continues to do so both when superimposed on an aversive baseline (when the CS increases behavioural responding) and on an appetitive baseline (when the CS decreases

behavioural responding), as was shown by Laroche *et al*. (1987). Berger *et al*. (1983, p. 1206) reported 'that 83% (40/48) of all pyramidal neurons significantly increased firing rate within either the CS period or the UCS period or both periods.' Some of their individual cells showed the same modelling of the conditioned response as the multiunit record (see their Fig. 6a), but others showed much more restricted firing which suggested that 'a complete unit representation of the conditioned NM [nictitating membrane] response may be produced by the simultaneous activities of many pyramidal cells' (Berger *et al*. 1983, p. 1208). We will return to this issue below.

A6.2.3 Correlates of discrimination learning

So far, the experiments we have discussed have mostly involved restrained animals. In this section, we discuss experiments in which the animal is free to move in any way it pleases. While some of its responses are usually monitored (e.g. lever presses), it will be very uncertain whether stimulus-related changes are the result of some unmonitored response. Freedom to move is also likely to have increased the number and type of hippocampal units actually responding (see discussion of head direction cells below). A further complication is that there has been no systematic comparison of responding across septo-hippocampal fields.

Hippocampal activity during discrimination learning was first reported by Olds and his colleagues, mainly working with a technique which required the rat to remain motionless for 1–2 s upon presentation of a signal and then to take food or water from a magazine. Using a tone CS for food, Olds and Hirano (1969) found that an initially inhibitory hippocampal response was transformed by conditioning into an excitatory one. Other than the fact that the signal generated an initial inhibition, this result is essentially identical to that found in the eyeblink conditioning studies. The size of this anticipatory type of response across a number of experiments could be shown to vary somewhat between anticipation of food versus water (Olds *et al.* 1969) but not between lever press for food versus lever press for shock avoidance (Fuster and Uyeda 1971). It was also greater for a CS+ than for a CS– (Hirano *et al.* 1970; Sideroff and Bindra 1976). Taken together, these results are all consistent with the idea that hippocampal reactions in area CA1 and CA3 are anticipatory of goals. For example, with the reinforcer case, food and drinking are different classes of goal and so produced different electrophysiological reactions, while in the food/shock case the immediate goal was a lever press in both cases and so produced a similar reaction despite the difference in reinforcer.

Segal and Olds (1972) found that, like Vinogradova's rabbits, rats presented with a nominal CS+, CS–, and food US showed marginal brief changes in CA3 firing during pseudoconditioning (equivalent to Vinogradova's habituation training). When the CS+ was made the signal for delivery of the US, dentate responses appeared (as a brief acceleration), followed (as training developed and as in the nictitating membrane experiments) by CA3 and then CA1 responses which continued throughout the CS–US interval. These responses were differential in that no conditioning to the CS– was observed. Only about half of the CA1 cells behaved in this fashion, consistent with some direct driving from entorhinal cortex.

Foster *et al*. (1987) investigated cell firing after training to criterion on a two-tone successive discrimination procedure. They classified cells as theta cells, complex spike cells (Appendix 5), and granule cells.[1] All three cell types increased their response rate to both the CS+ and CS–, with dentate granule cells and theta cells differentiating moderately between the two stimuli, as in the experiments described above. Complex spike cells did not appear to differentiate between the stimuli on an overall average. However, all three cell types were affected by local variations in reward density. Increasing numbers (1–5) of trials (either CS+ or CS–) of the same type increased granule cell responding on a subsequent CS+ trial. At the longest sequence, this effect was greater for CS+ than CS– (reminiscent of the effects seen by Vinogradova in the dentate). Short sequences (1–3) but not longer ones of CS– (but not CS+) trials depressed theta-cell responding on a subsequent CS+ trial. The complex spike cells did not appear to show any overall trend to an increase or decrease in CS+ response with increasing sequence but, at the longest sequence, showed the inverse of the granule cell discrimination effect: a depression of CS+ responding following the CS+ sequence, and an increase in CS+ responding following the CS– sequence. This granule cell–CA3/CA1 cell relation is reminiscent of Vinogradova's results.

It is worth mentioning here a study by John and Killam (1959). This used an interesting methodology which (to our knowledge) has not resulted in any further studies. They presented a flickering CS with the idea that the gross EEG response to the stimulus would be tagged by the specific flicker frequency used (10 Hz). Given the specific flicker frequency chosen, it is difficult to tell whether their hippocampal responses were non-theta activity entrained by the stimulus or theta activity reset by the stimulus. However, they found that, on initial presentation of the CS, hippocampal 10 Hz activity was seen and quickly habituated. During avoidance conditioning to the stimulus, hippocampal 10 Hz activity first waxed and then, as conditioning proceeded, waned. Finally, hippocampal 10 Hz activity appeared again during the early phases of extinction. Thus, apparent hippocampal access to the stimulus occurred specifically during the periods when the animal was likely to be changing its responses (i.e. in the middle rather than at the start of conditioning) and when autonomic output was likely to be highest (Coover *et al.* 1973), suggesting an involvement of aminergic systems (Appendix 10). This is very reminiscent of Vinogradova's habituation results. A similar effect is seen with release of acetylcholine (ACh) during simple barpress learning, where ACh is released in the hippocampus only during the period when the animal is altering its response strategy (Orsetti *et al.* 1996).

Segal (1975) studied further the basis for the unit responses to positive and negative CSs for food. Units in the entorhinal area showed differential responses to the CS+ and CS–, and in some cases the responses to CS+ were of very long duration, lasting up to a minute (matching Vinogradova's results). In the hippocampus, Segal noticed that, if the inter-trial interval (i.e. the interval between successive presentations of the CS+) was less than a minute, there was an augmentation of the unit response to the CS+. He suggested that this might be due to the sustained entorhinal input to the hippocampus lasting over this interval. This suggestion was supported by the finding (Segal 1975) that transection of the perforant path eliminated the augmented hippocampal response otherwise seen in CA1 and CA3 at inter-trial intervals less than a minute.

Segal (1977*a–d*; see also Doyère *et al*. 1995) also showed that transmission round the hippocampal circuit was facilitated by a CS (tone or light) for a US (either food or shock), and that similar effects could be produced by activation of either the noradrenergic input from the locus coeruleus or the serotonergic input from the median or dorsal raphe.

As we noted when considering the electrophysiology of the hippocampus, the effect of cholinergic, serotonergic, and noradrenergic input should not be viewed as simply excitatory or inhibitory. Rather, these inputs appear to change the signal-to-noise ratio, depressing the effects of weak inputs by inhibiting all inputs presynaptically, while effectively increasing the effects of stronger input by increasing postsynaptic excitability.

These 'paradoxical' aminergic effects can account for other data obtained by Segal and Bloom (1976). They found that, before conditioning, a tone elicited inhibitory responses in the hippocampus, mediated by noradrenergic input. When the tone was made a CS for food, the hippocampal unit responses became excitatory. Preceding the CS by locus coeruleus stimulation now *increased* the size of these excitatory responses. Thus the direction of the effect of noradrenergic input was opposite in the two cases. If the stimulus was of no particular consequence, noradrenergic stimulation increased the inhibition of unit firing; if the stimulus predicted food, it increased excitation. In both rats and monkeys, cells in the locus coeruleus (LC) increase their firing in response to 'sensory stimuli of many modalities . . . [and] the most effective and reliable stimuli for eliciting LC responses were those that disrupted behaviour and evoked orienting responses . . . [suggesting] a role for the LC system in regulating attentional state or vigilance . . . the cognitive complement to sympathetic function' (Aston-Jones *et al.* 1991, p. 501).

Results with a rather different technique, but with similar implications, have been reported by Deadwyler *et al.* (1979) and Lynch *et al.* (1978). They found that a tone CS for water-rewarded lever pressing produced a field potential in the outer molecular layer of the dentate gyrus (i.e. in the termination zone for the perforant path). This potential appeared only after the animal had learned to use the tone as a signal for the response, disappeared during extinction, and reappeared during reconditioning—these changes matching the changes in the animal's behaviour. Deadwyler *et al.* (1981) showed that these effects resulted from interactions between septal and entorhinal input.

So far, these results confirm the other demonstrations that conditioning facilitates the passage of sensory responses through the hippocampal formation. However, although the evoked potentials indicated that there was a large input to the dentate gyrus from the perforant path, this was not accompanied by reliable discharge of the dentate granule cells. For this to occur, it was necessary also to present a second, non-rewarded tone—imposing on the animal a requirement to discriminate between the two tones. The positive tone now produced a prolonged granule cell discharge, while the negative one produced an initial burst of spikes followed by a rapid return to baseline firing rates.

Thus, optimal passage of information through the dentate gyrus required not only the conditioning of a positive stimulus but also the formation of a discrimination between

positive and negative cues. This finding is perhaps related to the increased orienting reflex which is known to occur if a discrimination is substituted for a simple excitatory behavioural response (Sokolov 1960, 1963) and is likely to be mediated by the noradrenergic input to the hippocampus (see comments on the LC above).

An additional layer of complexity is suggested by the results of Doyère *et al*. (1995). They monitored the dentate response to a single perforant path stimulus during off-the-baseline conditioned emotional response training with both classical conditioning and pseudoconditioning trials. Consistent with the results we have reviewed so far, perforant path EPSPs increased during conditioning and decreased during pseudoconditioning, while population spike responses decreased under both conditions. The increase in EPSPs subsequently decreased with overtraining.

There are two features of these results that require comment. First, despite an increase in EPSPs, there was a decrease in population spike responses (and, unlike EPSPs, the population spike did not differentiate between conditioning and pseudoconditioning). This lack of increase in the population spike response is not consistent with the idea that output from the hippocampus supports learning. Second, conditioning trials resulted in any increase in a gross population response. This implies that a large number of a randomly selected (by the electrode position) bunch of nerve fibres *all* demonstrated increased transmission. This in turn implies that there is *no* coding of the specific learning stimuli by the hippocampus itself, and that any specificity in hippocampal cellular responses to natural stimuli is the result of gating (Appendix 5) by the hippocampus of input patterns which are already stimulus-specific (but see also Miller *et al*. 1995). These are not the synapse-specific effects which would be required if the hippocampus were storing ‘engrams’ (see McNaughton and Morris 1987).

Consistent with this argument, Stolar *et al*. (1989) found parallel development of discriminative responses in the dentate and areas such as the thalamus and cingulate, with little reduction in discrimination in the latter areas after subicular lesions. However, the dentate gyrus showed ‘massive brief-latency field potentials to . . . rare CS+ and CS– . . . [and] the enhancements of posterior cingulate cortical discharges and the suppression of the anteroventral thalamic discharges to rare CS+ presentation in intact rabbits did not occur in rabbits with hippocampal (subicular) lesions . . . [suggesting] that hippocampal inputs to the cingulate cortex and limbic thalamus are important and perhaps essential for novelty-induced modulation of neuronal firing in these structures’ (Stolar *et al*. 1989, p. 931).

A6.2.4 Habituation, simple conditioning, and discrimination combined

Overall, then, it appears that the medial septum provides an input which, because of its early occurrence and multimodality, is likely to be relatively uninformative, except for the fact that there may be a need to cope with a situation (i.e. a goal is present and subcortical, for example orienting, response mechanisms are primed). By analogy with the subcortical visual input to the amygdala (Fig. 6.1), this is a ‘quick and dirty’ pathway. In the absence of a suitable preprogrammed reaction (signalled via the entorhinal cortex), output from the hippocampus will elicit exploratory behaviour (cf. simple avoidance from the amygdala). After a number of occurrences of a stimulus,

neocortical areas build up a model of the stimulus and of any required responses. These goals are passed to the hippocampus by the entorhinal cortex, with the final step of model building (or at least plasticity) occurring in the dentate gyrus. An important point is that separate models must be passed simultaneously for all current potential goals if inappropriate exploration is not to be elicited.

In the absence of modulatory aminergic input, the coincidence of septal and entorhinal input eliminates hippocampal output (but if *either* input occurs alone, then an output is generated). This is the equivalent of the case where a primed amygdala avoidance reaction is cancelled by a cortical signal indicating that a threat is not in fact present.

In the presence of aminergic input, weak inputs are suppressed by presynaptic inhibition (matching the inhibition of spontaneous single-cell activity seen in paired-pulse paradigms), while strong inputs are facilitated by postsynaptic increases in excitability (matching the potentiation of population spikes seen in heterosynaptic paired-pulse paradigms). This results in potentiation continuing to progress into the hippocampus and increasing cellular responses (equivalent to complex avoidance conditioning in the amygdala).

The results of Foster *et al*. (1987), discussed above, indicate that the activating effects of reinforcement and local habituation-like changes resulting from predictable sequences can summate with each other.

We have discussed direct evidence for what could be called a logical (as well as a neural) gate only between the dentate on the one hand and CA1 and CA3 on the other. However, there appears to be a series of logical conditions which can result in augmented activity in dentate only, or dentate and CA3 only, or dentate and CA3 and CA1 only, or through the entire trisynaptic circuit, or, finally, in the targets of hippocampal output. No doubt more complex combinations are also possible.

It is important to note that Vinogradova's data on LTP, the data from Thompson's group on eyeblink conditioning, and the effects of hippocampal lesions (Appendix 8), all imply that the hippocampus is not the site at which a model of any goal is stored. Rather, the hippocampus receives a *copy* of the output from a number of models constructed elsewhere in the brain and is then a location at which the requirement for, for example, exploration is indicated by any mismatch between actual with modelled input.

We have concentrated on the role of LTP in the perforant path. It should be emphasized that virtually all excitatory inputs to the hippocampus support LTP. These include the medial septal input (see Appendix 5), with the possibility of complex mutual interactions with the perforant path input. As we noted in Chapter 6, the best current evidence for involvement of LTP in associative conditioning is in the amygdala. We must be prepared, therefore, for LTP (and LTD) to play a wide variety of roles.

A final point to note is that, matching the parallel septal and entorhinal inputs to all levels of hippocampus proper (demonstrated anatomically), we have seen good evidence that quite specific entorhinal information can frequently be passed directly

to area CA1, and that the same information, once filtered by the dentate gyrus and the septal inputs, can appear effectively degraded within area CA3 before being passed on 'to meet itself' in CA1. It is, of course, not 'the same information' and the entire purpose of the linear organization of hippocampal fields may be to provide a hierarchical series of logical gates, with output possible from each level of the system.

The experiments we have considered so far have used both simple stimuli and simple learning paradigms in, frequently restrained, rats and rabbits. Nonetheless we have discovered quite complicated hippocampal reactions and a number of cases where we could not extrapolate directly from the apparent stimulus or response correlate to the functional significance of cell firing in any one area. We have also uncovered systematic relations between the different components of the hippocampal formation. With our overview of these data as a foundation, and a warning, we now turn to data from more complex tasks for which, furthermore, we have much less information about the transformations occurring between the areas of the hippocampus.

A6.2.5 Correlates in memory tasks

We have already seen, even with as simple a task as nictitating membrane conditioning, that the hippocampus can be selectively activated by conditioning of a response. Given the involvement of hippocampal damage in amnesia in human beings, we would expect similar results to be obtained with complex tasks and stimuli. These have usually been investigated in monkeys to achieve as close an approximation to the human brain as possible.

