Appendix 9

Dissecting the septo-hippocampal syndrome

A9.1 Introduction

In Chapter 8 and Appendix 8 we treated the hippocampal formation as an inchoate blob, restricting our discussion to large lesions involving the hippocampus and surrounding cortex (H+) or, in human material, lesions involving, in addition to this, the amygdala and its surrounding areas (H+A+). In a number of key cases we also discussed fornix lesions (which cut both a major input to and a major output from the whole hippocampal formation) as if they were equivalent to this more extensive damage. Crude though this 'lumping' approach may have been, it was sufficient to allow us to compare and contrast the different theories of global hippocampal function, most of which do not in any case postulate any detailed intra-hippocampal machinery.

However, as we saw in Appendices 4–6, the hippocampal formation is neatly ordered and much is known about specific details of its physiology. The single-cell data, in particular, gave us a picture of sequential stages of processing, each carried out by a particular level of the hippocampal formation, with a variety of 'gates' controlling whether information is passed to the next level or not. The septal and entorhinal inputs appear to arrive at all levels (including each other) in parallel. Specific lesions of different inputs, outputs, or hippocampal fields should, therefore, have the potential to refine our overall theories of the functioning of the hippocampal formation considerably.

Unfortunately, truly selective lesions are not easy to achieve. They have only been approximated in recent times, and have been used only to address quite specific questions—often questions relating to one detail of one specific theory. There is not, then, a comprehensive body of data on any one selective lesion over the range of tasks we have already discussed. Rather, a number of studies have attempted to dissect a few tasks.

We first provide an overview of what is known about the effects of selective damage on memory-oriented tasks. Then, we discuss the fragmentary material on non-memory tasks. We will organize the data on a paradigm-by-paradigm basis. Our purpose is to functionally dissect the hippocampal formation itself, and we will therefore exclude from consideration dissection of H+A+ into its separate H and A components, since we have already covered the amygdala and the hippocampus separately, and the majority of the animal work has made relatively selective lesions of these structures. Where relatively discrete amygdaloid or hippocampal damage occurs in human beings, there appears to be a strong dissociation of the functions affected by these separate lesions (Bechara *et al.* 1995) of a kind predicted from the animal data (e.g. Peinado-Manzano 1990).

The possibility of further dissociation within the hippocampal syndrome is indicated, for example, by the fact that at least two underlying factors can be discriminated in the pattern of deficits produced by the individual variation in lesions across monkeys, all tested with a battery involving concurrent discrimination, two-pattern discrimination, delayed object retention, and delayed non-matching-to-sample, with the first two tasks loading on one factor, and the second two, on another (Zola-Morgan *et al.* 1995).

Before we discuss the dissection of specific tasks in relation to specific components of the septo-hippocampal system, it will be useful to take a look at the picture provided by a more global dissection of formally different tasks, each resulting in a conditioned nicititating membrane response.

A9.2 Analysis of nictitating membrane conditioning

The detailed analysis of the basic conditioned nictitating membrane response as a model system required 'the use of lesions, electrophysiological recordings, electrical microstimulation, microinfusion of drugs, and anatomical methods [to show] . . . that a region of the cerebellum ipsilateral to the trained eye (lateral interpositus nucleus) is essential for the learning and memory of the conditioned eye-blink response but not for the reflex response' (Thompson 1986, p. 942). However, while the nucleus interpositus appeared to be the primary location of plasticity and the primary area through which all types of conditioned responses were effected, there was evidence that the cerebellar cortex was also involved in conditioning and that different portions of the cerebellar cortex were involved with different conditioned stimuli (Knowlton *et al.* 1988). By contrast, acute decerebration had no effect on a previously established simple conditioned response (Mauk and Thompson 1987).

It is not surprising that the cerebellar circuitry is fairly complicated, since it appears to support not only simple but also delay conditioning. In this, the conditioned stimulus (CS) and unconditioned stimulus (UCS) still overlap in time, but the response is delayed well after CS onset. As noted earlier (Appendices 6 and 8), hippocampal lesions do not affect delayed nictitating membrane conditioning, but do affect both reversal of a discrimination (Orr and Berger 1985) and trace conditioning. The latter differs from delay conditioning in that the CS offset precedes the US by a substantial delay. In all these cases, lesions of the nucleus interpositus abolish conditioned responding.

In this context, it is particularly interesting that (as with conventional 'amnesia') hippocampal lesions impair trace conditioning only if the lesion is made soon after conditioning. Animals lesioned 1 day after conditioning lost the trace eyeblink response and failed to relearn it. Animals lesioned 1 month after conditioning retained the trace eyeblink response. 'The key question then is where the permanent memories are stored. Trace conditioning would seem to provide an animal model of this process of memory consolidation that is amenable to analysis because so

much is known about the neural substrates of eyeblink conditioning. The permanent store could be in the cerebellum, perhaps in the cortex, or in neocortical areas and could be localized or distributed' (Kim *et al.* 1995, p. 201).

There may be some attraction to the notion that the hippocampus can temporarily store complex stimuli and then transfer them to the cortex for longer-term storage. But the eye-blink response involves such simple stimuli and such a fixed response that it is difficult to see why the hippocampus should be required to store a trace delay when it is not needed to store a simple delay. It is also difficult to see how the hippocampus could transfer its memory of the delay to, say, the cerebellum for longer-term storage. So, how do we account for this dissection of the different aspects of eye-blink conditioning?

The hippocampus appears to communicate with the cerebellum via the connection between the subiculum and the retrosplenial cortex, which itself then projects to the ventral pontine nuclei. As might be expected from this anatomical link,

bilateral lesions of the retrosplenial cortex are associated with severe deficits in reversal learning that are very similar to those seen after bilateral damage to the hippocampal-subicular cortices. That is, lesions of either the retrosplenial cortex or the hippocampal formation produce no alteration in discrimination learning, but they do disrupt an animal's ability to reverse that discrimination. Moreover, animals with either lesion fail at the reversal phase of the task because of a continued high level of responding to the CS–; response rates to the CS+ are equivalent to those of control animals. These results also show that bilateral damage to the retrosplenial cortex produces deficits in reversal learning that are as severe in magnitude as those observed after bilateral hippocampectomy . . . animals with hippocampal damage display shorter latency and larger amplitude conditioned nictitating membrane responses than did control animals. (Berger *et al.* 1986, p. 804.)

Berger *et al.* (1986) present a model of cerebellar conditioning in which (as with Le Doux's description of fear conditioning; see Chapter 6) there 'is a hierarchical neuronal control of nictitating membrane movement: (a) The trigeminal-abducens system controls unconditioned, reflex responding, (b) the cerebellar system mediates the formation of learned responses that reflect simple associations (i.e. nonconditional relations) between environmental stimuli, and it interacts with the final common path through projections to the red nucleus, (c) the hippocampal system modifies those conditioned reflexes in a manner that allows the organism to respond to more complex relations among environmental events, such as reversal of a previously learned response or conditional relations among stimuli. The hippocampal system interacts with the cerebellar system through the retrosplenial–pontine projection' (Berger *et al.* 1986, p. 806). Although Berger *et al.* do not emphasize the fact, it is clear that the business of the hippocampal system in this case is to inhibit the production of responses which would otherwise occur. Not only are excess responses observed after hippocampectomy, but the circuitry requires this. Note that, in the early stages of reversal learning, the original CS+ (now CS–) will produce a conditioned response (CR) because of prior conditioning, but that the relation between the new CS+ (old CS–) and the UCS is such as should also produce conditioned responding using the basic cerebellar circuitry for new conditioning. Therefore, there is no need for the hippocampal system to produce the new response—this will happen anyway. What is required is for the hippocampal–retrosplenial system to inhibit the old response.

Let us see how this type of explanation fares with the case of trace conditioning. First, we must ask how a trace response can be generated at all. The simplest way to produce such a response is to feed the original stimulus through a selection of 'delay lines' tuned to different delays (see Miller 1991, especially pp. 160–2). Conditioning can then result when the output from one particular delay line arrives at the cerebellar circuitry at the same time as the UCS. From the point of view of the cerebellum, conditioning can then occur to this (delayed) stimulus in the normal way via some process such as long-term potentiation (LTP). It is tempting to see the delay lines as residing in the hippocampus (Miller 1991) and their output as being relayed via, for example, the retrosplenial cortex. However, there are several reasons for taking a more complicated position.

