5

Introduction to the lesion review

5.1. Nature and purpose of the review

IN this section of the book we review lesion and stimulation studies of the hippocampus. Throughout, animals with damage in the hippocampus or fornix are referred to as *hippocampal* or *fornical* animals, respectively. We have tried to include in this review every published study of the effects of hippocampal disruption on behaviour and apologize in advance for any omissions.* Given the large number of lesion studies on the hippocampus it is possible to group most of them according to the type of behaviour investigated. For each such group a table is provided in the Appendix which lists the relevant studies and their results. In the text a selection of studies from each group is discussed, including particularly those which document an important aspect of the hippocampal syndrome. We hope that the tables will provide an easy reference source for the reader and further that they redress any imbalance in the text resulting from our selection of studies for discussion. Some consideration of studies involving either electrical or chemical stimulation of the hippocampus is included in a separate chapter where the specific methodological problems raised by the use of these techniques can be considered.

Only those studies whose intent was to limit lesions to the hippocampus (or fornix) are included. No control, however, could be taken over the wide disparity in size and, perhaps more important, locus of lesion within the hippocampus. We assume, in this discussion, that the hippocampus throughout its length is a unitary structure *in the sense that it has an integrated function.* This is not to say that we are assuming complete equipotentiality of function within the hippocampus. One of us has suggested that there are differences in function between the dorsal and ventral parts of the hippocampus in rats (Nadel 1968); this possibility was noted at about the same time by several other investigators (e.g. Jackson 1968, Jarrard 1967). These regional differences could reflect the uneven distribution of CA fields within the hippocampus (see Lorente de No 1934, p. 155) and the different inputs and outputs of these fields. At various points in this review we shall confront the fact that the site of a hippocampal lesion can determine its effect upon behaviour. We have already seen that an

* Our review of the literature terminated in January 1976.

anatomical basis for differentiation exists within the hippocampus. What can presently be said about the specific functions of segments of the hippocampus?

The first thing that must be said is that much of our discussion is going to be simplified; we shall treat dorsal and ventral, anterior and posterior, lesions as the same, though it is clear that these are not equivalent in all respects. More pertinent, it now seems certain that fornix lesions cannot be treated as equivalent to hippocampal lesions, while neither is the same as entorhinal damage. However, there is enough commonality in all these lesions to allow us the assumption of a unitary system. While this totality undoubtedly comprises several separable subfunctions, we concentrate in this book on the mapping ensemble. The collection of interrelated functions we assign to the mapping system can, and should, be allocated to portions of that system. We choose not to attempt this fine-grain analysis here for two reasons. First, such an analysis would not affect the basic position adopted here; our chosen level of analysis does not require it. Second, there are not sufficient data at present to produce a consistent picture of the effects of lesions limited to one portion of the system or another.

Within each chapter in this section we discuss a particular aspect or type of behaviour and its modification, if any, following hippocampal disruption. Chapter 6 introduces the problem of reactions to novelty, and assesses the proposal that the hippocampus is critical for exploratory behaviour. We then examine the role of the hippocampus in discrimination and maze learning, concentrating upon the way in which animals utilize place hypotheses in these tasks (Chapter 7). Following this we examine the role of the hippocampus in behaviours based on reactions to threat, including fear, aggression, and avoidance (Chapter 8). In Chapter 9 we turn to a number of testing situations in which the role of the cognitive mapping system should be minimal, and this is followed by a consideration of reactions to reward shifts and extinction (Chapter 10). Next, we consider the general effects of hippocampal lesions upon such things as eating, drinking, and sexual behaviour (Chapter 11). This is followed by a brief discussion of stimulation studies (Chapter 12). The section is concluded with a chapter in which the role of the locale system in long-term memory is briefly assessed.

Prior to analysing the effects of hippocampal lesions upon any behaviour we attempt to uncover the factors underlying that behaviour in normal animals. In particular, we shall try to spell out the role of locale and taxon systems and to make predictions concerning the effects of hippocampal lesions. The verification of these 'predictions' does not, of course, constitute proof of the theory, at least in so far as they concern experiments already in the literature. We hope that sufficient, as yet unexamined, predictions will be suggested in the course of this review to provide adequate tests of

the theory. Our present aim is to incorporate all that is known about the effects of hippocampal lesions within a minimal set of basic postulates resting upon the cognitive approach to brain and behaviour discussed earlier. Further, these postulates must be consistent with what is known of the anatomical and physiological properties of the hippocampus as described in the previous section of the book.

In several cases data are discussed which cannot be explained without making unwarranted *post hoc* extensions to the theory; in such cases we present the data and discuss possible solutions to the problems they raise without settling on a final answer. In other cases the discussion raises interesting possibilities that go well beyond the scope of this book or the available data; here we have been content simply to point out these possibilities and leave it at that.