Before discussing these results, we should note that hippocampal cells can fire in relation to the spatial position of the animal (see below). However, like the rabbits we have just discussed, the monkeys are restrained. They sit in chairs during testing, with their heads clamped in a fixed position, and so, in the experiments we will consider in this section, the spatial position of the monkey itself cannot vary. The arms and eyes are free to move, and so the goal of the monkey's current response (usually reaching) could be related to spatial position. Given the results we have discussed so far, we would expect hippocampal unit firing to show spatially-related firing if reinforcement were correlated with spatial position. However, in the experiments described in this section, spatial position is deliberately uncorrelated with reinforcement because the experimenters wish to study memory for only those stimuli which they present to the monkey.

The use of working memory paradigms also allows us to pin down more closely what aspects of the stimulus and response may be controlling hippocampal activity. For example, Colombo and Gross (1994) tested monkeys in auditory–visual and visual–visual delayed matching-to-sample tasks. Inferotemporal cortex firing was stimulus-specific during the delay, whereas hippocampal firing was not stimulus-specific and incremented during the delay (about half of entorhinal cells may be stimulus-specific in such tasks; Suzuki *et al.* 1997). Colombo and Gross (1994, p. 452) noted that 'the increase in activity may represent some form of readiness potential not necessarily tied to any specific motor act' since the specific response to be made was not determined until the end of the delay.

This suggests that hippocampal cells are activated by *available* goals (perhaps signalled by the priming of response systems which could achieve those goals), rather than by a unique current goal (or corollary discharge from the release of current behaviour). In the nictitating membrane and simple discrimination experiments, there is only one available goal and so we see an apparent 'response modelling'. But during the working memory delay there are two available goals and so we should see 'modelling' by at least two separate populations of hippocampal neurons. At the end of the interval the test stimulus causes only one of the two concurrently primed goals to be activated. Certainly, the results show that the hippocampal activity does *not* simply encode the nature of the to-be-remembered stimulus (since its firing, unlike that of the inferotemporal cortex, was not stimulus specific); and it cannot be coding the specific response to-be-made either (since the nature of this response is not determined until the test stimulus is presented).

We should always remember that it is the subject not the experimenter that determines what is a goal; and so memory tasks can demonstrate not only fields that appear complex but also a number of such fields concurrently within any specific part of a particular task. For example, Brown (1982) recorded hippocampal units in rhesus monkeys required to perform a non-spatial conditional discrimination; certain of the units responded (or not) depending on the context in which a particular stimulus was presented. Riches *et al.* (1991; see also Watanabe and Niki 1985) tested monkeys in a visual delayed matching-to-sample task and found cells which responded to the sample stimulus, the delay, the test stimulus, and combinations of these (in perirhinal and parahippocampal as well as hippocampal cortex). Sakurai (1994) employed an auditory go–no-go working and reference memory task in rats and recorded cells in both auditory cortex and hippocampal formation. He reported that some units in all areas fired in relation to the stimuli employed in only one of the two tasks. More cells (40 per cent) fired in the reference memory task than the working memory task (10 per cent) and only auditory cortex neurons responded in both the working and reference tasks (50 per cent). About 30 per cent of units in all areas fired differentially during the delay period depending on the to-be-remembered stimulus ('sensory retention')—but *only* in the reference memory task. About 80 per cent of hippocampal cells fired after the presentation of the test stimulus and preceding the response about to be performed, some in the reference task, some in the working task, and some in both. This was also true for about 25 per cent of auditory cortex cells.

Here, we have a selection of experiments in which a variety of possible complex 'fields' have been searched for and indeed found. These could be the result of highly complex processing by the hippocampus. But they are also consistent with the 'available goal' fields we deduced from the simpler tasks, provided we can assume that different units code different successive subgoals within a complex sequence (see Wiener 1996, and below). Sakurai's results are of particular interest here. He found relatively similar fields in both auditory and hippocampal cortex, but with a much stronger bias to stimulus specificity in the auditory cortex and a much stronger bias to response anticipation in the hippocampus. In an earlier go–no-go experiment Sakurai (1990) found that dentate cells were often like motor cortex cells in firing whenever the animal made a response, whereas a proportion of CA1 and CA3 cells fired only when the animal made correct, but not incorrect, responses. A later study by Sakurai (1996), using auditory, visual, and auditory–visual configural variations on the same basic task, found that there were cells in the hippocampus which responded to one,

two, or all of the task combinations, and he argued that cell assemblies rather than single cells were coding unique information. This could well be true, but unique 'available goal' fields could also account for these results.

Recently, Eichenbaum and Cohen (1988; Cohen and Eichenbaum 1993) have attempted to integrate these obviously non-spatial fields with the equally obviously spatial fields we will consider below and with hippocampal involvement in human amnesia. Their key idea is that of 'relational processing'. A spatial task, by definition, requires the analysis of the relations between a number of stimuli (in this case angular relations). At least, where spatial tasks do not have this property (e.g. in the T-maze), they are not sensitive to hippocampal lesions (Appendix 8); and something of the same sort can be discerned in non-spatial paradigms.

The nub of Eichenbaum and Cohen's argument is that 'hippocampal neurons fire in association with various nonspatial task-relevant stimuli and conjunctions of such stimuli . . . In instrumental paradigms, some CA1 neurons have been observed to fire in association with discriminative stimuli in any sensory modality – auditory, visual or olfactory. Others have found CA1 cells to fire in relation to conditioned appetitive movements. . . [but not] in relation to simple sensory or motor events. [They] reflect higher-order relationships, beyond the multimodal processing of the neocortical areas that project to the hippocampal system . . . To our way of thinking, this reflects the processing of relationships among the task-constrained objects or events with which the animal is confronted, the task-defined relevance or significance of those objects or events, and the *behavioral responses* made under these constraints. This is truly relational processing' (Cohen and Eichenbaum 1993, pp. 115–18, our emphasis, a large number of citations omitted; see also Young *et al.* 1994).

While it appears true that in complex tasks hippocampal cells fire mostly as a result of memorial and relational processing, with spatial processing as a special case, we already have reason to believe that the cells also fire in minimally relational situations. It is remarkably difficult to see what is 'relational' about the nictitating membrane conditioning paradigm. Eichenbaum's own data suggest that this is true also within an odour-discrimination task in which he undertook a careful analysis of stimulus, behaviour, and electrographic features of the situation.

> Three major categories of cells were identified: (1) 'Cue-sampling' cells fired after onset of odor-cue sampling. Response magnitude was related to cue valence on both the current and past trials. (2) 'Goal-approach' cells fired prior to arrival at either the odor-sampling port or reward cup. A number of sampling and approach cells also had place correlates. However, detailed analyses indicated that specific behaviors associated with increased firing reliably occurred at the same place. Unit activity was at least as well described by behavioral as spatial parameters. (3) 'Theta' cells fired at high rates in strict relation to the ongoing limbic theta rhythm. (Eichenbaum *et al*. 1987, p. 716.)

Again, we see that, attractive as higher-order cognitive descriptions of hippocampal processing may seem, cell firing can relate to simple stimuli as well as complex ones, with a strong flavour of linkage to behavioural output rather than stimuli. Nonetheless, it is clear that cell firing is not a simple correlate of behaviour per se or even conditioned behaviour. This pattern of observations is consistent with the activation of hippocampal cells by available goals (or the priming of response systems which can direct responding to one or another of the alternative goals).

But, in drawing this conclusion, perhaps we have been moving too fast. Perhaps we have been considering (at least) two different populations of neurons, one that codes the relationships among various environmental stimuli and one among learned contingencies or responses. Yet, investigators using non-spatial learning paradigms find that nearly all complex-spike cells demonstrate responses to conditioned stimuli or behaviours, whereas those working with specifically spatial paradigms report that nearly all cells fire in relation to place. Best and Thompson even found that the same hippocampal units that have place fields in a radial-arm maze show conditioned responses to tone stimuli in a classical conditioning task. (Eichenbaum and Cohen 1988, p. 246.)

Likewise, Wiener *et al.* (1989) found that the same cell often had a conventional place field in a spatial task and a non-place (but quite complicated) field in an odour task; and Shapiro *et al.* (1997, p. 624) found that with

distal stimuli and with distinct local tactile, olfactory and visual cues covering each arm [of a four arm maze] . . . different hippocampal neurons encoded individual local and distal cues, relationships among cues within a stimulus set, and the relationship between local and distal cues. Double rotation trials, which maintained stimulus relationships within distal and local cue sets, but altered the relationship between them, often changed the responses of the sample neuronal population and produced new representations. After repeated double rotation trials, the incidence of new representations increased, and the likelihood of a simple rotation with one of the cue sets diminished. Cue scrambling trials, which altered the topological relationship within the local or distal cue set, showed that the cells that followed one set of controlled stimuli responded as often to a single cue as to a constellation. These cells followed the single cue when the stimulus constellation was scrambled, but often continued firing in the same place when the stimulus was removed or switched to respond to other cues. When the maze was surrounded by a new stimulus configuration, all the cells either developed new place fields or stopped firing.

They suggest that ‘hippocampal neurons encode a hierarchical representation of environmental information’. But we would argue that the apparent complexity of re-encoding not only destroys any simple meaning of the term ‘place field’, but also suggests that the apparent complexity arises from attempting to view the ‘receptive fields’ of the cells in purely stimulus terms when they are not purely stimulus related but include (or even are totally identifiable with) a potential response (or better ‘potential goal’) component.

A6.2.6 Correlates, from habituation to memory

The picture presented by the simpler paradigms suggests that fairly non-specific information, related to the priming of subcortical response systems, is sent from the medial septum to the hippocampal formation, and that this is more likely in the case of conditioned than unconditioned responses. Consistent with this inference, medial septal neurons in a non-spatial working memory task have activity which is occasionally correlated with stimulus presentation but more often correlated with response emission or reward delivery; and ‘incorrect responses are not associated with activation, indicating that the medial septal area is only active under conditions in which the appropriate response rule is retrieved for a given stimulus’ (Givens 1996; see also Kita *et al*. 1995).

Where reinforcement is present, the simpler paradigms suggest that the non-specific septal input and specific entorhinal input are combined to produce CA3 and CA1 responses. Consistent with this inference, there are hippocampal cells with highly specific, apparently ‘relational’ fields.

In all these cases, we have argued that hippocampal activity reflects relatively simple information about available goals (and hence choices) provided to it by other structures, gated by aminergic inputs, which indicate importance, and by mismatch (in either direction) between septal and entorhinal inputs, which indicate a need for information gathering. We suggested (following, for example, Wiener 1996) that distinct fields within a single task reflect distinct components of that task (subgoals, if you will). This suggestion, in the context of memory experiments, is distinctly ad hoc. But it appears more justifiable in the context of 'place fields'—probably one of the most dramatic and seductive correlates of hippocampal cell firing.

A6.2.7 Correlations with spatial position

In the simplest experiments we have described so far, the animal was unable to move itself through space. With the more complex experiments, the tasks (or at least predictors of reinforcement) have been non-spatial, and we have largely ignored the possible relationships between cell firing and spatial position. In a complex spatial environment, however, two main firing patterns are observed, both of which have a connection with place.

Some hippocampal units fire principally when the animal is moving from place to place, without any dramatic relation to its mode of movement or destination. Their firing, therefore, has a high rate. It is strongly correlated with movement theta (see below), and the cells often fire in bursts which are phase locked to theta (Feder and Ranck 1973; Ranck 1973; O'Keefe and Nadel 1978). As movement speed increases, previously non-rhythmic units become rhythmic and previously rhythmic units increase their rhythmicity (Rivas *et al*. 1996), and so it is not clear that these are a categorically distinct class of neurons as opposed to a set of neurons temporarily showing a particular mode of responding. O'Keefe and Nadel (1978) term the movement-related cells 'displace' units; these are 'identical to the theta units' in other reports (O'Keefe 1976).

By contrast, other hippocampal units appear to fire only when the animal is in a particular place. Descriptively, the unit has a 'place field'. As a result, these units are often called 'place cells' (for reviews, see O'Mara 1995; Wiener 1996). Although they do not show individual theta activity, the individual probability of their firing is related to the ongoing theta rhythm and their average firing as a population shows theta modulation (e.g. Skaggs *et al*. 1996, Fig. 2). The description of such units by O'Keefe and Dostrovsky (1971) provided the main impetus for the spatial theory of hippocampal function, although similar suggestions have been made on the basis of lesion experiments (e.g. Olton and Isaacson 1968; Mahut 1971). The early work on 'spatial fields' of hippocampal cells has been reviewed by O'Keefe and Nadel (1978), and Burgess and O'Keefe (1996*a*) provide a computer model of how place cells could contribute to navigation. More recently, the journal *Hippocampus* (1991, pp. 221–92) published a forum 'Is the hippocampal formation preferentially involved in spatial behaviour?', from which it is clear that there is still substantial room for interpretation of the data on this issue.

The correlations between firing patterns of hippocampal neurons, on the one hand, and spatial position, navigation, and head direction, on the other, have been discussed extensively in Chapter 7 of the printed text, and are therefore not discussed further

here. The chief conclusions we need to take forward from Chapter 7 to the rest of this appendix are that so-called place fields are better described as goal fields. They change their position, relative to other place fields, with changes in contingencies; and a cell that has a place field in a spatially oriented paradigm can have a non-spatial field in a non-spatial paradigm. Thus, as we write in Chapter 7 (p. 149): 'place field' is a convenient descriptive term within specific experimental paradigms rather than being functionally accurate; and the term 'place cell', in any literal sense, is a misnomer. If a cell has a place field in any particular environment at any particular time, this does not necessarily and uniquely indicate that the animal will be at that same point in allocentric space when the cell fires at any other time. There appears to be no appropriate spatial mapping in the hippocampus to allow decoding. The position (and indeed spatial nature) of the field can change dramatically in a spatially unchanged environment when response tendencies change. With cues which provide an additional spatial-like frame of reference, some cells code geographical space, some the cue space, and the majority code whichever frame of reference predicts reinforcement. In two or more shapes of apparatus, there is no obvious allocentric relation between the positions of spatial fields in one as compared to another.

We undertake a detailed theoretical account of these phenomena in Chapter 10, but for the moment we note that the processing of spatial goals seems as dependent on septal input, and as gated, as the processing of simple non-spatial ones.

It is important to note here that a septal/temporal, dorsal/ventral, 'where'/'what' separation must reflect only variations in the *proportions* with which dorsal and ventral trend information arriving in the entorhinal cortex is mixed as it is transferred to the hippocampus. It is in the nature of the concept of a goal that it must combine 'what' and 'where' to some extent; hence, perhaps, the otherwise peculiar anatomical fact that the hippocampus (which can be thought of as the remnant of the primordial evolutionary and developmental origin of the dorsal trend) receives a confluence of dorsal and ventral trend information (see Suzuki *et al.* 1997, p. 1080, for the suggestion that this mixing occurs in the perirhinal cortex). It is also in the nature of goals, as we normally refer to them, that some may be more concerned with 'what' the animal must do and some with 'where' it must do it.

