Appendix 8

Behavioural effects of large septo-hippocampal lesions

A8.1 Introduction

The arguments deployed in the book have led to the septo-hippocampal system as we have worked our way progressively higher within the defensive systems of the brain. However, at the level of the septo-hippocampal system, the question arises as to how far we are dealing with a primarily affective system and how far with perceptual and cognitive systems on which affective systems depend for at least part of their information. Appendices 5, 6, and 7 dealt far more with basic information processing than they did with affect, except at two points: the consistent impairments produced by all anxiolytics in the control of theta activity; and the emphasis, in the processing of information, on the specific processing of significant stimuli and the concomitant response component of such processing. We also previewed lesion data which suggest that the hippocampus often processes information fairly extensively without producing any output.

In this appendix we investigate the functions of the septo-hippocampal system as a whole, through a fairly coarse-grained review of the effects of large septal lesions and large fibre-interrupting lesions of the hippocampus. (A fine-grained review is not possible, as septal and hippocampal lesions have seldom been compared directly in identical tasks and—as we will see—quite minor task variations determine the results which are obtained.) While our review is fairly detailed, it is less so than its forerunners in the shape of Chapter 8 of the first edition (Gray 1982) and the article by Gray and McNaughton (1983). In regard to this earlier literature, the reader may wish to use those sources to supplement the present review. At the end of the appendix, we compare the pattern of the effects of both types of lesion, across tasks, with those of the anxiolytic drugs. This comparison provides us with our key conclusion: that the effects of lesions of the septo-hippocampal system produce a very good match to the effects of anxiolytic drugs, making this the best candidate (if we are to pick a single candidate) for the 'seat of anxiety', or at least for the seat of anxiolytic drug action.

To those who have looked only at the recent literature on the effects of hippocampal formation damage, the very small amount we have to say about memory in this appendix will come as something of a surprise. We downplay mnemonic tasks here because (a) the role of the hippocampus in memory requires fine-grained analysis of tasks which have not been used with septal lesions and anxiolytic drugs, an analysis undertaken in Chapter 8; and (b) in order to have a firm foundation for this memorial analysis, an overview of the non-mnemonic effects of hippocampal lesions forms an essential background. Careful dissection of types of memory may be rendered futile if one does not control for changes in more basic, non-memorial mechanisms. Indeed, we argue in Chapter 8 that the memorial effects of hippocampal lesions are no different in principle from the non-memorial effects emphasized here.

A8.2 Some methodology

In considering the behavioural effects of anxiolytic drugs, we were concerned to separate those related to specifically anxiolytic action from those representing side-effects. This task was simplified by the availability of at least some data on the behavioural effects of novel anxiolytic drugs that act on 5-HT_{1A} rather than GABA receptors and which hence do not share the muscle relaxant, anticonvulsant, or addictive properties of the classical anxiolytic drugs. The resulting description of the action of the anxiolytic drugs as a class covered the *common* effects of classical and novel anxiolytics, and specifically excluded any effects discrepant between the two groups of drugs (although we took into account a number of cases where only one group has been tested).

A similar problem arises when we search for the neurological site of action of these drugs by looking for an area which, when lesioned, produces similar effects. Destruction of a nucleus should produce behavioural effects similar to those of a drug which inactivates that nucleus. However, it will also produce 'side-effects' which result from damage to fibres of passage and to cells not affected by the drug. To a large extent, we have ignored this problem so far and will continue to do so until we come to deal, in Appendix 9, with the effects of specific neurotoxic lesions of subnuclei of the amygdala and the hippocampal formation.

Here we compare the behavioural effects of lesions to the hippocampal formation ('hippocampus' in the remainder of the appendix) with those of large lesions to the septal area ('septum'). Anatomy (see Appendix 4) tells us that the septum is both a major source of input to and a major relay of output from the hippocampus (Fig. 1.3). However, both structures make many other connections. Comparison of the effects of the two types of lesion delineates a 'septo-hippocampal syndrome', common to lesions of the two structures. This overlap provides a more coherent basis for comparison with the effects of anxiolytic drugs than would the necessarily wider range of behavioural effects of either type of lesion taken alone.

Our overview of the 'septo-hippocampal syndrome' covers a wide range of behavioural capacities. As such, it will provide not only a basis for comparison with the extensive anxiolytic profile of Appendix 1 but also a background for more detailed neural analysis. This background will be necessary as most of the more specific manipulations and measures (such as single-cell recording) which we considered in Appendices 5, 6, and 7 have been studied in only a

very limited range of tasks. Those studies can be viewed, then, as dissecting components of the septo-hippocampal syndrome defined here.

Many hundreds of experiments have examined the effects of septal or hippocampal lesions on behaviour in a wide variety of tasks. These experiments have been reviewed many times (e.g. Altman *et al*. 1973; Lubar and Numan 1973; Dickinson 1974; Ursin 1976; Grossman 1978; O'Keefe and Nadel 1978). In addition, as a companion to the first edition of this book, we made an explicit and detailed comparison of the septal and hippocampal syndromes in a review (Gray and McNaughton 1983) which required a complete re-evaluation of the literature on the effects of each of these lesions taken on its own. Where detailed references (or references to the first edition) are omitted from the present appendix, they can be found in this review paper.

Very few experiments have been concerned directly with the parallels between the effects of septal or hippocampal lesions, on the one hand, and anti-anxiety drug action on the other. There has been some cross-fertilization in the decade since the first edition of this book (e.g. Treit and Pesold 1990), but, by and large, the two lines of research have continued to go their separate ways. This is not surprising, since the theoretical preoccupations which have guided research in the two fields have been radically different. In consequence, for some kinds of behaviour we have information on drug effects but none on lesions, and for others the reverse is the case. There is also the problem that superficially similar experiments with drugs or lesions tend to be carried out in different laboratories, although, of course, direct comparisons within a single experiment would be much more informative. Experiments which administer anxiolytic drugs to lesioned animals would be still more informative (as has been shown by often surprising effects in the small number of experiments of this kind on the amygdala).

To aid comparison between drug and lesion effects, then, we will aggregate large numbers of experiments into general summary statements, as has already been done for the anxiolytic drugs, aiming always to assess underlying processes rather than superficial behaviour. In this way we hope to avoid the problems which would arise if we attempted direct experiment-by-experiment comparisons. We will also use the same format and section organization as in Appendix 1 and in the dorsal noradrenergic bundle section of Appendix 10 to facilitate comparison between the lesion and the drug effects.

As noted by Eichenbaum *et al*. (1994), there are dangers in 'straightforward tabulations' of large numbers of studies which derive conclusions based on the most common result for a particular class of experiment. 'Such an exercise inevitably leads to a sort of *psychoarithmetic* by which conclusions are made according to the simple majority of the data. In our view, this ignores the scientific rule that even single examples and counter examples within particular categories of paradigms are important and must be accounted for' (Eichenbaum *et al*. 1994, p. 458). With this, we agree. However, Eichenbaum *et al*. implicitly accuse us of falling into this error; yet, both in our original review (Gray and McNaughton 1983) and here, we have tried to subdivide groups of papers on the basis of key procedural features which control the variation in obtained results. We conclude, for example, that septo-hippocampal lesions do not affect simultaneous discriminations, not because this is a uniform finding but rather because we can demonstrate that special additional factors account for the discrepant cases. Where lumping and averaging has occurred, this is because we could find no obvious procedural detail to account for discrepancies between studies. Eichenbaum *et al*. also miss the point of the fact that, as they note, 'a mixture of data is observed within virtually every learning and memory task' (1994, p. 458). One cannot capture all the procedural variations which have given rise to the inconsistencies in the literature, since some of the critical features are so subtle that they are not reported. But, where the bulk of one class of task is affected by lesions and the bulk of a second class of task is not, it is reasonable to conclude that the difference between the two classes is directly or indirectly related to the source of the sensitivity to lesions.

There is, however, a danger here. It is tempting to see the procedural feature manipulated by the experimenter (usually driven by current theory) as giving rise to the observed differential sensitivity to lesion. Yet there may be other factors which, incidentally or necessarily, vary concomitantly and give rise to the observed pattern of results. This was elegantly demonstrated by Rawlins (1985), who showed that much of the variation in effects of hippocampal lesions between and within types of test could be accounted for by the extent to which temporal storage of information was required. Our theory will similarly conclude that the bulk of the results in the literature are determined, not by the paradigm officially imposed by the experimenter, but by other factors. Our predictions will overlap extensively with those of Rawlins, but we propose that the critical factor is, not time itself, but the degree to which specific elements of conflict have been introduced explicitly or implicitly. Thus, the pattern of results across tasks (and the fact that no task gives uniformly consistent results) arises because certain tasks are particularly likely to include such conflict, but mostly as a matter of high correlation rather than strict necessity.

Within each section, with its behavioural heading, we usually have three subsections dealing with septal lesions, hippocampal lesions, and the comparison between them. At the end of the appendix we compare the septo-hippocampal syndrome with the effects of anxiolytic drugs. Both this review and the comparison with anxiolytic drugs are summarized in Table 4.2 of the printed text.

A8.3 Responses elicited by appetitive stimuli

The most basic requirement, if we are to investigate higher-order processes, is that our treatments should not affect simple responses and simple learning. Neither septal nor hippocampal lesions impair basic appetitive responding. However, in the case of septal lesions there are numerous reports of increased water intake and some of increased

food intake. By contrast, hippocampal lesions do not generally alter either food or water intake (O'Keefe and Nadel 1978, Table A27). Given the latter lack of effect, it is unlikely that the features of the septo-hippocampal syndrome described below can be attributed to any simply change in reinforcement or appetitive behaviour. Medial septal lesions may increase and lateral septal lesions decrease sexual behaviour (Gogate *et al*. 1995).