It is a basic contention of the present theory that the hippocampus is not involved in fundamental motivational processes; that is, it is not a necessary link in eating, drinking, sexual behaviour, and so on. Evidence supporting this position is presented towards the end of this section. However, there are circumstances in which changes in aspects of these fundamental behaviours appear to follow upon hippocampal disruption and these are discussed at various points in the review. In these cases it can be seen that the absence of the cognitive-mapping system influences even the most simple behaviours in a specifiable way. Throughout the discussion of more complex learning situations, then, it is assumed that the absence of the hippocampus has a number of effects, but that the common thread linking these together is the lack of a cognitive-mapping system; it is this central defect that we shall concentrate upon.

5.2. Methodological considerations

Before turning to the lesion data we should comment on the validity of the lesion-cum-behavioural testing paradigm as a tool in the analysis of brain function. Strong biological and logical objections could be (and have been) raised against a heavy reliance upon this technique. From purely biological considerations one could argue either that *something more* than the removal of a discrete area of neural tissue has been effected by the lesion, or conversely, that *not even that* had been accomplished.

5.2.1. THE LESION AS SOMETHING MORE THAN FOCAL DESTRUCTION

5.2.1(a) Epileptic activity. Electrolytic lesions may produce an irritative focus which bombards distant structures with abnormal patterns of activity. It is now well established that such excitation produces long-lasting changes in these distant structures which may cause them to function abnormally (e.g. Morrell 1961, Goddard, McIntyre, and Leech 1969). More recent work has shown that abnormal epileptiform patterns can result from the de-afferentation that any lesion produces (Anderson *et al.*1971).

The hippocampus is a particularly epileptogenic structure and can be expected to be a likely generator of such abnormal barrages after electrolytic lesions. On the other hand, direct elicitation of epileptiform activity in the hippocampus through implantation of penicillin, or other irritating drugs, leads to a syndrome of behavioural defects demonstrably different from that produced by electrolytic or suction lesions of the hippocampus (e.g. Schmaltz 1971, Schmaltz, Wolf, and Trejo 1973).

5.2.1(b). Denervation hypersensitivity. The loss of afferent activity (rather than any trophic factor) which results from a lesion produces marked changes in nerve (Stavraky 1961, Sharpless 1964). In addition to the epileptiform bursting activity noted above, changes reported include collateral sprouting from neighbouring intact axons (Raisman 1969) and the potentiation of normally silent afferents (Wall and Egger 1971, Merrill and Wall 1972). In all of these examples the resultant reorganization of the target tissue would tend to be maladaptive and thus would exacerbate the damage produced by the primary lesion (see, however, the *not even that* argument below).

5.2.1(c). Hormonal and transmitter imbalance. Lesions in areas involved in hormonal regulation might shift the pattern of hormone secretion with consequent functional changes in the target areas for these hormones. As we note later (pp. 357-62), the hippocampus is involved in certain aspects of the pituitary-adrenocortical system, and lesions of the hippocampus might cause long-lasting changes in resting levels of the hormones produced by this system as well as in acute reactions to particular trigger events. One reported effect of this change in hormone function, for example, is a striking increase in liver glycogen levels in rats with hippocampal lesions (Murphy, Wideman, and Brown 1972). Other, perhaps more important, changes could involve alterations in neural excitability and neurotransmitter levels (cf. de Wied and Wiejnen 1970), which have been associated with changes in pituitary-adrenal function.

Further, lesions in one area might directly alter neurotransmitter levels in other areas to which it normally projects; Donoso (1966) has demonstrated such an effect of hippocampal lesions on noradrenaline levels in the hypothalamus.

5.2.1(d). Effects on sleep. Brain lesions frequently lead to changes in sleep patterns. In some instances paradoxical, or rapid-eye-movement (REM), sleep increases following a lesion; in the case of the hippocampus lesions decrease total sleep time (Jarrard 1968), but there are no data demonstrating marked changes in REM sleep. REM deprivation has global effects on brain function; it leads to increased amplitude of evoked potentials in entorhinal cortex following pre-pyriform stimulation (Satinoff, Drucker- Colin, and Hernandez-Peon 1971),

to decreased recovery cycles (Dewson *et al* 1967), and to decreased seizure thresholds (Cohen and Dement 1965). All these point to general changes in excitability of many different brain areas as an indirect result of a brain lesion which affects REM-sleep time.