First, the hippocampal response during nictitating membrane conditioning models the CR not the CS or the US (see Appendix 6), and this model is lost if nucleus interpositus is lesioned (Clark *et al.* 1984; Sears and Steinmets 1990, cited by Kim *et al.* 1995). If the hippocampus analysed stimuli and sent the results to the cerebellum, it should model the CS, and this neuronal model of the stimulus should not be disturbed by interpositus lesions. Second, the effect of hippocampal lesions on trace conditioning is much like their effects on reversal (in which over-responding to the CS– occurs). Some CRs occur (about 20 per cent) but their latency is greatly reduced, indeed they tend to occur before the offset of the CS. This pattern of results suggests that there are several different systems (including probably the cerebellar 'delay' system), all of which can potentially produce more or less delayed CRs and which compete for control of the response system. The hippocampus appears to receive input about primed CRs (hence its modelling of the CR in the simple conditioning case) and to decrease the effectiveness of those CS delay lines which are least appropriate.

The dissection of brain systems in the nictitating membrane case suggests a number of principles to bear in mind while analysing the more specific dissection of the hippocampus itself. First, we can expect a hierarchical organization with both lower and higher systems concurrently processing information and, potentially, controlling responding. In simple cases, 'quick and dirty' lower systems control responding. In more complex cases additional circuits can either supply the capacity to produce a particular response when this is impossible for the simple circuit, or allow engagement of other circuits when the response produced by the simple circuit would be inappropriate. In

general, the hippocampus appears to be involved in the inhibition of responding rather than its production. However, it is not involved in the simplest cases of this inhibition (as shown by the cerebellar control of delay conditioning and the lack of hippocampal sensitivity of tasks such as mirror drawing in which motor output may require alteration but there is no conflict between alternative goals to be achieved).
Having presented a model case with a simple system and the hippocampus treated as a whole, let us now turn to the much more difficult case of dissection of the components of the hippocampal system.

A9.3 Concurrent discriminations

Zola-Morgan and co-workers have analysed the contribution of different components of the septo-hippocampal system to concurrent discriminations in monkeys. Large lesions (H++) impaired the learning of simple discriminations when eight of these were learned concurrently. However, neither fornix nor mammillary body lesions produced this effect (Zola-Morgan *et al.* 1989*a*). The hippocampal impairment would appear, therefore, to relate largely to its cortical connections. Ischaemic damage to area CA1 had no effect on concurrent discrimination, despite impairing delayed matching-to-sample (Zola-Morgan *et al.* 1992). Moss *et al.* (1981) also found that fornix lesions did not affect concurrent discrimination. Hippocampal lesions which included some parahippocampal damage produced a deficit, as did entorhinal lesions. Anterior inferotemporal cortex lesions produced a deficit in visual but, unlike hippocampal lesions, not tactile concurrent discriminations. There was some suggestion of a greater deficit with lesions of hippocampus and inferotemporal cortex combined. In a slightly divergent result, Gaffan (1994) found that fornix lesions and perirhinal lesions both produced deficits on a concurrent scene discrimination with a 24-hour intertrial interval. Gaffan himself states that there was no significant difference between the lesions. However, only one of his perirhinal and all of the fornix animals reached criterion. It may be then that the apparent difference between fornix and cortical damage is quantitative rather than qualitative. Zola-Morgan *et al.* (1989*b*) found that perirhinal plus parahippocampal lesions produced as large a deficit in concurrent discrimination as H+A+ lesions, whereas Eacott *et al.* (1994) found only a modest non-significant difference with rhinal cortex lesions.
Overall, then, the data suggest a modest contribution to concurrent discrimination (at least at long delays) of the fornix–fimbria, with a major contribution from the perirhinal–parahippocampalentorhinal cortex. It remains to be seen to what extent perirhinal and parahippocampal effects are additive and to what extent inclusion of entorhinal cortex is important. Hippocampus proper may be relatively insignificant.

A9.4 Delayed matching

In contrast to concurrent discriminations, the effects of fornix lesions on delayed matching tasks are similar to those of hippocampal lesions. This is generally true with respect to both deficits and those cases where a deficit is not observed (e.g. Aggleton et al. 1992; Yee and Rawlins 1994). However, there are exceptions, with large hippocampal lesions producing greater effects than fornix lesions (Zola-Morgan et al. 1989a). With a visual delayed non-matching task using trial-unique objects (which might be expected to be particularly strongly weighted towards inferotemporal information and so minimize hippocampal involvement), combined perirhinal and entorhinal lesions have somewhat greater effects than perirhinal alone, which in turn have much greater effects than entorhinal alone (Meunier et al. 1993). ‘Paradoxically, . . . adding removal of the hippocampal formation and parahippocampal gyrus to a rhinal cortex lesion significantly reduces the recognition impairment produced by rhinal cortex alone’ (Meunier et al. 1996). So many factors are involved in determining whether deficits are seen with delayed matching tasks that it is difficult to isolate the interactions of lesions site with type of task; but it is possible (as discussed at the end of the appendix) that effects of fornix lesions are more likely to be seen in position-matching tasks and effects of cortical lesions in object- and visual-matching tasks.
In keeping with this general idea, delayed matching-to-place in the water maze shows a similar, large deficit with ibotenic acid lesions of hippocampus alone or hippocampus plus subiculum, while lesions limited to the subiculum had more modest effects (Morris *et al.* 1990). Nonetheless, ibotenic acid lesions of the entorhinal cortex can produce a deficit in delayed non-matching-to-place (Cho and Jaffard 1994), and this deficit was exacerbated if additional samples were interpolated between the sample and the test trials. Electrolytic lesions of the entorhinal cortex, hippocampus, and entorhinal cortex plus hippocampus all appear to produce equally severe deficits in this type of task (Hunt *et al.* 1994); although hippocampal lesions do not increase repeated incorrect choices in the same way that the other two lesions do. Electrolytic lesions of the entorhinal cortex also impair acquisition of delayed non-matching of body turns (Steward 1981). In the latter case, the deficit appeared to be due to the adoption of inappropriate position habits and, once these were broken by special training, the deficit disappeared.
Fornix lesions eliminate connections of the hippocampus with both the septum and the mammillary bodies. In one of the few studies in this literature to extract signal detection scores and to fit an exponential decay curve (see p. 166 of the printed text), Harper *et al.* (1994, p. 699) found that medial septal but not mammillary body lesions produced an increased rate of forgetting in delayed matching-to-position (see also Dunnett 1985). This is likely to be an effect at the medial septal nucleus itself, since medial septal injections of baclofen (which blocks transmission at type B GABA receptors) also affect delayed matching-to-position, at least in a radial-arm maze task (Stackman and Walsh 1994). Further, ibotenic acid lesions of the *horizontal* nucleus of the diagonal band appear to have greater effects even than entorhinal lesions (Johnson and Kesner 1994). ‘The lack of a [mammillary body] lesion effect on [delayed

matching-to-sample] performance appears inconsistent with several observations of deficits . . . (e.g. delay-dependent impairments in delayed alternation; and delay-independent impairments to memory performance in an eight-arm radial maze delayed-nonmatching-to-sample task). However, the lack of a mammillary body lesion effect in the current [delayed matching-to-sample] task is consistent with a number of studies that have failed to observe an impairment to memory following mammillary damage (e.g. in a Y-maze delayed-nonmatching-to-sample task and in an automated [delayed matching-to-sample] task very similar to that used here' (Harper *et al*. 1994; see also Aggleton *et al*. 1990). Béracochéa and Jaffard (1995, p. 51), in reporting a similar lack of effect of mammillary body lesions on delayed matching-to-position and contrasting it with a deficit in an (easier) delayed non-matching task, suggest that this is 'due, at least in part, to a difficulty to spontaneously engage in searching operations at the time of retrieval, a difficulty which is alleviated in a more demanding situation.'

We thus have a pattern of different cortical and subcortical connections of the hippocampus producing different components of a deficit which may, at least in some cases, be produced in full by selective lesions of the hippocampus proper. While there may be a qualitative difference between fornix and entorhinal lesions, it seems more likely that this difference is quantitative, especially as lesions of the horizontal nucleus of the diagonal band (HDBB) have greater effects than entorhinal lesions. Since the HDBB projections to the hippocampus do not all travel through the fornix (Appendix 4), it seems likely that a major deficit would be produced if the whole of the HDBB–ventral nucleus of the diagonal band (VDBB)–medial septal (MS) cholinergic input were lesioned. It has also been suggested that the full effects of anticholinergics on such tasks (e.g. Kirk *et al*. 1988) can only be reproduced if the nucleus basalis is also included in the lesions (Dunnett 1985), with the nucleus basalis making a major contribution at short delays and the MS/DBB complex increasing the rate of forgetting.

