List of appendices

Appendix 7

Electrical stimulation of the septo-hippocampal system, behaviour, and sleep

A7.1 Introduction

In this appendix we briefly consider the effects of electrical stimulation of the septo-hippocampal system on behaviour, with particular emphasis on the role of theta activity on consolidation-like processes. We also consider a related issue: the possible function of the theta rhythm during paradoxical sleep.

Electrical stimulation of the brain has the advantage over lesions that it manipulates an essentially intact organ and can be employed with parametric variations. It has the advantage over electrical recording that its approach is manipulative rather than correlational. It has the advantage over systemic drug injections that the direct effects of the manipulation can be quite localized. However, it suffers (as do all methods) from some peculiar disadvantages of its own. These are so complex that our strategy in this appendix is to select for brief comment only a few studies that appear to throw light on theoretically interesting issues, leaving aside the many which largely contradict each other or which (e.g. because of the production of epileptiform activity) lead to no obvious conclusions.

The major problem is that electrical stimulation of necessity imposes a specific pattern of activity on the affected network. This imposed pattern may mimic the normal activity of the system, degrade it, or produce some complex mixture of the two. For example, there is no reason why a particular stimulation should not enhance one pathway and impair a second pathway, at one and the same time, if both pass close to the electrode tip. Similarly, high-frequency stimulation can produce a ‘normal’ pattern of activity in each individual axon while, however, activating a particular set of axons which would never be coactivated by any natural stimulus or which would not be activated synchronously.

One way to ameliorate this problem is to compare the effects of electrical stimulation with the effects of lesions. If the two effects are the same, then the stimulation is presumably deleterious; if they are opposite, then it presumably enhances function; and if they are some mixture of the two, then something more complex is going on. However, arguments of this nature may often provide no more information than was available from the lesion studies themselves.

A particular problem, even using lesion data for comparison, is that apparently the same stimulation of areas such as the septum and hippocampus has been reported to produce lesion-like, opposite-to-lesion, or more complicated effects (e.g. O’Keefe and Nadel 1978, Table A29). This is not surprising since, as we shall see, the ‘same’

stimulation can have quite different effects depending on whether it elicits seizure discharge or not (see further O'Keefe and Nadel 1978, pp. 363–4); depending on the point in the pathway stimulated (high-frequency stimulation caudal to the supramammillary nucleus elicits theta, whereas high-frequency stimulation between the supramammillary nucleus, the medial septum, and the hippocampus blocks theta); and depending on whether high-frequency stimulation is continuous (theta blocking), as in most non-European studies, or phasic (potentially theta driving), as in some European studies. Some studies also use sinusoidal rather than brief pulse stimulation, which greatly increases the chances of additional effects due to ion deposition or lesion. Finally, since such stimulation can be used as a CS for conditioning, one must allow also for the possibility that the effects of stimulation on behaviour are due to state-change in general rather than any more specific effect of the treatment.

The solution we have adopted is to concentrate on those studies which monitor the neural effects of the stimulation, particularly with respect to hippocampal theta rhythm and seizure discharge, and studies which appear to present a clear picture for other reasons. We have divided the review into sections in terms of the nominally stimulated structure: perforant path, hippocampus, septum, and reticular formation. The order in which we treat these structures takes us, in effect, progressively backwards down the theta-generating pathways. We pay particularly close attention to studies linked to clear predictions as to effects on behaviour based on the known electrophysiology. Finally, we consider the potential role of theta activity during paradoxical sleep, as a natural equivalent of the effects of theta-eliciting stimulation.

A7.2 Perforant path/angular bundle stimulation

There is a large literature on relationships between long-term potentiation (LTP) and behaviour (see reviews by Morris *et al.* 1990; Morris and Baker 1984; Barnes 1995; Shors and Matzel 1997); but, except where this literature adds to information derived from either single-cell recording or lesions, we shall ignore it. Since all synapses in the septo-hippocampal system (and possibly all synapses in the brain) appear to be capable of LTP, many of the experiments, despite their technical sophistication, demonstrate merely that LTP could be important for behaviour, or that modifying LTP in the hippocampus occasionally has effects somewhat like a hippocampal lesion (see also Appendix 5). Here we will look specifically at the effects on behaviour of LTP-inducing stimulation of the input from the entorhinal cortex to the hippocampal formation.

Stimulation of the entorhinal cortex itself would be likely to have effects complicated by the number of cortical and hippocampal structures both orthodromically and antidromically activated. However, the perforant path input to the hippocampus travels in the angular bundle, where it can be activated by electrical stimulation in a somewhat more specific fashion. Equally important for behavioural studies, perforant path stimulation affects large areas of the hippocampus with relatively low levels of stimulation. Note, however, that it also affects (via antidromic invasion of entorhinal cortex) any extrahippocampal structures which receive entorhinal collaterals.

Experiments using angular bundle stimulation generally address the specific role of LTP in relation to behaviour and, by implication (because of the widely held view that LTP is a mechanism for memory storage), the question of whether the hippocampus

itself stores memories. The circuitry of the hippocampus potentially contains parallel distributed processing systems capable of a variety of memory storage functions (e.g. B. L. McNaughton and Morris 1987). A key point about such systems is that information is stored in the form of particular patterns of strengthened connections, and that storage of too many items, or strengthening of a substantial proportion of the available connections (saturation), will result in failure of the system. Also, of course, arbitrary strengthening of many connections, whether producing saturation or not, should degrade older memories. An obvious strategy for the testing of these hypotheses, then, is artificially to strengthen large numbers of connections and see if this impairs previously stored memories and prevents formation of new ones.

McNaughton *et al*. (1986) found that bilateral saturation of LTP produced impairments on the Barnes circular platform task, in which animals were given one trial per day on a brightly illuminated white platform . . . from which they could escape by finding a dark tunnel located beneath one of 18 peripherally located holes . . . [They] exhibited a pronounced, lasting deficit in the reversal of a previously learned spatial habit, a disruption of initial acquisition of spatial variables when the task was previously learned in a different environment, and disruption of recently stored spatial information. *Saturation produced no effect on performance of a previously learned spatial 'working memory' task*, despite the presumed requirement in this task of at least temporary storage of information about which locations had been recently visited. (Korol *et al*. 1993; our emphasis.)

Following on from the B. L. McNaughton *et al*. (1986) study, Castro *et al*. (1989) reported that saturation of the capacity of perforant path input to show LTP impaired learning in the Morris water maze and, importantly, that this impairment disappeared as LTP decayed. However, some subsequent studies (including those from the original laboratory) failed to replicate this effect (see *Hippocampus* 1993, pp. 123–64; see also Rioux and Robinson 1995 for similar results with the nictitating membrane response), although Jeffrey and Morris (1993) reported data which suggest that rats with more extensively saturated LTP of the EPSP (excitatory postsynaptic potential) were poorer at learning than rats in which the population spike but not the EPSP had saturated. (These authors interpret their data differently.) Inspection of the data from the other papers in the same issue of *Hippocampus* suggests that none conclusively demonstrated full saturation of the potentiation of the EPSP. More recent data suggest that the source of the failures may well be both the extent to which saturation is achieved *throughout* the hippocampus and an interaction of the effectiveness of saturation with specific task parameters (Barnes *et al*. 1994; see also Barnes 1995). Given the phenomenon of metaplasticity (Abraham and Bear 1996), one must also question what constitutes saturation in any case, rendering it difficult to interpret failures to demonstrate dysfunction after supposed saturation. It is also clear that seizures, which may have been induced in some of these experiments, can impair learning. The few apparent successes are, therefore, also in doubt. The issue must probably remain open until very carefully controlled experiments are carried out (Bliss and Richter-Levin 1993).

Whatever the outcome of future experiments in this area, it is clear that fairly extensive LTP of perforant path input to the hippocampus does not produce major impairments in many tasks sensitive to hippocampal lesions. Where impairments have been found, they tend not to involve erasure of pre-existing memories.

