11

Maintenance behaviours

IN discussing the effects of hippocampal damage upon various learning tasks we bypassed the question of the more general effects of brain damage upon such things as eating, drinking, and so on. We have assumed that none of these maintenance behaviours nor, for that matter, basic sensory and motor processes, are critically dependent upon the hippocampus. In our treatment of fear-based behaviour and aggression (see pp. 302-15) we concluded that any influence of hippocampal damage was indirect. In the present chapter we shall consider two broad areas of lesion effects: (1) influences upon drinking, eating, sexual, maternal, and social behaviours; (2) influences upon sensory, motor, autonomic, and endocrine function.

While the lesion data relating to these behaviours are reasonably clear, considerable data generated in studies using electrical or chemical stimulation techniques point to other, less clear-cut, conclusions. In the present chapter we largely restrict our discussion to the lesion data. Studies employing stimulation will be discussed in the following chapter.

11.1 Food and water intake, and related behaviours

In general, hippocampal lesions do not affect food or water intake in animals under either ad libitum (free access) or deprivation conditions (see Table A27).* Intake of sucrose, quinine water, and salt water (after adrenalectomy), seems normal in hippocampal animals. It is reasonable to assume on the basis of these data that the hippocampus is not critically involved in consummatory behaviours. However, Jarrard (1973) has proposed that the hippocampus does play a role in these and other such behaviours; the lesion data summarized in Table A27 would appear to render any general role for the hippocampus in consummatory behaviour highly unlikely.

Two recent studies have investigated the hoarding of food in hippocampal rats (Wishart, Brohman and Mogenson 1969, Wallace and Tigner 1972). This behaviour involves the transportation of food from

* Thomka, Murphy, and Brown (1975) have shown that hippocampal rats drop more food through their cage floors than do normal rats; this might account for any reports of increased food intake. The authors also point out that weight loss after hippocampal lesions could result if all animals are put on a diet involving a fixed, small amount of food, and the lesioned animals lose more through spillage.

an area outside the animal's living cage into the cage and would appear to reflect the action of several factors: deprivation of food, the relative insecurity of the location outside the cage containing the food, and a tendency to transport objects (cf. Munn 1950, Bindra 1959, for discussions of hoarding). An interesting possibility raised by these two studies, as noted by Wallace and Tigner, is that

'a difference in security does not have the same effect on the hoarding of hippocampals as it does on that of control animals' (p. 941).

Hoarding in the lesioned rats, as in the controls, was affected by the deprivation of the animals. The absence of an influence of the security–insecurity dimension on hippocampal animals is consistent with the finding that these animals begin to eat more rapidly in strange environments (eg. Jarrard 1968) than do normal animals. The absence of such place fear agrees with our conclusions formed from a consideration of aversively motivated behaviour (pp. 302-15).

11.2. Social, maternal, and sexual behaviour

Both sexual and maternal behaviour can be affected by hippocampal lesions. Early work suggested that hippocampal lesions in male rats prolong the time to the initiation of the first mount (Dewsbury *el al.* 1968) but then decrease the inter-mount interval, such that hippocampal rats mount more often per unit time (Kim 1960b, Bermant, Glickman, and Davidson 1968). However, Michal (1973) has reported that hippocampal lesions decrease mounting frequency in male rats. These data taken together indicate that hippocampal damage neither increases nor decreases sexual drive in a direct manner.

Michal computed measures of the predictability of behaviour sequences in his rats and found that hippocampal rats were markedly more predictable than were control rats; that is, they tended to perform the same sequences repeatedly. This facet of their behaviour could account for both the increased and decreased mounting observed in the studies noted above. Michal measured sexual behaviour in his rats for only 10 min; no normal rat managed to mount to ejaculation in this time. Given that hippocampal rats take longer to initiate the first mount, it is conceivable that with a longer test period Michal could have found increased rather than decreased mounting frequencies. The common thread in all these studies is the stereotypy in behaviour, be it mounting as in the early studies or attention to the head and body of the female without mounting, as observed by Michal.

While an early paper suggested that hippocampal lesions do not influence social behaviour (Glickman *et al.* 1970), three later reports (Kolb and Nonneman 1974, Nonneman and Kolb 1974, Ely, Greene, and Henry 1976) have noted marked changes in rat, cat, and mouse, respectively.