Despite there being no gross changes in eating behaviour and particularly in amounts of food consumed in hippocampal animals, there does seem to be some disturbance in the perception of interoceptive cues which can give rise to hunger. Thus Davidson and Jarrard (1993) found that hippocampal-lesioned rats were impaired on an interoceptive discrimination based on food deprivation level; and the classic amnesic patient 'H.M. appear[s] unable to detect or process certain types of information arising from his internal milieu. For example, H.M. had great difficulty identifying his state of food deprivation/satiation. When asked to rate his degree of hunger or satiety on a numeric scale H.M. was as likely to rate himself hungry after a meal as he was immediately before eating' (Davidson and Jarrard 1993, p. 167).

A8.4 Responses elicited by 'neutral' and aversive stimuli

A great diversity of observations fall under this heading. The stimuli used have belonged to many modalities (auditory, visual, olfactory, thermal, tactile, nociceptive) and the response measures have been very diverse (the startle response, locomotion, the galvanic skin response or GSR, EEG changes, bar-pressing, etc.). Gray and McNaughton (1983) classified the reported effects of septal and hippocampal lesions according to each of these variables, and also according to the direction of change in motor behaviour produced by the lesions.

There appear to be no systematic differences due to stimulus modality or the particular response measure used, provided this constituted an active response.

Septal lesions

If one asks the question 'was reactivity to stimulation increased, decreased, or unchanged by septal lesions?', a complex picture emerges. Order can be obtained, however, if one takes into account the degree to which the stimulus-elicited response consists of increased or decreased movement. Thus, out of a dozen or so observations of increased reactivity to shock after septal lesions, all but two involved an increase in motor behaviour (jumping or general reactivity); out of five reports of no change, four measured the detection threshold for shock; and when Blanchard and Fial (1968) used crouching as a measure of reactivity to shock, this was decreased by septal lesions, that is the animal moved more. A similar pattern is obtained with other stimuli. These data suggest that the effect of septal lesions is simply to increase movement in response to stimulation. This is not the whole picture, however. For example, Holdstock (1970) reported a reduction in the GSR and in heart rate acceleration after septal lesions. Since movement is normally accompanied by an increase in heart rate, this latter finding is unlikely to be secondary to changes in the amount of movement. The GSR is reduced whether auditory, visual, or shock stimuli are used (Holdstock 1969, 1970).

Shock-induced fighting between pairs of rats is reliably increased by septal lesions. A more confused picture emerges with other methods of eliciting aggression, perhaps as a result of species and other procedural differences (Gray 1982, Section 6.15). It is possible that both aggression and the lack of it could reflect hyperdefensiveness (where extremes of defence include attack), rather than the 'hyper-reactivity' with which the well-known 'septal syndrome' is labelled (Fried 1972).

Hippocampal lesions

The few observations on hippocampal animals fit the same general pattern, with the exception of aggression. The flinch threshold to shock is unaltered, the jump threshold is lowered, and the amount of crouching is reduced (Blanchard and Fial 1968; Eichelmann 1971). Results of the very limited number of studies using other aversive stimuli are generally consistent with those of the experiments using shock. Hippocampal lesions usually reduce aggression, no matter how this is produced.

Septal and hippocampal lesions compared

It is clear that neither lesion reduces reactivity to shock. This will be important when we consider the effects of these lesions on avoidance behaviour (see Sagvolden 1976). If anything, the picture is of increased reactivity to shock. But this is likely to be secondary to a general increase in motor reactions occurring as much with neutral as with aversive stimuli. Such increases are consistent with loss of behavioural inhibition, but have no obvious relation to memory or its supposed subtypes.

The two lesions differ in their effect on shock-induced aggression (increased after septal lesions, probably decreased after hippocampal lesions; see, in particular, Eichelmann 1971). When shock is not used, both lesions produce increased motor responses to stimuli in a number of modalities.

A8.5 Rewarded behaviour

Septal lesions

In straight alleys with continuous reinforcement (CRF) schedules, septal lesions do not usually affect running speed. Increases in speed have been obtained but these are unreliable and can be restricted to only part of the alley (Henke 1977; Feldon and Gray 1979). The only experiment to find a decrease in speed used water reward (Wolfe *et al*.

1967). In operant chambers, by contrast, the majority of studies have found elevated response rates in septal animals trained on CRF.

Most experiments on simultaneous discrimination have been concerned with brightness or position discriminations, although there have been occasional studies of other dimensions. Septal lesions most often have no effect on these tasks. The exceptions consist about equally often of reports of impairment and improvement.

These exceptions appear to result from the presence of existing response tendencies which can decrease or increase the probability of the required response (Singh 1973; Chin *et al*. 1976, experiment 2) depending on the precise experimental arrangements. A further important factor is the presence of additional cues which, again, can compete with, or enhance, discrimination of the required stimuli (Liss and Lukaszewska 1966; Dabrowska and Drzewiecka 1975; Chin *et al*. 1976, experiment 3; Sikorsky *et al*. 1977; Donovick *et al*. 1978, 1979).

Hippocampal lesions

When CRF schedules are used, hippocampal lesions do not generally affect either running speed in the alley or response rates in the operant chamber. Two exceptional experiments, which found increased rates in operant chambers, were the only ones to use water reward (Rabe and Haddad 1968; Van Hartesveldt 1973). However, in more complicated experiments the lesioned rats may learn the task as easily as controls but using a different strategy (Buzsáki *et al*. 1980).

Discrimination learning has been a much more popular subject of investigation after hippocampal lesions than after septal lesions, and a wide variety of stimulus dimensions has been studied. In the majority of cases, hippocampal lesions have no effects.

Where a difference is observed (in about a third of the reports), this is always in the direction of a hippocampal impairment. But in most cases it is possible to identify a special factor. The most important of these is the existence of an initial bias which works against the solution of the problem. This can occur in two slightly different ways. First (conceptually closer to extinction, which as we shall see shows a deficit), lesioned animals are impaired on simultaneous discriminations if they start with a response preference opposed to the correct choice. Second (conceptually closer to reversal learning, which also shows a deficit), they are impaired if they have previously learned a discrimination different from the one on which they are currently tested (see Gray 1982, Section 6.19). In both cases, there is then an element of conflict inherent in the situation even when this was not intended by the experimenter.

One case of considerable theoretical interest is that hippocampal system damage appears to impair simultaneous odour discrimination while leaving intact successive odour discrimination (see Cohen and Eichenbaum 1993), the opposite of the pattern observed with other modalities.

The odour discrimination case does not appear to conform directly to either the ‘extinction’ or ‘reversal’ analogues we have just discussed. However, there are two important features of the simultaneous odour discrimination task. First, prior to any choice, the animal must make a series of sampling responses to two odour ports in order to compare the stimuli and hence choose between them. This would not be true in a typical simultaneous visual discrimination (but see below). Second, the organization of the ports is such that the two discriminanda intermingle. Both of these features might give rise to an element of conflict between alternatives not present (or not to such an extent) with non-olfactory stimuli. Consistent with this possibility, after overtraining so that performance was equivalent for lesioned and control subjects, control but not lesioned rats showed slow response latencies with a differentiation in latency depending on whether the S+ was presented in the left or the right port. This pattern of results suggest that the control animals ‘sample both ports and make some comparative judgement at the time of their response decision’, in contrast to lesioned rats who ‘made their choices without comparative judgements at the time of their response decision’ (Cohen and Eichenbaum 1993, p. 140; Eichenbaum *et al.* 1989). It is possible, therefore, that for the lesioned animals the task was not in fact a simultaneous discrimination. Rather, a failure to switch responses (or a failure to withhold responding when sampling a port) meant that only one stimulus was sampled on each trial, and that the effective discrimination was therefore successive. However, this discrimination still differs from the pure successive olfactory case discussed later (in which no lesion-induced deficit is observed), in that on approach to the two ports a mixed rather than a pure stimulus will be encountered.

Similar conclusions can be drawn from an experiment by Hu and Amsel (1995). They used a simultaneous brightness discrimination in which they also measured ‘vicarious trial and error’ behaviour, ‘the rat’s conflict-like behaviour before responding to a choice’ (Hu and Amsel 1995, p. 5506). In their task hippocampal lesions produced a deficit in discrimination performance (possibly because of the procedure they used to break position habits, possibly because of the extensive trial-and-error behaviour generated); but, more importantly, they found that the hippocampal animals showed low levels of vicarious trial-and-error behaviour (i.e. movement of the head from the S+ to the S– or vice versa within a trial) compared to controls, with the high control levels dropping to lesion levels as their performance reached an asymptote.

Another interesting case of impaired brightness discrimination was reported by Han and Livesey (1977) in an experiment testing Douglas’s (1967) hypothesis that hippocampal-lesioned animals have difficulty gating out negative stimuli. Rats were trained to choose the brighter of two patches of light under three conditions: with both lights turned off as soon as the animal made its response; with S+ remaining lit for a short time after the response;

and with S– remaining lit for a short time after the response. Hippocampals were impaired only in the enhanced S– condition, fitting Douglas's hypothesis.
A similar result, which may be particularly relevant in relation to studies of maze learning (see below), was obtained by Douglas *et al*. (1969). They used one positive cue accompanied by either one, two, or four negative cues. Hippocampal monkeys were impaired only when more than one negative cue was used.
There are some reports of impaired pattern discrimination in hippocampal animals where no special factor is discernible. However, even these may be due to difficulties in controlling the response rather than perceptual difficulties. For example, Olton (1972) reports a hippocampal impairment in discriminating between vertical and horizontal rectangles in a choice box, with the hippocampal animals forming a position habit. Despite the resultant choice deficit, the response latencies of the hippocampals discriminated between the positive and the negative stimuli. This suggests the animals were sensitive to the significance of the stimuli but could not use this information to terminate an incorrect response.