While these results are problematic for the most basic forms of memory theory of hippocampal function, our discussion of the data of Appendix 6 suggests that they do not directly test the more general role of LTP in the hippocampus at all. We

concluded there from Vinogradova's data that changes in the dentate (and by implication in perforant path input to other areas) reflect a familiarity signal which cancels the CA3 and CA1 responses arriving via the septum as a result of presentation of novel stimuli. This signal depends substantially on cortical processing, with the dentate only a final stage (which direct entorhino-CA3/CA1 connections could in any case bypass). Furthermore, entorhinal cancellation of CA3/CA1 processing was shown to be critical only for habituation of hippocampal-induced exploration since, in the case of important stimuli, transmission of the relevant information to CA3 and CA1 occurred despite the building up of a dentate model. We also found reason to believe that the specific model of an external stimulus was built up in the cortex, and that the hippocampus simply analyses the intersection of subcortical and cortical 'versions' of the same information. It follows that saturation of perforant path input would be expected to be detectable only in a habituation paradigm (rather than the learning paradigms actually tested), and that, in such a paradigm, its predicted effect would be to enhance habituation of novelty-elicited exploration.

It also follows that the most appropriate stimulation to test the role of LTP in many hippocampal functions would be of the CA1 input to the subiculum. Unfortunately, saturation of this pathway would be almost impossible for technical reasons. Saturation of the CA3 input to the lateral septum, however, could be particularly informative.

A number of studies have successfully used low-intensity, moderate-frequency (in the 'LTP' range) stimulation of the perforant path as a CS in conditioning paradigms. Given that reinforcement opens the dentate–CA3 gate (Appendix 6), it is not entirely surprising that this stimulation can act as a CS. However, this type of experimental result does suggest that information can leave the hippocampus and then come to control behaviour even with paradigms which are not normally subject to the effects of hippocampal lesions. One study of particular interest is that of Matthies *et al*. (1986). These authors included a number of controls to demonstrate that conditioning to the perforant path stimulus was occurring (these controls are often omitted) and, in particular, they monitored perforant path responses across time and across rats. Unpaired perforant path stimulation produced a moderate but long-lasting depression of perforant path potentials. Rats which showed poor retention on the next day showed no increase in perforant path responses. Rats which showed better retention on the next day showed potentiation of the perforant path responses. The key point, to which we will return when considering the effects of post-trial and reticular stimulation, was that this potentiation was not immediately evident but developed steadily over a period of four hours. This is not what would be expected with a simple LTP-like control of conditioning, and suggests that some kind of reminiscence or consolidation effect is being evidenced.

A7.3 Hippocampal stimulation

Given what we now know about LTP, long-term depression, seizures, and the critical nature of the stimulus parameters required to produce these phenomena, it is not surprising that the effects of direct hippocampal stimulation on behaviour have been very mixed. Detailed reviews of these studies are available elsewhere (Izquierdo 1975; O'Keefe and Nadel 1978, Chapter 12). We will concentrate here on studies

which address the role of the hippocampus in movement, rather than the more complicated studies which address the issues of memory and consolidation.

As we will see in Appendix 8, hippocampal lesions give rise to an increase in motor activity (most obviously as a loss of inhibition). Consistent with this, there are several reports that hippocampal stimulation causes an arrest of movement (Kaada *et al.* 1953; MacLean 1957; Vanegas and Flynn 1968; Bland and Vanderwolf 1972; Buzsáki *et al.* 1978). The arrest of movement is fairly, but not completely, general. Bland and Vanderwolf (1972) disrupted a wide range of theta-related activities with dentate gyrus stimulation, but lapping, a non-theta behaviour, was not affected. These latter results support the theta-behaviour correlations discussed in the preceding appendix. However, at the same time, they reinforce the conclusions we drew from Appendix 6 that the function of the hippocampus is effectively the opposite of that implied by the correlations: the correlate of theta is movement, but the function implied by both lesions and stimulation is inhibition of movement. Furthermore, the Bland and Vanderwolf result implies that the inhibition could be limited to only those cases where movement is 'voluntary', that is where several different responses are concurrently primed and a choice has to be made between them (Appendix 6, particularly the discussion of Oddie *et al*. 1997).

A7.4 Septal stimulation

Research on the behavioural effects of septal stimulation has, surprisingly, not usually addressed the issue of memory. For this reason and in contrast to the hippocampal studies, post-trial stimulation has been little used and hippocampal activity has seldom been monitored. Since electrical stimulation of the septal area, especially when it is of high frequency, is a particularly effective way of provoking hippocampal seizures, this is a serious omission.

A second reason for concurrent recording from the hippocampus when stimulating the septum is the known effects of this stimulation on theta. To recapitulate, stimulation at theta frequencies and at sufficient intensity will drive theta; continuous high-frequency stimulation of sufficient intensity will block theta; and high-frequency stimulation containing gaps at theta frequencies, or integer multiples of those gaps (which can produce theta frequencies as harmonics), is likely to drive theta.

The effects of continuous high-frequency stimulation of the septum are theoretically the most difficult to interpret. Since such stimulation blocks theta, as do septal lesions, it should act like a lesion of the septum. But septal input has both phasic GABAergic and tonic cholinergic, serotonergic, and noradrenergic components (since the monoaminergic afferents to the hippocampus traverse the septal area). The high-frequency stimulation will produce tonic GABAergic coupled with tonic cholinergic, serotonergic, and noradrenergic input. This should produce paradoxical results, with the high-frequency stimulation of the GABA system blocking the normal theta activity, but the high-frequency stimulation of the cholinergic, serotonergic, and noradrenergic system producing effects which would normally accompany theta activity. Equally tricky is the fact that high-frequency septal stimulation can produce LTP of septal–dentate connections (McNaughton and Miller 1984), which could be either detrimental or facilitatory depending on a variety of factors. Taking all this into

account, we will treat high-frequency stimulation as equivalent to the effects of a septal lesion, but mention it only occasionally and with considerable reservations.

The effects of theta-eliciting stimulation are theoretically less difficult to interpret. With low-frequency stimulation which drives theta (Fig. 9.1 in the printed text), we might assume that the elicited theta would act in a more or less physiological manner, as we are imposing on the septum, and hence the hippocampus, essentially the same pattern of activity as occurs under normal physiological circumstances. However, there is one potential problem with this view. If the topographic pattern of septal activation carries critical information for use by the hippocampus, we can generate the opposite prediction. A septal stimulation pulse would, then, from the point of view of the hippocampus, be like shining a bright light in the eyes as opposed to presenting a normal visual scene. In theory, we can distinguish between these alternatives experimentally. However, if the frequency of septal input to the hippocampus is important, septal stimulation could also have detrimental effects, not because it eliminates a topographic organization of the information, but because it imposes a timing input of the wrong frequency. The only way to test this possibility would be to record from the supramammillary nucleus (from which the correct theta timing could be extracted), block the supramammillary input at the medial septum, and then stimulate the fornix superior to 'replace' the normal theta frequency. If this procedure resulted in a normally behaving animal, we could conclude that no important topographically coded information was normally transmitted. But, if the behaviour was not normal, one could probably not concluded anything useful at all!

We can clarify matters somewhat by noting that the phasic GABAergic component of septal input to the hippocampus is unlikely to carry topographic information. Its primary targets, whether via inhibition or disinhibition, are the GABAergic interneurons which have a one-many relation to projection cells and which, in any case, we assume produce hippocampal theta by inhibiting the firing of cells activated by other inputs. Provided that the topographic information in these inputs is maintained, the theta driving will provide the same type of non-specific phasic gating as the natural input. Since the minimum interval between driving pulses is around 100 ms, there is plenty of time for specific information to be transmitted to the hippocampus, and the net effect of a single septal pulse (recurrent one-to-many inhibition in the septum) will be the same as with natural phasic input. It is also highly likely that theta driving, by antidromically activating the supramammillary nucleus and hence its recurrent inhibitory interneurons, resets the system in a way which is functionally indistinguishable from its resetting by other nuclei involved in intensity–frequency transduction (Appendix 5).

A similar conclusion is available from an experiment performed by Turnbull *et al.* (1994). They made lesions of the fornix in rats which had been pretrained on a spatial working memory task in the water maze. Stimulation of the perforant path at 5 Hz was delivered to induce synchronicity of hippocampal firing. Fornix lesion produced an impairment in the spatial working memory task, the electrical stimulation produced about a 50 per cent reduction in this impairment, and when stimulation was omitted the impairment increased again. From this set of results we can draw two conclusions. First, synchrony by itself (of whatever origin and frequency) can be beneficial to hippocampal function. Second, synchrony at a single frequency is unable totally to repair the deficits induced by eliminating the natural frequency control or the other

information arriving from the septum. (In this context, the experiment proposed above to bypass the supramammillary nucleus would be particularly useful.)

From all of the above, we can draw the conclusion that septal theta-driving stimulation is most likely to be the functional opposite of a septal lesion and could have minimal lesion-like side-effects.