A9.5 Conditional, configural, and contextual tasks

We discussed the disagreement about configural tasks between, on the one hand, Jarrard and Davidson and, on the other, Rudy and Sutherland in Chapter 8 of the printed text (Section 8.8), and suggested that the difference between the studies was the use of partial or continuous reward, respectively. Another possibility is that there was some difference between the lesions. Jarrard used the same colchicine–kainate lesioning technique for their larger lesions, but these may not have been as extensive as Rudy and Sutherland's. That this, or some other incidental damage, could have been important is shown by the fact that ibotenic acid lesions of the hippocampus do not produce the deficit in Pavlovian conditional discrimination found with conventional hippocampal removal in the same task (Jarrard and Davidson 1991; see also Davidson and Jarrard 1989; Jarrard and Davidson 1990).

Conditional discriminations of the form 'food deprivation–go left, water deprivation–go right' are impaired both by loss of dentate granule cells due to neonatal X-ray irradiation and by transection of the component of the fornix destined for the anterior thalamus (Hirsh *et al.* 1978, 1979). Neurotoxic lesions of area CA1 in monkeys 'produce a severe impairment of the retention of a conditional task learnt prior to surgery and on the acquisition of several types of this task. The monkeys were equally impaired on conditional tasks that required a spatial response or an object choice in response to either visual or spatial cues. They were not impaired on simple visual discrimination tasks, simple spatial discrimination tasks or reversal learning of these tasks. This pattern of impairment resembles that seen in the same species with neurotoxic lesions within the vertical limb of the diagonal band of Broca or transection of the fornix. Monkeys with subtotal lesions of the adjacent [entorhinal cortex] were not consistently impaired on any of these tasks' (Ridley *et al*. 1995, p. 263). Consistent with the effects of diagonal band lesions, medial septal injections of scopolamine or muscimol (which reduce the power of theta rhythm) impair conditional discrimination (Givens and Olton 1994).

In a test of contextual fear conditioning, Phillips and Le Doux (1995) showed that lesions of the hippocampal system or surrounding cortex did not affect fear conditioning to an explicit stimulus, and that fornix–fimbria lesions, but not entorhinal or perirhinal lesions, impaired contextual fear conditioning. They conclude that 'as a result, the presumption that neocortical information is required for contextual fear conditioning, and perhaps other hippocampal-dependent functions, should be re-evaluated' (Phillips and Le Doux 1995, p. 5308).

There is little to go on in this section, but we are left with the impression that differential effects can be obtained within the septo-hippocampal system and that subcortical connections may be as important as cortical.

A9.6 Spatial tasks

Barnes (1988) reviewed a range of studies which allow comparison of effects in spatial and non-spatial (cued) forms of the standard spatial tasks, and on working and reference memory errors with lesions made before or after training. With lesions made prior to training, there were no reports of deficits in learning to approach a visual cue, or in working memory errors with such cues. By contrast, as far as could be told from the data at the time, lesions of any one of hippocampus proper, dentate gyrus, entorhinal cortex, or fornix–fimbria produced both reference and working memory errors in the spatial tasks. The effects of lesions made post-training are more difficult to assess, as deficits disappear with increasing acquisition–lesion intervals. However, subicular, entorhinal, and large hippocampal lesions appeared to produce transient losses of cue learning, while lesions of the fornix, dentate, and hippocampus proper did not. All the lesions, as in acquisition, affected spatial learning.

Sutherland and Rodriguez (1989) reported that fornix–fimbria transection totally abolished spatial learning, lesions of the nucleus accumbens or anterior thalamus produced a major impairment, while lesions of the medial septum or

mammillary bodies produced only transient effects on acquisition and small lesions in the cingulate cortex had no effect. Nor do cingulate lesions increase the effects of fornix transection (Greene *et al*. 1994). Lesions of the dorsal fornix have modest effects similar to those of septal lesions (M'Harzi and Jarrard 1992), and medial septal effects can also be obtained with injection of GABA agonists (Brioni *et al*. 1990). Lesions of the fimbria, sparing the dorsal fornix, also produce an impairment (M'Harzi *et al*. 1991), while lateral septal lesions produce an impairment that is somewhat smaller than that produced by medial septal lesions (M'Harzi and Jarrard 1992). Consistent with the involvement of output from (as well as input to) the hippocampus implied by these results, there is a small but significant correlation of performance with the number of intact CA1 cells (Olsen *et al*. 1994).

These data suggest that the effects of lesions of the fornix–fimbria reflect a summation of effects achieved through the different fibre tracts of which it is composed. Of particular interest here is that the deleterious effects of medial septal lesions can be reversed by cholinergic agonists and calcium channel blockers (see Bannon *et al.* 1993, and references therein). This pattern of results suggests some form of mass action effect, in which partial loss of some inputs to hippocampus can be corrected by enhancement of the remainder. In general terms, this type of finding is consistent with the synergy observed between the aminergic inputs to the hippocampus (Appendix 10). Unlike the case of delayed matching-to-sample, it appears that the nucleus basalis magnocellularis (NBM) does not contribute to spatial learning in the water maze (Hagan *et al*. 1988), but it may contribute to general, including spatial, learning in the radial-arm maze (Arendt *et al*. 1989). The combination of NBM and MS/DBB lesions does affect spatial performance (Waite *et al*. 1994).

Schenk and Morris (1985) found that combined lesions of the entorhinal cortex and subiculum produced smaller effects on spatial learning than those usually reported for total hippocampal lesions, while entorhinal lesion alone had smaller effects still. Nonetheless, small perirhinal lesions can produce a modest impairment (Wiig and Bilkey 1994), and it may be that the deficit is no bigger when perirhinal and entorhinal damage are combined (compare Nagahara *et al.* 1995). Parietal cortex lesions produce a larger deficit than do hippocampal lesions (DiMattia and Kesner 1988). Perforant path cuts, on the other hand, produce a substantial deficit (Skelton and McNamara 1992). It seems likely that we are dealing here, as with the fornix case, with a summation of effects. Certainly, ibotenic acid lesions of the hippocampus proper or the subiculum each produce modest effects, while a combined lesion produces much larger effects (Morris *et al.* 1990). In this case, neither of the smaller lesion groups demonstrated proper spatial navigation; and they showed different strategies for finding the platform (hippocampal animals swimming round in circles, and subicular animals swimming apparently at random).

However, substantial deficits can be obtained with quite restricted lesions to the hippocampus. Thus, effects on spatial learning in the water maze have been reported in rats with ischaemic lesions (after occlusion of the vertebral and carotid arteries) largely confined to CA1 pyramidal cells, with only small areas of additional damage in the hilus of the dentate gyrus and the caudate nucleus. The specificity of the spatial impairment to the loss of CA1 cells is called into question by the fact that correlations between the extent of cell loss and the size of the behavioural deficit are either lacking (Nunn *et al*. 1994) or weak (Nelson *et al*. 1997). This absence of a strong correlation suggests the involvement of additional structures. However, grafts of cells derived from foetal CA1, but not foetal basal forebrain, dentate, or CA3 regions, into the damaged adult CA1 area were sufficient to restore water-maze performance to normal levels (Netto *et al*. 1993; Hodges *et al*. 1996). Complete restoration of performance was observed also after transplantation of a murine line (MHP36) of conditionally immortalized neuroepithelial stem cells, which integrated only into the damaged CA1 and hilar regions (Sinden *et al*. 1997; Gray *et al*., in press). Similar findings have been reported after excitotoxic lesions confined to the CA1 region in marmosets trained on a conditional discrimination. The substantial deficit observed in performance on this task after the lesion was restored by transplants of either foetal marmoset CA1-derived cells or the murine MHP36 cells (Virley *et al*. 2000). The MHP36 cells, as in the experiments with rats (Sinden *et al*. 1997; Gray *et al*., in press), integrated selectively into the damaged CA1 region, many of them adopting apparently normal phenotypes (though of murine size) as pyramidal neurons. The results of these experiments strongly imply that a relatively small loss of CA1 pyramidal (and perhaps hilar) cells is capable of causing substantial deficits in spatial learning and conditional discrimination performance; and that these deficits can be reversed by cells which are either homotypic to (in the case of foetal grafts) or capable of adopting (in the case of neuroepithelial stem cells) a phenotype appropriate to the CA1 and hilar cell populations.