Septal and hippocampal lesions compared

The two lesions are alike in their general lack of effect on running in the alley. They may be similar in producing response increases in operant chambers with water reward. They differ in that septal, but not hippocampal, lesions elevate response rates on CRF schedules in operant chambers with a food reward.
The different effects observed in operant chambers as opposed to alleys may, of course, be attributable to the specific apparatus used. But alley experiments almost invariably use discrete trial procedures and measure the speed of traversing the alley once a response has been initiated, whereas operant chamber experiments almost invariably use free-operant procedures and measure the rate of response initiation. Thus, the critical difference may be between measures of response initiation and speed, respectively, as employed in these two types of apparatus. This interpretation would be consistent with the dissociation between choice and speed measures in Olton's (1972) experiment, described above.
Neither septal nor hippocampal lesions affect simultaneous discrimination learning in any general way. There are many reports of impairments after hippocampal lesions (although they are clearly in a minority compared to reports of no change) but hardly any after septal lesions. The most important factors giving rise to such impairments are the existence of a competing initial response bias or previously learned habit, and the existence of an excess of irrelevant stimuli or multiple negative cues.

A8.6 Responses elicited by frustrative non-reward

Septal lesions

In Appendix 1 we argued that anxiolytic drugs (in contrast to amygdala lesions, Appendix 2) do not impair responses to reward omission itself. This was in contrast to their effects on responses to stimuli which predict reward omission. The key evidence was the failure of the anxiolytics to alter the frustration effect in Amsel and Roussel's (1952) double runway. The same lack of effect is reported for septal lesions (Mabry and Peeler 1972; Henke 1977).
There is an operant analogue of the frustration effect, in which the reinforcer is omitted intermittently at the termination of the fixed interval of an otherwise standard FI (fixed interval) schedule. Normal animals respond faster after such reward omission than after reward. This 'FI omission effect' may be unaltered (Manning and McDonough 1974) or even increased (Poplawsky and Cohen 1977) by septal lesions.
Another phenomenon which has been linked to frustration (Gray and Smith 1969) is behavioural contrast (Reynolds 1961). This is an increase in response rate in the presence of S+ which occurs when an operant response is reinforced on a multiple schedule of which one component is either extinction or relatively low-density reinforcement. Like the frustration effect, behavioural contrast is unaffected by septal lesions (Dickinson 1973; Davison *et al*. 1975; Henke 1976; see also Gray 1982, p. 174).

Hippocampal lesions

These are reported to leave the double runway frustration effect unchanged (Swanson and Isaacson 1969) and to increase the FI omission effect (Manning and McDonough 1974). There appears to be no report of the effect of hippocampal lesions on behavioural contrast; but Gaffan (1973) found no effect of fornix lesions.

Septal and hippocampal lesions compared

Neither lesion alters the double runway frustration effect. This result may appear surprising, given the increases which the lesions produce in response to neutral and aversive stimuli (above) and the many similarities between reward omission and shock presentation (below). It tends, however, to confirm our conclusions that septal and hippocampal lesions do not affect the aversiveness of shock as such, but rather that they increase the behavioural response to any (neutral or aversive) sensory stimulus. It appears that the putative operant analogue of the frustration effect (the FI omission effect) may be increased by both lesions. However, interpretation of any increase is complicated by two issues. First, the FI omission effect may have nothing to do with frustration (Staddon 1970, 1972). Second, the observed changes in response rate may simply be a variant of the tendency of septal lesions, in particular, to increase responding in simple free-operant lever pressing while leaving simple running in the alley untouched.

A8.7 One-way active avoidance and escape

There is no consistent pattern of change with septal or hippocampal lesions in studies of skilled escape (Gray 1982, Section 6.4). However, there is a general impairment in one-way active avoidance with large septal lesions. This impairment may be secondary to the hyper-reactivity usually produced by such lesions. There is no clear impairment with hippocampal lesions and special factors may be operative. For example, in experiments by Olton and Isaacson (1969), a deficit appeared if avoidance training was preceded by pseudoconditioning trials in which the future CS was presented in random association with the shock, whereas an improvement was produced if avoidance training was preceded by 10 trials of fear conditioning (paired presentations of CS and shock). This latter result could be linked to the impairment produced by hippocampal lesions in conditioning of freezing to background cues (see below); such an impairment would remove a source of interference expected to be present in control animals.

A8.8 Classical conditioning of fear

Septal lesions

The evidence for a general impairment of classical conditioned responses with aversive unconditioned stimuli is slight. Experiments measuring responses such as heart rate, GSR, and nictitating membrane closure have been negative or at best mixed. Trace eyeblink conditioning is more reliably affected than simple eyeblink conditioning but, as with other memory paradigms, lesions affect only recently acquired conditioning and have no effect if they are made a month after training (Kim *et al.* 1995) or if a short delay is used (Moyer *et al.* 1990).

Off-the-baseline conditioned suppression (unaffected by anxiolytic drugs) does not appear to have been tested with septal lesions. However, Dickinson and Morris (1975) studied off-the-baseline conditioned acceleration. In this paradigm a CS, previously paired with shock, is presented to an animal engaged in active avoidance behaviour, and causes it to increase its response rate. Dickinson and Morris (1975) found no effect of septal lesions on conditioned acceleration.

With other responses there is some evidence for changes in fear conditioning. Conditioned freezing, for example, is fairly reliably reduced by septal lesions (Brady and Nauta 1953; Trafton 1967; Duncan 1971; Mattingley *et al.* 1979). Deficits in on-the-baseline conditioned suppression have also been reported, but only under limited conditions (Brady and Nauta 1955; Harvey *et al.* 1965; see also Gray 1982, Section 6.3). In a study in which shock was adjusted individually to produce fixed amounts of suppression, McNaughton (1990) found that septal-lesioned animals showed faster acquisition of suppression over the first four sessions when shock levels were being increased and that they then required greater levels of shock to maintain them at their asymptotic suppression ratio. This pattern of results suggests that, rather than a loss of the capacity to show behavioural inhibition as such, the septal animals showed an increase in the tendency (also shown by controls) to desuppress once initial acquisition is complete.

In one recent study (Sparks and Le Doux 1995) conditioned freezing to a tone was not affected by septal lesions, while conditioned freezing in the period prior to the tone (taken as a measure of conditioning to contextual cues) was increased.

Hippocampal lesions

There have been few studies of classical aversive conditioning after hippocampal lesions, and there is little evidence of any impairment. There are reports of reduced (Blanchard and Blanchard 1972) or more rapidly extinguished (Kaplan 1968) freezing and, at least with very small dorsal hippocampal lesions, an indication that conditioned freezing is only affected if there is a substantial interval between conditioning and testing (Kim *et al.* 1993). Of particular interest, Phillips and Le Doux (1994; see also Phillips and Le Doux 1995) showed a selective effect of hippocampal lesions on conditioning of freezing to contextual cues as opposed to explicit phasic stimuli. This lesion effect was not mirrored by any effect on conditioning of freezing to the same static cues when there was no phasic cue, and hence when the static cues are no longer contextual. (Phillips and Le Doux, themselves, refer to these latter as ‘foreground contextual’ cues, but this seems to us a distortion of the normal meaning of ‘context’.) Consistent with this failure to affect conditioned fear as such, McNish *et al.* (1997) found that, within the same animals and test situation, hippocampal lesions impaired conditioned ‘contextual’ freezing but had no effect on fear-potentiated startle, thus demonstrating a disruption ‘of the freezing response but not of contextual fear itself’ (McNish *et al.* 1997, p. 9353).

Off-the-baseline conditioned suppression has produced all three possible outcomes after hippocampal lesions: increased suppression (Antelman and Brown 1972), no change, and reduced suppression (Freeman *et al.* 1974). The discrepancy between the two findings reported by Freeman *et al.* (1974) was the result of differences in reward magnitude: reduced suppression with large but not small reward. The increased suppression reported by Antelman and Brown (1972) is likely to be an artefact. They tested conditioned suppression to the CS from a shuttle-box avoidance task after asymptotic learning had been reached. Since hippocampals learnt the task faster (4 versus 8 days for controls, see also below), they had fewer exposures to the CS.

On-the-baseline conditioned suppression has been tested in three studies. They reported no change (Solomon 1977; Garrud *et al.* 1984) and a non-significant trend to reduced suppression (Rickert *et al.* 1978) respectively. On-the-

baseline conditioned acceleration of Sidman avoidance (Micco and Schwartz 1971) was unaffected by hippocampal lesions.
Of particular importance to our final theoretical analysis, dorsal hippocampal lesions do not block fear-potentiated startle (McNish *et al.* 1997). In this case the evidence is in favour of this effect of anxiolytic drugs being produced by an action on the amygdala.

Septal and hippocampal lesions compared

Neither septal nor hippocampal lesions produce general reductions in conditioned fear. However, they both appear to reduce conditioned freezing under selected circumstances, particularly when the conditioning is to true contextual stimuli, i.e. stimuli which provide a background to the conditioning of freezing to an explicit phasic stimulus. Septal but not hippocampal lesions appear to reduce on-the-baseline conditioned suppression.