If one simply elicits theta by driving it from the septum and observes the animal's behaviour, there is little to see (Gray 1972*a*; Kramis and Routtenberg 1977; Wetzel *et al.* 1977). Upon the first few occasions of stimulation the animal usually searches around as though something has aroused its curiosity. This is consistent with the observed correlations between theta and orienting or attentive behaviour (Appendix 6), and is equivalent to, but much weaker than, the effects of cholinergic septal activation. However, the same type of searching behaviour is elicited by stimulation at many other sites in the brain. With repeated stimulation, the animal rapidly habituates and comes to ignore it; it may even curl up in a corner and go to sleep. Wetzel *et al*. (1977) imply there is a much closer relationship than this between elicited theta and orienting. It is possible that their observations were due to the use of relatively ventral placements within the septum, which may have produced theta in the ventral as well as dorsal hippocampus. Even in their experiments, however, orienting did not occur whenever theta was present. This capacity of theta to produce sensitization to environmental stimuli, followed by tolerance, is something to which we will return.

Given the observed correlations between theta and movement (Appendix 6), it is important to note that, except for the initial exploration, there is no tendency for theta-driving stimulation to elicit movement. This is true even if the driven frequency is as high as 10 or 11 Hz. The same is true with 10 Hz theta produced by brief periods of 100 Hz stimulation in ideal reticular stimulation sites (N. McNaughton, personal observations).

The only occasion on which there appears to be any relation between septally elicited theta and motor behaviour is after systemic administration of the anticholinergic drug scopolamine, when driven theta is only observed if the animal simultaneously moves (McNaughton *et al*. 1977). In this case, it is not the theta that produces the movement, but the movement that permits the theta. Conversely, tonic cholinergic activation of the septum elicits both theta and intense exploratory activity (Monmaur and Breton 1991). These effects probably arise because the cholinergic activation not only elicits theta (as does septal stimulation), but also concurrently produces a high level of activation of septal cholinergic neurons, so opening a hippocampal cholinergic gate as well as a gate in the lateral septum as a result of diffusion and thereby allowing hippocampal outflow to subcortical exploration control systems (Appendix 5). However, as with septal stimulation, the behavioural syndrome reverts to relaxed immobility and automatic movements while theta remains present in the EEG, presumably because the output gates become closed before the activation of the hippocampus completely dissipates.

Several experiments have investigated the interaction of septal driving of theta with various ongoing behaviours. Klemm and Dreyfus (1975) saw no effect of driving theta in the rabbit on activity in a box, or ambulation in the open field. Gray (1972*b*) found that such stimulation did not affect drinking, and similar observations were

reported by Kramis and Routtenberg (1977). Gray (1972*b*) found that theta driving at 7.7 Hz decreased the rat's speed of running for water reward in the alley; and Glazer (1974*a*) and Klemm and Dreyfus (1975) similarly found a reduction in the rate of fixed-ratio (FR) bar-pressing. These data are consistent with the idea that theta is an active state of the hippocampus and that the function of the latter is essentially inhibitory of ongoing behaviour, since hippocampal lesions increase the FR response rate.

These data, taken together, fit well with the fact that anxiolytic drugs impair production of theta, exploratory behaviour such as rearing, and the inhibition of ongoing behaviour. It should be noted that septal driving does not produce any of the autonomic responses associated with fear or anxiety. This lack of effect is consistent with the fact that, unlike anxiolytic drugs, septal and hippocampal lesions do not block such responses.

A7.5 Septal stimulation and non-reward

A series of experiments, starting with Gray (1970) and Gray and Ball (1970), have studied the effects of septal stimulation on behaviour that is empirically and theoretically more complex than that considered so far in this appendix. In their most general formulation, these experiments have been concerned with the development of tolerance for aversive stimulation.

If animals are exposed repeatedly to aversive events, especially in the context of reward, they develop behavioural tolerance to them (Amsel 1962, 1972, 1992; Gray 1987). One example of this phenomenon is the partial reinforcement extinction effect (PREE). In the most typical version of this paradigm (although the PREE is ubiquitous and occurs under very varied conditions), two groups of rats receive food reward for running down a straight alley, one with food on every trial (continuous reinforcement, CRF), the other with reward on a random 50 per cent of trials (partial reinforcement, PRF). The PREE is shown by greater resistance to extinction (i.e. continued running for more trials when reward is discontinued) in the PRF group relative to the CRF group. Much evidence shows that the PREE reflects, at least in part, tolerance for the aversive event of frustrative non-reward (i.e. the non-delivery of expected reward; see Chapter 3 of the printed text) during training on the PRF schedule. Furthermore, since, for example, training on a PRF schedule gives rise to increased resistance to punishment and training on a schedule of mixed reward and punishment gives rise to increased resistance to extinction (see Gray 1987 for review), it seems that the PREE reflects a general increase in tolerance for aversive events, rather than a specific tolerance limited only to non-reward.

The experiments using septal driving of theta described in this appendix stem from a series of specific hypotheses, some of which have been drastically modified in the present edition of the book. Notably, in the 1982 edition it was proposed that the theta rhythm plays a substantive role in the selection of information for processing, and that this role varies as a function of theta frequency. In the present edition, by contrast, the working hypothesis is that the theta rhythm acts more generally to enhance the temporal precision with which the hippocampal system undertakes information processing, and that this more limited role does not vary as such with theta frequency. Thus, in the preceding appendix, evidence was assembled to show that the

correlations between the occurrence of theta and particular forms of behaviour are not frequency-specific; and that the putative division of theta frequency into a low (cholinergic) and high (non-cholinergic) frequency band is incorrect. Nonetheless, the experiments described in the present section were derived from a series of hypotheses so tightly interwoven with a frequency-specific analysis of theta that we shall here recount them within that framework. Furthermore, as we shall see, the degree to which very detailed predictions derived from these hypotheses have been experimentally verified requires us to leave open the possibility that, with further understanding, a frequency-specific view of hippocampal theta may yet undergo a renaissance.

The origin of the theta-driving experiments lay in three observations: that the measured theta frequency in rats exposed to non-reward as part of a PRF schedule in the straight alley occurred at 7.7 Hz; that there is a minimum threshold of the current required for septal driving of theta at this same frequency; and that the anxiolytic drugs increase the theta-driving threshold with a maximum rise at this frequency (Gray 1970; Gray and Ball 1970; McNaughton *et al*. 1977). These observations have been discussed already at several points throughout both the printed text and the appendices. Here, we consider only the experiments on the behavioural effects of septal driving of theta to which they gave rise. A further key previous observation was that the anxiolytics, given during acquisition on a PRF schedule, block the PREE (e.g. Feldon *et al*. 1979; Feldon and Gray 1981). Putting together these observations, Gray (1970, 1972*b*) predicted and found that the driving of theta at 7.7 Hz in the goal-box of a straight alley on a quasi-PRF schedule (but with the rats actually receiving food reward on every trial) mimicked a PREE in that animals so treated were subsequently (in the absence of any further septal stimulation) more resistant to extinction than controls. This result was taken as evidence that the specific frequency of 7.7 Hz theta elicited by non-reward forms part of the causal chain that leads to the PREE; that anxiolytic drugs block the PREE by impairing this frequency-specific theta response to non-reward; and that 'injecting' it by means of septal driving of theta activates the causal chain in the absence of objective non-reward. Further support for the same conclusion was that theta-blocking, high-frequency (100 Hz) septal stimulation delivered in the goal-box on the non-rewarded trials of a genuine PRF schedule blocked the PREE (Gray *et al.* 1972); although this last piece of evidence is relatively weak, since such stimulation eliminates theta totally rather than merely shifting its frequency.

The supposition in these early experiments was that the 7.7-Hz theta response to non-reward, or its experimentally 'injected' equivalent, underwent counterconditioning (Amsel 1962, 1972, 1992) because of its proximity to reward on the interleaved trials of the PRF schedule. This part of the overall hypothesis needed to be changed in the light of observations reported by Glazer (1974*a*,*b*). Using a lever-press procedure (food reward on an FR5 schedule), this author replicated the finding that induction of 7.7-Hz theta during acquisition increases resistance to extinction, but showed that this effect can be also obtained if theta induction occurs *prior* to acquisition of the lever-press response. In the latter experiment, Glazer induced theta by rewarding the animal for producing it within a specified frequency band centring on 7.7 Hz. Thus, his results could still be accounted for in terms of counterconditioning of the 7.7-Hz frustration-related response by the immediately following food reward. Holt and Gray (1983), however, took Glazer's experiment one step further by using septal

stimulation to drive theta prior to acquisition of the lever-press response with no accompanying reward: again, resistance to extinction was proactively increased by the septal stimulation. Further replication of this effect has since been reported both using Glazer's FR5 paradigm (Williams and Gray 1996) and in the original runway situation (Snape *et al.* 1996). These experiments from Gray's laboratory (reviewed by Williams *et al.* 1989) also showed that the frequency of the septal driving current (and the elicited theta response) could vary between 7.7 and 8.3 Hz without change of the behavioural effect. Thus, the process engaged by 7.7–8.3-Hz theta-driving septal stimulation appeared from these experiments to be akin to the non-associative 'toughening-up' deduced by Neal Miller (1976) from behavioural experiments; these had shown that exposure to repeated stressors can lead to tolerance for stress in general, with no role played by cue-controlled conditioning.