Behaviourally, recovery of performance in medial septal-lesioned rats is accompanied by the adoption of stereotypic strategies which do not reduce with repeated testing; furthermore, if the animal is required to use non-stereotypic strategies, then permanent deficits remain despite repeated testing (Janis *et al.* 1994). This pattern of results suggests that the different components of the fornix–fimbria may control different aspects of response flexibility.

The possible complexities of response in the water maze are similarly shown in an experiment by McDonald and White (1994). They found that fornix, but not dorsal striatal, lesions impaired water maze acquisition in which cued trials were interspersed with occasional purely spatial probe trials (with a submerged platform present in the standard cued location). However, on transfer from the original spatial task to a visual task with the platform in a new place, 50 per cent of the controls visited the old spatial location before swimming to the new visual one. All the striatal animals went to the old spatial location, while all the fornix animals went to the new visual location. This suggests that striatal and fornix animals were learning about two separate aspects of the task, both of which were learned by the controls. However, only in the case of the fornix animals did these changes in behavioural strategy

result in an initial deficit. In both cases, the changed performance in the transfer task appeared to be a failure of inhibition of the prior response rather than a loss of the capacity to discriminate as such.
What is important to note, in this plethora of effects, is that both efferent and afferent fibre systems appear to make partial contributions to the overall hippocampal deficit. There is a general impression that the more hippocampal system damage there is, the greater the deficit. On the output hand, this seems easiest to explain in terms of the availability to the rat of distinct strategies (each determined by an output target), with the observed deficits depending on how many of the available alternatives have been lost. There also appears to be a bias towards the involvement of subcortical as opposed to cortical connections of the hippocampus.

A9.7 Punishment, conditioned suppression, and avoidance

In Appendix 6 we noted that there is a strong correlation between the frequency of theta rhythm and the distance about to be jumped in a jump avoidance task (Morris *et al*. 1976). We also noted that dorsal fornix lesions, which abolish theta in the hippocampus, had no effect on jump avoidance (Myhrer 1975). This is not surprising, given the general lack of effect of all our key treatments on active avoidance. More surprising, however, is that electrolytic medial septal lesions do not impair punishment-induced or on-the-baseline conditioned suppression (see Gray *et al.* 1979), and neurotoxic lesions do not impair extinction either (see below). This is a particularly interesting set of results, since the electrolytic lesions *did* increase resistance to extinction and increased responding during the pre-punishment baseline, while lateral septal lesions impaired punishment and conditioned suppression but did not affect extinction. An apparently similar pattern of septal-related reduction of *pain-free* anxiety coupled with insensitivity of *pain-induced* anxiety is shown with intraseptal injections of the benzodiazepine, midazolam. These increase open-arm entries in the plus maze test of anxiety, but do not impair shock prod avoidance (while intra-amygdala injections produce the opposite pattern; Pesold and Treit 1994).
A similar separation of unimpaired punishment-induced suppression and impaired extinction has been seen with intrahippocampal injections of atropine (Ross *et al.* 1975). This pattern was apparently obtained with both septal and temporal placements within the hippocampus. However, Blozovski (1979) found a similar lack of effect on passive avoidance with atropine injected into the septal pole of the hippocampus, but observed an effect with temporal injections. His temporal placements were much more so than Ross *et al*.'s and encroached on the entorhinal cortex. To confuse the issue somewhat, Bailey *et al.* (1986) found impaired passive avoidance and *impaired* two-way active avoidance with *septally* located hippocampal atropine. (They attribute the unusual effect on two-way avoidance to the use of a small door between the compartments.)
Overall, we may conclude that medial septal lesions do not, and lateral septal lesions do, impair punishment-induced suppression.

A9.8 Extinction, the partial reinforcement extinction effect, and latent inhibition

In the first edition, a seemingly coherent picture was presented of extinction being controlled by the passage of signals of non-reward via the medial septum to the hippocampus, and of the counterconditioning of those signals, necessary for production of the partial reinforcement extinction effect (PREE), returning via CA3 to the lateral septum. Furthermore, it was proposed that the anxiolytic drugs block the fundamental process of counterconditioning (and so the PREE) by disrupting the passage of information around this septo-hippocampal circuit. This model, for a variety of reasons, must now be abandoned.
First is the issue of counterconditioning itself. It is now clear that anxiolytic drugs do not reduce shock–food counterconditioning (Gray and McNaughton 1983) nor non-reward-food counterconditioning even with a 24-hour intertrial interval (McNaughton *et al*., submitted). Thus, such a blockade of counterconditioning cannot be used to account for the effects of the drugs on either the PREE or the partial punishment effect (i.e. the increased resistance to extinction observed in animals trained on a partial punishment plus continuous reward schedule). We have argued elsewhere that the drugs instead reduce a non-associative 'toughening up' process (McNaughton 1989, Chapter 7). How far septal and hippocampal lesions share the precise profile of action of the anxiolytic drugs is not clear, but certainly septal lesions do not impair Pavlovian counterconditioning either (Gray and McNaughton 1983). Furthermore, as we saw in Appendix 7, septal stimulation can have quite marked non-associative proactive effects on extinction.
Second is the nature of the pathways which are now known to be involved. A detailed analysis of the relevant experimental results has been undertaken by Rawlins and his co-workers, and the results are summarized in Table A9.1.
Table A9.1 The effects on rate of extinction in the straight alley after training on continuous reinforcement (CR) or partial reinforcement (PR) schedules of various lesions of the septo-hippocampal system or its connections
CR PR PREE Trials/day
Total hippocampus (aspiration) – + abolished multi
Total septum (electrolytic) – + abolished multi
Hippocampus + subiculum + entorhinal cortex (neurotoxic) – + abolished
Fornix–fimbria (cut)* –? + abolished

Lateral septum (electrolytic) –? + abolished multi, one
Subiculo-accumbens pathway (cut) 0 + abolished multi
Accumbens – + abolished multi
Total septum (neurotoxic) + + spared multi
Total hippocampus (neurotoxic) – – spared
Temporal hippocampus + subiculum (aspiration) – – spared multi
Medial septum (electrolytic) – – spared
Fimbria only (cut) 0 0 spared multi
Descending columns of the fornix (cut) – 0 reduced multi
Anxiolytics – + reduced multi
Anxiolytics – + abolished one
Dorsal bundle lesions – + abolished multi, one

Adapted from Table 1 of Rawlins *et al.* (1989), with additions from Clark *et al.* (1992) or as referenced in the table. PREE, partial reinforcement extinction effect; EC, entorhinal cortex; –, rate of running decreased; +, rate of running increased; multi, multiple trials per day; one, 1 trial per day.

*Histology of these lesions reassessed by Clark *et al.* 1992, the inclusion of the entorhinal cortex was not previously emphasized.

Let us first consider extinction in continuously reinforced rats. Extinction is retarded (i.e. behavioural inhibition is impaired) with both fibre-sparing and conventional lesions of the hippocampus proper, by electrolytic but not neurotoxic lesions of the septum, by section of the fornix–fimbria or descending columns of the fornix, and by lesions of the dorsal ascending noradrenergic bundle, which sends a major projection to the hippocampus through the septum. Extinction is not impaired in continuously reinforced animals by lesions of the fimbria or by cutting the pathway connecting the subiculum to the nucleus accumbens. Total septal lesions which spare fibres of passage actually speed up extinction.

We can accommodate many of these data by the proposal that an intact input from the locus coeruleus to the hippocampus and an intact output from the subiculum via the descending columns of the fornix are critical for speedy extinction. Hippocampal cells appear to build models of responses; noradrenergic input appears to enable activity to transfer from one level of the hippocampus to the next (Appendix 5); and the final stage for behavioural control is the transfer of information to the subiculum. Hence lesions of the hippocampus proper or of the dorsal noradrenergic bundle prevent the relevant information from reaching the subiculum and hence prevent the inhibition of the previously learned running response. Similarly, lesion of the descending columns of the fornix prevents output of the relevant information. This could well be destined for the mammillary bodies or the anterior thalamus, since the outputs to the accumbens and lateral septal nucleus are both ruled out by the data.