A8.9 Passive avoidance, two-way active avoidance, non-spatial active avoidance

The data on passive avoidance after hippocampal lesions have served as ground for a particularly fierce battle between defenders of the behavioural inhibition theories of hippocampal function (Altman *et al*. 1973) and defenders of spatial mapping theories (Black *et al.* 1977; O'Keefe and Nadel 1978, pp. 313–15). This is an important issue for the theory presented here and required extensive analysis in the first edition (Gray 1982, Section 6.2) which will not be reiterated here. This analysis reached somewhat different conclusions to those of O'Keefe and his collaborators, partly because it excluded, and they did not, experiments in which only partial lesions of the hippocampus were made, or in which afferents to or efferents from the hippocampus were lesioned. The differences between the behavioural effects of such lesions and those of large hippocampal lesions are discussed in Appendix 9.
The effects of septal and hippocampal lesions are very similar in passive avoidance tasks. Both lesions produce deficits across a range of tasks, with particularly pronounced effects in tasks in which anticipation of shock conflicts with locomotion towards a positive reinforcer. One experiment using fornix–fimbria lesions is of particular interest in this context. Okaichi and Okaichi (1994) tested rats in a running wheel *in which there was little spontaneous running*. They found no deficit in active avoidance or passive avoidance as such. However, in animals trained in active avoidance and then switched to passive avoidance, there was a transient passive avoidance deficit. Thus, when a prepotent response tendency was introduced (in this case by active avoidance training), a deficit was obtained; but when the animals had very little tendency to make the response (as when passive avoidance preceded active), then passive avoidance was intact.
With both septal and hippocampal lesions, the effects on punished drinking are more reliable with footshock than with shock to the mouth; these effects are reduced by prolonged prior experience of the shock, and by long intervals between shocks or between training and retention tests. Even with footshock, hippocampal lesions may have no effect on punished drinking while still having strong effects on place avoidance (Selden *et al*. 1991). (Note that this study found a double dissociation between hippocampal and amygdala lesions in producing these two effects.) Conversely, for both septal and hippocampal lesions, prolonged prior reward training increases the observed effects. In almost all of these cases, then, the effects of the lesions are greatest in those conditions in which there is the greatest conflict between the approach and avoidance responses. (Okaichi and Okaichi, however, interpret their data, described above, in terms of the presence or lack of a spatial element in the task.)
Of particular interest are the effects of septal lesions observed by Treit and Pesold 1990). They used the shock-probe burying test, which (unlike many of the other tests studied with lesions) has been shown to be a reliable screening test for anxiolytic drugs. Septal lesions totally eliminated burying behaviour, but had no effect on the tendency to approach the shock-prod as indexed by the number of shocks received. Treit and Pesold (1990, p. 370) comment: 'why septal lesions produce passive avoidance deficits in more traditional paradigms and not in the shock probe test is a question for further study. One possibility is that in the shock probe test the aversive stimulus comes from a spatially restricted and well defined object in the test environment, i.e. the wire-wrapped probe, whereas in more traditional passive avoidance tasks the shock is usually more diffusely localized . . . Although septal lesions have also been observed to produced passive avoidance deficits in tests where drinking is inhibited with mouth shocks.' It seems more likely that the critical factor is the level of approach–avoidance conflict generated. In the shock-probe test, the animal has no overwhelming reason to approach the prod and so inhibition of this tendency will be much easier than in the case of a thirsty rat approaching a water spout (especially if the shock is delivered to the feet in the latter test).
The effects of septal lesions appear more reliable than those of hippocampal lesions in tasks which involve a minimum of prior learning of the to-be-punished response. Septal lesions impair step-down and step-through passive avoidance whether or not the shock can be escaped. Hippocampal lesions only do so if the shock is escapable. This difference could be due to the hyper-reactivity of the septal animals, as we suggested for the effects on active avoidance.
As would be expected from the observed impairment in passive avoidance and inconsistent effects on active avoidance, both septal and hippocampal lesions produce highly reliable improvements in two-way active avoidance. In the case of septal lesions, Gray and McNaughton (1983) list 51 reports of this facilitation, making it one of the best replicated results in physiological psychology. The exceptions are similar for both lesions: lesioning after

acquisition of the task and the use of darkness as a safety signal both reduce the effects. In a direct comparison of the effects of the two lesions on Sidman avoidance in the shuttle-box, Capobianco *et al*. (1977) could not distinguish between them. This effect of the lesions is identical to that of anxiolytic drugs and opposite to that seen with amygdala lesions.

As was the case with anxiolytic drugs, the improvement in two-way active avoidance with septal and hippocampal lesions appears to be paralleled by improvements in non-spatial active avoidance, particularly Sidman avoidance (Gray 1982, Section 6.6).

A8.10 Conditioned taste aversion

In conditioned taste aversion, the animal is allowed to ingest a novel distinctively flavoured substance and then is made sick (by a poison such as lithium chloride or by X-ray irradiation). It subsequently shows reluctance to ingest substances flavoured in the same way. This paradigm has some of the features of conditioned fear and some of passive avoidance. But it has special features of its own (such as the long CS–UCS intervals which can be used) and so has been given a special section here.

Reduced taste aversion and more rapid extinction have been reported after hippocampal lesions (Miller *et al.* 1971, 1975; Thomka and Brown 1975; Krane *et al*. 1976; McFarland *et al*. 1978). In one report of retarded extinction (Kimble *et al*. 1979) the rats were given 5-days pre-exposure to the to-be-conditioned flavour. This could have generated latent inhibition in the control rats, which would be likely to be blocked by the lesions (see Section A8.15 below). In many reports, however, hippocampal lesions have been found to have no effect on taste aversion conditioning.

There appears to be no report of the effects of large septal lesions; but McGowan *et al*. (1969, 1972) reported *increased* aversion after both lateral and medial septal lesions. On the other hand, Siegel (1976) reported more rapid extinction after medial septal lesions, which parallels the hippocampal results.

A8.11 Reward omission and successive discrimination

Septal lesions

Septal lesions increase resistance to extinction of responses which have previously been rewarded on a CRF schedule, both in alleys and in operant chambers. They also increase resistance to satiation (Henke 1975), running speed being measured with goal-box baited but the animal sated. This parallel is consistent with the general behavioural similarities between reward omission and satiation (Morgan 1974).

It is possible to block the normal increase in resistance to extinction by interpolating a satiation test between acquisition and extinction (Henke 1975). Similarly, Rawlins (1977) found that rats with medial septal lesions tested in the alley after previous experience with non-reward failed to show increased resistance to extinction, although they did when tested before this experience. This may be the same kind of phenomenon that we encountered above, where we saw that the passive avoidance deficit normally produced by septal lesions disappears with repeated exposure to shock (e.g. Beatty *et al*. 1973). It also probably relates to the partial reinforcement extinction effect (see Appendix 9).

As would be expected from the above, septal lesions produce a highly reliable impairment in position reversal. Since they produce no impairment in simple position learning, this effect is specific to the reversal element.

Experiments on brightness reversal have produced a much more mixed picture. Schwartzbaum and Donovick (1968) and Dabrowska and Drzewiecka (1975) found no effect of the lesion on brightness reversal, even though position reversal was impaired in both experiments. These null results may have been due to the method of assessing performance. In later reports from Donovick's laboratory, there was no impairment as assessed by initial errors (i.e. errors on first entering each section of the maze), but there was an impairment as assessed by repeated entry into incorrect arms (Chin *et al*. 1976; Sikorsky *et al*. 1977).

Another experiment from Donovick's group investigated the effect of an irrelevant dimension on reversal (Donovick *et al*. 1978). In the acquisition phase of the experiment, rats learned a discrimination with black and right as perfectly correlated positive cues; they were then reversed to white positive with position irrelevant or to left positive with brightness irrelevant. Septals were impaired on both reversals, and to a greater extent on brightness than position reversal.

The results of experiments on successive discrimination in septal animals have been very mixed. There have been about equal numbers of reports of impairments or no change. In addition, three experiments actually obtained improved successive discrimination after septal lesions (Carlson and Vallante 1974; Carlson, Carter and Vallante 1972; Vom Saal *et al*. 1975); these all used olfactory or gustatory stimuli.

Intermittent schedules can be considered as varieties of successive discrimination in which time, as opposed to an explicit stimulus, provides the continuing cue for response inhibition. As would be expected from this parallel, septal lesions reduce the FI scallop (that is, the tendency of response rate to increase over the fixed interval), and the post-reinforcement pause on FR (fixed ratio) schedules. They also impair performance on DRL (differential reinforcement of low rates of response), shortening inter-response times, with a consequent loss of reinforcement. These effects can all be regarded as an impairment in behavioural inhibition, since response probability is in each case increased with either no increase or an actual loss of reinforcement. However, in contrast and unlike anxiolytic drugs (Feldon *et al*. 1979), septal lesions appear to increase the difference between rewarded and non-rewarded

responding on a single alternation schedule. A runway experiment of this kind (Carlson *et al*. 1972) used wet mash as a reward without controlling for the effects of odour. However, this potential artefact was absent in a second experiment (Carlson and Norman 1971) from the same laboratory, in which an operant conditioning procedure was used (reward being delivered only after response completion) at an intertrial interval (ITI) of 10 s. These conditions also reveal improvement in single alternation performance after hippocampal lesions (see below).

In two experiments (Beatty and Schwartzbaum 1968; Ross and Grossman 1975) septal lesions increased responding at the end of the FI interval as well as at the beginning. This pattern of change may indicate a general response-increasing effect rather than a specific loss of response inhibition; the same effect may be produced by anxiolytic drugs (Zhu and McNaughton 1995). The disruption in DRL performance can be overcome if the animal is very gradually shaped through successive increments in the DRL interval (De Noble and Caplan 1977) or if a cue, used to signal the end of the DRL interval, is gradually faded out of the procedure (Ellen *et al.* 1977). Both these procedures can be interpreted as reducing the requirement for behavioural inhibition.

There have been four experiments on the Crespi depression effect, that is, reduced running speed in the alley to a reward of a given size if the animal has previously been given a larger reward for the same response. Three found no effect of septal lesions (Pubols 1966; Flaherty and Hamilton 1971; Hammond and Thomas 1971). In the fourth (Flaherty *et al*. 1973) septal lesions reduced the depression effect if there was a 4-day interval between the pre- and post-shift exposures to reward, but not with a 1-day interval.

Hippocampal lesions

Hippocampal lesions give rise to increased resistance to extinction after CRF with as much regularity as do septal lesions. They also, again like septal lesions, produce resistance to satiation (Henke 1975).

The effects of hippocampal lesions on resistance to extinction apparently last through repeated testing to a greater extent than the comparable septal effects. Thus Henke and Bunnell (1971) found increased resistance to extinction in a second test after interpolated CRF reacquisition; and Schmaltz and Isaacson (1967) found the same effect in three such tests. Given these results, it is perhaps surprising that hippocampal lesions have minimal effects on progressive ratio schedules (in which the required ratio of operant responses to reinforcement is steadily increased).