Glazer (1974*a*,*b*) had supposed that his FR5 operant schedule (used also by Holt and Gray 1983) was the equivalent of a runway CRF schedule. However, Williams *et al*. (1990) demonstrated a series of parallels between this schedule and a runway *PRF* schedule (see also McNaughton 1984 for supportive data). Accordingly, Williams and Gray (1996) and Snape *et al*. (1996) re-examined, using both the operant task and the original runway paradigm, the effects of proactive septal 7.7-Hz theta driving, varying both the acquisition schedule by which this stimulation was followed and the timing of the stimulation relative to the periods of acquisition and extinction. The results of these experiments were very clear and caused us to re-evaluate completely the nature of the proactive theta-driving effect on behaviour. Given prior to acquisition on a PRF schedule, 7.7-Hz theta driving increased resistance to extinction, confirming Glazer's and Holt and Gray's original findings. However, given prior to acquisition on a CRF schedule, the opposite effect was obtained: resistance to extinction was weakened. These results can be interpreted as follows: the proactive effect of 7.7-Hz theta driving is to increase the sensitivity of the animal to non-reward when this next occurs; if this in on a PRF schedule, the magnitude of the PREE is increased (as is known to occur, for example, when a large reward is contrasted with a small reward on the rewarded trials of a PRF schedule; Amsel 1992); if, however, non-reward next occurs during extinction (after acquisition on a CRF schedule), then extinction takes place more rapidly. This interpretation was supported by other results from the same series of experiments (Snape *et al*. 1996; Williams and Gray 1996). If 7.7-Hz theta driving stimulation was applied, not prior to acquisition, but between acquisition and extinction, then even after a PRF acquisition schedule resistance to extinction was weakened, the reverse of the effect observed when this stimulation occurred prior to acquisition. Again, therefore, the animal's sensitivity to non-reward, when it next occurred (now during extinction), was enhanced.

Taken together, then, these experiments demonstrate that septal driving of theta in the range 7.7–8.3 Hz proactively sensitizes the rat to the behavioural effects of non-reward (including to the *associative* counterconditioning on a PRF schedule that gives rise to the PREE). We must not forget, however, the experiments reported by Gray (1970, 1972*b*), in which such stimulation, given in the goal-box on a quasi-PRF schedule but with no actual non-rewarded trials, gave rise to a pseudo-PREE. This result forces us to suppose (in line with Gray's original interpretation) that, besides any proactive sensitizing effects, the immediate effects of 7.7-Hz theta-driving include the elicitation of a state sufficiently like frustration for counterconditioning to the actual reward to occur.

Other data provide an important clue as to the mechanism underlying the proactive effects of theta-driving in the 7.7–8.3 Hz band. Recall that the 7.7-Hz minimum threshold for septal driving of theta is selectively raised, not only by anxiolytic drugs, but also by destruction of the noradrenergic afferents to the septo-hippocampal system travelling in the dorsal ascending noradrenergic bundle (Gray *et al*. 1975; McNaughton *et al*. 1977). Destruction of these afferents also blocks the PREE (Owen *et al*. 1982). One may therefore think of 7.7-Hz theta driving as being in some sense the opposite of destruction of the noradrenergic input to the septo-hippocampal system. Consistent with this formulation, Graham-Jones *et al*. (1985) demonstrated that septal stimulation of this kind proactively increases the activity of the rate-limiting enzyme in noradrenaline synthesis, tyrosine hydroxylase, in the hippocampus, with a time course (the enzyme changes were measured 15 days after termination of the stimulation regime) similar to that observed in the experiments in which septal theta driving proactively affected the PREE. Thus, it is possible that the proximate mechanism underlying the increased sensitivity to non-reward proactively caused by 7.7-Hz theta driving consists of an augmented intra-hippocampal noradrenergic response to this behavioural event.

It could be argued that these results have all been obtained by use of a highly unphysiological treatment, that of septal electrical stimulation (see above), and should therefore be treated with great scepticism. There is, however, one further line of research which escapes this criticism and which has produced concordant results. We have observed that a single systemic dose of nicotine proactively enhances tyrosine hydroxylase mRNA production in the locus coeruleus (the nucleus of origin of the dorsal ascending noradrenergic bundle) a few days later, that this is followed a 2–3 weeks later by increased levels of tyrosine hydroxylase activity in a number of forebrain sites, including the hippocampus, and that 4 weeks after nicotine administration a second nicotine challenge causes a greater release of noradrenaline (measured by *in vivo* microdialysis) relative to animals given the challenge but not the prior nicotine injection (Mitchell *et al*. 1993). This same single-dose regime of nicotine administration also gives rise, 4 weeks later, to enhanced long-lasting potentiation in the dentate gyrus (slice preparation) response to a second, challenge dose of nicotine (Hamid *et al.* 1997). Given these results, and particularly the similarity in enhanced activity in hippocampal noradrenergic function observed weeks after septal theta-driving stimulation (Graham-Jones *et al*. 1985) and a single dose of nicotine (Mitchell *et al*. 1993), respectively, we predicted that this same drug regime applied to rats prior to training on CRF and PRF schedules in the straight alley would, like theta driving (Snape *et al*. 1996), enhance the PREE. This, indeed, is exactly what we found (Grigoryan and Gray 1996). In further as-yet unpublished experiments, moreover, we have preliminary evidence that this proactive effect of nicotine is indeed mediated by way of the noradrenergic afferents to the hippocampus: like the enhanced long-lasting potentiation seen in the dentate gyrus 4 weeks after a single dose of nicotine (Hamid *et al*. 1997), it is sensitive to systemic propranolol (a beta-noradrenergic antagonist); and it is also sensitive to lesion of the dorsal noradrenergic bundle.

A considerable amount of data, then, supports the hypothesis that septal theta-driving stimulation in the 7.7–8.3 Hz range has a dual effect: at the time of stimulation, it mimics in some degree the effects of frustrative non-reward; and proactively it enhances the behavioural response to subsequent non-reward. The second of these

effects (and possibly also the first) appears to be due to an augmentation of the intra-hippocampal noradrenergic response to non-reward. Given the general behavioural literature concerning non-reward (Amsel 1992), it is likely that these effects should be generalized from non-reward to stressors more widely. Indeed, we have evidence that this is so. Holt and Gray (1985) showed that 7.7-Hz driving prior to acquisition of a punishment schedule produced, first, greatly increased suppression (attributable to the hypothesized sensitization) and then (as the controls started to lose suppression, i.e. to show tolerance) greatly decreased suppression (attributable to increased counterconditioning). Similarly, in an accompanying conditioned emotional response experiment (in which the shock was now non-contingent), they found a very brief greater suppression in previously stimulated rats followed by prolonged lesser suppression. Thus, the proactive effects of 7.7-Hz theta driving extend to responses to shock as well as non-reward.

We have described the above results as relating to a specific band within the septal stimulation range, namely 7.7–8.3 Hz (Williams *et al*. 1989). This description does not reflect mere caution in staying close to the experimental parameters employed in the experiments, because, strikingly, exactly opposite results are obtained if the stimulation (and elicited theta) frequency is very slightly reduced: from 7.7 to 7.5 Hz, that is from an inter-pulse interval of 133 ms to one of 130 ms (Williams *et al*. 1989; Snape *et al*. 1996; Williams and Gray 1996). In both the FR5 lever-press and the alley-running paradigms, the same experimental manoeuvres as described above (varying the timing of stimulation relative to acquisition and extinction, and following the stimulation regime by either CRF or PRF training) give rise to a pattern of results which, if we follow the lines of interpretation (but in reverse) used for 7.7-Hz theta, is consistent with the view that 7.5-Hz theta driving proactively *reduces* sensitivity to non-reward when this next occurs. Thus, if the stimulation is given before training on a CRF schedule, subsequent resistance to extinction is enhanced; if it is given before training on a PRF schedule, resistance to extinction is weakened; if it is given between training on a PRF schedule and extinction testing, resistance to extinction is enhanced—all these effects being in the direction opposite to what is observed after stimulation at 7.7 Hz.