In rats, hippocampal damage drastically reduced contacts between pairs of lesioned animals in both large and small fields. In cats, lesions seemed to make the animals submissive to intact cats. The authors commented on the fact that the lesioned cats seemed uninterested in other cats, preferring to eat if allowed to do so. However, when presented with a silhouette model of a cat, lesioned animals seemed quite interested in it, though their responses to this model do not decrement normally. In mouse, a failure to develop social dominance hierarchies was observed in conjunction with decreased aggression. All these data could, as Ely *et al.* suggested, be explained in terms of a loss of cognitive mapping. The possibility that the hippocampus is more directly involved in social behaviour must be left open. At least one aspect of (anti) social behaviour remains intact after hippocampal damage in rats: mouse-killing (De Castro and Marrone 1974, Kolb and Nonneman 1974).

Hippocampal lesions in female rats can affect various components of maternal behaviour, including nursing, retrieving, and nest building (Kim 1960a; Kimble, Rogers, and Hendrickson 1967), while in the cat these lesions affect oestrous behaviour (Peretz 1967). These changes are not directly predicted from the present theory, and we can only assume that they are attributable to other defects that are directly predicted. For example, the deficit in retrieving and nursing might be due to the mother's inability to locate the pups accurately. Thus, Kimble *et al.* give an example of a lesioned dam who

'executed perfect hovers, but several inches away from any of the pups' (p. 406).

11.3. Sensory and motor function

No gross motor or sensory defects of a permanent nature are seen in animals after bilateral hippocampal lesions.* However, two studies have suggested that unilateral lesions can lead to a subtle motor defect (Greene, Saporta, and Walters 1970, Saporta and Greene 1972). Rats with unilateral lesions were found to have both a turning and orienting bias ipsilateral to the lesion. This bias persisted in the visual mode after optic chiasm section, indicating that it rests on a motor, rather than sensory, effect. According to the present model the hippocampus has no direct motor role that would account for these results. Such biases are seen after many subcortical lesions, and it must remain a possibility that they are not directly attributable to the hippocampal locus of the lesion.

No particular bias has been reported after bilateral lesions, though one can assume that damage in these cases is often quite asymmetrical. What is often seen, on the other hand, is a strong preference for turning to one side or another in two-choice situations; these preferences persist for

* We have already noted that the hippocampus can modulate sensory evoked potentials (see pp. 138-9) and that hippocampals might by hyper-reactive to intense sensory inputs (pp. 248-50).

abnormally long periods in hippocampal animals, as we have seen. However, it is not unusual for hippocampals to demonstrate one turning preference at an early stage and then switch to the opposite preference, maintaining this for a long time as well. Thus, it seems unlikely that the persistent turning tendencies so often noted in hippocampal animals are related to the effects reported by Greene and his colleagues; this possibility must be left open until further work clarifies the nature of the motor effects of unilateral lesions.

We have noticed some remarkable short-term motor-changes in rats with electrolytic or mechanical lesions of the dorsal fornix (O'Keefe and Nadel, unpublished observations).* For the first few days after the lesion these animals are profoundly catatonic. When placed on a table or turned on their backs and left unrestrained they will maintain the unnatural posture for several minutes. Abnormal limb postures are also maintained in this way. In a few of these animals extreme catatonia resembling the waxy flexibility described by Stein (1971) after injections of 5-hydroxydopamine is seen; these animals retained unusual standing postures for 15 min or more. The absence of whisker movements reported by Gray (1970) after lesions in the septum does not occur after fornix section unless the septum is also damaged.

This condition, it should be noted, resembles that reported by Bures, Buresova, and Weiss (1960) after bilateral placement of potassium chloride (KCL) crystals in the dorsal hippocampus of rats (e.g. the elicitation of spreading depression) and by MacLean (1957b) after direct deposition of crystalline carbachol in the hippocampus of the cat. MacLean noted that after his injections

'sometimes the animal may be draped into various postures, which it will maintain for minutes at a time (p. 130).

In our experience this condition clears within a few weeks of operation, although the experienced investigator can often tell the difference between normal and hippocampal rats when they are lifted up; the hippocampal rat appears 'looser' and more relaxed. The cause of the initial gross change is unknown; one could speculate that it results from surgical trauma and/or seizures associated with the surgical or stimulation procedure. Whatever its cause, this phenomenon would appear to be relatively unimportant in assessing the results of lesion studies, most of which are carried out after a recovery period during which this abnormality subsides.

* De Castro and Marrone (1974) have described similar effects of hippocampal lesions. They reported the same changes noted above, as well as the fact that these effects are ameliorated by the passage of time. They argued that these changes did not underlie the behavioural change they were investigating (shock-induced fighting). The report of increased 'tonic immobility' in rabbits (Woodruff, Hatton, and Meyer 1975), after the lesioned animals were turned on their backs, is probably another example of this effect.