There remains the question why fibre-sparing total septal lesions should increase the rate of extinction. Our analysis of the single-cell data suggested that the medial septal input to the hippocampus reflects orienting reactions. In both of the experiments demonstrating an effect of ibotenic acid lesions of the septum (Coffey *et al.* 1989), the lesion produced an increase in the rate of acquisition of the response, an effect that was significant in the second experiment. It seems possible, therefore, that a loss of some aspect of orienting reactions led to the lesioned rats concentrating more on the availability of reward and less on extraneous aspects of the apparatus. As a result, they would learn the response earlier, thus receiving overtraining in comparison to the controls. In the second experiment (which shows the greater lesion effect on extinction) acquisition appeared complete by the third day, and so the lesion but not the control rats received 5 days (270 per cent) of overtraining. Overtraining is known to increase the rate of extinction (see Mackintosh 1974), which could therefore account for the lesion effect in extinction. If this suggestion is correct, the lesion difference both in acquisition and extinction would probably be eliminated by extensive prior handling of the animals and habituation to the apparatus. The opposite effects of electrolytic lesions might be attributable to a predominating influence of noradrenergic (or other) fibres of passage.

A similar increase in the rate of acquisition is seen with lesions of the descending columns of the fornix (Rawlins *et al.* 1989), but in this case a moderate increase in resistance to extinction occurred. Here it seems likely that the overtraining (which was less, involving only 3 days at asymptote) would have simply subtracted somewhat from the direct effect on extinction of interrupting the subicular outflow. These arguments give rise to a picture of the medial septal nucleus as conveying information leading to an orienting reaction, and the noradrenergic input conveying information about frustration to the hippocampus, with the resultant control of the orienting response and of extinction depending on the subiculum and its output in the descending columns of the fornix.

Let us now consider the effects of lesions on partially reinforced rats and on the partial reinforcement extinction effect. Neither neurotoxic lesions of the septum, neurotoxic lesions of the entire hippocampus proper (sparing subiculum and entorhinal cortex), nor aspiration lesions which included most of the subiculum as well as hippocampus proper, but spared the septal pole of both, reduced the PREE. This set of results suggests that the hippocampus proper and the subiculum as a whole are not involved. By contrast, neurotoxic lesions which included the entorhinal cortex, or lesions which damaged the pathway connecting the entorhinal cortex to the nucleus accumbens, or the nucleus accumbens itself all reduced or abolished the PREE (see Table A9.1).

Taken as a whole these data show that the increased resistance to extinction seen in partially reinforced rats is completely independent of the increased resistance produced by septo-hippocampal lesions. This is consistent with

the conclusion we came to above, that the PREE cannot result from counterconditioning. The data also suggest that the PREE depends on output from the entorhinal cortex to the accumbens. But what could this output signify?
We saw in our analysis of the single-cell data that, in the absence of special reinforcement conditions, the input from the entorhinal cortex to the hippocampus constituted a 'familiar–ignore this' signal. If we assume that the output to the accumbens has the same effect, then the result could well be to prevent interruption of the current motor programme (running) by the introduction of non-reward.
That the output to the accumbens may prevent interruption of motor programmes by otherwise salient events in a more general fashion is suggested by the effects of lesions on latent inhibition (Lubow 1989). This is the reduction in subsequent learning produced by prior unreinforced pre-exposure to a stimulus (see Clark *et al.* 1992 and references therein; also Section A8.15 in the previous appendix). In every case tested so far, lesions which impair latent inhibition also impair the PREE, consistent with a suggestion originally made by Joram Feldon (personal communication, 1985) that these two phenomena are closely related. The reverse is not the case, as dorsal bundle lesions impair the PREE (Owen *et al*. 1982) but do not impair latent inhibition (Tsaltas *et al*. 1984). The effect of dorsal bundle lesions on the PREE is likely to be due to a more specific impairment of reactions to reward omission of the type which accounts for their effects on extinction.
The assumption (see above) that the input from the entorhinal cortex to the nucleus accumbens constitutes a 'familiar–ignore' signal is supported by studies from Ina Weiner's and Feldon's laboratories on the effects of accumbal lesions on latent inhibition. They have proposed a model (Weiner and Feldon 1997) of latent inhibition in which there is a mechanism in the nucleus accumbens responsible for switching between different motor programmes or the stimuli engaging such programmes. In a latent inhibition paradigm, pre-exposure has the consequence that the switch to the requirements imposed by the CS–UCS contingency (encountered in the conditioning phase of the paradigm) is inhibited by a second 'non-switch' mechanism, also located in the nucleus accumbens. In a series of elegant experiments, Weiner *et al*. (1996, 1999) showed that the two mechanisms are located in the core (switch) and shell (non-switch) subterritories of the nucleus accumbens respectively. Lesions of the core gave rise to 'undisruptable' latent inhibition, that is, latent inhibition which (unlike the normal case) survives context shift between pre-exposure and conditioning; while lesions of the shell abolished latent inhibition. Weiner points out that the former pattern of results is also obtained after excitotoxic lesions restricted to the hippocampus proper (Honey and Good 1993; and see discussion in Appendix 8, Section A8.15), while the latter is seen after lesions to the entorhinal cortex (Yee *et al*. 1995). She proposes (Weiner, in press), therefore, that the projection from the entorhinal cortex to the shell subterritory of the nucleus accumbens activates the non-switch mechanism, causing this to inhibit the switch mechanism in the core subterritory. This hypothesis is clearly compatible with our description of the entorhinal–accumbens projection as carrying a 'familiar–ignore' signal. There may be, in addition, a projection from the hippocampus proper to the core of the accumbens, which would directly activate the switch mechanism under conditions of context shift. This hypothesis would account for the undisruptable latent inhibition seen after lesions of both the hippocampus proper and the accumbens core.
There is one aspect of the data which is not entirely consistent with the model we have just produced. The lesions of the descending columns of the fornix described by Rawlins *et al*. (1989), which reduced but did not eliminate the PREE, included the same area as their more selective 'subiculo-accumbens pathway' cut—which abolished the PREE. We deal with this issue in two parts. First, why is it that descending column lesions impair but do not eliminate the PREE? Although we have ignored this issue so far, in the interests of clarity, it has been shown that there are at least three quite distinct mechanisms which can co-occur and give rise to the PREE: conditioning of after-effects of non-reward, associative effects of stimuli of frustration, and non-associative 'toughening up'—with anxiolytic drugs reducing the effects of the latter two (see McNaughton 1989, pp. 88–90). It is possible that lesions of the descending columns of the fornix leave one of these three processes intact. Second, given the above argument, why does the smaller lesion abolish the PREE? Here, we should note that the lesioned partially reinforced rats showed much slower acquisition than the continuously reinforced rats (which, like the rats with lesions of the descending columns of the fornix described above, were faster than controls). Thus, the small lesion produced a change in behaviour in the partially reinforced rats during acquisition which was blocked in some way by the additional damage in the rats with larger lesions of the descending columns of the fornix. This change in behaviour during acquisition could have eliminated one of the normal components of the PREE, or might simply have resulted in much lesser response strength and so an altered PREE due to incomplete acquisition.
A second explanation is offered by Rawlins *et al*. (1989, p. 159), that: 'destruction of the descending columns of the fornix alone would have produced increased resistance to extinction in both CR and PR trained rats: adding the basolateral septal cut would then presumably decrease resistance to extinction in the PR group alone (judging from the results seen in the septum cut group in the present experiments). Thus a combined lesion of the kind that our procedure produces would increase resistance to extinction in descending column-CR rats, but would have little effect on persistence in the descending column-PR rats, because the two elements of the lesions would tend to cancel each other out in this respect.'
An important feature of the link between the PREE and latent inhibition is that it provides an 'inhibitory' explanation both of a decreased rate of extinction in CR animals and an increased rate of extinction in PR animals. In the latter case we see the effects, in extinction, of an override of inhibition of responding, learned during acquisition.

A9.9 Integration

Let us now see if we can put all of the above 'dissections' together into an at least moderately coherent story.

Consider first the entorhinal, perirhinal, and parahippocampal cortices. These are, anatomically, very high-order polymodal association cortex. Not surprisingly, therefore, they appear relatively important for sensory discriminations. While it is not clear whether the hippocampus proper is required for the solution of concurrent discriminations in a single modality, fornix lesions produce a relatively smaller impairment than entorhinal, perirhinal, and parahippocampal lesions. With delayed matching-to-sample tasks, perirhinal and parahippocampal cortex appear relatively more important than entorhinal, while the addition of damage to hippocampus proper even appears to ameliorate the effects of rhinal damage (Meunier *et al*. 1996). By contrast, rhinal cortex appears relatively unimportant for spatial tasks, but has not been investigated in relation to punishment. Entorhinal cortex is important for the partial reinforcement extinction effect and latent inhibition, both of which can be viewed as inhibitory forms of sensory discrimination.