This pattern of results strongly suggests that hippocampal theta does different things at different frequencies, a hypothesis which occupied a central position in the first edition of this book, but which has now become part only of a larger picture: one that includes anxiolytic effects on the reticular control of theta and on the amygdalar control of arousal.

The mechanism underlying the difference between the effects observed after stimulation at 7.7 and 7.5 Hz, respectively, is unknown. Indeed, we do not even at present have a coherent hypothesis as to how the effects of 7.5-Hz stimulation are produced. A possible line of argument makes use of the serotonergic gate discussed in Appendix 5. There appears to exist a circuit, tuned to approximately 6.9 Hz, which is normally inhibited by serotonergic input to the septo-hippocampal system from the dorsal raphe. Driving at frequencies below 7.7 Hz may perhaps activate this circuit, producing effects equivalent to those of a serotonergic lesion. Since serotonergic and noradrenergic lesions tend to produce similar behavioural effects (where they produce effects at all), it follows that 6.9-Hz (and hence possibly 7.5-Hz) driving should have effects opposite to those of 7.7-Hz and 8.3-Hz driving. (If these suggestions are right,

future experiments would be advised to use 6.9-Hz rather than 7.5-Hz driving for the best effects.) In general terms, therefore, this line of argument perhaps provides a rationale for the opposition between the behavioural effects of theta driving in these two different frequency bands. However, given the cogent arguments advanced elsewhere in this book for casting aside altogether a frequency-specific view of hippocampal theta, we shall need to await fuller clarification of the mechanisms underlying the results described in this section before assessing whether the hypothesis of frequency specificity has been abandoned too readily.

If we leave aside the issue of frequency specificity and consider only the effects of stimulation within the 7.7–8.3 Hz range, the picture that emerges from the experiments described in this section fits well with the overall theory put forward in this book. It appears that there is a noradrenergically mediated resonance (centring on 7.7 Hz) in the circuitry controlling the frequency of hippocampal theta; that activation of theta at this resonance forms part of the manner in which the septo-hippocampal system responds to non-reward (and probably other stressors too); that activity in this circuit sensitizes the animal to the effects of signals of non-reward (and other stressors); and that (given other data reviewed in this book) the anxiolytic drugs exert some of their behavioural effects (including impairment of the PREE) by opposing this resonance.

A7.6 Septal stimulation: other paradigms

There are a variety of other findings to which arguments such as those deployed in the previous section are perhaps applicable. Thus, Klemm and Dreyfus (1975) produced the superficially surprising result that 8-Hz driving impairs both escape and active avoidance. These are tasks which are not normally affected by septal or hippocampal lesions and which were not affected by theta blocking stimulation within the same experiment. However, we should remember that septo-hippocampal lesions do impair passive avoidance. We can, then, explain Klemm and Dreyfus' result as being due to sensitization (as in the experiments by Williams and Gray 1996 and Snape *et al*. 1996 using 7.7-Hz stimulation) to the background passive avoidance tendencies inherent in the situation. This account treats Klemm and Dreyfus' task as analogous to the mixture of active and passive avoidance tendencies seen in two-way active avoidance, a form of behaviour which septo-hippocampal lesions improve. The lack of effect of theta blocking may also be accounted for, if the background passive avoidance tendencies were (in the absence of stimulation) below the threshold to impair active avoidance.

A similar result was obtained by Landfield (1977) with stimulation applied after acquisition, during a putative consolidation phase. Driving at 7.7 Hz improved passive avoidance. This result may perhaps be attributable to sensitization, as above. However, in a companion experiment, Landfield found that 7.7-Hz stimulation *enhanced* consolidation of *one-way active* avoidance. Here we need to note that, unlike the passive avoidance experiment, Landfield's active avoidance training was carried out over two days, both with stimulation; and, unlike Klemm and Dreyfus, his stimulation followed training on each day. It is possible, therefore, that in this second experiment he induced tolerance to footshock. Such tolerance would be tantamount to a reduction in objective shock intensity, a change which at least under some circumstances can improve active avoidance. Further experiments (for example with

only a single stimulation session between acquisition and retention) are required to settle this issue.

The stimulation frequency in these experiments lay in the higher, 7.7–8.3 Hz, range of the two frequency bands studied by Holt, Williams and Snape (see references in the previous section). In other experiments, frequencies in their lower range (around 7.5 Hz) have been used. Thus, Wetzel *et al*. (1977) showed enhanced consolidation with 7.0-Hz stimulation applied between acquisition and retention testing of what was, in effect, two-way active avoidance. On the analogy of 7.5-Hz stimulation applied in the non-reward experiments described in the preceding section, this stimulation regime should have given rise to desensitization to the passive avoidance component inherent in the two-way active avoidance task, a change which would be expected to manifest itself as improved active avoidance and therefore apparent enhanced consolidation (the authors' interpretation of these results). Similarly, Deupree *et al*. (1982) reported that 7.5-Hz driving before acquisition speeded acquisition of a visual discrimination in which rats were trained to go to the lit arm of a T-maze to collect food. Since rats initially avoid lit arms in favour of dark ones, the observed improvement learning might again have been the result of desensitization to the implicit passive avoidance tendency.

A7.7 Reticular stimulation

The reticular formation is often treated as if it were a large undifferentiated net (indeed the name itself implies this). However, it is probably better to view it as a highly interconnected (e.g. Lambertz *et al*. 1986) but nonetheless functionally separable (see, for example, Langhorst *et al.* 1986; Süpple *et al.* 1987; Klingberg *et al.* 1989; Müller and Klingberg 1989*a*,*b*, 1990;) set of networks. However, for the purposes of the present section, we too will treat the reticular formation as if it were homogeneous, for three reasons. First, we need to discuss only very limited parts of the reticular formation. Second, our findings in the previous appendices suggest that the ascending theta control systems, while they have a reticular organization, are fairly homogeneous functionally and, in any case, usually co-activated. Third, variations in the site of stimulation do not appear, in practice, to produce different results.

Stimulation of most areas of the midbrain reticular formation elicits theta (as we saw in Appendix 5), and can also facilitate retention of material learned just prior to the stimulation (Bloch 1970). In cases where initial learning is not itself affected, post-trial stimulation during learning of one task can facilitate generalization to a second, related task (Ammassari-Teule *et al.* 1984). Post-trial stimulation also facilitates the development of classically conditioned multiunit activity in the dentate gyrus but not the entorhinal cortex (Laroche *et al.* 1983); and, possibly because of the change in the dentate, such stimulation also increases CA3 multiunit activity during classical conditioning (Bloch and Laroche 1981). Reticular stimulation also increases entorhinal evoked potentials in the dentate (Bloch and Laroche 1981) and, as would be expected from this effect, greatly increases the amount of LTP (Bloch and Laroche 1985). Note that, by contrast, LTP is normally suppressed by spontaneous theta (see Appendix 5).

A7.8 Sleep

We now have reason, from both theta driving and reticular stimulation experiments, to link theta not only with the processing of current events but also with proactive enhancement of the effects on learning of aversive stimuli and, possibly through the same mechanism, with enhancements of consolidation. An involvement in the processing of memories could account for one of the few entirely reliable correlates of theta rhythm across species: paradoxical sleep.

Sleep is highly structured (see, for example, Pinel 1997, Chapter 12) and involves a cycling, approximately every 90 min, through phases of 'slow wave sleep' (SWS) and 'paradoxical sleep' (PS; 'dream sleep'). During PS, the brain is highly active and

> it would seem unlikely that the extensive cortical activity during sleep does not have some purpose; however, there is still no consensus on why we need to sleep. One intriguing possibility is that information acquired during the day is compared during sleep with older memories. Previous neural network models included such a 'sleep phase' to calibrate the storage of memories acquired by Hebbian mechanisms. Recent recordings from the hippocampus, and a new neural network model, lend experimental support and computational motivation to the possibility that we may sleep in order to organize efficient cortical representations of experience.
>
> Cortical representations of objects and events are widely distributed in the cerebral cortex. . . . Problems arise when new experience and objects must be integrated with existing information that is widely distributed. Learning algorithms designed for artificial neural networks that use such distributed representations can suffer from 'catastrophic interference' when new information is stored in the same neural circuits as old information. Therefore, the brain must solve two problems during learning: where to make the changes to create a new memory; and how to make changes that are compatible with previous stored memories. (Sejnowski 1995, p. 832.)