From these considerations, we conclude that the septal input (carrying rather degraded 'what' information, including information about, for example, the generation of saccades; Sobotka and Ringo 1997) must be integrated with *both* dorsal ('where') *and* ventral ('what') trend information by the hippocampus. This integration may be achieved via the topography we have already discerned. But there is another possibility. The distinction between low-firing-rate place cells and high-firing-rate 'theta' cells may reflect a separation of dorsal and ventral trend information. It has been argued that 'theta' cells are interneurons, and this may be true in spatially extended arrays. However, Vinogradova's results suggest either that there are occasions when theta cells are also principal cells or that the theta interneurons can pass the information they are encoding on to subsequent levels of the septo-hippocampal system. In either case, the interaction of high-frequency and low-frequency cells could produce the integration of dorsal and ventral trend information.

One final suggestive observation is worth mentioning. Where cues are rotated so that different cells' place fields provide conflicting information, it appears that these

conflicting representations tend to suppress each other in young but not in old memory-impaired rats (Tanila *et al.* 1997; see also Mizumori *et al.* 1996). It could be that this observation reflects at the single-cell level the inhibitory conflict resolution which, we argue, is at the core of hippocampal function (Chapter 10).

So far, we have not discussed in any detail the correlates of individual theta cells, except to note that their firing is strongly related to more general theta activity throughout the hippocampal formation. In the remainder of this appendix we consider their population correlates in the form of theta rhythm, before attempting an integration of all of the data.

A6.3 The behavioural correlates of theta

The earliest substantial work on the behavioural correlates of theta was that of Vanderwolf. He showed an extremely strong relation between movement and theta in rodents (Vanderwolf 1969, 1971). The key observations are summarized by Vanderwolf *et al*. (1975) and are reproduced in Fig. 10.1 in the printed text. These observations have been replicated many times and are so reliable that they are used by one of us in an undergraduate practical class: certain types of movement are almost invariably accompanied by theta in rats, and this theta is of quite consistent frequency. As movement increases in speed, previously non-rhythmic hippocampal units become rhythmic and rhythmic units increase their rhythmicity (Rivas *et al*. 1996). We will discuss shortly the fact that theta can also occur during non-movement. Almost all the work on the behavioural correlates of theta activity has measured theta rhythm rather than single-cell firing, but since the rhythm is generated by the synchronous firing of many hippocampal cells (Appendix 5), it is particularly good evidence for large-scale, behaviour-related changes in the hippocampus as a whole.

Interpretation of the observations is more difficult. What is it that distinguishes those classes of movement which are accompanied by theta from those which are not? Vanderwolf (1971) initially suggested that theta accompanies *voluntary* movements but not *automatic* ones—a pleasingly simple suggestion which captures large amounts of the rodent data. Unfortunately, this simple hypothesis had to be abandoned.

Vanderwolf (1971) defined voluntary behaviour as that which can accomplish a number of different types of goal, and automatic behaviour as that which is associated with only one particular motivational state. Our final view of theta (including immobility theta) will be very close to this. However, when rats are trained to lick at a tube to avoid a shock, irregular activity is usually seen, not theta. Thus the hippocampal electrical activity in this case of shock-avoidance is that which accompanies normal licking during drinking (Black and Young 1972; Young 1976), not that which accompanies responses such as lever pressing to avoid shock; and yet lick avoidance would seem as ‘voluntary’ as lever press avoidance. Equally, passive rotation of the animal, eliciting reflexive head movements and nystagmus, and optokinetic stimulation, which elicits nystagmus alone, result in 7.0–8.5 Hz theta in rats (Gavrilov, Weiner and Berthoz, 1995*a*, 1995*b*). This behaviour does not seem to be voluntary.

Note that while these results conflict with the idea of *voluntariness*, they greatly strengthen the relation reported by Vanderwolf between electrical activity and specific *movements*. It appears not to matter *why* the animal performs a given movement; the fact that the movement is performed is sufficient to guarantee theta or its lack (although we qualify this conclusion below). Not only, therefore, does this create problems for the idea that theta relates to voluntary movement, it also drastically limits *any* hypothesis which seeks to link the occurrence of theta to psychological processes such as learning, attention, or frustration (Black 1975).

A second complication for the voluntary movement hypothesis is that movement is not necessary for theta to occur. In this context, we can probably ignore the fact that theta occurs during REM sleep (see Table A11 in O'Keefe and Nadel 1978) since, when a lesion is placed just caudal to the acetylcholinergic neurons of the dorsolateral pons [to eliminate the peripheral paralysis which accompanies REM] 'to a naïve observer, the cat, which is standing, looks awake since it may attack unknown enemies, play with an absent mouse, or display flight behavior although the animal does not respond to visual or auditory stimuli. These extraordinary episodes are a good argument that 'dreaming' occurs during [REM sleep] in the cat.' (Carlson 1994, p. 287). The theta activity during REM sleep can, therefore, be viewed as movement theta with atonia rather than non-movement theta. However, especially in the cat and rabbit, theta is frequently seen in states of alert immobility (e.g. Harper 1971; Kemp and Kaada 1975; Kramis *et al.* 1975; Arnolds *et al*. 1979*a*; and see Table A8,b in O'Keefe and Nadel 1978).

In the rat, immobility-associated theta is less obvious but is seen when the rat is sniffing (Gray 1971), preparing to jump (Whishaw and Vanderwolf 1973), or presented with a CS signalling footshock (Whishaw 1972; Graeff *et al.* 1980). In a series of studies of immobility theta which are of particular theoretical significance, Sainsbury (personal communication) could observe theta as high as 12 Hz during immobility. An example of large-amplitude, high-frequency (>10 Hz) immobility theta in a guinea-pig faced with a snake is shown in Fig. 1 of Sainsbury and Montoya (1984). Consistent with the electrophysiological data discussed in Appendix 5, then, there is no necessary relationship between frequency and 'Type' of theta.

The key finding in Sainsbury's studies, however, is that immobility theta 'is elicited in response to sensory stimuli which are processed when the animal is in an aroused state' (Sainsbury 1985, p. 19). In many cases the stimuli to be processed are also innate sources of arousal: snakes, ferrets, and owl calls. It is technically difficult to confirm or disconfirm Sainsbury's claim that it is the *combination* of sensory stimulation and arousal that is critical. However, his group showed that a number of procedures can convert a normally ineffective stimulus into one that elicits theta if it is presented during immobility: a preceding owl-sound (Sainsbury and Montoya 1984), or presentation of a shock or a predator (Montoya *et al*. 1989; Sainsbury *et al*. 1987*a*). The presentation of shock is particularly illuminating. 'Three conditioning paradigms (delay, trace, random) were utilized. [Immobility] theta production increased over time as a function of the number of shocks and was not due to conditioning [to the CS]. There were no differences in the three groups in the occurrence of [immobility] theta during CS presentations or during the inter-stimulus intervals. Previously neutral sensory stimulation also produced [immobility] theta after conditioning in all groups. The inescapable shocks placed the rat in a high state

of arousal which subsequently sensitized the animal to produce [immobility] theta' (Sainsbury *et al*. 1987*b*). A similar explanation could account for the variations in theta frequency with exploration of different parts of an enclosure by rabbits (Fontani and Maffei 1997).

It is clear that an animal can process stimuli in a state of high arousal also when it is moving. The combination of these two functional attributes is perhaps paralleled by the deduction, in Appendix 5, that, physiologically, cholinergic and serotonergic theta can occur concurrently. Furthermore, acetylcholine is released in the hippocampus, not only when an animal is stationary but also at the point in training at which it acquires a motor response (Orsetti *et al*. 1996). This set of circumstances allows us to account for one of the more troubling species differences in the literature. Not only does the cat show apparently more immobility-related theta than the rat, but also the behavioural correlates of its movement-related theta are different from the rat's. In the cat, movement theta is 'correlated with various psychological processes such as the orienting reflex, attention or memory. . . . [So,] it is possible that the cat has totally different theta correlates than the rat, rabbit or guinea pig. . . . [But] administration of 50 mg/kg of atropine sulfate abolishes all theta activity in the cat' (Sainsbury 1985, pp. 11, 16, 17, 19). Thus, in the majority of experiments in the literature, the cat does not appear to have serotonergic theta. But, as suggested by Sainsbury (1985), during movement in species such as the rat, cholinergic and serotonergic ('Type 1' and 'Type 2') theta can occur concurrently, and some bursts of movement-related theta are purely cholinergic in all species.

The species difference between rat and cat may in any case not be as large as implied in the previous paragraph. Robinson (1980) has cogently argued that non-cholinergic theta is often obtained only from recording sites where large-amplitude theta can be observed.[2] In the majority of cat experiments, amplitudes have not been high; and, when large amplitudes have been recorded from the cat, they show the same movement relation as in the rat (except that, unlike the rat, movement theta is of much lower amplitude than immobility theta). The difference between cats and rats, then, appears to be quantitative rather than qualitative. These results imply that cholinergic and non-cholinergic gating have different topographies within the hippocampus, which may well be a consequence of the mapping of function-related zones in the hippocampal formation (Appendix 4).

We now have all the clues that will allow us to produce an integrated view of theta occurrence. Before doing so, let us review the one other recent attempt to resolve the species-dependency and behavioural correlates of theta in a unitary fashion.

Winson (1972, 1990) has suggested that theta activity occurs during behaviours which are 'pivotal to the animal's survival' (Winson 1990, p. 45)—and that its occurrence during sleep 'reflected a neural process whereby information essential to the survival of a species . . . was reprocessed into memory' (Winson 1990, p. 44, see also Appendix 7). This suggestion has the advantage of appearing to cover many of the species differences in theta occurrence, as well as spanning movement and non-movement. In particular, his hypothesis includes theta during REM by postulating that in this state survival-related information is being processed 'off-line' (a notion to which we return in Appendix 7). This view is consistent with the suggestions we made in Appendix 5 about the relations between theta and LTP and LTD.

Unfortunately, it is post hoc and circular since ‘survival-related’ is difficult to define. It is not clear why drinking (non-theta) and eating (non-theta) are not survival-related; it is not clear why monotonous running in a running wheel (theta) should be survival-related; and it is also not clear that Winson’s approach can encompass the contrast between lick-avoidance (non-theta) and lever press-avoidance (theta).

Before we present our own view, it will be useful to be reminded of the crucial basis for distinguishing types of theta (since neither ‘movement’ nor ‘frequency’ can be used for this; Appendix 5). Theta is partially resistant to systemic injections of anti-muscarinic drugs (e.g. atropine, scopolamine) and is also partially resistant to anaesthetics such as urethane. However, the combination of anaesthetic (or anti-serotonergic) and anti-muscarinic abolishes all theta. Especially given the apparent independence of the phasic aspects of theta from these pharmacological influences (Appendix 5), we must see theta as depending on two separate gates which, if either is open, allow the hippocampus to be entrained by a single source of rhythmic input. Thus, non-movement theta usually depends on phasic GABAergic input to the hippocampus being supplemented by concurrent release of acetylcholine. Movement theta usually depends on the same phasic GABAergic input being supplemented by concurrent release of both acetylcholine and serotonin. Both types (cholinergic, serotonergic) of theta are abolished by medial septal lesions which destroy the GABAergic pacemaker; both types of theta are elicited by reticular stimulation; and both types of theta can be ‘driven’ by septal stimulation.

In the previous edition of this book, and in much of Vanderwolf’s work, great emphasis was placed on possible relationships between theta frequency and type of theta: non-cholinergic theta often being of high frequency and cholinergic theta often being of low frequency. However, it is now clear (particularly from Sainsbury’s work) that there is no *necessary* relation between frequency and type. The observed *correlations* between type and frequency result from the experimental conditions *normally* used to elicit the two types of theta. High-frequency purely cholinergic theta is not usually seen because only Sainsbury has used stimuli which can concurrently produce high levels of arousal and immobility. Equally, reticular stimulation can elicit very low-frequency theta even in the presence of anticholinergic drugs, with the frequency obtained being the same as that in the absence of the drug (McNaughton and Sedgwick 1978).

The idea of a cholinergic gate and the independence of theta type and frequency are nicely demonstrated by one of Vanderwolf’s earliest figures. In this figure (Vanderwolf 1975, Fig. 5), electrical stimulation in the undrugged rat produces theta in the absence of movement. In the presence of atropine, the same stimulation initially produces no response, and then produces theta when the animal moves. The key point to note is that the theta frequency observed is identical in the two cases. This suggests that the frequency control mechanism was activated identically in the two cases. But, in the absence of a cholinergic (blocked by atropine) or serotonergic (blocked by lack of movement) enabling signal, it could not affect the hippocampus. When the animal moved, the serotonergic-enabling signal allowed the hippocampus to be entrained to the pre-existing phasic drive from the supramammillary–septal system and to show theta. It should be noted particularly that the atropine-sensitive non-movement theta (shown in the pre-atropine case) was essentially the same frequency as the atropine-resistant movement theta.

But, if theta frequency depends on the same fundamental circuitry whether it is gated by acetylcholine or by serotonin, can we see it as the simple result of stimulus processing interacting with arousal level (Sainsbury's hypothesis for immobility theta) in both cases?[3]

There is good agreement that more vigorous movements are associated with higher frequencies of theta (O'Keefe and Nadel 1978, Table A6, a and c). This is true whether the movement is natural (Whishaw and Vanderwolf 1973), or provoked by electrical stimulation of the hypothalamus (Bland and Vanderwolf 1972). This relationship relates to velocity or the size of a planned displacement in space, and not to force or rate of acceleration (Morris *et al.* 1976; see O'Keefe and Nadel 1978, pp. 179–82). However, if an animal is forced to run in a wheel, it is only the initial frequency of theta that relates to speed of running. As movement continues, theta settles down to a constant value independent of speed (Whishaw and Vanderwolf 1973). Furthermore, Arnolds *et al*. (1979*b*) reported that theta frequency related to speed of movement through space when the subject (a dog) was pulled along in a cart; and Gavrilov, Weiner and Berthoz. (1995*a*, 1995*b*) obtained clear bursts of theta in response to whole-body rotation of rats passively transported in a robot.

A similar explanation is probably required for the occurrence of intermediate frequency theta in response to frustration in the alley (Gray 1970; Gray and Ball 1970). Upon first entry into the alley, during exploratory behaviour, the observed theta had a mean frequency of 7.7 Hz. When the animal was well trained and running fast towards the goal, the frequency rose to 8–10 Hz. When it entered the goal and consumed the water reward, the frequency fell to 6–7.5 Hz. (Note that in this particular experiment consumption of water was accompanied by theta, not irregular activity—despite the fact that the subject is a rat, see above.)

On non-rewarded trials, the frequency in the goal box rises to 7.7 Hz both during extinction and on non-rewarded trials of a partial reinforcement schedule. Morris and Black (1978) showed that it is possible to predict, with a high degree of accuracy, the theta frequency elicited by non-reward if one takes into account the motor patterns observed (sniffing, walking, rearing, etc.). As we noted previously in the case of lick-avoidance, the EEG response is likely to be the same, and of the same frequency, however the behaviour is elicited. This conclusion is strengthened by the fact that the frequency of frustration-induced theta depends on the apparatus. In the alley (Gray and Ball 1970; Kimsey *et al.* 1974) and when a thirsty rat is presented with an empty water tube (Soubrié *et al.* 1978) it is 7.7 Hz. In the operant chamber it is lower, at about 7 Hz (James and Gray, unpublished), but represents a similar increase in frequency from the rewarded baseline as in the alley (N. McNaughton, unpublished). Non-reward for a jump-up response elicits theta at 8.0 Hz. The specific frequency observed, then, appears to relate less to the nominal psychological state, frustration, than it does to the specific behaviour of the subject. However, in each case the change in theta reflects a change in behaviour that is a response to frustration. These data also seem to rule out any simple relation of theta frequency to arousal (even if we were in a position to clearly define this rather slippery term).