All of these data are consistent with the single-cell analysis of Appendix 6. This suggested that the entorhinal cortex builds a model of expected goals, which has the net effect of an 'ignore' signal with respect to septal input unless additional aminergic input indicates that action is required. In the case of concurrent discriminations, this signal would be necessary for the suppression of the interference which would otherwise occur when there are many similar stimulus sets and the responses to be performed do not differ across the sets. The relative lack of effect of fornix lesions on concurrent discriminations suggests that the effect of the entorhinal cortex on concurrent discriminations depends on output to cortical areas. By contrast, latent inhibition and the PREE depend on the subcortical connections of the hippocampal system. It is probably best to view the PREE as a special case of latent inhibition to stimuli associated with reward omission, with latent inhibition of all types involving the transfer from the entorhinal cortex to the nucleus accumbens of an 'ignore' signal.

Next, consider the hippocampus proper. This does not appear to be particularly important for concurrent discriminations, in which the main problem for goal selection seems to be a multiplicity of stimuli to which a particular single class of response could be made. However, the hippocampus proper is involved in delayed matching-to-sample, spatial learning, and runway extinction. In all these cases correct performance can be viewed as depending on the capacity to devalue prior goals (in the case of delayed matching, this process takes place on a very brief time-scale). As we saw with nictitating membrane conditioning, there are certain types of response inhibition which appear to involve only simple inhibition rather than choice between alternatives, and these are not affected by hippocampal lesions. Contrary to the view expressed in the first edition, the involvement of the hippocampus proper (i.e. excluding the subiculum and entorhinal cortex) in extinction is not matched by any involvement in the PREE, and is unrelated to lesion effects on the PREE.

Given the fornix lesion data, we can assume that medial septal input is relatively unimportant for concurrent discriminations. Loss of medial septal input produces an apparent increased rate of forgetting in delayed matching-to-sample, whereas lesions of the horizontal nucleus of the diagonal band have much more extensive effects, and cholinergic blockade as a whole produces a major deficit in performance without any accompanying apparent increase in rate of forgetting. Consistent with this subtotal effect on delayed matching, medial septal lesions have only modest effects on spatial learning (and these can be reversed by cholinergic agonists), while neurotoxic damage to the medial septum does not appear to affect extinction at all. (We have recently obtained similarly modest effects on spatial learning with supramammillary blockade; Pan and McNaughton, in preparation.) Nor does the medial septum appear to be involved in punishment. The most likely role for this input appears to be in the control of orienting and related reactions.

Lateral septal lesions can be presumed to be unimportant for concurrent discriminations, their role in delayed matching is unknown, and they have only a modest effect on spatial learning. These lesions impair punishment-induced and conditioned suppression, while having no effect on extinction.

The effects of lesions to the fornix–fimbria often appear to reflect the sum of separate effects produced by disruption of the different sets of fibres of which it is composed. The dissociation of the effects of fornix–fimbria and rhinal cortex lesions, respectively, on conditional and delayed matching tests of memory in subhuman animals is particularly interesting, given the report of a patient with 'a significant and persistent anterograde amnesia . . . [after] a lesion that involved the region of the proximal, posterior portion of both fornices without evidence of damage to other hippocampal pathways or to other structures known to be critical for memory, such as the hippocampus, thalamus or basal forebrain' (D'Esposito *et al*. 1995; see also Calabrese *et al*. 1995). Fornix–fimbria lesions have only weak effects on concurrent discrimination (suggesting, as we noted, a mainly cortical mediation of an output from the entorhinal and related isocortex), but have effects equivalent to those of large hippocampal lesions on delayed matching, spatial learning, extinction, the PREE, and latent inhibition. The latter two effects appear to be due solely to destruction of fibres running from the entorhinal cortex to nucleus accumbens. The spatial learning deficit can be attributed to damage to fibres travelling to the hippocampus from the medial septum in the dorsal fornix, to fibres travelling from the hippocampus in the fimbria, and to fibres travelling from the subiculum (or possibly the entorhinal cortex) to the mammillary bodies. This same pattern appears to be obtained with more spatial or response-oriented delayed matching or non-matching-to-sample, but the mammillary bodies do not appear to be

involved in less response-oriented matching tasks. The effects on extinction appear attributable to fibres travelling in the descending columns of the fornix and destined for the mammillary bodies and/or the anterior thalamus.

As reviewed in Appendix 10, noradrenergic input to the hippocampus is important in enabling output from the hippocampus in relation to non-reward, while serotonergic input is important in relation to punishment. Given the above results, these can be seen as separable, if partially overlapping, with some lesions producing a double dissociation of extinction and punishment.

There is a key conclusion from all of the above. While we may be (and in Chapter 10 we argue that we are) able to characterize the septo-hippocampal system as having an essentially coherent set of functions, it produces its effects on behaviour through a variety of distinct outputs to the cortex, accumbens, mammillary bodies, thalamus, etc., each of which makes its own specialized contribution. While some specific tests may be successful in partially isolating one of these outputs, in the majority of cases several are involved concurrently in any one task.

Above all, and crucially for the theory developed in Chapter 10, hippocampal outputs can be seen as inhibitory (or as controlling information-gathering consequent on inhibition), and inhibitory primarily of goals. This is clear for many of the cases we have discussed. But we should note the role of the cortical connections of the hippocampal formation in concurrent discriminations, where the output must suppress the largely stimulus-based interference from the concurrent tasks. There is also the role of the entorhinal–accumbens connection in latent inhibition, in which, in effect, the output must suppress the capacity of a stimulus to enter into a future association. In both these cases we can view what is being achieved as control of orienting responses or their internal equivalent in relation to retrieval from memory. The multiplicity of cortical and subcortical outputs which can be involved concurrently in mediating hippocampal control of behaviour makes it difficult to view this process as a simple memory storage device feeding information to the cortex. As against this view, not only are critical functional outputs of the hippocampus subcortical, but also the components of the isocortex most closely connected to the archicortex of the hippocampus proper appear to provide input more than they receive output. Moreover, all of the different subcortical outputs we have considered (mammillary bodies, anterior thalamus, accumbens) contribute more to the motor control structures of the anterior cortex than to the perceptual analytic structures of the posterior cortex. These facts argue for a role of the hippocampus in inhibitory aspects of the planning of responses and the selection of goals.

References

Aggleton, J.P., Hunt, P.R., and Shaw, C. (1990) The effects of mammillary body and combined amygdalar-fornix lesions on tests of delayed non-matching-to-sample in the rat. *Behavioral Brain Research*, **40**,145-157

Aggleton, J. P., Keith, A. B., Rawlins, J. N. P., Hunt, P. R., and Sahgal, A. (1992). Removal of the hippocampus and transection of the fornix produce comparable deficits on delayed non-matching to position by rats. *Behavioural Brain Research*, **52**, 61–71.

Arendt, T., Allen, Y., Marchbanks, R. M., Schugens, M. M., Sinden, J., Lantos, P. L., *et al.* (1989). Cholinergic system and memory in the rat: effects of chronic ethanol, embryonic basal forebrain brain transplants and excitotoxic lesions of cholinergic basal forebrain projection system. *Neuroscience*, **33**, 435–62.

Bailey, E. L., Overstreet, D. H., and Crocker, A. D. (1986). Effects of intrahippocampal injections of the cholinergic neurotoxin AF64A on open-field activity and avoidance learning in the rat. *Behavioral and Neural Biology*, **45**, 263–74.

Bannon, A. W., McMonagle-Strucko, K., and Fanelli, R. J. (1993). Nimodipine prevents medial septal lesion-induced performance deficits in the Morris water maze. *Psychobiology*, **21**, 209–14.

Barnes, C. A. (1988). Spatial learning and memory processes: the search for their neurobiological mechanisms in the rat. *Trends in Neuroscience*, **11**, 163–9.

Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., and Damasio, A. R. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science*, **269**, 1115–18.

Béracochéa, D. J. and Jaffard, R. (1995). The effects of mammillary body lesions on delayed matching and delayed non-matching to place tasks in the mice. *Behavioural Brain Research*, **68**, 45–52.

Berger, T. W., Weikart, C. L., Bassett, J. L., and Orr, W. B. (1986). 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.

Blozovski, D. (1979). PA-learning in young rats with dorsal hippocampal- and hippocampo-entorhinal atropine. *Pharmacology, Biochemistry and Behavior*, **10**, 369–72.

Brioni, J. D., Decker, M. W., Gamboa, L. P., Izquierdo, I., and McGaugh, J. L. (1990). Muscimol injections in the medial septum impair spatial learning. *Brain Research*, **522**, 227–34.