11.4. Autonomic and endocrine functions

Basic autonomic and endocrine functions appear to be intact in hippocampal animals. Thus, basal metabolic rate (Kim 1960a), heart rate Jarrard and Korn 1969), and galvanic skin response (Bagshaw *et al.* 1965) are all normal and there is

'no essential defect in pituitary-adrenal function in . . . hippocampus-ablated rats' (Coover et al. 1971b, p. 731).

The absence of 'essential' defects does not mean, however, that either autonomic, or particularly endocrine, functions are always normal in hippocampal animals. We have already noted that abnormal heart rate responses to supra-threshold shocks occur in these animals. Similarly, the evidence that certain hormonal systems are influenced by, and in turn can influence, the hippocampus is now quite strong. This evidence relates primarily to the pituitary-adrenocortical system (involving ACTH and corticosterone in the rat); there is little evidence that other hormone systems, such as those involving the gonadal hormones for instance, are modulated by the hippocampus.

The evidence concerning this hormone-hippocampus interaction falls into three categories: (1) the uptake of radioactively labelled hormone by the hippocampus; (2) the effects of systemic injections of various hormones upon the activity of hippocampal neurones; (3) the effects of hippocampal lesions or stimulation on pituitary-adrenal function. The studies providing this evidence are listed in Table A28.

11.4.1. UPTAKE STUDIES

In a series of experiments McEwen, Weiss, and their colleagues have demonstrated that the hippocampus is a potent site of uptake for corticosterone in the rat (e.g. McEwen, Weiss, and Schwartz 1969, McEwen, Magnus, and Wallach 1972, Gerlach and McEwen 1972); this finding has been replicated in other laboratories (Ford, Rhines, and Steig 1971, Knizley 1972). The binding of corticosterone, which is primarily nuclear (Gerlach and McEwan 1972, Warembourg, 1975), appears to be maximal about one hour after injection (McEwen *et al.* 1972, Ford *et al.* 1971). The intensity of uptake varies among the different hippocampal fields, with CA1 and CA2 showing the most intense labelling (Gerlach and McEwen 1972, Warembourg 1975); the latter study showed strong labelling in the fascia dentata as well. This strong uptake of corticosterone by the hippocampus can be contrasted with its general failure to concentrate gonadal hormones (Stumpf and Sar 1971, Zigmond and McEwen 1970, but see Luttge, Chronister, and Hall 1973 and Pfaff and Keiner 1973 for conflicting reports).

11.4.2. EFFECTS ON SINGLE UNITS AND EEG THETA

Pfaff, Silva, and Weiss (1971) have shown that corticosterone can reduce the firing rates of neurones in the dorsal hippocampus. ACTH, on the other hand, can increase hippocampal neurone firing rates; some units were found which were affected by both ACTH and corticosterone. These results were seen in chronic and acute preparations in both intact and hypophysectomized rats. The ACTH-induced increases usually began 3-10 min after injection and lasted 25-30 min, whereas the corticosterone induced decreases began 10-40 min after injection and lasted at least 2 h. In contrast, Dafny *et al.* (1973) found that the hippocampus was the least reponsive limbic area to injections of cortisol, a related corticosteroid. Whereas over 80 per cent of units in areas such as the anterior hypothalamus, ventromedial hypothalamus, and mesencephalic reticular formation changed firing pattern, only 13 of 28 units in the dorsal hippocampus were affected. Of these, seven increased activity, while five decreased activity.

Several studies (Martin, Moberg and Horowitz 1975, Urban and De Wied 1975, Urban *et al.* 1974) have reported an effect of adrenal hormones on hippocampal EEG. Urban *et al.* (1974) found that $ACTH_{4\text{-}10}$ significantly reduced the frequency of the hippocampal theta in the dog while the animal waited for a visual signal to press a lever for food reward. The effect was only seen under conditions of mild deprivation when the animal's performance was low and erratic and not during strong food deprivation when its performance was high and consistent. In another study from the same laboratory, Urban and De Wied (1975) found that $ACTH_{4\text{-}10}$ *increased* the frequency of theta elicited by stimulation of the reticular formation in unrestrained rats. The maximum changes occurred 60-120 min after the injection.

Martin *et al.* (1975) looked at the spontaneous and sensory elicited theta in the unrestrained rabbit. They found an increase in the amount of spontaneous theta 60-90 min after injection of corticosteroid but no change in the theta evoked by auditory stimuli. It is unfortunate that in the latter two EEG studies and in the chronic part of the Pfaff *et al.* unit study behaviour was neither monitored nor controlled, so that one cannot rule out an intermediary effect of the hormone on behaviour.