The emphasis must be placed here on the preparation for, rather than the execution of, responses. In Morris *et al*.'s (1976) experiment, theta frequency predicted the height of the jump rather than merely accompanying the jump itself. Likewise,

Preobrazhenskaya (1990) has shown that frequency of theta is related to probability of reinforcement in dogs. The highest frequency of theta is obtained at intermediate probabilities. This suggests that theta frequency is related to the number of alternative responses being considered by the animal (lower at very low levels of reinforcement where no responses are emitted, and also lower at very high levels of reinforcement where there is a single clear goal) rather than arousal level per se. Furthermore, if the animal is tested to exhaustion, the occurrence of theta (or at least high-frequency theta) fails on the same trials as the response fails (Vanderwolf and Cooley 1974)—when one can assume that all the situational factors are the same, and only the willingness to respond is lacking. On the other hand, arousal and attention are often emphasized because, for example, when the animal is forced to run in a running wheel or on a moving belt at a fixed speed, we can imagine that the arousal or certainly the task demands are greatest when the animal has to accelerate in order to cope with the moving belt. This problem will be greatest with high speeds initially. But once running has adjusted to the speed of the belt, it could be argued that the same amount of attention is required, whatever the speed—hence the observed changes in theta frequency. Perhaps the simplest resolution would be to suggest that the frequency of theta reflects the load on a motor programming system.

The relationship between theta and responding is also illustrated by a preliminary experiment of ours (McNaughton and MacMillan, in press). The problem addressed was that, on the evidence of Appendix 5, the anxiolytic benzodiazepines reduce the frequency of theta. A superficial view of the correlational evidence of the present appendix might suggest that increasing *rates* of motor behaviour might be expected to produce increasing frequencies of theta. However, it is also known that chlordiazepoxide increases the rate of lever pressing on a variety of non-reward and punishment schedules (Appendix 1). We therefore recorded theta during a fixed interval schedule in animals treated with either chlordiazepoxide or given control injections.

Theta frequency in the 0.75 s immediately before each lever press did not increase as response rate increased during the fixed interval; indeed, towards the end of training it appeared to increase when response rate was lowest in the control animals. This result is not, in fact, surprising, since the lever press response and the events leading up to it are likely to have been fairly stereotyped; and the increase in theta frequency can be attributed to the increased requirement for inhibition.

More importantly, at all points of the interval, chlordiazepoxide reduced the frequency of theta by about 1 Hz. This was true both when chlordiazepoxide increased responding throughout the interval and when it increased responding only in the initial, most suppressed part of the interval. The drug thus decreased frequency, while increasing the overall rate of behaviour. This shows, in relation to frequency, the same type of dissociation as is implied when we compare the effects of lesions on behaviour to the correlations between behaviour and theta. The use of systemic injections makes any causal attribution impossible, but the data are consistent with the idea that, during normal lever pressing, the rat is processing many alternative goals (because of the omission of reward in the schedule) and this leads to a hippocampally-mediated inhibition of lever pressing. When the frequency of theta is reduced (altering the receptive field properties of the hippocampal cells) the hippocampus no longer receives the tightly time-locked information it needs about alternative goals and so

fails to inhibit lever pressing to the same extent as before. A similar result was obtained by Iwahara *et al*. (1972) who used 20 mg/kg chlordiazepoxide to reduce spontaneous alternation and theta frequency. They found that the drugged rats ran faster than controls given saline, presumably because of a loss of inhibition resulting from the loss of theta. Recently we have found (Senior *et al*., in preparation) that reducing theta frequency quite specifically by injecting chlordiazepoxide into the supramammillary nucleus has the same effect on both theta frequency and behaviour in the fixed interval schedule as does systemic administration of the drug.

A related illuminating result was obtained many years ago by Elazar and Adey (1967) using cats in a light–dark discrimination. They found that theta power (at low frequency) was particularly high *well in advance* of execution of incorrect responding, and suggested that this was associated with 'a confused state with exaggerated reactions' (Elazar and Adey 1967, p. 232). Thus, if theta is associated with the selection of responses through the suppression of all but the most favoured, we may have here an example of oversuppression of ongoing plans and their replacement by exploratory/risk analysis behaviour. In superficial contrast to this interpretation, Holmes and Beckman (1969) found that whether a cat would run or not in a go–no-go paradigm was highly predictable from the hippocampal record (up to 98 per cent correct in one case), with theta predicting movement and non-theta predicting no movement. In these two apparently conflicting results, we may have a critical clue as to why theta needs its extensive control system: too much theta (suppressing even the correct response) may be just as detrimental to performance of some tasks as too little theta (failing to suppress incorrect responses) is to others.

This general position is reinforced by recent results from Bland's laboratory (Oddie *et al*. 1997). These authors placed pairs of rats together so that one could steal food from another. In this situation 'the victim dodges from the robber with a latency, distance, and velocity dependent upon the size of the food, elapsed eating time, and proximity of the robber [so that] the movement requires sensory integration and planning' (Oddie *et al*. 1997, p. 169). Blockade of theta by temporary medial septal inactivation blocked dodging, but not more simple responses, while stimulation of the posterior hypothalamus in an eating rat, without a robber, elicited both theta rhythm and dodging. This suggests a tight relationship between theta and the selection of movements, as opposed to the production of movements where little selection is required.

The observations we have considered so far attempt to relate the occurrence of theta, or its frequency averaged over some period of time, to the behaviour by which it is accompanied. This attempt has been very successful in producing a tight relationship between highly specific motor patterns (including visual scanning in the cat and sexual behaviour in the rat and dog) and specific frequencies of theta or the occurrence of non-theta. There have also been more ambitious attempts to relate the microstructure of behaviour to particular theta waves, or to a particular instant (phase) within a train of theta waves. These have also been surprisingly successful.

Thus, Komisaruk (1970) and Macrides (1975) noted that movements of the rat's vibrissae tend to stay in phase with theta. Consistent with this observation, medial septal lesions which abolish theta appear to eliminate the rhythmicity of vibrissal movement and the normal synchrony between movements of the vibrissae on the two

sides of the snout (Gray 1971). Phase locking has also been noted between bar pressing and theta (Buño and Velluti 1977; Semba and Komisaruk 1978); and between momentary changes in theta frequency and amplitude, on the one hand, and individual acts of sighing or stepping in the dog on the other (Arnolds *et al*. 1979*b*). Macrides's extensive analysis of sniffing indicates that sniffing entrains to the ongoing theta rather than the other way round.

Of particular interest is the fact that 'place cell' firing (see above) shows a progressive shift in the phase of theta at which it fires as the animal traverses the place field (see O'Keefe 1993). 'When the animal enters the place field, the firing occurs late in the cycle but moves progressively earlier with each successive cycle' (O'Keefe 1993, p. 918). O'Keefe himself (1993, p. 917) claims that this shows how theta activity 'clocks part of the spatial code'. However, this 'clocking' is not directionally specific (Skaggs *et al*. 1996); and it seems more likely, given the other evidence, that this change in phase reflects the means whereby a primarily inhibitory phasic component of theta can 'tighten up' hippocampal fields. Thus, maximal firing is obtained in the middle of the theta cycle (as would be expected since inhibition is least then; see Skaggs *et al*. 1996, Fig. 6), and minimal firing is obtained as inhibition starts to occur (when it will delete what would have been the latest spikes of a burst) and as it wears off (when it will delete the earliest spikes of a burst). The phase shift, then, is a result of the inhibitory aspects of theta, and would be expected to occur with non-spatial as with spatial fields. In the absence of theta input (after fornix lesion), field sizes often expand, or fields disappear, attributable to a loss of this inhibition. The purpose of the phasic component of theta activity, then, appears to be to inhibit firing except when this occurs at a fixed point in time (see Tsodyks *et al*. 1996 for a specific detailed model of this general type of process, in which excitation between cells with related fields is important). We argue, in Chapter 10, that this type of system is required because of recursive processing between the hippocampus and its target structures, which, without phasic inhibition, would show interference between one cycle of calculation and the next.

A6.3.1 Accounting for cholinergic gating of theta

Theta rhythm is the result of theta activity: the synchronous firing of many hippocampal cells. Cholinergic theta appears to be the result of the concurrence of an underlying phasic inhibitory input with input from the ascending cholinergic system which, even in its control of theta, involves a complex 'reticulum' of centres such as the pedunculopontine tegmental nucleus (PPT), superior colliculus, substantia nigra pars compacta, amygdala, and probably several more.

This reticular anatomy suggests that cholinergically-gated theta is just one consequence of the activation of centres which increase processing of external immediate stimuli, at the expense of internal stimuli and of previous external stimuli. Cholinergically-gated theta would, therefore, affect areas which control the orienting response, but its activation would *not* necessarily have behavioural output and, even when it does, 'orienting' could be limited to eye movements. This suggestion fits with the nuclei involved in the PPT-associated 'reticulum', in which even the substantia nigra has been implicated in some form of attention; and with the suggestion that '[PPT] is required for learning or implementing new associations if these are to be used to guide appropriate actions. Where there are few competing outputs lesions do

not affect responding, but as the task difficulty increases and response choices multiply, the [PPT] becomes crucial for funnelling out inappropriate actions. . . . [Alternatively,] motor outflow from the cortex and extrapyramidal sites might direct actions themselves, leaving the [PPT] to recruit those autonomic events which are their necessary corollaries' (Inglis and Winn 1997, p. 23).

Relating these considerations to theta, we note that, in the cat, in which theta during immobility has been seen particularly often (O'Keefe and Nadel 1978, Table A8,b), it is clearly associated with attentive postures and visual exploration or alert scanning (e.g. Kemp and Kaada 1975; Bennett and French 1977). As noted above, Sainsbury has pointed out that, in this species, most of the theta which has been recorded appears to be cholinergic and the movement correlates of theta appear to relate to orienting and directed attention. In the rabbit, the strong theta response to novel sensory stimuli formed the basis for Green and Arduini's (1954) classic description of slow wave activity in the hippocampus. In the immobile rat, theta has been observed during vigorous movement of the vibrissae (Gray 1971), in response to an aversive CS (Whishaw 1972; Graeff *et al*. 1980); and, in guinea-pigs, at high frequency, in response to a direct innate threat (Sainsbury and Montoya 1984). In the latter case we can argue that there is extreme focusing of attention on a single, immediate and important object: the predator.

We can integrate all of these data, then, by suggesting that cholinergic theta is the hippocampal component of orienting, and probably more generally risk assessment, and that its eliciting conditions overlap with, and hence from a correlational point of view are masked by, non-cholinergic theta. As with Sainsbury's arousal plus stimulation hypothesis: 'this particular interpretation of the behavioural correlates of [cholinergic] theta readily explains the common observation of habituation of [cholinergic] theta in all species studied' (Sainsbury 1985, p. 19). Note that in Sainsbury's formulation (with which we concur) it is neither arousal, per se, nor the stimulus which elicits theta, but the combination of the two (see also Preobrazhenskaya 1974). Sainsbury's description is stimulus-oriented. However, we would argue that cholinergic theta has a more direct relation with behavioural output, which is masked by two things. First, this relationship reflects the presence of available goals, and hence only the priming of responses that are not necessarily released (as in freezing to a predator, when both flight and fight are highly primed). Second, orienting is inherently internal—a narrowing of processing (Appendix 10) to allow careful evaluation of potentially important stimuli. It will only produce, for example, eye movements, if the critical object is not already in the centre of the visual field. The cat appears to provide examples of purely cholinergic theta with identifiable behaviour. In this species, what we see is probably best thought of as behavioural manifestations of attempts to foveate important stimuli.

However, cholinergic theta probably reflects much broader information gathering than just orienting. Injections of carbachol into the medial septum not only elicit theta, they also result in 'a behavioural syndrome resembling intense exploratory behaviours and consisting in walking, rearing, sniffing, head displacements and very large vibrissae movements' (Monmaur and Breton 1991). As we note in Appendix 8, exploratory behaviours such as these, particularly rearing, are disrupted by septal and hippocampal lesions. Given the fact that septal procaine can abolish wheel-running as well as theta elicited by hypothalamic stimulation (Oddie *et al*. 1996), it seems likely

that it is output from the hippocampus that generates the exploratory behaviours. A strong cholinergic signal is also likely to be important, since septal driving of theta rhythm does not by itself produce either intense or reliable exploration.

As suggested by Bennett *et al.* (1978), if there is in fact a major difference between the rat, on the one hand, and the cat and rabbit, on the other, this is likely to reflect species-specific modes of exploratory behaviour. The rat tends to explore by moving slowly round its environment so that it can make use of information received by the vibrissae, the cortical representation of which is large and highly ordered. The rat's vision, particularly in laboratory albino animals, is poor. The cat and rabbit, by contrast, tend to explore visually, remaining immobile. It is almost certainly for this reason that the frequency of theta during 'exploratory behaviour' tends to be in the mid-point of the range in the rat, but near the lower end of the range in the cat, paralleling the different degrees of movement accompanying such behaviour in the two species.

Thus, cholinergic theta appears to reflect the presence of significant goal objects which may require orienting, exploration, and risk analysis (hence Sainsbury's stimulus plus arousal rule). In the cat, purely cholinergic theta can be accompanied by orienting behaviour, but in the rat it is usually accompanied by immobility (we discuss why this may be when we consider non-cholinergic theta below). Where a novel stimulus is unimportant, the hippocampal activity and orienting and exploration undergo concurrent habituation. The occurrence of this hippocampal activity to a novel or threatening stimulus appears to be critical for initial responses (e.g. exploration) to that stimulus; and, furthermore, cholinergic activation by itself, even in rats, appears to elicit exploration. This link between cholinergic activation and novel or threatening stimuli is the mirror image of the fact that place fields (which do not show the habituation characteristic of cholinergic theta) are unaffected by cholinergic blockade; and that restraint, which eliminates place fields, leaves cholinergic theta intact (Foster *et al.* 1989).

A6.3.2 Accounting for non-cholinergic gating of theta

We have concluded above that purely cholinergic theta is related to response tendencies ('goals'/'plans') which are often behaviourally silent. We now argue that the true correlate of 'non-cholinergic' theta is not the action observed but the set of potential (planned) actions.

First, note that the cholinergic and serotonergic gates can be open concurrently. If we conclude, as in essence we did above, that these relate to different types of action tendency, then it follows that more than one such tendency can activate hippocampal theta, despite the fact that only one can currently control behaviour.

Second, note that, with forced running (and other situations), the frequency of theta is initially high and then decays to a lower value, largely independently of the changes in the motor action with which the activity is loosely correlated.