Calabrese, P., Markowitsch, H. J., Harders, A. G., Scholz, M., and Gehlen, W. (1995). Fornix damage and memory: a case report. *Cortex*, **31**, 555–64.

Cho, Y. H. and Jaffard, R. (1994). The entorhinal cortex and a delayed non-matching-to-place task in mice: emphasis on preoperative training and presentation procedure. *European Journal of Neuroscience*, **6**, 1265–74.

Clark, A. J. M., Feldon, J., and Rawlins, J. N. P. (1992). Aspiration lesions of rat ventral hippocampus disinhibit responding in conditioned suppression or extinction, but spare latent inhibition and the partial reinforcement extinction effect. *Neuroscience*, **48**, 821–9.
Clark, G. A., McCormick, D. A., Lavond, D. G., and Thompson, R. F. (1984). Effects of lesions of cerebellar nuclei on conditioned behavioral and hippocampal neuronal responses. *Brain Research*, **291**, 125–36.
Coffey, P. J., Feldon, J., Mitchell, S., Sinden, J., Gray, J. A., and Rawlins, J. N. P. (1989). Ibotenate-induced total septal lesions reduce resistance to extinction but spare the partial reinforcement extinction effect in the rat. *Experimental Brain Research*, **77**, 140–52.
Davidson, T. L. and Jarrard, L. E. (1989). Retention of concurrent conditional discriminations in rats with ibotenate lesions of hippocampus. *Psychobiology*, **17**, 49–60.
D'Esposito, M., Verfaellie, M., Alexander, M. P., and Katz, D. I. (1995). Amnesia following traumatic bilateral fornix transection. *Neurology*, **45**, 1546–50.
DiMattia, B. D. and Kesner, R. P. (1988). Spatial cognitive maps: differential role of parietal cortex and hippocampal formation. *Behavioral Neuroscience*, **102**, 471–80.
Dunnett, S. B. (1985). Comparative effects of cholinergic drugs and lesions of nucleus basalis or fimbria–fornix on delayed matching in rats. *Psychopharmacology*, **87**, 357–63.
Eacott, M. J., Gaffan, D., and Murray, E. A. (1994). Preserved recognition memory for small sets, and impaired stimulus identification for large sets, following rhinal cortex ablations in monkeys. *European Journal of Neuroscience*, **6**, 1466–78.
Gaffan, D. (1994). Scene-specific memory for objects: a model of episodic memory impairment in monkeys with fornix transection. *Cognitive Neuroscience*, **6**, 305–20.
Givens, B. and Olton, D. S. (1994). Local modulation of basal forebrain: effects on working and reference memory. *The Journal of Neuroscience*, **14**, 3578–87.
Gray, J. A. and McNaughton, N. (1983). Comparison between the behavioural effect of septal and hippocampal lesions: a review. *Neuroscience and Biobehavioral Reviews*, **7**, 119–88.
Gray, J. A., Rawlins, J. N. P., and Feldon, J. (1979). Brain mechanisms in the inhibition of behaviour. In *Mechanisms of learning and motivation* (ed. A. Dickinson and R. A. Boakes), pp. 295–316. Erlbaum, Hillsdale, NJ.
Gray, J. A., Grigoryan, G., Virley, D., Sinden, J. D., and Hodges, H. (2000) Conditionally immortalised multipotential and multifunctional neural stem cell lines as an approach to clinical transplantation. *Cell Transplantation*, **9**, 153-168.
Greene, P. L., Cassel, J.-C., Kelche, C., Jeltsch, H., Bratt, A. M., and Will, B. E. (1994). Differential behavioral effects of supracallosal and infracallosal lesions of the septohippocampal pathways: no ameliorative effects of oxotremorine or pilocarpine on radial-maze performance. *Behavioral and Neural Biology*, **62**, 4–14.
Hagan, J. J., Salamone, J. D., Simpson, J., Iversen, S. D., and Morris, R. G. M. (1988). Place navigation in rats is impaired by lesions of medial septum and diagonal band but not nucleus basalis magnocellularis. *Behavioural Brain Research*, **27**, 9–20.
Harper, D. N., McLean, A. P., and Dalrymple-Alford, J. C. (1994). Forgetting in rats following medial septum or mammillary body damage. *Behavioral Neuroscience*, **108**, 691–702.
Hirsh, R., Holt, L., and Mosseri, A. (1978). Hippocampal mossy fibers, motivation states, and contextual retrieval. *Experimental Neurology*, **62**, 68–79.
Hirsh, R., Davis, R. E., and Holt, L. (1979). Fornix-thalamus fibers, motivational states, and contextual retrieval. *Experimental Neurology*, **65**, 373–90.
Hodges, H., Sowinski, P., Fleming, P., Kershaw, T. R., Sinden, J. D., Meldrum, B. S., *et al.* (1996). Contrasting effects of fetal CA1 and CA3 hippocampal grafts on deficits in spatial learning and working memory induced by global cerebral ischaemia in rats. *Neuroscience*, **72**, 959–88.
Honey, R. C. and Good, M. (1993). Selective hippocampal lesions abolish the contextual specificity of latent inhibition and conditioning. *Behavioral Neuroscience*, **107**, 23–33.
Hunt, M. E., Kesner, R. P., and Evans, R. B. (1994). Memory for spatial location: functional dissociation of entorhinal cortex and hippocampus. *Psychobiology*, **22**, 186–94.
Janis, L. S., Bishop, T. W., and Dunbar, G. L. (1994). Medial septal lesions in rats produce permanent deficits for strategy selection in a spatial memory task. *Behavioral Neuroscience*, **108**, 892–8.
Jarrard, L. E. and Davidson, T. L. (1990). Acquisition of concurrent conditional discriminations in rats with ibotenate lesions of hippocampus and of subiculum. *Psychobiology*, **18**, 68–73.
Jarrard, L. E. and Davidson, T. L. (1991). On the hippocampus and learned conditional responding: effects of aspiration versus ibotenate lesions. *Hippocampus*, **1**, 107–17.
Johnson, D. L. and Kesner, R. P. (1994). The effects of lesions of the entorhinal cortex and the horizontal nucleus of the diagonal band of broca upon performance of a spatial location recognition task. *Behavioural Brain Research*, **61**, 1–8.