The impairment produced by hippocampal lesions in position reversal is as reliable as that produced by septal lesions and is, again, not accompanied by impairment in the acquisition of the original position habit. Hippocampal-lesioned animals also show impairment in reversal when tested with a variety of other dimensions. However, as with septal lesions, impairments in brightness reversal are less substantial than impairments in position reversal (Gray 1982, Section 6.22). Object reversal in rhesus monkeys does not appear to be sensitive to the lesions (Mahut 1971; Jones and Mishkin 1972). This variation of sensitivity in reversal learning may be related to the results of Yee and Rawlins (1994). They found no deficit in delayed non-matching-to-sample with complex stimuli, but they demonstrated a deficit when simple stimuli were used.

The impairment seen in nictitating membrane response reversal occurs with cross-modal as well as intra-modal reversal (Berger and Orr 1983; Weikart and Berger 1986) and is accompanied by a change in response topography which does not occur with simpler tasks (Orr and Berger 1985). This latter result is important for our interpretation of the data on single-cell responses in the hippocampus (see Appendix 6).

The effects of hippocampal lesions on successive discrimination are much less variable than those of septal lesions, and there is a clear preponderance of impairments (see Gray 1982, Section 6.20). Probably the most interesting exception is that of olfactory successive discrimination (Eichenbaum *et al.* 1986, 1988; see Cohen and Eichenbaum 1993), which shows no deficit with hippocampal system damage despite a deficit in simultaneous discrimination with the same stimuli.

Three out of five experiments on FI performance have found rate increases after hippocampal lesions, but of these only one (Beatty and Schwartzbaum 1968) found a reduction in the FI scallop. However, DRL is as clearly impaired by hippocampal lesions as by septal lesions. Increases ‘in rate of pressing cannot be attributed to differences in food motivation . . . since subjects with hippocampal lesions did not eat more in the food consumption study’ which accompanied one such result (Jarrard 1965, p. 116).

Schmaltz and Isaacson (1966) showed that the impairment is only obtained if rats are trained on CRF before being shifted to DRL. This is the conventional procedure. If the rats were trained from the start on DRL, hippocampal lesions failed to produce a deficit. Braggio and Ellen (1976) showed that the hippocampal deficit could be ‘repaired’ by a period of training with a cue to signal the end of the DRL period; unlike the case of animals with septal lesions, for which the cue must be faded out gradually (Ellen *et al*. 1977), the cue can be removed abruptly.

The results of experiments on single alternation after hippocampal lesions have been very mixed. In the operant chamber, the important variables seem to be the inter-trial interval and the type of lever, retractable or non-retractable. With a retractable lever, hippocampals are inferior to controls at an ITI of 80 or 40 s, equivalent to controls at an ITI of 20 s, and better than controls at an ITI of 10 s (Means *et al*. 1970; Walker *et al*. 1970, 1972). With a non-retractable lever, a hippocampal impairment has been seen with ITIs ranging from 5 to 30 s (Warburton 1969; Walker and Means 1973; White 1974). In the alley, Franchina and Brown (1971) found a hippocampal impairment at a 20-s ITI. Under similar conditions, Cogan *et al*. (1976) found no effect of hippocampal lesions, although they did observe a deficit with a single alternating schedule of reward and delayed reward.

Of four experiments on the Crespi depression effect, two found no change (Kramarcy *et al*. 1973; Van Hartesveldt 1973); but Murphy and Brown (1970) and Franchina and Brown (1971) both report that this effect is absent after hippocampal lesions (see Gray 1982, p. 175).

Septal and hippocampal lesions compared

Septal and hippocampal lesions both cause increased resistance to extinction under a wide variety of conditions. Both lesions impair position and brightness reversals, but the latter appears to be somewhat less sensitive than the former. Both also tend to impair successive discriminations, hippocampal lesions with greater consistency than septal.

The most interesting exception to this last rule is that of olfactory successive discrimination and reversal, upon which fornix lesions have no effect, despite their capacity to impair simultaneous discrimination. We attributed their effect on simultaneous discrimination, above, to a loss of the vicarious trial-and-error behaviour which would be an important feature of the solution of the task by the control animals. Similarly, we should notice an important feature of the olfactory discrimination task compared to most successive discriminations. In this task 'the two odors in each problem were presented successively on separate trials, and the animal simply had to learn which odor was the one for which they should stay in the odor port to receive reward. Successful performance on each problem could be achieved by coming to appreciate that one of the odors was "good" and choosing to stay in the odor port for it, or that one of the odors was somehow undesirable and choosing not to stay around in the odor port upon its presentation. . . . In such a case, the representation guiding performance need *not* be flexible or promiscuous' (Cohen and Eichenbaum 1993; see also Eichenbaum *et al*. 1986). Furthermore, in contrast to conventional successive discriminations, the S– does not occur against the background of ongoing responding for reward.

In the case of reversal of the olfactory successive discrimination, control rats take longer to learn the reversal than to learn the original discrimination, while fornix-lesioned rats take fewer trials, but still show some slowing of learning relative to learning of a completely new pair of odours. This pattern of results suggests that the fornix-lesioned rats learned the original discrimination in a different way than did the controls, and that the rule used by the lesioned rats did not depend as greatly on the specific association of odour with reward learned by the controls.

Both septal and hippocampal lesions impair DRL performance in a way which is consistent with a loss of behavioural control by signals of non-reward. For septal but less so for hippocampal lesions, the same is true of FI and FR schedules. The septal effect on DRL is more robust than the hippocampal one. In the hippocampal case, the deficits appears to be accompanied by generally greater motor activity not confined to increased lever pressing, and there is evidence that the hippocampal rats treat the lever area as less aversive than do control rats in the early part of the interval (Acsádi *et al*. 1986).

Meck (1988) reports a particularly interesting result, in relation to the DRL deficits, on a peak-interval procedure. In this task 'after an intertrial interval a signal occurs and the rat is free to make a lever response at any time while the signal is present. On a random half of the trials, the first lever response after a fixed duration has elapsed (e.g. 20 s) terminates the signal and produces food reinforcement. On the remaining trials, no reinforcement is primed, and the signal continues for a relatively long time' (Meck 1988, p. 54). The non-rewarded trial allows analysis of the animal's capacity to tell when the reward would have occurred. Meck trained animals post-operatively on a 20-s peak interval followed by a 10-s one. 'Rats with sham operations were maximally responsive about the time that reinforcement was sometime made available (10 or 20 s) and showed an oscillation of successive peak-time values similar to biological feedback control systems. In contrast, rats with fimbria–fornix lesions were maximally responsive at a time about 20% earlier than the time that reinforcement was made available (8 or 16 s) and showed no control of successive peak time values' (Meck 1988, p. 54). If a gap of 5 s is inserted 10 s into the signal on a random selection of the no-reinforcement trials, control animals behave as if they are timing the whole of the interrupted interval (i.e. their peak responding occurs 5 s later than it would have relative to the start of the interval), while the lesioned animals respond as if the gap resets the interval (i.e. their peak responding occurs 15 s later than it would have, equating with 10 s of initial stimulus plus 5 s of gap). Note that in this case the lesioned rats are responding much later than the controls (Meck *et al.* 1984).

A key point about these results is that, while the lesioned rats showed premature responding within each schedule, they adjusted from the 20 s to the 10 s schedule. Nonetheless, their response to the gap suggests that their strategy for timing was quite different from that of the controls. It is also noteworthy that, despite their other differences, the conformation of their response rate curves was identical to that of controls, suggesting that, as in DRL, they knew the timing rule. Similarly, Dietrich *et al.* (1997) found that, when hippocampal lesions were made after acquisition of the peak-interval schedule, there was no effect, showing 'that the hippocampus is neither necessary for timing behaviour nor for the memory of temporal events' (Dietrich *et al.* 1997, p. 255).

Septal lesions appear to improve single alternation, while hippocampal lesions have mixed effects, with delay being one of the critical parameters.

The Crespi depression effect is inconsistently impaired after hippocampal lesions, but there is little evidence of any change after septal lesions.

A8.12 Maze learning

As we have noted, neither septal nor hippocampal lesions impair simple position discrimination in the T-maze. By contrast, both septal and hippocampal lesions impair spontaneous alternation.

There have not been as widespread investigations of maze learning after septal lesions as after hippocampal lesions, but these present a consistent picture of impairment: in the Lashley maze, Olton's radial-arm maze, and Maier's three-table 'reasoning' task; in spatial (left–right) alternation; and in Morris's water maze (the latter effect being observed even with excitotoxic lesions of the medial septum; Waite *et al*. 1994). The effect on left–right alternation contrasts with the improvement which septal lesions produce in single alternation (see above).

It is also of particular interest for our theory that extensive training can apparently remove the septal deficit on the radial-arm maze. This change occurs because the animals adopt a consistent pattern of arm choices. Recent analysis has shown that the implied inability to use flexible strategies produces a permanent impairment if flexibility is a requirement of the task (Janis *et al.* 1994), and that control rats appear to use a multiple-arm-sampling strategy, rather than a cognitive map strategy, in the conventional form of the task (Brown 1992). A radial-arm maze deficit is also not observed in hippocampal animals if each arm contains a unique visual pattern (Winocur 1982).

The spatial deficits after hippocampal lesions are now legendary (e.g. Thomas and Otis 1958; Kaada *et al*. 1961; O'Keefe and Nadel 1978, Table A20). The apparatus used to demonstrate the deficit has included Lashley, Hebb–Williams, and Dashiell mazes, Olton's radial-arm, multiple T, multiple U, and Maier's three-table task, as well as, most convincingly, Morris's water maze (Morris 1981, 1984). We analyse the specifically spatial nature of these deficits in more detail in Chapter 8. The link between the hippocampus and space has also been made by the fact that food-storing birds have relatively larger hippocampi than those which do not store (Krebs *et al*. 1989; Hampton *et al*. 1995; see also Sherry *et al.* 1992; Doupe 1994), and that the size of the mossy fibre system in the hippocampus of the mouse is correlated to spatial learning (see Schwegler and Crusio 1995, Table 2). (However, in the latter case, it is clear that similar correlations can also be found for non-spatial tasks.) 'By depriving hand-raised marsh tits of the opportunity to store food until different ages (day 59, 83 or 115), and measuring the volume of the hippocampus after different amounts of deprivation and/or experience, we showed that experience of storing and retrieving results in an increase in relative hippocampal volume and neuron number' (Clayton and Krebs 1995, see also for a general review; see also Clayton 1995).