Third, let us consider the voluntary–automatic distinction made by Vanderwolf to account for the differences between theta-related and non-theta-related behaviours. It cannot be voluntariness, per se, that results in theta, since conditioned licking is not

accompanied by theta. What then distinguishes 'voluntary' behaviour at the behavioural level itself? In Vanderwolf's original formulation, it is the opposite of a fixed action pattern: namely, potentially variable behaviour accompanied (from the animal's point of view) by many behaviourally silent choices. We would argue, therefore, that theta is not the correlate of the behaviour actually seen, but of the number and intensity of the many additional alternative behaviours which the animal is tempted to produce concurrently under the circumstances. The rat can press a lever in many ways, but licking is more stereotyped.[4]

Fourth, theta can show strong correlations with types of behaviour which are totally insensitive to hippocampal lesions. With a few important exceptions, such as rearing, theta-related behaviours are not lost after hippocampal lesions; instead the animal appears incapable of inhibiting those same behaviours (Appendix 8). This lack of change in behaviour after hippocampal lesions holds even for the case of jump–avoidance, despite the fact that, in the intact rat, theta frequency is particularly tightly related to the distance about to be jumped (Myhrer 1975). As with the single-cell data, then, we must invoke a gate (e.g. CA1–subiculum or CA3–lateral septum) which blocks the functional output from CA1 and CA3 until other conditions are met. We discuss what these conditions are in Chapter 10.

We now have an extensively gated view of the theta control system. Phasic information arises in the supramammillary area (and other related nuclei) and is sent to the medial septum. We have evidence for at least a cholinergic gate there and so, unless certain conditions are met, the hypothalamic intensity–frequency transducer will not entrain the septal pacemaker. We also have evidence that there are cholinergic and serotonergic gates which, if closed, prevent the septal pacemaker from entraining theta in the hippocampal formation (including the posterior cingulate). We can also now infer that, even when CA3 and CA1 show theta activity, they will still need additional input if they are to produce behaviourally significant output via the lateral septum and subiculum.

Peck and Vanderwolf (1991) showed that stimulation of the dorsal raphe produced both theta and a variety of movements. These 'included a variety of head movements; walking or running; leaping off the platform; and circling. . . . Treatment with scopolamine had no consistent effect on any of the behaviours' (Peck and Vanderwolf 1991, p. 246), nor did it block the production of theta. However, in contrast to the behaviours which appear to accompany cholinergically-elicited theta, an extensive reduction in this dorsal raphe-induced theta (produced by combining scopolamine with parachlorophenylalanine) did not alter these induced behaviours, although the rats 'would often walk off the edge of the recording platform, usually without pausing on approaching the edge' (Peck and Vanderwolf 1991, p. 249; see also Robertson *et al.* 1991). These observations strongly suggest that serotonergic theta is a corollary rather than a cause of the behaviour, and that when the theta is reduced by drug treatment the animals lose some form of behavioural inhibition.

This state of affairs contrasts with theta elicited by cholinergic stimulation of the septum, which, we noted, appears to cause exploratory behaviour. The latter observation suggests that pure cholinergic movement-related theta can occur in the rat. Rearing is elicited by cholinergic activation of the septum, and blocked by systemic anticholinergics.

What, then, distinguishes the cholinergic from the non-cholinergic theta? We would argue that cholinergic theta is more stimulus-oriented. That is, it signals the presence of stimuli which require goal-oriented behaviour and, if no such behaviour is being prepared, it activates motor programmes the purpose of which is to gather information and, particularly, to assess risks within the environment. Serotonergic theta is more response-oriented. That is, it signals the priming of multiple motor programmes, the purpose of which is to allow the animal to approach available goals. Since, in Appendix 10, we conclude that serotonergic activation is the result of the priming of repetitive motor programmes, it seems likely that noradrenergic activation, associated with the priming of phasic motor programmes, would also gate theta (although this has never been demonstrated). It is possible, however, that noradrenergic input, by itself, is insufficient and that it potentiates either or both of the cholinergic and serotonergic inputs (see Amassari-Teule *et al.* 1991. Indeed, we provide evidence in Appendix 10 to suggest that all three aminergic inputs operate synergistically. But noradrenergic, cholinergic, and serotonergic factors determine only whether theta will occur, they do not determine its frequency. What then is our account of the phasic component of theta?

A6.3.3 Accounting for phasic activity

With both the cholinergic and serotonergic gates we are dealing with inputs which affect hippocampus but only as one of many brain structures which must be adjusted along a continuum of modes of processing. At one extreme there will be processing which involves a very broad selection of, often, rather unimportant stimuli. At the other extreme there will be processing limited to only one or two crucial stimuli. The greater the activation of the aminergic systems, the more processing will favour the latter rather than the former. In the specific case of the hippocampus, this aminergic input results in an increase in input-wise ‘signal-to-noise’ ratio, causing only certain inputs to be processed. We would argue that the phasic inhibitory input from the septal pacemaker produces an equivalent narrowing of the temporal focus of attention, causing inputs to be processed only in certain narrow time windows (this postulate proves important for the details of our theory in Chapter 10).

In our view, the critical outputs of the hippocampal formation are to goal-oriented structures (including sensory areas analysing current goals). The phase locking of the responses such as whisker movement or lever pressing can be attributed, then, to the entrainment of activity in those areas by hippocampal theta activity. Note that, on our theory, this entrainment will only occur when the hippocampus is actively engaged in selecting between competing goals or generating information-gathering activity (see also Schmajukj’s 1997 view of theta as an error signal which can be directed at ‘association cortex’).

But what is the significance of theta frequency? We accounted, in Appendix 5, for the phasic nature of theta as output from an intensity–frequency transducer consisting of a complex of nuclei which integrate ‘reticular inputs’. Other than the supramammillary nucleus, it is unclear which nuclei comprise the intensity–frequency transducer. Even less clear is which nuclei provide input to this system. We concluded that *frequency* is independent of the cholinergic and serotonergic gates; and the one known input to the nuclei that control frequency, the nucleus reticularis pontis oralis, is not essential for theta, and its precise function in the awake rat is obscure.

If we take our cue from Vinogradova's work on the septum, it seems likely that the intensity–frequency transduction system receives direct or indirect input from all subcortical areas which detect the presence of available goals. We have already concluded that this system calculates the sum of its inputs. Such a simple summation across modalities is consistent with the lack of modality specificity in septal activation. It follows that frequency will depend, indiscriminately, on both the number and the intensity of activation of representations of available goals. Thus, frequency is high in the immobile animal when the animal is faced with a predator (when we know from the Blanchards' work that it is prepared for both explosive attack and explosive escape). But note that 'intensity' here cannot relate simply to the vigour of the anticipated movement, since jumping theta frequency is related to distance not force. Rather, intensity of activation of a goal representation may relate to the speed with which the animal is shifting its attention between the available alternatives or to some other factor reflecting cognitive as opposed to muscular load.

On this view, theta should result from activation arriving from a wide range of different sites, each concerned with a particular kind of goal. This approach fits better with the view of Robinson and Vanderwolf (1978), that there are many sites contributing to theta, than with that of Vertes (e.g. Vertes *et al*. 1993), that the nucleus reticularis pontis oralis is the primary brain stem source of theta (see also Faris and Sainsbury 1990, for the lack of effect on theta of lesions of this nucleus). It also fits with our recent data (McNaughton *et al*. 1997) showing that the ascending cholinergic control of theta involves a polysynaptic, widely diverging reticulum.

It is possible that changes in frequency of theta are just epiphenomena of a more basic requirement to generate phasic hippocampal activity. However, if this were so, the various nuclei involved in frequency control would merely require inhibitory interconnections (to ensure phase locking), but not the excitatory interconnections which provide the capacity to summate their joint input (Appendix 5) and which must also require complex circuitry to prevent explosive positive feedback. It seems likely, therefore, that the specific frequency of theta is of functional importance (see also Miller 1991).

We will look at this suggestion more closely in relation to the effects of septal driving of theta on behaviour (Appendix 7), but we can note here that it is consistent with the effects of manipulations of specific aspects of theta control. First, injections of chlordiazepoxide directly into the supramammillary intensity–frequency transducer produce a modest reduction in theta frequency and a similarly modest impairment of specifically spatial learning in the water maze (Pan and McNaughton 1997), but a large reduction in theta frequency and a large impairment of behaviour on a fixed interval schedule (Woodnorth and McNaughton 1999). Second, intraperitoneal injections of chlordiazepoxide produce greater effects on both theta and spatial learning. Third, ethanol, at doses which should greatly reduce theta frequency, reduces the specificity of place fields (Matthews *et al.* 1996). Fourth, partial fornix lesions, which increase theta frequency, impair radial-arm maze learning, and this deficit is reversed when frequency is normalized with clonidine (Ammassari-Teule *et al.* 1991). Fifth, there is a loss of spatial performance in genetically modified mice with a loss of LTP specific to stimulation frequencies in the theta range (Bach *et al*. 1995). Sixth, Buzsáki *et al*. (1992) found that septal grafts reinstate cholinergic innervation of the hippocampus, but do not reinstate theta, and also do not reinstate

normal water maze behaviour. All of these data suggest that the presence of phasic theta activity and its precise frequency are functionally significant.

In this context, the results of Givens (1995) are particularly interesting. He showed that choice accuracy in a delayed alternation task was affected at a threshold dose of 0.75g/kg of ethanol, at which time there was a reduction in theta prevalence but not frequency; and that a significant effect at the smallest delay was seen at 1.0 g/kg, at which point theta frequency was reduced. The loss of theta prevalence is consistent with the fact that septal driving of theta at 7.7 Hz (close to the 7.5 Hz observed by Givens) is similarly and substantially reduced by 0.6 g/kg and 1.2 g/kg of ethanol (McNaughton *et al*. 1977), while the frequency of reticular-elicited theta is not reduced until a dose above 1.4 g/kg (Coop *et al*. 1990). This suggests that the electrophysiological tests predict theta changes in behavioural tasks, and that both reduction in amount of theta without a change in frequency and (given the results in the previous paragraph) reductions in frequency are functionally significant.

A6.4 Overview

There is a wide array of correlates of hippocampal activity: novel stimuli, responses, rewards, complex stimuli in memory paradigms, etc. In human beings in a face-recognition task, hippocampal single units have been shown to respond to faces, specific facial expressions, combinations of facial expression, and sex, and yet more complex attributes (Fried *et al.* 1997). We have argued that these are all corollaries of the perception of available goals of one type or another. We define ‘goal’ more tightly in Chapter 10 (see also Fig. 1.7), but for our present purposes it can be thought of as both a stimulus complex with innate or acquired response-eliciting properties and the priming of a response system which, if released, would result in behaviour directed at a specific stimulus complex. ‘Goal’ here includes what many would call a ‘subgoal’, that is a step in a sequence of directed actions; and does not equate with ‘reinforcer’, since in a choice paradigm the alternative goals both potentially lead to the same reinforcer.[5] Note also, that ‘perceived available goal’ implies a *current* choice—essentially between subgoals. We do not suggest that hippocampal cells code for the ultimate goal of a current response chain (see Burgess and O’Keefe 1996*b*, p. 661); that is more likely to be held in the prefrontal cortex (Appendix 3).

We have two reasons for attempting to conflate together the various single-cell correlates and further to conflate single-cell correlates with theta correlates. First is sheer parsimony. If we can achieve it, a unitary account is scientifically preferable to a set of ad hoc piecemeal accounts, the boundaries between which may be very blurred. Second is the nature of the data. We have tended towards ‘stimulus’ descriptions of single-cell fields (albeit with caveats about relationships with reinforcement) and ‘response’ descriptions of theta correlates (albeit with caveats derived from non-movement theta and Sainsbury’s work). Yet, theta modulation (if not complete rhythmic activity) can, apparently, be shown by the bulk of cells in the hippocampal formation under appropriate conditions and may be quite general. Certainly, theta rhythm must result from the concurrent synchronous activity of many cells. The correlates of observable theta rhythm, then, must be the correlates of at least the average of the fields of the single cells active in any particular situation. Likewise, we have concentrated on simple stimulus relations in high-rate neurons, but

similar results can be obtained with low-rate complex spike cells (Korshunov *et al*. 1996).

What, then, are the parallels between the results of the single-unit experiments and the theta-activity experiments?

First, firing in the medial septal area occurs on presentation of important stimuli. This firing appears to be closely related to cholinergic theta activity. It is likely, therefore, to originate in the reticular formation. It is multimodal and so can as readily be thought of as a summation of stimulus intensities as a summation of the priming of systems which could produce reflexive responding to those stimuli.

Second, firing in CA1 and CA3 occurs to some novel stimuli, but quickly habituates. We argued that this activity reflects production of information-gathering behaviour, rather than processing of the stimuli, inasmuch as these two concepts can be separated. At least some part of this activity must contribute to the production of cholinergic theta rhythm, which also shows ready habituation. Following Sainsbury, we see this cholinergic theta as depending on the need to process certain stimuli under conditions of arousal. The cholinergic gating signal arises in a complex of areas, including the superior colliculus, substantia nigra and amygdala, all of which can be viewed as controlling preliminary responses, such as gaze direction, to important stimuli. (In the context of the theory of this book, it is significant that the superior colliculus is thought to be the location at which simple threatening stimuli are detected visually and from which an alarm signal is sent directly to the periaqueductal grey, see Chapter 6.) In the absence of input from the entorhinal cortex, septal (particularly cholinergic) input elicits information-gathering activity, including both internal risk assessment and exploratory behaviour. With neutral stimuli, the entorhinal cortex and dentate gyrus pass a cortical ‘model’ of the stimulus (or more strictly a model of the fact that the programmed response is to do nothing or ignore the stimulus) to the hippocampus, which cancels the activation of CA3 and CA1 which would otherwise have elicited information gathering.

Third, in conditioning experiments and more complex stimulus arrays, firing in CA1 and CA3 reflects the receipt by the hippocampus of information related to priming of responses to multiple available goals. The prevalence of ‘place fields’ in the hippocampus is due to the fact that in many tasks a potential goal and a place are essentially the same thing.

We have already seen that the information received by CA1 and CA3 cells depends on integration of both septal and entorhinal input. The subcortical input must, therefore, provide general information related to the subcortical processing of goals in much the same way that entorhinal input provides specific information about the cortical processing of goals. In conditioning experiments, a non-specific medial septal signal indicating the presence of an important stimulus (or possibly the subcortical priming of a simple innate response such as gaze direction to that stimulus) would be accompanied by a specific entorhinal/dentate signal indicating proposed action. In the simple nictitating membrane case, this signal can have the temporal morphology of the emitted response in at least some cells; in trace conditioning of the nictitating membrane response, results are more varied and apparently ‘different hippocampal

neurons are mediating different aspects of the conditioned response' (Weiss *et al*. 1996, p. 204).