Both the integration of new information and the maintenance of old, relatively little used, information (e.g. Kavanau 1994, 1997) could be undertaken during sleep.

A variant on this idea which fits particularly well with our theoretical approach is

> the provocative theory of Crick and Mitchison (1983) [which] states that we have REM [rapid eye-movement] sleep (and dreams) in order to forget. . . . It addresses a long-standing problem in neuropsychology: how brains distinguish between trivial and important associations and memories. . . . Declarative memories might be reinforced . . . through interaction with fixed action programs of affective and vegetative behaviors programmed in the limbic system. Our dreams clearly reflect some integrative process, combining both recent and remote experiences in an emotional climate often fraught with strong feelings of anxiety and fear. (Hobson 1990, p. 376.)

Consistent with the general effects of septal driving of theta, and of reticular stimulation, Winson (1990) has suggested that theta rhythm during paradoxical sleep is a form of off-line processing of memories which reduces the extent to which waking processing must be taken up with consolidation. Reticular formation stimulation, which would be expected to elicit theta, 'suppresses the characteristic increase of paradoxical sleep which is normally consecutive to learning. Moreover, such stimulation has been found to compensate for the deleterious effects of experimental deprivation of paradoxical sleep on acquisition performance' (Ammassarie-Teule *et al.* 1984, p. 1027). Stimulation during paradoxical sleep also improves learning in animals that are not deprived of sleep, an effect which is produced neither by stimulation during waking (other than in the 10 min or so

immediately post-trial) nor by stimulation during slow wave sleep (Hennevin *et al.* 1989). The authors link their failure to affect learning by stimulation applied during slow wave sleep to the fact that the capacity of the hippocampus to show LTP is reduced at this time, whereas it is equivalent to waking capacity during paradoxical sleep (indeed LTP may be more easily obtained during paradoxical sleep theta than waking theta; Bramham *et al.* 1994). REM and theta appear to be functionally tightly linked, since 'the two most effective theta trigger zones in the brain stem are the rostral pontine reticular formation and the cholinergic pedunculopontine tegmentum. These are also sites for the cholinergic induction of REM sleep' (Quattrochi 1996).

In its simplest form, then, the idea emerging from these considerations is that, during sleep, the hippocampus is involved in the formation of memories. However, as with the single-cell correlates of Appendix 6, we can find reasons for believing that exactly the opposite is the case.

During SWS the interrelations between the firing patterns of different hippocampal cells suggest that they may be replaying their newly acquired 'place fields' (Wilson and McNaughton 1994; Skaggs and McNaughton 1996). Furthermore, during SWS there is a release of growth hormone. These data are consistent with the idea that during SWS major alterations are made to brain circuitry (with the help of growth hormone) and that these alterations ultimately lead to improved memory. But if this is the case, why does selective deprivation of *PS* impair memory, and why is there a PS phase at all?

Perusal of the figures shown by Wilson and McNaughton (1994) suggests that, during post-learning SWS, there are *more* relations between cell pairs than occur during the original learning. This pattern of results suggests that a large number of connections are being strengthened or adjusted. Intensive strengthening of connections in this way would allow the formation of higher-order associations ('deductions' or 'extrapolations', if you will) by integrating new information with old. Just such an excess of new connections, some of which are likely to be potentially inappropriate, might account for the poor memory displayed by animals deprived of PS. Like conventional 'amnesia' (see Chapter 8), this poor memory would then in fact be the result of hypermnesia, that is the recall of inappropriate items in excessive quantities.

On this scenario, the value of PS, and of reticular stimulation during PS, might lie in the pruning back of excessive connections (the memorial equivalent of behavioural inhibition). Consistent with this suggestion, SWS always precedes PS. Phylogenetically speaking, inactivity preceded SWS, which preceded PS (Winson 1990; see also Kavanau 1997). Thus, PS may have evolved to supply some improvement on the functions for which SWS had previously evolved.

A strongly related scenario is that proposed by Gardner-Medwin and Kaul (1995). Their proposal fits particularly well with the observation that the capacity for LTP is reduced during SWS. In their model, confusable stimuli (of the type likely to generate intrusion errors) are 'replayed' during SWS. A process of this kind would activate most extensively those connections that are common to the two stimuli. Given the downregulation of LTP, these connections will not, however, be strengthened but, rather, fatigued. During REM sleep, the same circuits are likely to be activated, but now under conditions where LTP is unusually easy to produce. The unique

connections for each stimulus will therefore be strengthened, but the common connections will not, because they have just previously been fatigued. There are difficulties with this theory. It does not account for the release of growth hormone during SWS; it has no explicit role for theta activity; and it is not clear that 'fatigue' of any conventional sort would last sufficiently long to play the role required for it during REM sleep. However, the theory is not incompatible with the one outlined in the previous paragraph; and either, both, or a combination of the two could provide a plausible account of how the two phases of sleep might be complementary in their effects on the off-line processing of memories.

These considerations suggest the following evolutionary scenario. SWS evolved as the result of a capacity to use the circadian inactive period for the off-line processing of information. Because this process depends on the release of growth hormone, a poorly localized mechanism, there might be a general growth of many synapses, including the formation of entirely new ones. This process, therefore, would be relatively inefficient, allowing the strengthening of some just-sub-threshold synapses. Given the general metabolic nature of the process and the random nature of spikes during SWS, there would be no requirement for specific analysis of information. PS would have evolved subsequently to improve on this rather inefficient consolidation process (see Kavanau 1997). During PS, circuits would be activated in a more or less meaningful manner, with a high degree of focusing of attentional systems and of negative bias so as to reject incorrect alternatives thrown up in the general pandemonium (see Wright 1990). The net effect would be a successive, recursive pruning of the connections newly formed in the preceding SWS phase.

In Chapter 10 we argue that the way in which the hippocampus achieves inhibition of future behaviour is by increasing the weighting of affectively negative associations. We also argue that this inhibition only occurs when there is a conflict between mutually incompatible goals. The process we have just outlined (building on concepts proposed by the other theorists mentioned above) in relation to the consolidation of memories during sleep is of essentially the same kind.

A7.9 Conclusions

We have briefly reviewed some highly selected data which, because of their selection, must be treated with caution. However, they suggest that:

1. Sub-saturation perforant path LTP does not affect previously formed memories, and has only modest effects on the acquisition of new information, even in hippocampal dependent tasks. These findings are contrary to the idea that such LTP mediates the formation of detailed memories based on stimulus information supplied by the entorhinal cortex. On the other hand, with the appropriate task and with saturation of the entire hippocampus, it seems that deficits can be obtained. Such findings are consistent with the idea that LTP is important for hippocampal processing (although this may be in a relatively non-specific 'attentional' role rather than a specific 'memorial' role; Shors and Matzel 1997). We suggested (on the basis of the single-cell data) that saturation of perforant path input would be more likely to have observable effects on habituation of exploration, where it would constitute a virtually instantaneous 'familiar–ignore' signal. (This signal would, of course, be

overridden in the normal learning experiments by the presence of a reinforcer, as in the case of naturally habituated stimuli; Appendix 6.)

2. Experiments involving stimulation of the hippocampus suggested that hippocampal output is inhibitory of movement rather than producing movement. These findings are consistent with the lesion data; and they are only superficially at variance with the observed correlations between hippocampal electrical activity and movement.
3. Septal driving stimulation appeared to produce essentially normal theta activity and, consistent with the lesion data, had little effect on ongoing learning or behaviour. There was some production of orienting and exploration and occasional slowing of movement; this is consistent with an inhibitory function of the hippocampus.
4. Experiments in which septal theta driving stimulation has been applied in experiments involving frustrative non-reward have provided a strong body of evidence suggesting that there is a noradrenergically mediated resonance (centring on 7.7 Hz) in the circuitry controlling the frequency of theta, and that activation of theta at this resonance forms part of the manner in which the septo-hippocampal system responds to non-reward (and probably to other stressors too). Stimulation at this resonance not only has immediate effects on behaviour but also proactively sensitizes the animal to non-reward when this next occurs. This sensitization extends to a greater susceptibility to associative counterconditioning of the response to non-reward, if this is then followed by reward. All these effects appear to be strongly frequency dependent, since stimulation at 7.5 Hz has proactive effects on behaviour that are opposite in sign to those produced by stimulation at the very slightly higher frequencies of 7.7 or 8.3 Hz. This apparent frequency dependence is in theoretical and empirical tension with the major position (based upon evidence reviewed in Appendices 5 and 6) adopted in this edition of the book, in which no particular significance is attached to theta frequency. Further clarification of the mechanisms underlying the effects reported in these experiments is required to resolve this tension. However, the main findings in this series of experiments, relating theta at around 7.7 Hz to the processing of aversive stimuli, provide strong support for the overall theory of the book, relating, as it does, septo-hippocampal function to anxiety.
5. Reticular stimulation of a type which could produce theta (but this was not demonstrated within the experiments themselves) improved consolidation in a number of tasks. It also, at least in some sites, produced inhibitory effects. Of particular interest was the fact that this stimulation had effects when delivered specifically during paradoxical sleep. We argued that, in all these cases, the effect of reticular activation and of theta production was to inhibit incorrect memory formation against a background of the formation of novel associations by other processes.