Kim, J. J., Clark, R. E., and Thompson, R. F. (1995). Hippocampectomy impairs the memory of recently, but not remotely, acquired trace eyeblink conditioned responses. *Behavioral Neuroscience*, **109**, 195–203.
Kirk, R. C., White, K. G., and McNaughton, N. (1988). Low dose scopolamine affects discriminability but not rate of forgetting in delayed conditional discrimination. *Psychopharmacology*, **96**, 541–6.
Knowlton, B. J., Lavond, D. G., and Thompson, R. F. (1988). The effect of lesions of cerebellar cortex on retention of the classically conditioned eyeblink response when stimulation of the lateral reticular nucleus is used as the conditioned stimulus. *Behavioral and Neural Biology*, **49**, 293–301.
Lubow, R. E. (1997). Latent inhibition as a measure of learned inattention: some problems and solutions. *Behavioural Brain Research*, **88**, 75–83.
Mackintosh, N. J. (1974). *The psychology of animal learning.* Academic Press, New York.
Mauk, M. D. and Thompson, R. F. (1987). Retention of classically conditioned eyelid responses following acute decerebration. *Brain Research*, **403**, 89–95.
McDonald, R. J. and White, N. M. (1994). Parallel information processing in the water maze: evidence for independent memory systems involving dorsal striatum and hippocampus. *Behavioral and Neural Biology*, **61**, 260–70.
McNaughton, N. (1989). *Biology and emotion.* Cambridge University Press.
Meunier, M., Bachevalier, J., Mishkin, M., and Murray, E. A. (1993). Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. *The Journal of Neuroscience*, **13**, 5418–32.
Meunier, M., Hadfield, W., Bachevalier, J., and Murray, E. A. (1996). Effects of rhinal cortex lesions combined with hippocampectomy on visual recognition memory in rhesus monkeys. *Journal of Neurophysiology*, **75**, 1190–205.
M'Harzi, M. and Jarrard, L. E. (1992). Effects of medial and lateral septal lesions on acquisition of a place and cue radial maze task. *Behavioural Brain Research*, **49**, 159–65.
M'Harzi, M., Jarrard, L. E., Willig, F., Palacios, A., and Delacour, J. (1991). Selective fimbria and thalamic lesions differentially impair forms of working memory in rats. *Behavioral and Neural Biology*, **56**, 221–39.
Miller, R. (1991). *Cortico-hippocampal interplay and the representation of contexts in the brain.* Springer-Verlag, Berlin.
Morris, R. G. M., Black, A. H., and O'Keefe, J. (1976). Hippocampal EEG during a ballistic movement. *Neuroscience Letters*, **3**, 102.
Morris, R. G. M., Schenk, F., Tweedie, F., and Jarrard, L. E. (1990). Ibotenate lesions of hippocampus and/or subiculum: dissociating components of allocentric spatial learning. *European Journal of Neuroscience*, **2**, 1016–28.
Moss, M., Mahut, H., and Zola-Morgan, S. (1981). Concurrent discrimination learning of monkeys after hippocampal, entorhinal, or fornix lesions. *The Journal of Neuroscience*, **1**, 227–40.
Myhrer, T. (1975). Normal jump avoidance performance in rats with the hippocampal theta rhythm selectively disrupted. *Behavioural Biology*, **14**, 489–98.
Nagahara, A. H., Otto, T., and Gallagher, M. (1995). Entorhinal–perirhinal lesions impair performance of rats on two versions of place learning in the Morris water maze. *Behavioral Neuroscience*, **109**, 3–9.
Nelson, A., Lebessi, A., Sowinski, P., and Hodges, H. (1997). Comparison of effects of global cerebral ischaemia on spatial learning in the standard and radial water maze: relationship of hippocampal damage to performance. *Behavioural Brain Research*, **85**, 93–115.
Netto, C. A., Hodges, H., Sinden, J. D., Le Peillet, E., Kershaw, T., Sowinski, P., *et al.* (1993). Effects of fetal hippocampal field grafts on ischaemic-induced deficits in spatial navigation in the water maze. *Neuroscience*, **54**, 69–92.
Nunn, J. A., Le Peillet, E., Netto, C. A., Hodges, H., Gray, J. A., and Meldrum, B. S. (1994). Global ischaemia: hippocampal pathology and spatial deficits in the water maze. *Behavioural Brain Research*, **62**, 41–54.
Olsen, G. M., Scheel-Krüger, J., Moller, A., and Jensen, L. H. (1994). Relation of spatial learning of rats in the Morris water maze task to the number of viable CA1 neurons following four-vessel occlusion. *Behavioral Neuroscience*, **108**, 681–90.
Orr, W. B. and Berger, T. W. (1985). Hippocampectomy disrupts the topography of conditioned nictitating membrane responses during reversal learning. *Behavioral Neuroscience*, **99**, 35–45.
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.
Pan, W.X. and McNaughton, N. (1997) The medial supramammillary nucleus, spatial learning and the frequency of hippocampal theta activity. *Brain Research* **764**:101-108
Peinado-Manzano, M. A. (1990). The role of the amygdala and the hippocampus in working memory for spatial and non-spatial information. *Behavioural Brain Research*, **38**, 117–34.
Pesold, C. and Treit, D. (1994). The septum and amygdala differentially mediate the anxiolytic effects of benzodiazepines. *Brain Research*, **638**, 295–301.

Phillips, R. G. and Le Doux, J. E. (1995). Lesions of the fornix but not the entorhinal or perirhinal cortex interfere with contextual fear conditioning. *The Journal of Neuroscience*, **15**, 5308–15.
Rawlins, J. N. P., Feldon, J., Tonkiss, J., and Coffey, P. J. (1989). The role of subicular outputs in the development of the partial reinforcement extinction effect. *Experimental Brain Research*, **77**, 153–60.
Ridley, R. M., Timothy, C. J., MacLean, C. J., and Baker, H. F. (1995). Conditional learning and memory impairments following neurotoxic lesion of the CA1 field of the hippocampus. *Neuroscience*, **67**, 263–75.
Ross, J. F., McDermott, L. J., and Grossman, S. P. (1975). Disinhibitory effects of intrahippocampal or intrahypothalamic injections of anticholinergic compounds in the rat. *Pharmacology, Biochemistry and Behavior*, **3**, 631–9.
Schenk, F. and Morris, R. G. M. (1985). Dissociation between components of spatial memory in rats after recovery from the effects of retrohippocampal lesions. *Experimental Brain Research*, **58**, 11–28.
Sinden, J. D., Rashid-Doubell, F., Kershaw, T. R., Nelson, A., Chadwick, A., Jat, P. S., *et al.* (1997). Recovery of spatial learning by grafts of a conditionally immortalized hippocampal neuroepithelial cell line into the ischaemia-lesioned hippocampus. *Neuroscience*, **81**, 599–608.
Skelton, R. W. and McNamara, R. K. (1992). Bilateral knife cuts to the perforant path disrupt spatial learning in the Morris water maze. *Hippocampus*, **2**, 73–80.
Stackman, R. W. and Walsh, T. J. (1994). Baclofen produces dose-related working memory impairments after intraseptal injection. *Behavioral and Neural Biology*, **61**, 181–5.
Steward, O. (1981). Evaluation of short-term cue recollection following entorhinal cortical lesions in rats. *Behavioral and Neural Biology*, **31**, 187–97.
Sutherland, R. J. and Rodriguez, A. J. (1989). The role of the fornix/fimbria and some related subcortical structures in place learning and memory. *Behavioural Brain Research*, **32**, 265–77.
Thompson, R. F. (1986). The neurobiology of learning and memory. *Science*, **233**, 941–7.
Tsaltas, E., Preston, G. C., Rawlins, J. N. P., Winocur, G., and Gray, J. A. (1984). Dorsal bundle lesions do not affect latent inhibition of conditioned suppression. *Psychopharmacology (Berlin)*, **84**, 549–55.
Waite, J. J., Chen, A. D., Wardlow, M. L., and Thal, L. J. (1994). Behavioral and biochemical consequences of combined lesions of the medial septum/diagonal band and nucleus basalis in the rat when ibotenic acid, quisqualic acid, and AMPA are used. *Experimental Neurology*, **130**, 214–29.
Weiner, I. (2000) The latent inhibition model of schizophrenia. In *Contemporary issues in modeling psychopathology* (ed. M. Myslobodsky and I. Weiner). Kluwer Academic Publishers, Boston/Dordrecht/London.
Weiner, I., Gal, G., Rawlins, J.N., and Feldon, J. (1996). Differential involvement of the shell and core subterritories of the nucleus accumbens in latent inhibition and amphetamine-induced activity. *Behavioral Brain Research*, **81**, 123-33.
Weiner, I. and Feldon, J. (1997). The switching model of latent inhibition: an update of neural substrates. *Behavioural Brain Research*, **88**, 11–25.
Weiner, I., Gal, G., and Feldon, J. (1999). Disrupted and undisruptable latent inhibition after shell and core lesions. *Annals of the New York Academy of Sciences*, **877**, 723–27.
Wiig, K. A. and Bilkey, D. K. (1994). Perirhinal cortex lesions in rats disrupt performance in a spatial DNMS task. *NeuroReport*, **5**, 1405–8.
Yee, B. K. and Rawlins, J. N. P. (1994). The effects of hippocampal formation ablation or fimbria–fornix section on performance of a nonspatial radial arm maze task by rats. *The Journal of Neuroscience*, **14**, 3766–74.
Yee, B. K., Feldon, J., and Rawlins, J. N. P. (1995). Latent inhibition in rats is abolished by NMDA-induced neuronal loss in the retrohippocampal region, but this lesion effect can be prevented by systemic haloperidol treatment. *Behavioral Neuroscience*, **109**, 227–40.
Zola-Morgan, S., Squire, L. R., and Amaral, D. G. (1989*a*). Lesions of the hippocampal formation but not lesions of the fornix or the mammillary nuclei produce long-lasting memory impairment in monkeys. *The Journal of Neuroscience*, **9**, 898–913.
Zola-Morgan, S., Squire, L. R., Amaral, D. G., and Suzuki, W. A. (1989*b*). Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. *The Journal of Neuroscience*, **9**, 4355–70.
Zola-Morgan, S., Squire, L. R., Rempel, N. L., and Clower, R. P. (1992). Enduring memory impairment in monkeys after ischemic damage to the hippocampus. *The Journal of Neuroscience*, **12**, 2582–96.
Zola-Morgan, S., Squire, L. R., and Ramus, S. J. (1995). The role of the hippocampus in declarative memory: a reply to Nadel. *Hippocampus*, **5**, 235–9.