Surprisingly, the results obtained with spatial alternation tasks are more mixed, although the majority report impairments after hippocampal lesions. An improvement in alternation with hippocampal lesions was reported by Stevens and Cowey (1972) using a visual cue to indicate the correct one of two levers to press; hippocampals were superior to controls only if this visual cue was spatially separate from the lever. A particularly surprising result was obtained by Jackson and Strong (1969). In their task, the basic response unit was a pair of lever presses, one left and then one right, with reward consequent on the second press. Hippocampals were superior at learning this basic unit, as well as more complicated sequences of the same general type.

Jarrard (1975) reported that hippocampal rats were unimpaired at spatial alternation even with delays of 4 min; but, if they ran in a running wheel during the interval, then an impairment was produced.

It appears, then, that both types of lesions produce impairments in specifically spatial, especially spatial navigation, tasks. There are several reports, surprising in this context, of hippocampal superiority in operant spatial alternation tasks. This finding could be related to the hippocampal superiority sometimes seen in operant single (go–no-go) alternation. O'Keefe and Nadel (1978, p. 325) suggest that this type of result reflects the ease with which hippocampal animals acquire and execute bar-pressing. If so, we would expect septal lesioned animals to do the same, since, if anything, operant over-responding is even more frequent in these. Unfortunately, neither spatial nor single alternation has been much studied in operant experiments after septal lesions.

An alternative possibility is suggested by the results of McDonald and White (1995) in the radial-arm maze. In this experiment rats were given one acquisition trial per day in which, on successive days, they were confined in either one food arm or in one non-food arm. On later testing with both arms available, fornix-lesioned animals showed superior learning of the spatial position of the rewarded arm. Thus, spatial learning in the absence of a requirement to choose between alternatives was intact and, indeed, improved. A second experiment gave rise to a contrasting set of results. In this, the animals were allowed to run in the maze to choose either the food arm or one of two alternative non-food arms (at 10 trials per day). Now fornix-lesioned animals showed a major deficit if the food and non-food arms were consistently adjacent to each other, but not if they were well separated. Thus, passive learning (in which minimal movement through the environment is required, akin to the situation in an operant chamber) was improved by fornix lesions, while active learning (involving greater self-initiated motion through the environment) was affected only when adjacent arms in the maze were one baited and the other not. This pattern of results suggests that it is not the spatiality of the discrimination as such that determines impairment, but the requirement to select between two closely adjacent goal locations.

A8.13 Responses elicited by novelty

This section concerns the distribution of activity in different parts of the environment. Description of observations of this kind suffers from the problem that the distinctions between measures of general activity, reactivity to stimulation, and exploration, respectively, are very cloudy, and all of these can be confounded by lesion-induced changes in affectivity. In particular, hippocampal lesions appear to produce a fairly general increase in activity as

such (while both septal and hippocampal lesions increase activity in the shuttle-box without increasing it in the running wheel; Gray 1982, Section 6.11; Gray and McNaughton 1983).
Septal lesions reduce defecation in the open field, as well as in the runway and the shuttle-box during avoidance training. This can be viewed as resulting from a reduction in fear (Gray 1971, 1979). Hippocampal lesions, however, do not affect defecation or other similar putative measures of fear such as urination and wall clinging. The sole indications of reduced fear after hippocampal lesions are the reports by Jarrard (1968) of increased eating in the open field and by Krane *et al*. (1976) of reduced neophobia.
The effects of septal lesions on ambulation in the open field are complex, depending on number of test sessions, length of test session, etc. However, as argued by Gray (1982, p. 149) the pattern of results is that which would be predicted if septal lesions decreased an animal's score on Whimbey and Denenberg's (1967) factor of 'emotionality', i.e. fearfulness (for a recent genetic analysis of this factor, see Flint *et al*. 1995). By contrast, rearing is reliably reduced by septal lesions.
Of particular interest for the comparison with anxiolytic drugs is a study by Treit and Pesold (1990). They tested the effects of septal lesions in the elevated plus maze, which has become a very popular test of anxiolytic drug action (despite its tendency not to show effects with buspirone). These authors found that large posteriorly-placed septal lesions produced an 'anxiolytic' profile in this test. However, more anterior lesions (which on the histology they present could well have eliminated theta rhythm) did not produce this effect. In a similar vein Dringenberg *et al*. (in press) found no effect of hippocampal lesions in the black–white box; and Treit and Menard (1997) found no effect of hippocampal lesions on defensive burying, although there is an effect of septal lesions on the latter (Treit *et al*. 1998).
Hippocampal lesions produce a general increase in ambulation but decreased rearing in only two out of four experiments (Strong and Jackson 1970; Murphy *et al*. 1975; Köhler 1976), and fornix–fimbria lesions have been reported to increase rearing (Whishaw *et al*. 1994). Whishaw *et al*. (1994) have attributed both the increased rearing and the increased ambulation which they observed to a shift in the 'mobility gradient' of the rats; that is, the main cause of increases in both measures appeared to lie in a reduced tendency for the lesioned animals to remain motionless rather than any increase in the speed or distance of travel on individual trips. Although Whishaw *et al*. (1994) do not say this, their results are consistent with a loss of behavioural inhibition, and (as suggested by the Blanchards in relation to anxiolytic drugs) could be due to an effective reduction in anxiety against the background of the more defensive end of the U-shaped relationship between rearing and defensive distance (see Chapter 2). This account might also apply to the results reported by Köhler *et al*. (1978), who exposed their rats to 60 dB white noise and found inverted-U-shaped relationships with time for the activity measures in their control but not lesioned animals.
Social interaction has not been tested after septal or hippocampal lesions with the degree of formality provided for the anxiolytic drugs by File's (File and Hyde 1978) social interaction test. Septal lesions increase social contact in a variety of species and situations, but there is little evidence in relation to hippocampal lesions.
The two lesions are alike in reducing spontaneous alternation (see Section 8.12 on maze learning) and other measures of the animal's tendency to explore its environment.

A8.14 Habituation

One process which adds complexity to studies of exploration and reactions to novelty is habituation. The reaction to novelty itself is measured against a background of decreasing response due to habituation. In this sense, habituation can be viewed as sharing with extinction and satiation the loss of a response as a result of removal of a reinforcing value. However, most formal analyses of habituation view it as one of the simplest forms of learning and, like simple associative conditioning and sensitization, it can be demonstrated at single synapses. Given the lack of effect of septal and hippocampal lesions on moderately complex classical and instrumental conditioning, one might expect them to have no effect on habituation. This is not the case.

Septal lesions

Habituation has been studied in a variety of situations. Generally it has been reported to be retarded by septal lesions. In most cases, this results in greater vigour of motor activity (Gray and McNaughton 1983), as is the case for the one experiment which obtained more rapid habituation. In this case (Raphelson *et al*. 1965) the response measured was *suppression* of running in the alley. However, changes in motor response alone do not provide the basis for all results. De Noble and Caplan (1977) trained rats to bar-press for food on either a DRL or a DRH (differential reinforcement of high rates of response) schedule, and then superimposed free food on a variable time schedule. This gave rise to rate acceleration in the DRL condition, but rate deceleration in the DRH condition. Despite the opposite change in motor performance in the two cases, septal lesions blocked habituation in both cases.

Hippocampal lesions

Retarded habituation is equally apparent after hippocampal lesions. Once again, most cases involved increased motor behaviour, and the most obvious exceptions (Mitchell *et al.* 1993; Köhler 1976) involved suppression (of drinking). Once again, also, there are cases of retarded habituation even when this involved reduced motor activity (Douglas and Pribram 1969; Gustafson and Koenig 1979).

An interesting analysis of habituation to a novel environment was carried out by Mitchell *et al*. (1993). They reasoned that 'in the frequently used open-field task . . . the absence of a choice between novel and familiar alternatives . . . precludes meaningful assessment of neotic preference' (Mitchell *et al*. 1993, p. 194). They, therefore, tested animals for their tendency to enter and explore a novel straight alley from a nest box in which the animals had lived for the previous 24 hours. On several measures (including rearing), hippocampal-lesioned animals showed no differences in either neophobia or habituation during a 1-hour session. However, their pattern of exploration was not like controls in that they made a larger number of shorter visits to the novel environment (for an equal total amount of time exploring). 'The hippocampal lesioned rats were not simply more active than controls; they typically showed a characteristic sequence of stereotyped behaviours as they shuttled between the familiar nest box and the novel alley. In the typical case, animals with more extensive lesions would repeatedly emerge from the nest box, traverse the alley, rear off the floor for a moment, then rapidly return to the nest box. Moreover, for any given hippocampal lesioned animal, the details of this emergence pattern were remarkably consistent across trials: If such an animal stopped in the middle of the alley on a given visit, it almost always stopped at the same place on preceding or subsequent visits' (Mitchell *et al*. 1993, p. 199).

Septal and hippocampal lesions compared

Both lesions generally retard habituation, with some occasional exceptions when the response being measured is itself a response suppression. Some key failures (e.g. with habituation of drinking neophobia), coupled with the general pattern of results described above, suggest that the lesions do not affect habituation directly (which is in any case inherently unlikely, given that this can occur in monosynaptic systems) but rather some other process, for example an increase in response stereotypy, which affects the measured rate of habituation.

A8.15 Conditioned inhibition, latent inhibition, blocking

Habituation is one of the simplest ways of robbing a stimulus of its capacity to elicit a response. Classical conditioning provides us with a variety of other ways which are slightly more complicated, but allow more arbitrary choice of stimulus and response.