Entorhinal input must also provide a more stimulus-biased (or at least 'where' as opposed to 'what') model (this will be important when we account for the role of the hippocampus in memory). This bias to the stimulus aspects of goals is most obvious in the septal/entorhinal cancelling of responses to 'neutral' stimuli. The results of Foster *et al*. (1987) suggest that, on occasion, stimulus-biased (habituating) and response-biased (augmenting) information will interact on a trial-by-trial basis. In the habituation case, multiple potential goals must always be signalled in parallel to prevent elicitation of exploration; and we have some evidence that the same is true in conditioning experiments. Activation of a sufficient number of concurrent goals/subgoals would be accompanied by the release of serotonergic theta activity. Thus 'voluntary' behaviour will tend to open the serotonergic gate because of the number of alternative subgoals continuously primed, but 'automatic' behaviour could also do so if it were accompanied by sufficient priming of alternative response systems. Note that on this view 'voluntary' and 'automatic' are not linked to any particular observed behaviour but to the extent to which the animal must choose between multiple concurrent alternatives. Thus, in theory, 'voluntary' behaviour could be rendered 'automatic', and hence not open the serotonergic gate, if it were rendered stereotypical by overtraining. Likewise, 'automatic' behaviour could be rendered 'voluntary' by sufficient priming of concurrent alternative behaviour. We postulate that this is what occurred in the rat experiments in which drinking was associated with theta activity.

Fourth, the septo-hippocampal system contains a series of logical gates which interact to determine the conditions under which it will produce functional output. This would be impossible if it did not have a largely unidirectional transmission of information. There is good evidence for a (possibly noradrenergic) gate between the dentate gyrus and CA3 which determines whether the dentate effectively excites or inhibits CA3. There is also evidence for a cholinergic gate within the medial septum (gating input from areas such as the supramammillary nucleus) and for independent cholinergic and serotonergic gates within the hippocampus (gating input from the medial septum and probably other areas). There also appeared to be a gate between CA3 and CA1 and, for consistency, we also postulate a gate between CA1 and its outputs, including the subiculum, and between the subiculum and its outputs such as the mammillary bodies. One, at least, of the latter two exists, since the eye-blink-related firing of CA1 is not transferred to the mammillary bodies. A subicular-related gate (on input to or output from the subiculum) is particularly important, theoretically, as it could account for the many instances where single-cell or theta correlates (recorded in CA1) do not map to the effects of hippocampal lesions (Appendix 8). In these cases, the hippocampus is receiving information with which it *could* control behaviour, but which does not result in significant functional output unless some other condition is fulfilled, so opening the final subicular gate (Chapter 10). A similar gate in the lateral septum is likely to determine the functional consequences of CA3 activity (see Garcia *et al*. 1993). There may also be gates related to the specific output targets of the hippocampus, with the potential for the appearance of theta activity in certain areas only when they are both involved in a particular class of task and the form of that task requires hippocampal disambiguation.

Finally, it should be noted that a number of the steps in the pathway may be gated, not only by the presence or absence of some tonic (e.g. cholinergic) signal, but also by the temporal ordering of natural events (for example the depression of response to the second of two closely spaced tones shown by Miller *et al*. 1995, and as suggested by the phase precession of cell firing as the animal passes through a place field).

Given this array of postulated gates, it is of interest that septal inactivation (which can produce deficits in spatial tasks) disrupts CA3 place fields extensively, subicular and entorhinal place fields to some extent, but CA1 cell firing not at all (see Mizumori *et al.* 1992). This pattern of results shows that the logical gates in the system are not simply sequential. Certain information (represented by place fields in this case) is sent directly to all levels of the system and then the operation of the various gates determines which levels (CA3, subiculum, etc.) of the system can produce functional output.

It is in the essence of the methods used that cell firing must be analysed in terms of correlation with an observable stimulus or an observable response. Yet we have suggested that the true correlate of hippocampal cell firing is not just internal activity, but internal activity which often reflects the priming of response systems which are not in fact released. This makes the true correlates inherently invisible at the behavioural level. Surely this inference breaks the central canon of the whole research area, permitting one to explain anything in a totally ad hoc fashion?

This is a charge that must be treated seriously, but we think it can be completely answered. While one cannot usually use introspection in scientific psychology, there can be little doubt in the mind of anyone who does introspect that there are thoughts, and hence brain processes, which are behaviourally silent at the time they are occurring. The same can be demonstrated in animals in, for example, the case of sensory preconditioning, in that later testing with a reinforcer can demonstrate that pairing of two neutral stimuli caused them to becomes associated (Chapter 3). Thus, while our proposed ‘correlations’ cannot normally be directly observed, they can be inferred across multiple conditions (as we have done above) and should be directly observable under at least some special conditions.

First, if there is only one primed goal it should become behaviourally visible since hippocampal activity will, in this case, always be followed by behaviour directed to that goal. If, in addition, the goal can be characterized by the temporal topography of goal-directed responding (as in the case of the nictitating membrane conditioning experiments), then it can be recognized even if no response is emitted. For example, let us imagine a situation in which there were only two responses available, each able to vary only in the temporal dimension (for example, with a highly restrained rabbit trained to produce the eyeblink and jaw movement responses). These responses would be few enough for us to keep track of their co-occurrence and would be identifiable, one from the other, by their distinct temporal morphology. Cells could then be classified in relation to their response morphology and ‘pure nictitating’ and ‘pure jaw movement’ cells selected for further experiment. We would predict that both types of cell would respond in their characteristic fashion if their CSs were presented concurrently and that some previously silent cells would respond to the conjunction of the two. It is also probable that priming could be demonstrated by some form of delay firing between an ambiguous readiness signal and a discriminatory imperative signal

(as suggested by the experiments of Colombo and Gross 1994, discussed earlier). In such an experiment, trace conditioning would first be undertaken with separate CSs for each of the responses and the delay-related firing characterized (Weiss *et al*. 1996). Then the ambiguous warning–imperative form of the task would be substituted. Here we would predict that the ambiguous warning stimulus should produce firing in both types of cell simultaneously, independent of which response was ultimately emitted.

Second, priming of responses could be detected by recording from the appropriate brain area (probably the deep cerebellar nucleus and red nucleus in the case of nictitating membrane conditioning). Thus, concurrent single-cell recording in the periaqueductal grey, ventral tegmental area, tegmental nuclei, amygdala, anterior cingulate, posterior cingulate, or prefrontal cortex should show a linkage with the firing of particular hippocampal cells that is much tighter than that shown by observable behaviour.

It might be thought, at this point, that we have just run foul of the same problem as an absolute spatial map theory. If the hippocampus codes for so many different goals, how can one ever record in the right place? There are two answers to this. First, we do not view the hippocampus as *coding* for the information apparently contained in its correlates. For the hippocampus as a whole we presume a relatively indiscriminate summing of all available inputs similar to that which we know occurs with the subcortical control of theta frequency. Second, we invoke a dynamic ‘lateral inhibition-like’ process which determines, in essence, how many functional lamellae the hippocampus may demonstrate at any particular point in time (Appendix 4). While the cell-sampling procedure used by Berger *et al*. (1983) in their classical conditioning procedure was such that they would have missed cells with a very low spontaneous firing rate, their estimate that over 80 per cent of pyramidal cells increased their firing rate during conditioning suggests that hippocampal cells receive convergent input from an enormous variety of sources. It is likely, therefore, that the apparent specificity and complexity of hippocampal cell fields in some experiments is the result of quite marked adjustments in signal-to-noise ratio (Appendix 10). This inference is important for our theory.

A final point is that, while our hypothesis (that the fields of hippocampal cells represent available goals) is admittedly difficult to test directly using only single-cell techniques, its validity can also be judged in terms of the place it occupies within our overall theory. This theory is open to many different kinds of test of many of its different facets. In the next appendix, for example, we look at the effects of electrical stimulation of the inputs to the hippocampus, a quite different means of assessing the functions of the septo-hippocampal system.

References

Alger, B. E. and Teyler, T. J. (1976). Long-term and short-term plasticity in the CA1, CA3, and dentate regions of the rat hippocampal slice. *Brain Research*, **110**, 463–80.

Ammassari-Teule, M., Maho, C., and Sara, S. J. (1991). Clonidine reverses spatial learning deficits and reinstates theta frequencies in rats with partial fornix section. *Behavioural Brain Research*, **45**, 1–8.

Apostol, G. and Creutzfeldt, O. D. (1974). Crosscorrelation between the activity of septal units and hippocampal EEG during arousal. *Brain Research*, **67**, 65–75.

Arnolds, D. E. A. T., Lopes da Silva, F. H., Aitiak, J. W., and Kamp, A. (1979*a*). Hippocampal EEG and behaviour in dog. III. Hippocampal EEG correlates of stimulus–response tasks and of sexual behaviour. *Electroencephalography and Clinical Neurophysiology*, **46**, 581–91.

Arnolds, D. E. A. T., Lopes da Silva, F. H., Aitiak, J. W., and Kamp, A. (1979*b*). Hippocampal EEG and behaviour in dog. II. Hippocampal EEG correlates with elementary motor acts. *Electroencephalography and Clinical Neurophysiology*, **46**, 571–80.

Aston-Jones, G., Chiang, C., and Alexinsky, T. (1991). Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance. *Progress in Brain Research*, **88**, 501–20.

Bach, M. E., Hawkins, R. D., Osman, M., Kandel, E. R., and Mayford, M. (1995). Impairment of spatial but not contextual memory in CaMKII mutant mice with a selective loss of hippocampal LTP in the range of the Φ frequency. *Cell*, **81**, 905–15.

Bennett, T. L. and French, J. (1977). Electrical activity of the cat hippocampus during the species-typical gape response: evidence against the voluntary movement hypothesis. *Behavioural Biology*, **21**, 432–7.

Bennett, T. L., French, J., and Burnett, K. N. (1978). Species differences in the behavior correlates of hippocampal RSA. *Behavioural Biology*, **22**, 161–77.

Berger, T. W. and Alger, B. (1976). Neuronal substrates of classical conditioning in the hippocampus. *Science*, **192**, 483–5.

Berger, T. W. and Thompson, R. F. (1978*a*). Neuronal plasticity in the limbic system during classical conditioning of the rabbit nictitating membrane response. I. The hippocampus. *Brain Research*, **145**, 323–46.

Berger, T. W. and Thompson, R. F. (1978*b*). Neuronal plasticity in the limbic system during classical conditioning of the rabbit nictitating membrane response. II. Septum and mammillary bodies. *Brain Research*, **156**, 293–314.

Berger, T. W., Rinaldi, P. C., Weisz, D. J., and Thompson, R. F. (1983). Single-unit analysis of different hippocampal cell types during classical conditioning of rabbit nictitating membrane response. *Journal of Neurophysiology*, **50**, 1197–219.

Berger, T. W., Berry, S. D., and Thompson, R. F. (1986*a*). Role of the hippocampus in classical conditioning of aversive and appetitive behaviors. In *The hippocampus* (ed. R. L. Isaacson and K. H. Pribam), pp. 203–39. Plenum, New York.

Berger, T. W., Weikart, C. L., Bassett, J. L., and Orr, W. B. (1986*b*). Lesions of the retrosplenial cortex produce deficits in reversal learning of the rabbit nictitating membrane response: implications for potential interactions between hippocampal and cerebellar brain systems. *Behavioral Neuroscience*, **100**, 802–9.

Best, M. R. and Best, P. J. (1976). The effects of state of consciousness and latent inhibition on hippocampal unit activity in the rat during conditioning. *Experimental Neurology*, **51**, 564–73.

Black, A. H. (1975). Hippocampal electrical activity and behavior. In *The hippocampus*, *Vol. 2*, *Neurophysiology and behaviour* (ed. R. L. Isaacson and K. H. Pribam), pp. 129–67. Plenum, New York.

Black, A. H. and Young, G. A. (1972). Electrical activity of the hippocampus and cortex in dogs operantly trained to move and to hold still. *Journal of Comparative and Physiological Psychology*, **79**, 128–41.

Bland, B. H. and Vanderwolf, C. H. (1972). Diencephalic and hippocampal mechanisms of motor activity in the rat: effects of posterior hypothalamic stimulation on behaviour and hippocampal slow wave activity. *Brain Research*, **43**, 67–88.

Blaxton, T. A., Zeffiro, T. A., Gabrieli, J. D. E., Bookheimer, S. Y., Carrillo, M. C., Theodore, W. H., *et al.* (1996). Functional mapping of human learning: a positron emission tomography activation study of eyeblink conditioning. *The Journal of Neuroscience*, **16**, 4032–40.

Brown, M. W. (1982). Effect of context on the response of single units recorded from the hippocampal region of behaviourally trained monkeys. In *Neuronal plasticity and memory formation* (ed. C. A. Marsan and H. Matthies), pp. 557–73. Raven Press, New York.

Buño, W., Jr. and Velluti, J. C. (1977). Relationships of hippocampal theta cycles with bar pressing during self-stimulation. *Physiology and Behavior*, **19**, 615–21.

Burgess, N. and O'Keefe, J. (1996*a*). Cognitive graphs, resistive grids, and the hippocampal representation of space. *The Journal of General Psychology*, **107**, 659–62.

Burgess, N. and O'Keefe, J. (1996*b*). Neuronal computations underlying the firing of place cells and their role in navigation. *Hippocampus*, **6**, 749–62.

Buzsáki, G., Hsu, M., Horváth, Z., and Gage, F. H. (1992). Physiological and behavioral consequences of delayed septal grafts in the subcortically denervated hippocampus. *Restorative Neurology and Neuroscience*, **4**, 369–80.

Carlson, N. R. (1994). *Physiology of behavior.* Allyn and Bacon, Boston.

Caudarella, M., Durkin, T., Galey, D., Jeantet, Y., and Jaffard, R. (1987). The effect of diazepam on hippocampal EEG in relation to behavior. *Brain Research*, **435**, 202–12.

Cohen, N. J. and Eichenbaum, H. (1993). *Memory*, *amnesia*, *and the hippocampal memory system.* The MIT Press, Cambridge, MA.

Colombo, M. and Gross, C. G. (1994). Responses of inferior temporal cortex and hippocampal neurons during delayed matching to sample in monkeys (*Macaca fascicularis*). *Behavioral Neuroscience*, **108**, 443–55.

Coop, C. F., McNaughton, N., Warnock, K., and Laverty, R. (1990). Effects of ethanol and Ro 15–4513 in an electrophysiological model of anxiolytic action. *Neuroscience*, **35**, 669–74.

Coover, G.D., Ursin, H., and Levine, S. (1973) Plasma corticosterone levels during active avoidance learning in rats. *Journal of Comparative and Physiological Psychology,* **82**, 170-174

Deadwyler, S. A., West, M., and Lynch, G. (1979). Synaptically identified hippocampal slow potentials during behavior. *Brain Research*, **161**, 211–25.

Deadwyler, S. A., West, M. O., and Robinson, J. H. (1981). Entorhinal and septal inputs differentially control sensory-evoked responses in the rat dentate gyrus. *Science*, **211**, 1181–3.

Doyère, V., Negro, C. R.-D., Dutrieux, G., Le Floch, G., Davis, S., and Laroche, S. (1995). Potentiation or depression of synaptic efficacy in the dentate gyrus is determined by the relationship between the conditioned and unconditioned stimulus in a classical conditioning paradigm in rats. *Behavioural Brain Research*, **70**, 15–29.

Eichenbaum, H. and Cohen, N. J. (1988). Representation in the hippocampus: what do hippocampal neurons code? *Trends in Neuroscience*, **11**, 244–8.

Eichenbaum, H., Kuperstein, M., Fagan, A., and Nagode, J. (1987). Cue-sampling and goal-approach correlates of hippocampal unit activity in rats performing an odor-discrimination task. *The Journal of Neuroscience*, **7**, 716–32.