11.4.3 EFFECTS OF LESIONS OR STIMULATION

A large number of studies (listed in Table A28) have investigated the effects of lesions or stimulation of the hippocampus on pituitary-adrenal function. These can be split up into two categories: (1) those investigating the physiological functioning of the pituitary-adrenal system, that is, resting levels and/or cyclic variations; (2) those investigating

pituitary-adrenal responses to various experimental treatments, typically involving stressful or novel stimulation.

11.4.3(a). Physiological functions. While a number of authors have claimed that fornix section or hippocampal lesions abolish the normal diurnal rhythm of plasma corticosteroids* (Mason 1958, Nakadate and de Groot 1963, Moberg *et al.* 1971, Endroczi 1972), there have been many negative reports (Galicich, *et al.* 1965, Endroczi and Nyakas 1971, Wilson and Critchlow 1973/4, Kearley, Van Hartesveldt, and Woodruff 1974, Lanier *et al.* 1975). Some of the confusion could relate to the time of testing after operation. Lengvari and Halasz (1973) have shown a disruption of the diurnal cycle with fornix lesions at 1 week, but not 3 week, postoperative testing. Most of the positive reports indicate that the effect consists of a smoothing out of the normal cyclic rhythm such that lesioned animals have abnormally high levels in the morning and abnormally low levels in the evening, though one study (Endroczi 1972) reported an absolute increase throughout the day. In most of these studies no attempt was made to correlate corticosteroid levels with behavioural activity, in spite of the known relationship between the two, and the fact that hippocampal damage usually alters activity levels, in particular attenuating cyclic activity changes (e.g. Jarrard 1968).

Chemical or prolonged electrical stimulation of the hippocampus has been reported either to increase basal ACTH secretion (Bohus, Nyakas, and Lissak 1968) or to decrease plasma corticosteroid levels (Mason 1959 Rubin, Mandel, and Crandall 1966, Kawakami *et al.* 1968), though there have been negative results (e.g. Endroczi and Lissak 1960). The extent to which these results are due to the spread of after discharges to other structures is not clear, as most of these studies failed to provide controls for this possibility. To add to the confusion, the effects of stimulation have been shown to be critically dependent upon frequency parameters; low-frequency stimulation inhibits ACTH release while high-frequency stimulation facilitates it (Endroczi and Lissak 1962). These data do not allow any firm conclusion concerning the nature of hippocampal influence upon resting pituitary-adrenal function. However, if we assume that low-frequency stimulation mimics physiological function while high-frequency stimulation acts as a functional lesion, these data are consistent with the idea that the hippocampus normally acts to inhibit ACTH release.**

11.4.3(b). Behavioural functions. While the data concerning resting levels are somewhat confused, a clearer picture is emerging from a consideration

* This cycle consists in high levels in the evening and low levels in the morning, and is related to, though lagging behind, cyclic changes in activity levels (Endroczi 1972).

** This assumption, taken in conjunction with the rapid potentiating effect of ACTH on hippocampal neurones, suggests that there is a negative feedback loop maintaining resting ACTH levels.

of the kinds of environmental manipulations which elicit pituitary-adrenal activity and the way in which the hippocampus might exert its influence upon this hormonal system.

Much of the work concerned with pituitary-adrenal responses to environmental factors has concentrated upon physically unpleasant stimuli such as extreme cold, physical restraint, anaesthesia, electric shock, and so on. The view arose that pituitary-adrenal mobilization was nonspecific, related to any stressful situation (cf. Selye 1950). While there is little doubt that such extreme stimuli mobilize the pituitary-adrenal system, there is increasing evidence that other, less extreme, stimuli might also be able to mobilize the system. Thus, Mason (1971), in criticizing the traditional view, stated that:

'it appears highly advisable that we view with skepticism the conclusions drawn from all those past and future studies of the role of "physiological" or "physical" stimuli in endocrine regulation in which no rigorous efforts were made to minimize or assess the possible role of associated psychological reactions' (p. 238).

Among the psychological, or *neurogenic,* factors that seem important in mobilizing the pituitary-adrenal system several stand out as particularly interesting in the present context. There is little doubt, for instance, that fear provokes an endocrine response; ACTH and other pituitary peptides, as well as corticosterone, all have an influence upon behavioural reactions in fear-provoking situations (cf. de Wied *et al.* 1972 for a review). It is worth noting that this influence appears strongest in situations of 'mild' fear (e.g. Weiss *et al.* 1969, 1970), where mild fear is usually taken as *situational* or place defined.