Some idea of the extent and magnitude of these global changes following central lesions can be obtained from physiological studies on the spinal cord or sensory relay nuclei following chronic lesions. Septal lesions, for example, lead to increased evoked potentials in the trigeminal nucleus upon stimulation of the trigeminal nerve (Rose and Frommer 1971). Perhaps more interesting is the finding of Griffin (1970) that the decreased habituation in spinal reflexes following frontal lesions in the rat persists after spinal-cord transection. This indicates a long-term change consequent upon the lesion in the frontal area.

5.2.2. THE NOT EVEN THAT ARGUMENT

In contrast to the above arguments, adherents of the *not even that* position suggest that structural and functional reorganizations following a lesion might act to ameliorate the behavioural defect. Evidence for this position comes from (1) the recovery of the lost behavioural capacity with experience, (2) the attenuation of the effect when the lesion is produced in several stages separated in time, as opposed to the usual single-stage lesion (e.g. Stein *et al.* 1969), and (3) the reduced or absent effect when the same lesion is produced in neonatal animals. All these examples have implications for what is known as the *recovery of function* phenomenon (see Rosner 1970, 1974, Dawson 1973, LeVere 1975), and several explanations for this `recovery' can be noted. Basically, these explanations fall into two broad categories: those suggesting that new brain structures take over the functions of the lost tissue and that no behavioural capacities are lost, and those suggesting that there is little neural take-over of function but that alternative behavioural capabilities are utilized to solve certain tasks.

The take-over notion would appear unlikely on purely anatomical grounds. Although one bit of cortex might conceivably substitute for another, the unique machinery of a structure such as the hippocampus is not so easily replaced or simulated. To demonstrate that true take-over of function occurs would require that lesioned animals recover all the capabilities of intact animals, including the ability to solve the same problem in precisely the same way. We have already stressed, and will continue to emphasize, the point that most tasks put to experimental animals can be solved through the use of any of several different strategies, some of which will be dependent upon different brain structures. Recovery of function could thus represent a switch to alternative modes of solution dependent upon intact brain tissue, rather than the actual reorganization of brain function. Neonatal and/or serial lesions, on this view, would permit a gradual adjustment to the use of these alternative hypotheses which

typically would not have been used in the intact animal. According to this analysis recovery of function should not appear with behavioural tasks dependent solely upon the types of hypotheses subserved by the damaged structure; we present evidence later supporting this contention for animals with hippocampal lesions (pp. 377-9). Further, recovery of function, when it occurs, should be dependent upon a change to a new mode of task solution. We discuss shortly a way in which this possibility could be tested.

Some recovery of function might be due to the amelioration of certain of the *something more* effects noted above, either with the passage of time, or because serial and/or neonatal lesions have less traumatic effects. One cannot, in this sense, ascribe recovery to anything like a take-over of function, and the constraints concerning alternative behavioural modes of solution mentioned above should apply to this form of recovery as well. On the other hand, by potentially avoiding some of the *something more* effects such techniques as the serial lesion might come closest to producing neither more nor less than the intended damage.

5.2.3. LOGICAL OBJECTIONS

At a logical level problems have been raised about the interpretation of changes in behaviour following lesions; one tends to impute to a structure removed by lesion just those functions missing or aberrant in the operated animal (cf. Gregory 1959). Thus, in the case of the hippocampus a consistent attempt has been made to link this structure with some manner of inhibitory function, based primarily on the fact that animals with hippocampal lesions often appear to lack the ability to inhibit certain responses (or behaviours, or hypotheses) (cf. Kimble 1968, Isaacson and Kimble 1972, Altman *et al.* 1973, see Nadel and O'Keefe 1974, Nadel *et al.* 1975 for a discussion of these models). Gregory points out that such techniques lead to a position where a resistor is labelled a hum-suppressor because its removal from a radio leads to a hum. This, and other examples like it, attest to the fact that one must utilize lesion data with extreme care. On the other hand, there are cases where the imputation of function based on `what's missing' following a lesion is a useful method for proceeding. In a trivial sense the absence of vision after section of the optic tracts is one such example, and it seems clear that the nearer one is to the periphery the better this procedure works. The hippocampus, however, is not a peripheral structure; rather it appears to sit somewhere in the middle, concerned directly, we assume, with neither sensory input processes nor motor output mechanisms. The use of the missing-function technique here is more open to question.