Elazar, Z. and Adey, W. R. (1967). Spectral analysis of low frequency components in the electrical activity of the hippocampus during learning. *Electroencephalography and Clinical Neurophysiology*, **23**, 225–40.

Elliott, K. and Whelan, J. (1978). *Functions of the septo-hippocampal system.* Ciba Foundation Symposium 58 (New Series). Elsevier, Amsterdam.

Faris, P. D. and Sainsbury, R. S. (1990). The role of the pontis oralis in the generation of RSA activity in the hippocampus of the guinea pig. *Physiology and Behavior*, **47**, 1193–9.

Feder, R. and Ranck, J. B., Jr. (1973). Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. II. Hippocampal slow waves and theta cell firing during bar pressing and other behaviours. *Experimental Neurology*, **41**, 532–55.

Fontani, G. and Maffei, D. (1997). Hippocampal electrical activity in rabbits during exploration of a semi-natural environment. *Behaviour Processes*, **40**, 121–8.

Foster, T. C., Christian, E. P., Hampson, R. E., Campbell, K. A., and Deadwyler, S. A. (1987). Sequential dependencies regulate sensory evoked

responses of single units in the rat hippocampus. *Brain Research*, **408**, 86–96.

Foster, T. C., Castro, C. A., and McNaughton, B. L. (1989). Spatial selectivity of rat hippocampal neurons: dependence on preparedness for movement. *Science*, **244**, 1580–2.

Fried, I., MacDonald, K. A., and Wilson, C. L. (1997). Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron*, **18**, 753–65.

Fuster, J. M. and Uyeda, A. A. (1971). Reactivity of limbic neurons of the monkey to appetitive and aversive signals. *Electroencephalography and Clinical Neurophysiology*, **30**, 281–93.

Garcia, R. and Jaffard, R. (1996). Changes in synaptic excitability in the lateral septum associated with contextual and auditory fear conditioning in mice. *European Journal of Neuroscience*, **8**, 809–15.

Garcia, R., Vouimba, R. M., and Jaffard, R. (1993). Spatial discrimination learning induces LTP-like changes in the lateral septum of mice. *NeuroReport*, **5**, 329–32.

Gavrilov, V. V., Wiener, S. I., and Berthoz, A. (1995*a*). Enhanced hippocampal theta EEG during whole body rotations in awake restrained rats. *Neuroscience Letters*, **197**, 239–41.

Gavrilov, V. V., Wiener, S. I., and Berthoz, A. (1995*b*). Whole body rotations enhance hippocampal theta rhythmic slow activity in awake rats passively transported on a mobile robot. In *New directions in vestibular research* (ed. S. M. Highstein, B. Cohen, and J. A. Buttner-Ennever), Annals of the New York Academy of Sciences, New York. pp. 1–20.

Givens, B. (1995). Low doses of ethanol impair spatial working memory and reduce hippocampal theta activity. *Alcoholism (NY)*, **19**, 763–7.

Givens, B. (1996). Behavioral correlates of single units in the medial septal area: the effect of ethanol. *Neuroscience*, **71**, 417–27.

Graeff, F. G., Quintero, S., and Gray, J. A. (1980). Median raphe stimulation, hippocampal theta rhythm and threat-induced behavioral inhibition. *Physiology and Behavior*, **25**, 253–61.

Gray, J. A. (1970). Sodium amobarbital, the hippocampal theta rhythm and the partial reinforcement extinction effect. *Psychological Review*, **77**, 465–80.

Gray, J. A. (1971). Medial septal lesions, hippocampal theta rhythm and the control of vibrissal movement in the freely moving rat. *Electroencephalography and Clinical Neurophysiology*, **30**, 189–97.

Gray, J. A. and Ball, G. G. (1970). Frequency-specific relation between hippocampal theta rhythm, behavior and amobarbital action. *Science (NY)*, **168**, 1246–8.

Green, J.S. and Arduini, A. (1954) Hippocampal electrical activity in arousal. Journal of Neurophysiology 17,533-557

Harper, R. M. (1971). Frequency changes in hippocampal electrical activity during movement and tonic immobility. *Physiology and Behavior*, **7**, 55–8.

Hirano, T., Best, P., and Olds, J. (1970). Units during habituation, discrimination learning and extinction. *Electroencephalography and Clinical Neurophysiology*, **28**, 127–35.

Holmes, J. E. and Beckman, J. (1969). Hippocampal theta rhythm used in predicting feline behavior. *Physiology and Behavior*, **4**, 563–5.

Inglis, W. L. and Winn, P. (1997). The pedunculopontine tegmental nucleus: where the striatum meets the reticular formation. *Progress in Neurobiology*, **47**, 1–29.

Iwahara, S., Oishi, H., Yamazaki, S., and Sakai, K. (1972). Effects of chlordiazepoxide upon spontaneous alternation and the hippocampal electrical activity in white rats. *Psychopharmacologia (Berlin)*, **24**, 496–507.

John, E. R. and Killam, K. F. (1959). Electrophysiological correlates of avoidance conditioning in the cat. *Journal of Pharmacology and Experimental Therapeutics*, **125**, 252–74.

Jung, M. W. and McNaughton, B. L. (1993). Spatial selectivity of unit activity in the hippocampal granular layer. *Hippocampus*, **3**, 165–82.

Jung, M. W., Wiener, S. I., and McNaughton, B. L. (1994). Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat. *The Journal of Neuroscience*, **14**, 7347–56.

Kemp, I. R. and Kaada, B. R. (1975). The relation of hippocampal theta activity to arousal, attentive behavior and somato-motor movements in unrestrained cats. *Brain Research*, **95**, 323–42.

Kimsey, R. A., Dyer, R. S., and Petri, H. L. (1974). Relationship between hippocampal EEG, novelty, and frustration in the rat. *Behavioural Biology*, **11**, 561–8.

Kita, T., Nishijo, H., Eifuku, S., Terasawa, K., and Ono, T. (1995). Place and contingency differential responses of monkey septal neurons during conditional place–object discrimination. *The Journal of Neuroscience*, **15**, 1683–703.

Komisaruk, B. R. (1970). Synchrony between limbic system theta activity and rhythmical behaviours in rats. *Journal of Comparative and Physiological Psychology*, **70**, 482–92.

Korshunov, V. A., Wiener, S. I., Korshunova, T. A., and Berthoz, A. (1996). Place- and behavior-independent sensory triggered discharges in rat hippocampal CA1 complex spike cells. *Experimental Brain Research*, **109**, 169–73.

Kramis, R., Vanderwolf, C. H., and Bland, B. H. (1975). Two types of hippocampal rhythmical slow activity in both the rabbit and the rat: relations to behavior and effects of atropine, diethyl ether, urethane, and pentobarbital. *Experimental Neurology*, **49**, 58–85.

Laroche, S., Neuenschwander-El Massioui, N., Edeline, J.-M., and Dutrieux, G. (1987). Hippocampal associative cellular responses: dissociation with behavioral responses revealed by a transfer-of-control technique. *Behavioral and Neural Biology*, **47**, 356–68.

Lidsky, A., Levine, M. S., and MacGregor, S., Jr. (1974*a*). Tonic and phasic effects evoked concurrently by sensory stimuli in hippocampal units. *Experimental Neurology*, **44**, 130–4.

Lidsky, A., Levine, M. S., and MacGregor, S., Jr. (1974*b*). Hippocampal units during orienting and arousal in rabbits. *Experimental Neurology*, **44**, 171–86.

Llinas, R. R. and Simpson, J. I. (1981). Cerebellar control of movement. In (ed. A. L. Towe and E. S. Luschei), *Handbook of behavioral neurobiology. Vol. 5*, *Motor coordination.* Plenum Press, New York.

Logan, C. G. and Grafton, S. T. (1995). Functional anatomy of human eyeblink conditioning determined with regional cerebral glucose metabolism and positron-emission tomography. *Proceedings of the National Academy of Sciences of the United States of America*, **92**, 7500–4.

Lynch, G. S., Rose, G., and Gall, C. M. (1978). Anatomical and functional aspects of the septo-hippocampal projections. In *Functions of the septo-hippocampal system*, Ciba Foundation Symposium 58 (New Series), (ed. K. Elliott and J. Whelan), pp. 5–20. Elsevier, Amsterdam.

Macrides, F. (1975). Temporal relationships between hippocampal slow waves and exploratory sniffing in hamsters. *Behavioural Biology*, **14**, 295–308.

Mahut, H. (1971). Spatial and object reversal learning in monkeys with partial temporal lobe ablations. *Neuropsychologia*, **9**, 409–24.

Matthews, D. B., Simson, P. E., and Best, P. J. (1996). Ethanol alters spatial processing of hippocampal place cells: a mechanism for impaired navigation when intoxicated. *Alcohol Clinical Experimental Research*, **20**, 404–7.

Mauk, M. D. and Thompson, R. F. (1987). Retention of classically conditioned eyelid responses following acute decerebration. *Brain Research*, **403**, 89–95.

Mays, L. E. and Best, P. J. (1975). Hippocampal unit activity to tonal stimuli during arousal from sleep and in awake rats. *Experimental Neurology*, **47**, 268–79.

McNaughton, B. L. and Morris, R. G. M. (1987). Hippocampal synaptic enhancement and information storage within a distributed memory system. *Trends in Neuroscience*, **10**, 408–15.

McNaughton, N. and MacMillan, F. (1994). Effects of chlordiazepoxide on hippocampal rhythmical slow activity during a fixed interval schedule. *International Journal of Neuroscience*, **74**, 133-134

McNaughton, N. and Miller, J. J. (1984). Medial septal projections to the dentate gyrus in the rat: electrophysiological analysis of distribution and plasticity. *Experimental Brain Research*, **56**, 243–56.

McNaughton, N., Forster, G. L., Swain-Campbell, N. R., and Ripandelli, F. M. (1997). Cholinergic relays in superior colliculus, substantia nigra and amygdala co-operate to gate theta activity. *Society for Neuroscience Abstracts*, **23**, 487.

McNaughton, N., James, D. T. D., Stewart, J., Gray, J. A., Valero, I., and Drewnowski, A. (1977). Septal driving of hippocampal theta rhythm as a function of frequency in the male rat: effects of drugs. *Neuroscience*, **2**, 1019–27.

McNaughton, N. and Sedgwick, E.M. (1978) Reticular stimulation and hippocampal theta rhythm in rats: effects of drugs. *Neuroscience,* **2**, 629-632

Miller, C. L., Bickford, P. C., Wiser, A. K., and Rose, G. M. (1995). Long-term potentiation disrupts auditory gating in the rat hippocampus. *The Journal of Neuroscience*, **15**, 5820–30.

Mizumori, S. J. Y., Ward, K. E., and Lavoie, A. M. (1992). Medial septal modulation of entorhinal single unit activity in anaesthetized and freely moving rats. *Brain Research*, **570**, 188–97.

Mizumori, S. J. Y., Lavoie, A. M., and Kalyani, A. (1996). Redistribution of spatial representation in the hippocampus of aged rats performing a spatial memory task. *Behavioral Neuroscience*, **110**, 1006–16.

Monmaur, P. and Breton, P. (1991). Elicitation of hippocampal theta by intraseptal carbachol injection in freely moving rats. *Brain Research*, **544**, 150–5.

Montoya, C. P., Heynen, A. J., Faris, P. D., and Sainsbury, R. S. (1989). Modality specific type 2 theta production in the immobile rat. *Behavioral Neuroscience*, **103**, 106–11.

Morris, R. G. M. and Black, A. H. (1978). Hippocampal electrical activity and behavior elicited by nonreward. *Behavioural Biology*, **22**, 524–32.

Morris, R. G. M., Black, A. H., and O'Keefe, J. (1976). Hippocampal EEG during a ballistic movement. *Neuroscience Letters*, **3**, 102.

Myhrer, T. (1975). Normal jump avoidance performance in rats with the hippocampal theta rhythm selectively disrupted. *Behavioural Biology*, **14**, 489–98.

Nieber, D. and Schlegel, S. (1992). Relationships between psychomotor retardation and EEG power spectrum in major depression. *Neuropsychobiology*, **25**, 20–3.

Oddie, S. D., Stefanek, W., Kirk, I. J., and Bland, B. H. (1996). Intraseptal procaine abolishes hypothalamic stimulation-induced wheel-running and hippocampal theta field activity in rats. *The Journal of Neuroscience*, **16**, 1948–56.

Oddie, S. D., Kirk, I. J., Whishaw, I. Q., and Bland, B. H. (1997). Hippocampal formation is involved in movement selection: evidence from medial septal cholinergic modulation and concurrent slow-wave (theta rhythm) recording. *Behavioural Brain Research*, **88**, 169–80.

O'Keefe, J. (1976). Place units in the hippocampus of the freely moving rat. *Experimental Neurology*, **51**, 78–109.

O'Keefe, J. (1993). Hippocampus, theta, and spatial memory. *Current Opinion in Neurobiology*, **3**, 917–24.

O'Keefe, J. and Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Research*, **34**, 171–5.

O'Keefe, J. and Nadel, L. (1978). *The hippocampus as a cognitive map.* Clarendon Press, Oxford.

Olds, J. and Hirano, T. (1969). Conditioned responses of hippocampal and other neurons. *Electroencephalography and Clinical Neurophysiology*, **2**, 159–66.

Olds, J., Mink, W. D., and Best, P. J. (1969). Single unit patterns during anticipatory behavior. *Electroencephalography and Clinical Neurophysiology*, **26**, 144–58.

Olton, D. S. and Isaacson, R. L. (1968). Hippocampal lesions and active avoidance. *Physiology and Behavior*, **3**, 719–24.

O'Mara, S. M. (1995). Spatially selective firing properties of hippocampal formation neurons in rodents and primates. *Progress in Neurobiology*, **45**, 253–74.

Orsetti, M., Casamenti, F., and Pepeu, G. (1996). Enhanced acetylcholine release in the hippocampus and cortex during acquisition of an operant behavior. *Brain Research*, **724**, 89–96.

Pan, W. X. and McNaughton, N. (1997). The medial supramammillary nucleus, spatial learning and the frequency of hippocampal theta activity. *Brain Research*, **764**, 101–8.

Peck, B. K. and Vanderwolf, C. H. (1991). Effects of raphe stimulation on hippocampal and neocortical activity and behaviour. *Brain Research*, **568**, 244–52.

Preobrazhenskaya, L. A. (1974). Hippocampal electrical activity and different types of conditioned reflexes in dogs. *Acta Neurobiologica Experimentalis*, **34**, 409–22.

Preobrazhenskaya, L. A. (1991). Dependence of the electrical activity of the hippocampus on the probability of reinforcement of an alimentary conditional stimulus. *Neuroscience and Behavioral Physiology*, **21**, 296–302.

Ranck, J. B., Jr. (1973). Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. *Experimental Neurology*, **41**, 461–555.

Riches, I. P., Wilson, F. A. W., and Brown, M. W. (1991). The effects of visual stimulation and memory on neurons of the hippocampal formation and the neighboring parahippocampal gyrus and inferior temporal cortex of the primate. *The Journal of Neuroscience*, **11**, 1763–79.