Perhaps more pertinent, strong pituitary-adrenal responses are triggered by uncertainty, novel situations, and the failure to confirm expectancies. Thus, Mason (1959) showed that endocrine mobilization occurred in 'first-experience' situations, even when these did not involve pain or an obvious threat to the animal. Endroczi (1972) has shown that the pituituary-adrenal system responds strongly to unmet expectancies, such as the withdrawal of expected rewards or closing down an alley normally used to get to water in a maze. Similarly, Bohus (1973), Coover *et al.* (1971a) and Coover, Ursin, and Levine (1973) have all provided evidence that

'one of the conditions which will activate the neuroendocrine mechanisms leading to subsequent release of ACTH is a change in expectancies' (Coover el al. 1973, p. 174).

These studies indicate that environmental uncertainty, or novelty, is a crucial factor in endocrine release.

The fact that uncertainty and environmental mismatch can be singled

out as potent triggers for pituitary-adrenal mobilization brings our discussion back to the possible nature of the hippocampal influence upon this endocrine system. The one situation in which hippocampal rats fail to demonstrate normal plasma corticosterone elevations concerns the extinction of an appetitive response (Coover *et al.* 1971b). Thus, mismatch mobilizes the pituitary-adrenal system in normal, but not hippocampal, animals. This deficiency could account for many of the effects of hippocampal disruption upon pituitary-adrenal reactions to stress.

11.4.4. CONCLUSIONS

These data suggest that an important interaction exists between the hippocampus and the pituitary-adrenal system. One possible way of conceiving of this interaction is as follows: the pituitary-adrenal system is under direct control of portions of the hypothalamus (and other pituitary hormones), as well as being controlled from feedback through basal levels of ACTH and corticosteroids themselves. This system undergoes patterned circadian rhythms which are related to, and affected by, other circadian rhythms, including those involved with activity and temperature regulation. Triggering of this endocrine system, as part of a mobilization pattern in preparation for behavioural exertion, can be effected by several brain systems (cf. Krieger and Krieger (1971) for evidence that there are several brain systems capable of independently mobilizing the endocrine response). One particularly effective triggering system is connected with the hippocampal novelty detection-mismatch function; stress would be another trigger. As part of its output in mismatch situations, the hippocampus will activate the release of ACTH.

The presence of corticosterone-binding cells in the hippocampus and the predominance of these in CA1, coupled with the responsiveness of hippocampal neurones to ACTH and corticosterone, could all reflect part of a feedback loop maintaining basal levels of these hormones, whilst enabling the pituitary-adrenal system to respond to novelty. This simple version of an admittedly complex function is rather vague, but it would not seem particularly useful at present to specify this system in any greater

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* There are a number of interesting possibilities, none of which are supported by much evidence. These fall into two classes, concerned with short-term and relatively long-term effects. The pituitary peptides and the corticosteroids have been implicated in the modulation of behavioural responses to fearful situations; they can clearly influence performance in a variety of such tasks, as we noted above. McEwen (personal communication) has suggested that these effects are maximal when fear is related to places rather than objects. Thus, it might be possible to draw a connection between pituitary-adrenal modulation of place-dependent fear and the hippocampal role in the definition of such places.

Another, related, possibility is suggested by the time course of corticosterone binding in the hippocampus, on the one hand, and the effects of ACTH and corticosterone on hippocampal neurone activity on the other. While ACTH has a rapid potentiating effect on hippocampal neurones (and markedly increases the sensitivity

detail. We are thus leaving open numerous questions, including those concerning specific effects of the pituitary peptides and corticosteroids on the neural elements themselves.* **

of hypophysectomized rats to places in avoidance situations), corticosterone has little effect for 30-60 min, at which time it depresses neural activity in the hippocampus. This coincides with a period during which the previously learned avoidance behaviour can suffer from relatively poor performance, the so-called Kamin effect. The fact that corticosterone concentrates in cell nuclei during this time and has been implicated in protein synthesis (McEwen et al. 1969) raises the exciting possibility that this hormone is in some way involved in the plasticity underlying long-term memory changes in the mapping system. The failure to find an effect of hippocampal lesions upon the Kamin pattern (Klein et al. 1975) argues against this possibility.

** Several recent review articles treat the interaction between the hippocampus and various hormone systems (McEwen, Gerlach, and Micco 1975, Bohus 1975, McGowan-Sass and Timiras 1975, Van Hartesveldt 1975). The last of these gives a thorough view of the problem and should be consulted by interested readers.