For example, Lockhart and Moore (1975) and Powell *et al*. (1976) used a differential conditioning paradigm to study the rabbit's nictitating membrane response after septal lesions. In both experiments, the lesion disinhibited response to the CS–. The results with hippocampal lesions are more murky, since Solomon (1977) saw no change in Pavlovian conditioned inhibition, whereas Micco and Schwartz (1971) found impaired conditioned inhibition of a Sidman avoidance schedule.

Similar results can be obtained with other paradigms in which a stimulus loses its capacity to elicit a response. Of particular interest is work on latent inhibition, that is the weakening of the capacity of a conditioned stimulus (CS) to enter into association with an unconditioned stimulus (UCS) if it has first been repeatedly presented without reinforcement ('pre-exposure') prior to its use in a conditioning experiment (Lubow and Moore 1959; Lubow 1997). Early studies reported impairments in latent inhibition after both septal and hippocampal lesions (Ackil *et al*. 1969; Weiss *et al*. 1974; Solomon and Moore 1975; see brief review in introduction to Schmajuk *et al.* 1994). More recent work has concentrated on the effects of hippocampal lesions, with widely diverse results. These appear to depend (at least) upon the nature of the lesion (large lesions of the hippocampal formation versus selective excitotoxic lesions of the hippocampus proper), whether or not there is a context shift between pre-exposure and conditioning, and a number of procedural details, including the total time of CS pre-exposure (Buhusi *et al*. 1998). Table A8.1, reproduced from Buhusi *et al*. (1998), summarizes this diversity of findings. Using a neural network model of latent inhibition proposed by Schmajuk *et al*. (1994), together with specific hypotheses as to the effects within that model of lesions of the hippocampus proper and the wider hippocampal formation respectively, Buhusi *et al*. (1998) were able to simulate the great majority of the effects summarized in Table A8.1 (see their article for details). The assumptions used were that: (1) lesions of the hippocampus proper eliminate the capacity to modify associations between different CSs, which are themselves (according to the model) computed in the neocortex; and (2) lesions of the wider hippocampal formation in addition eliminate the capacity to compute the 'aggregate prediction' of the UCS, that is taking into account associations between all potential CSs and the context, on the one hand, and the UCS, on the other. With these assumptions, together with parametric computation of the effects within the model of the specific procedural details of each experiment, Buhusi *et al*. (1998) show that it is possible to account for all the effects (varying from blockade to enhancement of latent inhibition) summarized in Table A8.1. It remains for future computational analysis to determine whether the assumptions used in these simulations as to the roles played in latent inhibition by the hippocampus proper and the wider hippocampal formation are compatible with the more general assumptions used in this book to account for hippocampal involvement across a much wider range of phenomena.

Comparison Between Experimental Data and Simulations Obtained with the Schmajuk, Lam and Gray (SLG: 1996) Model

(From; Buhusi C V, Gray J A & Schmajuk N A. Perplexing effects of hippocampal lesions on latent inhibition: a neural network solution. Behavioural Neuroscience 1998 112, 316-351.

Reference	Lesion	Lesion	Paradigm	Procedure	CS	Total	Result	Model

	Method	Type				Time(s) of Preexposure (ms)		
Ackil et al (1969)	Aspiration	HFL	Avoidance	BS	Tone	150	Impaired LI	Impaired LI
Solomon & Moore (1975)	Aspiration	HFL	Eyeblink	BS	Tone	225	Impaired LI	Impaired LI
McFarland et al (1978)	Electrolytic	HFL	Taste Aversion	BS	Flavor	30	Impaired LI	Impaired LI
Schmajuk et al (1994)	Aspiration	HFL	Eyeblink	BS	Tone	225	Impaired LI	Impaired LI
Kaye & Pearce (1987a, 1987b)	Electrolytic	HFL	Foodcup entry	BS	Light	720	Impaired LI	Impaired LI
Kaye & Pearce (1987a)	Electrolytic	HFL	Foodcup entry	BS	Light	720	No OR decrease	Small OR decrease
Honey & Good (1993)	Ibotenic	HPL	Foodcup entry	BS	Tone	720	Preserved LI	Preserved LI
Han et al (1995)	Ibotenic	HPL	Foodcup entry	WS	Light	400	Impaired LI	Impaired LI
Honey & Good (1993)	Ibotenic	HPL	Foodcup entry	WX	Tone	720	No CX effect	No CX effec
Reilly, Harley et al (1993)	Ibotenic	HPL	Taste aversion	BW	Flavor	7,200	Facilitated LI	Facilitated L
Purves et al (1995)	Electrolytic	HFL	Taste aversion	WW	Flavor	7,200	Facilitated LI	Facilitated L
Gallo & Candido (1995)	Electrolytic	HFL	Taste aversion	BW	Flavor	900/5,400	Preserved LI	Facilitated L
Christiansen & Schmajuk (1993)	Aspiration + Haloperidol	HFL	Eyeblink	BS	Tone	225	Restored LI	Restored LI
Yee et al (1995)	NMDA[a] + Haloperidol	HFL	CER	WS	Light	450	Restored LI	Restored LI

Note: CS = conditioned stimulus: HFL = hippocampal formation lesion: induced BS = between-subject procedure: LI – latent inhibition: OR = orienting response: HPL = hippocampus proper lesion: WS = within-subject procedure: WX = within-subject procedure with context (CX) change: BW = between-subject procedure with interspersed water presentations: WW = within-subject procedure with interspersed water presentations: CER = conditioned emotional response.

[a]N-methyl-D-aspartate lesions of the subiculum/entorhinal cortex.

Another way to rob a stimulus of the capacity to control behaviour is to pair it with a UCS only in the presence of an additional, previously conditioned, CS for the same UCS. This is Kamin's (1968) 'blocking' effect. The blocking effect can be eliminated by hippocampal lesions (Solomon 1977; Rickert *et al*. 1978) even with taste aversion conditioning in animals which show no loss of latent inhibition (Gallo and Cándido 1995). However, both blocking and the related phenomenon of overshadowing are sometimes left intact (Garrud *et al*. 1984), and it seems likely that critical procedural differences, influencing, for example, the extent of orienting responses to the stimuli used, determine the result (see, for example, discussion in Garrud *et al*. 1984).

Septal lesions have not been tested on blocking paradigms using a classical conditioning procedure. However, Donovick *et al*. (1979) reported an experiment in which rats were trained on a discrimination with one dimension relevant (brightness or position) in stage 1; then trained with both dimensions relevant and perfectly correlated in stage 2; and finally tested, in stage 3, with either the original positive cue or the positive cue that had been added in stage 2. Animals with septal lesions were no different from controls in stage 3 when tested with the original positive cue, but they were impaired when tested with the cue added in stage 2. (This result is very similar to the effect of sodium amylobarbitone described by McGonigle *et al.* 1967.) Thus septal lesions prevented the added redundant cue from gaining control of behaviour.

In all of these cases (loss of conditioned inhibition, loss of latent inhibition, disruption of the blocking effect), the lesioned animals continue to respond actively to a stimulus which has lost its effectiveness for the normal animal. This general kind of result, like the failure of habituation, is predicted by theories which emphasize the inhibitory functions of the septo-hippocampal system (see especially Douglas 1967).

A8.16 Distraction experiments

This section is concerned with the effects of novel stimuli presented to animals while they are engaged in other behaviour. The amount of novelty involved is therefore limited, in comparison to the previous sections where the entire environment is likely to have been novel. In such experiments, one may measure either the effect of the new stimulus in distracting the animal away from its ongoing behaviour or the direct response to the new stimulus.

Septal lesions

There have been few experiments of this kind with septal animals, and there appears to be no report of the effect of the ongoing behaviour on the direct response to the distractor. In experiments where the response to the distractor is measured by a change in the baseline (distracted) behaviour, septal lesions can increase or decrease this response or leave it unchanged. As with other cases of mixed septal results, here again the critical factor appears to be the direction of change in motor behaviour: this is always increased by septal lesions.

A particularly instructive pattern of results was obtained by P. E. Gray (1976). He trained rats to bar-press for sucrose on an FI schedule and then presented a distractor early or late in the fixed interval. Presented early, when bar-pressing was most inhibited, the distractor increased bar-pressing: and this effect was greater in septal animals. Presented late during the interval, the distractor decreased bar-pressing rate; this effect was unchanged by septal lesions (see also De Noble and Caplan 1977). In other experiments (Harvey *et al*. 1965; Schwartzbaum and Kreinick 1974) a distractor reduced bar-pressing rate in controls and this effect was smaller in septal animals. Thus the only generalization which fits all the data is that septal lesions tend to increase motor responding.

Hippocampal lesions

Observations of changes in the baseline behaviour in hippocampal animals show more clearly the same picture as that seen after septal lesions. There have been many reports of reduced distraction after hippocampal lesions, but in every case this involves increased motor activity.

There are also several observations of the response directly elicited by the distractor. Five out of nine of these show a *reduced* response to the novel stimulus. This is the direct opposite of the result obtained when the animal is not engaged in other behaviour at the time of presentation of the novel stimulus (see previous section). This pattern of results suggests that the confused picture otherwise seen when non-motor response to stimuli have been measured (Gray and McNaughton 1983) might appear more orderly if the animal's behaviour at the time of measurement was better recorded or controlled (see also Gray 1982, p. 146); and it again fits with the view that a critical feature of the situation is the extent to which it provokes conflicting response tendencies.

Septal and hippocampal lesions compared

Reduced distraction has been reported more frequently after hippocampal than septal lesions. However, this probably does not represent a difference between the syndromes, since in all cases the results appear to fit the general rule that motor activity is increased. This interpretation gains support from the fact that changes in distraction are easily seen if the baseline response has a large motor element (bar-pressing, running), whereas a licking baseline is relatively refractory to change after either septal (Weiss *et al.* 1974) or hippocampal (Gustafson 1975) lesions.