Rivas, J., Gaztelu, J. M., and García-Austt, E. (1996). Changes in hippocampal cell discharge patterns and theta rhythm spectral properties as a function of walking velocity in the guinea pig. *Experimental Brain Research*, **108**, 113–18.

Robertson, B., Baker, G. B., and Vanderwolf, C. H. (1991). The effects of serotonergic stimulation on hippocampal and neocortical slow waves and behavior. *Brain Research*, **555**, 265–75.

Robinson, T. E. (1980). Hippocampal rhythmic slow activity (RSA; theta): a critical analysis of selected studies and discussion of possible species-differences. *Brain Research Reviews*, **2**, 69–101.

Robinson, T. E. and Vanderwolf, C. H. (1978). Electrical stimulation of the brain stem in freely moving rats: II. Effects of hippocampal and neocortical electrical activity, and relations to behavior. *Experimental Neurology*, **61**, 485–515.

Ruusuvirta, T., Korhonen, T., Penttonen, M., Arikoski, J., and Kivirikko, K. (1995). Behavioral and hippocampal evoked responses in an auditory oddball situation when an unconditioned stimulus is paired with deviant tones in the cat: Experiment II. *International Journal of Psychophysiology*, **20**, 41–7.

Sainsbury, R. S. (1985). Type 2 theta in the guinea pig and the cat. In *Electrical activity of the archicortex* (ed. G. Buzsáki and C. H. Vanderwolf), pp. 11–22. Akademiai Kiado, Budapest.

Sainsbury, R. S. and Montoya, C. P. (1984). The relationship between type 2 theta and behavior. *Physiology and Behavior*, **33**, 621–6.

Sainsbury, R. S., Harris, J. L., and Rowland, G. L. (1987*a*). Sensitization and hippocampal type 2 theta in the rat. *Physiology and Behavior*, **41**, 489–93.

Sainsbury, R. S., Heynen, A., and Montoya, C. P. (1987*b*). Behavioral correlates of hippocampal type 2 theta in the rat. *Physiology and Behavior*, **39**, 513–19.

Sakurai, Y. (1990). Hippocampal cells have behavioural correlates during the performance of an auditory working memory task in the rat. *Behavioral Neuroscience*, **104**, 253–63.

Sakurai, Y. (1994). Involvement of auditory cortical and hippocampal neurons in auditory working memory and reference memory in the rat. *The Journal of Neuroscience*, **14**, 2606–23.

Sakurai, Y. (1996*a*). Population coding by cell assemblies—what it really is in the brain. *Neuroscience Research*, **26**, 1–16.

Sakurai, Y. (1996*b*). Hippocampal and neocortical cell assemblies encode memory processes for different types of stimuli in the rat. *The Journal of Neuroscience*, **16**, 2809–19.

Schmajuk, N. A. (1997). Stimulus configuration, long-term potentiation, and the hippocampus. *Behavioural and Brain Sciences*, **20**, 629–31.

Segal, M. (1973). Flow of conditioned responses in limbic telencephalic system of the rat. *Journal of Neurophysiology*, **36**, 840–54.

Segal, M. (1974). Convergence of sensory input on units in the hippocampal system of the rat. *Journal of Comparative and Physiological Psychology*, **87**, 91–9.

Segal, M. (1975). Hippocampal conditioned responses in the absence of entorhinal input. *Physiology and Behavior*, **15**, 381–4.

Segal, M. (1977*a*). The effects of brainstem priming stimulation on interhemispheric hippocampal responses in the awake rat. *Experimental Brain Research*, **28**, 529–41.

Segal, M. (1977*b*). Changes of interhemispheric hippocampal responses during conditioning in the awake rat. *Experimental Brain Research*, **29**, 553–65.

Segal, M. (1977*c*). Changes in hippocampal evoked responses to afferent stimulation during conditioning. *Brain Research*, **127**, 382 (abstract).

Segal, M. (1977*d*). Excitability changes in rat hippocampus during conditioning. *Experimental Neurology*, **55**, 67–73.

Segal, M. and Bloom, F. E. (1976). The action of norepinephrine in the rat hippocampus. IV. The effects of locus coeruleus stimulation on evoked hippocampal unit activity. *Brain Research*, **107**, 513–25.

Segal, M. and Olds, J. (1972). Behavior of units in hippocampal circuit of the rat during learning. *Journal of Neurophysiology*, **35**, 680–90.

Semba, K. and Komisaruk, B. R. (1978). Phase of the theta wave in relation to different limb movements in awake rats. *Electroencephalography and Clinical Neurophysiology*, **44**, 61–71.

Shapiro, M. L., Tanila, H., and Eichenbaum, H. (1997). Cues that hippocampal place cells encode: dynamic and hierarchical representation of local and distal stimuli. *Hippocampus*, **7**, 624–42.

Sideroff, S. and Bindra, D. (1976). Neural correlates of discriminative conditioning: separation of associational and motivational processes. *Brain Research*, **101**, 376–82.

Skaggs, W. E., McNaughton, B. L., Wilson, M. A., and Barnes, C. A. (1996). Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus*, **6**, 149–72.

Sobotka, S. and Ringo, J. L. (1997). Saccadic eye movements, even in darkness, generate event-related potentials recorded in medial septum and medial temporal cortex. *Brain Research*, **756**, 168–73.

Sokolov, E. N. (1960). Neuronal models and the orienting reflex. In *The central nervous system and behaviour*, 3rd Conference (ed. M. A. B. Brazier), pp. 187–276. Josiah Macy Jr Foundation, New York.

Sokolov, E. N. (1963). *Perception and the conditioned reflex.* Pergamon Press, Oxford.

Soubrié, P., Thiébot, M. H., Simon, P., and Boissier, J. R. (1978). Benzodiazepines and behavioural effects of reward (water) omission. *Psychopharmacology*, **59**, 95–100.

Steward, O. (1976). Topographic organization of the projections from the entorhinal area to the hippocampal formation of the rat. *The Journal of Comparative Neurology*, **167**, 285–314.

Stolar, N., Sparenborg, S., Donchin, E., and Gabriel, M. (1989). Conditional stimulus probability and activity of hippocampal, cingulate cortical and limbic thalamic neurons during avoidance conditioning in rabbits. *Behavioral Neuroscience*, **103**, 919–34.

Stumpf, C. (1965). Drug action on the electrical activity of the hippocampus. *International Review of Neurobiology*, **8**, 77–138.

Suzuki, W. A., Miller, E. K., and Desimone, R. (1997). Object and place memory in the macaque entorhinal cortex. *Journal of Neurophysiology*, **78**, 1062–81.

Tanila, H., Shapiro, M. L., and Eichenbaum, H. (1997). Discordance of spatial representation in ensembles of hippocampal place cells. *Hippocampus*, **7**, 613–23.

Tsodyks, M. V., Skaggs, W. E., Sejnowski, T. J., and McNaughton, B. L. (1996). Population dynamics and theta rhythm phase precession of hippocampal place cell firing: a spiking neuron model. *Hippocampus*, **6**, 271–80.

Tulving, E., Markowitsch, H. J., Kapur, S., Habib, R., and Houle, S. (1994). Novelty encoding networks in the human brain: positron emission tomography data. *NeuroReport*, **5**, 2525–8.

Vanderwolf, C. H. (1969). Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalography and Clinical Neurophysiology*, **26**, 407–18.

Vanderwolf, C. H. (1971). Limbic–diencephalic mechanisms of voluntary movement. *Psychological Review*, **78**, 83–113.

Vanderwolf, C. H. (1975). Neocortical and hippocampal activation in relation to behavior: effects of atropine, eserine, phenothiazines, and amphetamine. *Journal of Comparative and Physiological Psychology*, **88**, 300–23.

Vanderwolf, C. H. (1987). Near-total loss of ‘learning’ and ‘memory’ as a result of combined cholinergic and serotonergic blockade in the rat. *Behavioural Brain Research*, **23**, 43–57.

Vanderwolf, C. H. and Cooley, R. K. (1974). Hippocampal electrical activity during long-continued avoidance performance: effects of fatigue. *Physiology and Behavior*, **13**, 819–23.

Vanderwolf, C. H., Kramis, R., Gillespie, L. A., and Bland, B. H. (1975). Hippocampal rhythmical slow activity and neocortical low voltage fast activity: relations to behavior. In *The hippocampus*, *Vol. 2. Neurophysiology and behavior* (ed. R. L. Isaacson and K. H. Pribram), pp. 101–28. Plenum Press, New York.

Vertes, R. P., Colom, L. V., Fortin, W. J., and Bland, B. H. (1993). Brainstem sites for the carbachol elicitation of the hippocampal theta rhythm in the rat. *Experimental Brain Research*, **96**, 419–29.

Vinogradova, O. S. (1975). Functional organization of the limbic system in the process of registration of information: facts and hypotheses. In *The hippocampus*, *Vol. 2. Neurophysiology and behavior* (ed. R. L. Isaacson and K. H. Pribram), pp. 3–69. Plenum Press, New York.

Vinogradova, O. S. (1995). Expression, control, and probable functional significance of the neuronal theta-rhythm. *Progress in Neurobiology*, **45**, 523–83.

Vinogradova, O. S. and Brazhnik, P. S. (1978). Neuronal aspects of septo-hippocampal relations. In *Functions of the septo-hippocampal system*, Ciba Foundation Symposium 58 (New Series), (ed. K. Elliott and J. Whelan), pp. 145–171. Elsevier, Amsterdam.

Vinogradova, O. S., Brazhnik, E. S., Kichigina, V. F., and Stafekhina, V. S. (1993). Theta modulation of neurons of the hippocampus of the rabbit and its interrelationship with other parameters of spontaneous and evoked activity. *Neuroscience and Behavioral Physiology*, **23**, 226–39.

Watanabe, T. and Niki, H. (1985). Hippocampal unit activity and delayed response in the monkey. *Brain Research*, **325**, 241–54.

Weiss, C., Kronforst-Collins, M. A., and Disterhoft, J. F. (1996). Activity of hippocampal pyramidal neurons during trace eyeblink conditioning. *Hippocampus*, **6**, 192–209.

Whishaw, I. Q. (1972). Hippocampal electroencephalographic activity in the Mongolian gerbil during natural behaviours and in wheel running and conditioned immobility. *Canadian Journal of Psychology*, **26**, 219–39.

Whishaw, I. Q. and Vanderwolf, C. H. (1973). Hippocampal EEG and behavior: changes in amplitude and frequency of RSA (theta rhythm) associated with spontaneous and learned movement patterns in rats and cats. *Behavioural Biology*, **8**, 461–84.

Wiener, S. I. (1996). Spatial, behavioral and sensory correlates of hippocampal CA1 complex spike cell activity: implications for information processing functions. *Progress in Neurobiology*, **49**, 335–61.

Wiener, S. I., Paul, C. A., and Eichenbaum, H. (1989). Spatial and behavioral correlates of hippocampal neuronal activity. *The Journal of Neuroscience*, **9**, 2737–63.

Wilson, M. A. and McNaughton, B. L. (1993). Dynamics of the hippocampal ensemble code for space. *Science*, **261**, 1055–8.

Winson, J. (1972). Interspecies differences in the occurrence of theta. *Behavioural Biology*, **7**, 479–87.

Winson, J. (1990). The meaning of dreams. *Scientific American*, **263**, 42–8.

Woodnorth, M.-A. and McNaughton, N. (1999). Anxiolytic action on the supramammillary nucleus reduces theta frequency and increases fixed interval responding. *Society for Neuroscience Abstracts*, **25**, 1641.

Yadin, E. (1989). Unit activity in the medial septum during differential appetitive conditioning. *Behavioural Brain Research*, **33**, 45–50.

Young, B. J., Fox, G. D., and Eichenbaum, H. (1994). Correlates of hippocampal complex-spike cell activity in rats performing a nonspatial radial maze task. *The Journal of Neuroscience*, **14**, 6553–63.

Young, G. A. (1976). Electrical activity of the dorsal hippocampus in rats operantly trained to lever press and to lick. *Journal of Comparative and Physiological Psychology*, **90**, 78–90.

Notes

1. This classification of granule cells was on the basis of a number of criteria relating to perforant path stimulation, including the fact that this 'elicited a single action potential from isolated units recorded in the granule cell layer even at high stimulation intensities' at the latency of the population spike. However, the baseline rate of firing of 17 spikes/s contrasts with Jung and McNaughton's (1993) view that granule cells are characterized by very low (0.15 spike/s) firing rates, and that high-rate 'theta' cells have a baseline rate of 4 spikes/s. Given the single spike activation by perforant path stimulation, it seems less likely that Foster *et al*. (1987) were recording simultaneously from many units than that the nature of the behavioural paradigm greatly changed the firing characteristics of granule cells.

2. This would be above 1 mV within hippocampus proper. But both cholinergic and non-cholinergic theta are easily recorded in the subiculum, where the amplitude is low. This may be because of the relative lack of fast activity in the subiculum.

3. Vanderwolf (1987) presents data on the behavioural effects of combining cholinergic and serotonergic blockade which could be taken to suggest that total blockade of theta has quite extensive effects. However, the treatments were systemic, and the effects included an abolition of active avoidance which is never seen with hippocampal lesions. The relation of the drug effects to changes in theta is therefore open to question.

4. It follows that if you could record activity from a pigeon hippocampus similar to that from a rat hippocampus, then key pecking would be accompanied by large irregular activity (LIA), since in pigeons key pecking is a stereotyped 'eating' or 'drinking' response which varies only in relation to the reinforcer. It is also possible, but not necessarily likely, that sufficient training of a rat on a simple continuously reinforced lever press response could render this stereotypical and hence eliminate the accompanying theta. The occasional cases where theta accompanies licking may be ones in which alternative action tendencies are concurrently activated. This could explain some results of Caudarella *et al*. (1987). They found that administration of diazepam, which reduces the frequency of theta, greatly increased the tendency of animals on a treadmill to walk quickly and then stop repeatedly rather than walking steadily. This walking was usually accompanied by LIA, and the immobility which followed was accompanied by theta. It seems possible that the reduction in theta frequency produced by the drug had reduced the capacity for high-speed selection between alternative flexible walking responses and had replaced this behaviour with something akin to a fixed action pattern. It seems unlikely that the treatment had disturbed the theta–walking relationship as such since, during self-paced walking in an open field, benzodiazepine treatment reduces theta frequency without apparently disrupting ambulation (Pan and McNaughton, in preparation).

5. The precise term to describe the information being imparted to the hippocampus is difficult to choose. This information does not involve copies of the simple motor programmes which might be conceived to produce the different responses. Nor does it involve copies of the 'intended movement vectors' (Llinas and Simpson 1981), which are a computationally respectable equivalent to the English-

language term ‘goals’ in a pure response sense. Rather, the incoming information must contain elements, not only of the general class of responses to be performed (presumably coded topographically), but also the importance attached to that class (coded by intensity of input and theta frequency), as well as elements of the expected result if the response is performed. Thus, discrepancies in the stimulus information received by the hippocampus (for example when the stimulus is entirely novel and there is no pre-programmed response) will cause information/risk assessment output from the hippocampus. This could not happen with an affectively neutral stimulus if the hippocampus received only response-modelling information. As we will see when we come to our theory, the stimulus, response, and importance information are not all tightly linked with each other.