In general, then, these highly selected data, when viewed from the right perspective, can provide a relatively coherent, if speculative, view of the effects of activation of the hippocampus, of theta rhythm, and of long-term potentiation. Potentiation of dentate synapses represents an ‘ignore’ signal. This is suppressed during slow wave sleep, during which time many synapses receive semi-permanent strengthening through a growth-hormone-dependent process. During awake consolidation and paradoxical sleep, dentate potentiation is enabled and, as a result of this and other

changes, memory networks can be refined through a recursive process of inhibition of incorrect alternatives. Loss of this inhibitory process gives rise to excess connections and, as a result, retrieval of incorrect information. This is technically a hypermnesia, but will appear behaviourally as amnesia.

References

Abraham, W. C. and Bear, M. F. (1996). Metaplasticity: the plasticity of synaptic plasticity. *Trends in Neuroscience*, **19**, 126–30.

Ammassari-Teule, M., Fombon, A.-M., and Bloch, V. (1984). Facilitation of generalization performances in spatial learning problems by posttrial stimulation of the mesencephalic reticular formation. *Physiology and Behavior*, **32**, 1027–31.

Amsel, A. (1962). Frustrative nonreward in partial reinforcement and discrimination learning: some recent history and a theoretical extension. *Psychological Review*, **69**, 306–28.

Amsel, A. (1972). Behavioural habituation, counterconditioning, and a general theory of persistence. In *Classical conditioning II: current research and theory* (ed. A. H. Black and W. F. Prokasy), pp. 409–26. Appleton-Century-Crofts, New York.

Amsel, A. (1992). *Frustration theory: an analysis of dispositional learning and memory.* Cambridge University Press.

Barnes, C. A. (1995). Involvement of LTP in memory: are we 'searching under the street light'? *Neuron*, **15**, 751–4.

Barnes, C. A., Jung, M. W., McNaughton, B. L., Korol, D. L., Andreasson, K., and Worley, P. F. (1994). LTP saturation and spatial learning disruption: effects of task variables and saturation levels. *The Journal of Neuroscience*, **14**, 5793–806.

Bland, B. H. and Vanderwolf, C. H. (1972). Electrical stimulation of the hippocampal formation: behavioral and bioelectrical effects. *Brain Research*, **43**, 89–106.

Bliss, T. V. P. and Richter-Levin, G. (1993). Spatial learning and the saturation of long-term potentiation. *Hippocampus*, **3**, 123–6.

Bloch, V. (1970). Facts and hypotheses concerning memory consolidation. *Brain Research*, **24**, 561–75.

Bloch, V. and Laroche, S. (1981). Conditioning of hippocampal cells: its acceleration and long-term facilitation by post-trial reticular stimulation. *Behavioural Brain Research*, **3**, 23–42.

Bloch, V. and Laroche, S. (1985). Enhancement of long-term potentiation in the rat dentate gyrus by post-trial stimulation of the reticular formation. *Journal of Physiology*, **360**, 215–31.

Bramham, C. R., Maho, C., and Laroche, S. (1994). Suppression of long-term potentiation induction during alert wakefulness but not during 'enhanced' REM sleep after avoidance learning. *Neuroscience*, **59**, 501–9.

Buzsáki, G., Grastyan, E., and Lenard, L. (1978). Hippocampal inhibition and the fornix. *Behavioural Biology*, **22**, 67–76.

Castro, C. A., Silbert, L. H., McNaughton, B. L., and Barnes, C. A. (1989). Recovery of spatial learning deficits after decay of electrically induced synaptic enhancement in the hippocampus. *Nature*, **342**, 545–8.

Deupree, D., Coppock, W., and Willer, H. (1982). Pretraining septal driving of hippocampal rhythmical slow activity facilitates acquisition of visual discrimination. *Journal of Comparative and Physiological Psychology*, **96**, 557–62.

Feldon, J. and Gray, J. A. (1981). The partial reinforcement extinction effect after treatment with chlordiazepoxide. *Psychopharmacology*, **73**, 269–75.

Feldon, J., Guillamon, A., Gray, J. A., De Wit, H., and McNaughton, N. (1979). Sodium amylobarbitone and responses to nonreward. *Quarterly Journal of Experimental Psychology*, **31**, 19–50.

Gardner-Medwin, A. R. and Kaul, S. (1995). Possible mechanisms for reducing memory confusion during sleep. *Behavioural Brain Research*, **69**, 167–175.

Glazer, H. I. (1974*a*). Instrumental response persistence following induction of hippocampal theta frequency during fixed-ratio responding in rats. *Journal of Comparative and Physiological Psychology*, **86**, 1156–62.

Glazer, H. I. (1974*b*). Instrumental conditioning of hippocampal theta and subsequent response persistence. *Journal of Comparative and Physiological Psychology*, **86**, 267–73.

Graham-Jones, S., Holt, L., Gray, J. A., and Fillenz, M. (1985). Low-frequency septal stimulation increases tyrosine hydroxylase activity in the hippocampus. *Pharmacology, Biochemistry and Behavior*, **23**, 489–93.

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

Gray, J. A. (1972*a*). The structure of the emotions and the limbic system. In *Physiology, emotion and psychosomatic illness*, Ciba Foundation Symposium No. 8 (New Series) (ed. R. Porter and J. Knight), pp. 87–130. Associated Scientific Publishers, Amsterdam.

Gray, J. A. (1972*b*). Effects of septal driving of the hippocampal theta rhythm on resistance to extinction. *Physiology and Behavior*, **8**, 481–90.

Gray, J. A. (1987). *The psychology of fear and stress.* Cambridge University Press, London.

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

Gray, J. A., Araujo-Silva, M. T., and Quintao, L. (1972). Resistance to extinction after partial reinforcement training with blocking of the hippocampal theta rhythm by septal stimulation. *Physiology and Behavior*, **8,** 497–502.

Gray, J. A., McNaughton, N., James, D. T. D., and Kelly, P. H. (1975). Effect of minor tranquillisers on hippocampal theta rhythm mimicked by depletion of forebrain noradrenaline. *Nature (London)*, **258**, 424–5.

Grigoryan, G. and Gray, J. A. (1996). A single dose of nicotine proactively enhances the partial reinforcement extinction effect in the rat. *Psychobiology*, **24**, 136–46.

Hamid, S, Dawe, G. S., Gray, J. A., and Stephenson, J. (1997) Nicotine induces long-lasting potentiation in the dentate gyrus of nicotine-primed rats. *Neuroscience Research*, **29**, 81–5.

Hennevin, E., Hars, B., and Bloch, V. (1989). Improvement of learning by mesencephalic reticular stimulation during postlearning paradoxical sleep. *Behavioral and Neural Biology*, **51**, 291–306.

Hobson, J. A. (1990). Sleep and dreaming. *The Journal of Neuroscience*, **10**, 371–82.

Holt, L. and Gray, J. A. (1983). Septal driving of the hippocampal theta rhythm produces a long-term, proactive and non-associative increase in resistance to extinction. *Quarterly Journal of Experimental Psychology*, **35B**, 97–118.

Holt, L. and Gray, J. A. (1985). Proactive behavioral effects of theta-driving septal stimulation on conditioned suppression and punishment in the rat. *Behavioral Neuroscience*, **99**, 60–74.

Izquierdo, I. (1975). The hippocampus and learning. *Progress in Neurobiology*, **5**, 37–75.