A8.17 Counter-conditioning and toughening up

Septal lesions

Septal lesions block the partial reinforcement extinction effect (PREE; described in some detail in the previous appendix) in the alley with both short and long intertrial intervals (Gray 1982, Section 6.17); but long training (96 trials) with a short intertrial interval can eliminate the effect (Henke 1974). The lesion appears simply to delay rather than eliminate the occurrence of the normal partial reinforcement effect, since Henke's (1974) partially reinforced group developed, albeit later than controls, the variability in running times which is characteristic of acquisition on this schedule (Amsel 1962).

Septal lesions produce increased resistance to extinction in operant chambers with acquisition under CRF, FR, FI, VI (variable interval), or DRL schedules. This increased resistance to extinction can be blocked by an interpolated satiation test (Henke 1975), and the increased responding on a progressive ratio schedule is not seen on a second occasion of testing (Rawlins 1977), paralleling in both cases effects seen in the alley. However, lateral septal lesions, which block the PREE in the alley, do not block counterconditioning in a classical conditioning procedure (McNaughton and Gray 1983). Fallon and Donovick (1970) showed that septal resistance to extinction could be converted into a reduction in resistance if the drive was changed from food to water deprivation between acquisition and extinction. This results suggests that the usual septal effect is closely tied to the context in which the response is acquired (see also Winocur and Olds' 1978 experiments with reversal learning).

Hippocampal lesions

Hippocampal lesions reduce the PREE in the alley, but this effect may be slightly less robust than with septal lesions (see Rawlins *et al*. 1980 and discussion therein). Resistance to extinction is observed after operant chamber training on CRF, FR, and FI, but not DRL schedules. It also survives repeated reacquisition and extinction (Schmaltz and Isaacson 1967; Henke and Bunnell 1971).

Septal and hippocampal lesions compared

Both lesions abolish the PREE in the alley. Since this effect of the lesions combines a reduction in responding in partially reinforced rats with an increase in responding in CRF-trained rats, increased motor activity cannot explain the result. In the septal case, the lesion effect is not the result of a block of the basic process of counterconditioning (McNaughton and Gray 1983).

There is some suggestion (again from data only available in the septal case) that a key factor in determining resistance to extinction may be the context of learning. We consider 'contextual' theories of hippocampal function in Chapter 6, but here we note two features. First, the evidence for context relates to internal motivational cues, and we have already suggested that perception of these may be impaired (see Section A8.3). Second, more general contextual features are unlikely to reflect specifically spatial aspects of reward location. If this were so, we would expect the effects of lesions to be more marked, the further the animal is from the goal (on the grounds that, close to the goal, simple proximal cues as opposed to spatial navigation would be sufficient). Yet Rawlins *et al.* (1980) found that both the increased resistance to extinction in CRF-trained animals and the decreased resistance in partially reinforced animals were similar in all parts of the alley (see also Winocur and Bindra 1976).

A8.18 Conditional, delayed, and configural discriminations and related memory tasks

We give detailed consideration to these tasks in Chapter 8. However, for the sake of comparison with anxiolytic drug effects we note here that both conditional discriminations and delayed matching-to-sample are impaired by hippocampal lesions. Introduction of a delay is a frequent method of inducing a hippocampal deficit in a variety of tasks. However, delay per se is not the critical feature, as a number of variations in the precise procedure used can unmask or eliminate lesion effects

A8.19 Comparison between the septal, hippocampal, and anxiolytic syndromes

Table 4.2 in the printed text summarizes the septal and hippocampal syndromes as they have been described in this appendix, and also by Gray and McNaughton (1983) and in Chapter 6 of the first edition of the book. It should be noted that: (a) this summary is based on large lesions of the septum and relatively large lesions of the hippocampus, both of which are likely to have interfered with fibres of passage; (b) our major concern here is to define a 'septo-hippocampal syndrome' which is based on the overall points of agreement between the two types of lesion; and (c) we have excluded the extensive literature analysing the involvement of the hippocampus in memory, because there are few equivalent data on anxiolytic drugs. This omission is redressed in Chapter 8.

Our reasons for comparing septal with hippocampal lesions are that there are extensive interconnections between the two areas (described in detail in Appendix 4); and that the septum controls hippocampal theta, through which we postulate that anxiolytic drugs produce critical behavioural effects. It is, therefore, not surprising that the septal and hippocampal syndromes should resemble each other to some extent. However, in view of the pitfalls of the lesion technique and the extensive connections of the hippocampus to the cortex, it is perhaps surprising that they resemble each other so closely. We have commented on the specific resemblances in detail above. The third column of Table 4.2 identifies the 'septo-hippocampal syndrome' which results. The cases where septal and hippocampal lesions have different effects from each other are discussed in detail in Gray (1982, Section 6.24); here we are concerned only with the cases where they are concordant.

Of course, the 'septo-hippocampal syndrome' so defined may be due in part to fortuitous concurrence, or to interruption by septal lesions of hippocampal afferents or efferents which do not relay in the septum (as has been shown for the effects on latent inhibition and the PREE—Appendix 9). However, for our present purposes, this syndrome is only a stepping stone to more detailed analysis and a high degree of anatomical precision is not essential. The same is true of our behavioural categories. Throughout our review we have found that the presence or absence of a deficit can be produced with any nominal behavioural task depending on quite detailed features of the procedure or of the animals' inherent response tendencies. Nonetheless, in the absence of similarly detailed analysis of all the treatments to be compared, we must take a coarse-grained average and compare groups of tasks in terms of whether an effect or a lack of effect is most likely to be observed for that particular type of task.

The anatomical interconnections between the septal area and the hippocampus provide strong a priori grounds for expecting the septal and hippocampal syndromes to resemble each other, irrespective of any particular theory of their behavioural functions. However, there are no a priori grounds for expecting any similarity between the septo-hippocampal syndrome and the effects of anxiolytic drugs. But it is clear when we compare the third and fourth columns of Table 4.2 that the concordance here is also remarkably strong.

Since the value of science is often held to reside in its predictive power, it should be noted that the overwhelming majority of the data which support this concordance in Table 4.2 were collected *after* the original proposal of the links between anxiolytics and septal and hippocampal lesions (Gray 1970). This is the foundation of our theory and has withstood, and indeed been strengthened by, three decades of research.

The degree of concordance between the anxiolytic and septo-hippocampal syndromes is particularly surprising in the case of benzodiazepines because their receptors are widely distributed throughout the brain (and areas such as the pineal). Their muscle relaxant effect, at least, might have been expected to produce many effects which decreased the concordance with the septo-hippocampal syndrome. However, where it has been tested in the tasks we have considered, buspirone almost invariably shares the effects of the benzodiazepines and hence of septal and hippocampal lesions. This suggests that the battery of tests we have reviewed are not, by and large, sensitive to the

muscle relaxant, anticonvulsant, hypnotic, depressant, or addictive properties of the benzodiazepines, since buspirone's side-effects do not include any of these properties.

The striking feature of Table 4.2 is that, with few exceptions, *wherever* the effects of septal and hippocampal lesions are the same as each other, the effects of the anxiolytic drugs are the same again (although there are many cases where relevant data are simply not available and the magnitude of the drug effect is usually smaller). The main exception is aggressive behaviour.

Although the effects of the drugs on aggression are very variable (Gray 1977), there is reason to suppose that there is a real divergence on this measure between their effects and those of septal and hippocampal lesions. Both septal and hippocampal lesions usually reduce aggression if this is induced by means other than shock (usually by isolating animals). When shock is not used, all the classical anxiolytic drugs have been reported to increase aggression, particularly at low doses. As the blank spaces of Table 4.2 are filled in, we may expect more cases like this, but for the moment, surprisingly, aggression may be the only major case of divergence of the anxiolytics from the septo-hippocampal syndrome (although many more data on the 5-HT_{1A} agonists would be welcome).

There are also few discrepancies in the reverse direction. Those that exist can be attributed to one effect of anxiolytic drugs which appears to be missing from the septo-hippocampal syndrome and which is of particular importance for the account of the symptoms and syndromes of anxiety proposed in Chapter 11. The drugs impair all three postulated outputs of the behavioural inhibition system: behavioural inhibition itself, increased attention to novel stimuli, and increased level of arousal. The septo-hippocampal syndrome includes the first two of these, but there is no evidence that lesions of the septo-hippocampal system lower the level of arousal.

Two experiments suggest more definitely that they do not have this effect: those by Dickinson (1975) and Raphelson *et al*. (1965). These are discussed in detail in Chapter 6 of the printed text (pp. 116–17), to which the reader is referred. A similar account may also apply to behavioural contrast, which is reduced by anxiolytics but (as noted above) is immune to the effects of septal or fornix lesions. On the assumption that this phenomenon results from conditioned frustration, it is likely to reflect an increment in the level of arousal (Gray and Smith 1969). But perhaps the most significant result in this category is the fact that hippocampal lesions do not reduce fear-potentiated startle. The evidence (Appendix 2) strongly suggests that this effect of the anxiolytic drugs (including buspirone) is achieved through a direct action on the amygdala. If this is so, the same analysis may apply to all of the cases in which anxiolytics affect arousal and septo-hippocampal damage does not.

Overall, then, inspection of Table 4.2 shows that the similarities in terms of decreases, increases, and, particularly important for theoretical analysis, lack of effect cover a very wide range of behaviour. The lesions share the pattern of the drug's effects in tasks that seem to rule out any general effects on memory as opposed to emotion (e.g. passive avoidance compared to one-way active avoidance). Similarly, the drugs share the lesions' effects on tasks which seem to involve memory more than emotion (water maze, delayed conditional discrimination). In addition, there is one similarity which is less well established: under certain conditions all three treatments reduce the animal's capacity to attend to and take in information about novel features of its environment. Overall, the similarities between the treatments are formidable and offer strong support for the hypothesis that the anxiolytic drugs produce at least some of their effects by impairing the functioning of the septo-hippocampal system, directly or indirectly.

A8.20 Conclusion

At this stage of our analysis, then, we conclude that the effects of the anxiolytic drugs are very well matched by the effects of septo-hippocampal lesions. Indeed, given the likely side-effects of each of the treatments used, the match is quite surprisingly good.

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