Jeffrey, K. J. and Morris, R. G. M. (1993). Cumulative long-term potentiation in the rat dentate gyrus correlates with, but does not modify, performance in the water maze. *Hippocampus*, **3**, 133–40.

Kaada, B. R., Jansen, J., and Andersen, P. (1953). Stimulation of the hippocampus and medial cortical areas in unanesthetized cats. *Neurology (Minneapolis)*, **3**, 844–57.

Kavanau, J. L. (1994). Sleep and dynamic stabilization of neural circuitry: a review and synthesis. *Behavioural Brain Research*, **63**, 111–26.

Kavanau, J. L. (1997). Memory, sleep, and the evolution of mechanisms of synaptic efficacy maintenance. *Neuroscience*, **79**, 7–44.

Klemm, W. R. and Dreyfus, L. R. (1975). Septal- and caudate-induced behavioral inhibition in relation to hippocampal EEG of rabbits. *Physiology and Behavior*, **15**, 561–7.

Klingberg, F., Mager, P., and Mager, R. (1989). The mesencephalic reticular formation as a link in the cortical control of exploratory and goal-directed behaviour. *Acta Physiologica Hungarica*, **74**, 121–34.

Korol, D. L., Abel, T. Y., Church, L. T., Barnes, C. A., and McNaughton, B. L. (1993). Hippocampal synaptic enhancement and spatial learning in the Morris swim task. *Hippocampus*, **3**, 127–32.

Kramis, R. C. and Routtenberg, A. (1977). Dissociation of hippocampal EEG from its behavioral correlates by septal and hippocampal electrical stimulation. *Brain Research*, **125**, 37–49.

Lambertz, M., Kluge, W., Schulz, G., and Langhorst, P. (1986). Principles of functional organisation of a common system in the reticular formation for

cardiorespiratory and somatomotor regulation. Computer simulations based on physiological data. *Journal of the Autonomic Nervous System (Suppl.)*, 269–74.

Landfield, P. W. (1977). Different effects of posttrial driving or blocking of the theta rhythm on avoidance learning in rats. *Physiology and Behavior*, **18**, 439–45.

Langhorst, P., Schulz, G., and Lambertz, M. (1986). Integrative control mechanisms for cardiorespiratory and somatomotor functions in the reticular formation of the lower brain stem. In *Cardiorespiratory and cardiosomatic psychophysiology* (ed. P. Grossman, K. H. Janssen, and D. Vaitl), pp. 9–39. Plenum, Berlin.

Laroche, S., Falcou, R., and Bloch, V. (1983). Post-trial reticular facilitation of associative changes in multiunit activity: comparison between dentate gyrus and entorhinal cortex. *Behavioural Brain Research*, **9**, 381–7.

MacLean, P. D. (1957). Chemical and electrical stimulation of hippocampus in unrestrained animals. II. Behavioural findings. *Archives of Neurological Psychiatry (Chicago)*, **78**, 128–42.

Matthies, H., Ruethrich, H., Ott, T., Matthies, H. K., and Matthies, R. (1986). Low frequency perforant path stimulation as a conditioned stimulus demonstrates correlations between long-term synaptic potentiation and learning. *Physiology and Behavior*, **36**, 811–21.

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, B. L., Barnes, C. A., Rao, G., Baldwin, J., and Rasmussen, M. (1986). Long-term enhancement of hippocampal synaptic transmission and the acquisition of spatial information. *The Journal of Neuroscience*, **6**, 563–71.

McNaughton, N. (1984). Effects of anxiolytic drugs on the partial reinforcement extinction effect in runway and Skinner box. *Quarterly Journal of Experimental Psychology*, **36B**, 319–30.

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., 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.

Miller, N. E. (1976). Learning, stress and psychosomatic symptoms. *Acta Neurobiologica Experimentalis*, **36**, 141–56.

Mitchell, S. N., Smith, K. M., Joseph, M. H., and Gray, J. A. (1993). Increases in tyrosine hydroxlase messenger RNA in the locus coeruleus after a single dose of nicotine are followed by time-dependent increases in enzyme activity and noradrenaline release. *Neuroscience*, **56**, 989–97.

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

Morris, R. and Baker, M. (1984) Does long term potentiation / synaptic enhancement have anything to do with learning and memory ? In: *The neuropsychology of memory*, edited by Squire, L.R. and Butters, N.New York:Guilford Press, p. 521-535.

Morris, R. G. M., Davis, S., and Butcher, S. P. (1990). Hippocampal synaptic plasticity and NMDA receptors: a role in information storage? *Philosophical Transactions of the Royal Society of London, Series B*, **329**, 187–204.

Müller, G. and Klingberg, F. (1989*a*). Lesions of the caudal pontine reticular nucleus reduce spontaneous behavioural activity of rats differently in dorsal and ventral parts of the nucleus. *Biomedica Biochimica Acta*, **48**, 807–16.

Müller, G. and Klingberg, F. (1989*b*). Learning and retention of active avoidance are differently impaired after dorsal and ventral lesions of the nucleus reticularis pontis caudalis of rats. *Biomedica Biochimica Acta*, **48**, 817–27.

Müller, G. and Klingberg, F. (1990). Learning and retrieval are impaired after lesions of the ventral part of rat's nucleus reticularis pontis oralis. *Biomedica Biochimica Acta*, **49**, 51–8.

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

Owen, S., Boarder, M. R., Gray, J. A., and Fillenz, M. (1982). Acquisition and extinction of continuously and partially reinforced running in rats with lesions of the dorsal noradrenergic bundle. *Behavioural Brain Research*, **5**, 11–41.

Pinel, J. P. J. (1997). *Biopsychology.* Allyn and Bacon, Boston.

Quattrochi, J. J. (1996). Theta rhythm: a systems approach to neuromodulation of behavioural state. *NeuroReport*, **7**, ii.

Rioux, G. F. and Robinson, G. B. (1995). Hippocampal long-term potentiation does not affect either discrimination learning or reversal learning of the rabbit nictitating membrane response. *Hippocampus*, **5**, 165–70.

Sejnowski, T. J. (1995). Neural networks: sleep and memory. *Current Biology*, **5**, 832–4.

Shors, T. J. and Matzel, L. D. (1997). Long-term potentiation: what's learning got to do with it? *Behavioural and Brain Sciences*, **20**, 597–613.

Skaggs, W. E. and McNaughton, B. L. (1996). Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science*, **271**, 1870–3.

Snape, M., Grigoryan, G., Sinden, J. D., and Gray, J. A. (1996). Dependence of the proactive behavioral effects of theta-driving septal stimulation on stimulation frequency and behavioral experience. 2. Continuously and partially reinforced running. *Psychobiology*, **24**, 22–32.

Süpple, M., Muller, G., and Klingberg, F. (1987). Reduced behavioural inhibition after lesions in the dorsomedial pontine reticular formation of rats. *Biomedica Biochimica Acta*, **46**, 521–5.

Turnbull, J., Jiang, F., and Racine, R. (1994). Hippocampal stimulation of fornical-lesioned rats improves working memory. *The Canadian Journal of Neurological Sciences*, **21**, 100–3.

Vanegas, H. and Flynn, J. P. (1968). Inhibition of cortically-elicited movement by electrical stimulation of the hippocampus. *Brain Research*, **11**, 489–506.

Wetzel, W., Ott, T., and Matthies, H. (1977). Hippocampal rhythmic slow activity ('theta') and behavior elicited by medial septal stimulation in rats. *Behavioural Biology*, **19**, 534–42.

Williams, J. H. and Gray, J. A. (1996). Dependence of the proactive behavioral effects of theta-driving septal stimulation on stimulation frequency and behavioral experience. 1. Leverpress experiments. *Psychobiology*, **24**, 9–21.

Williams, J., Gray, J. A., Snape, M., and Holt, L. (1989). Long-term effects of septohippocampal stimulation on behavioural responses to anxiogenic stimuli. In *Psychopharmacology of anxiety* (ed. P. Tyrer), pp. 80–108. Oxford University Press.

Williams, J. H., Gray, J. A., Sinden, J., Buckland, C., and Rawlins, J. N. (1990). Effects of GABAergic drugs, fornicotomy, hippocampectomy and septal lesions on the extinction of a discrete-trial fixed ratio 5 lever-press response. *Behavioural Brain Research*, **41**, 129–50.

Wilson, M. A. and McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science*, **265**, 676–9.

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

Wright, J. J. (1990). Reticular activation and the dynamics of neuronal networks. *Biological Cybernetics*, **62**, 289–98.