A second point about the logic of the lesion technique concerns the question of control groups. To ablate a subcortical structure such as the hippocampus, using a suction method, it is necessary to remove a considerable amount of overlying tissue. Lesion control groups which have suffered damage only to the neocortex are therefore usually included in such studies. It is hard to know what conclusions to draw when the performance of these controls falls between the performance levels of the experimental lesion group and the intact control group, as is often the case. Even when the two control groups perform at the same level there are objections to the conclusion that any deficit in the experimental animals is wholly attributable to the subcortical damage. If there is both neocortical and hippocampal involvement in the generation of behaviour, then this simply is not so. In that case a lesion in either the neocortex or hippocampus will have no effect, while a lesion of both areas will have an effect. Thus, one could argue that the subcortical structure can be involved, but not that its involvement is essential. The double-dissociation technique would seem to offer a more solid base for reasonable inference.*

We shall close this discussion with a more general critique of the lesion method as it is most frequently used. As one reads through the literature one cannot help but be surprised at the small amount of information that is generated by each individual experiment and at the general absence of any important relationship between different experiments, even when they are done in the same laboratory. We think this is due to a fundamental misconception concerning appropriate methodology; that is, to the almost exclusive reliance upon an inappropriate experimental paradigm, the *crucial experiment* (cf. Platt 1964). The crucial experiment is designed to decide between two strong hypotheses where they can be shown to make mutually exclusive predictions. As such, it assumes a considerable prior knowledge of the phenomenon under study and seeks to control or eliminate all the relevant variables except those pertinent to the distinction between the two hypotheses under test. The crucial experiment produces very little information, but what it does produce is held to be extremely important; it is an 'uptight' business, the serious side of a 'mature' science.

At earlier stages in the development of a science different, more information-rich, paradigms are needed. Here it is necessary to make fewer assumptions about existing knowledge, and the emphasis is on the careful observation of natural phenomena and the selective interference with these processes in an attempt to understand them. Emphasis is placed not on the individual isolated experiment but on the accumulation of information about the phenomenon through the accretion of many small experiments. The atmosphere, one might say, is that of play rather than that of work.

Most of the experiments reported in this section follow the crucial-experiment paradigm although they were not designed specifically to place in opposition two strong hypotheses. Typically, animals are studied in artificial environments constructed to eliminate most stimuli and calculated

* In the double-dissociation technique at least two experimental lesion groups are included and several behavioural tests employed. The hope is to demonstrate a defect in some tasks with one lesion and in other tasks with the second lesion, thereby doubly dissociating the lesioned areas.

to force the animals to learn a particular task in a specific way. Differences between groups are (or are not) found and it is concluded that the group with a certain lesion lacked (or retained) a given function. Information generated in this way is useful only if the conceptualization of behaviour guiding the research is correct. If such things as response inhibition do not exist then experiments testing the effects of lesions on response inhibition cannot be very helpful.

The more ethological approach suggested above would, in our view, be preferable at this stage of our knowledge. Rather than mask the fact that different animals learn the same task in different ways, this could be exploited and studied. Animals would be trained on tasks which utilize their natural repertoires as much as possible, with as much information available as could reasonably be provided. Following (or in some cases during) learning, the experimental situation could be systematically manipulated with the aim of determining how each animal solved the task. This emphasis on intra-animal differences would suggest that each animal be run through a series of studies so that any consistent pattern of learning strategies could be revealed.

Among the few lesion studies using this approach are those by Means and Douglas (1970) and Hamilton (1972). In experimental work using intact animals such techniques are used more often, as in transfer studies in discrimination learning and in transfer-of-control studies in avoidance learning. Of course, such techniques can be criticized; in particular one can object that they yield data contaminated either by new learning or some manner of interference from one situation to another.

We have been developing an experimental paradigm, which we call the *probe technique,* in order to assess whether brain-damaged animals learn in the same manner as do normal animals, without respect to learning rates. Animals are trained on a task to a loose criterion and then given a small number of additional trials on post-criterion days. Interspersed amongst these trials are the `probe' trials in which certain aspects of the situation are manipulated**.** Normal trials are given both before and after these probe trials to determine whether the probes have had any residual effects upon criterion performance. Using this technique we have been able to show that equivalent learning rates can mask qualitatively different modes of learning; some of these results are described in the course of this review.

In sum, a cognitive approach to brain-behaviour interaction demands the use of experimental techniques which allow for the possibility that a given task can be solved in any of several ways. Though we are aware of the objections one can raise concerning the use of lesion techniques, we feel that these techniques can be used profitably so long as the shortcomings are kept firmly in mind. In this review we rely heavily upon the lesion data, partly because of the great wealth of it and partly because much of it can be accounted for within our theoretical framework. The striking

thing about the accumulated lesion data on the hippocampus, in fact, is the consistency of results across different lesion techniques, sizes, and sites when viewed from what we consider to be an appropriate theoretical perspective. In the discussion which follows we attempt to analyse the syndrome resulting from hippocampal damage both in terms of the putative `missing function' of the hippocampus and in terms of the functions of what is left to the animal's brain.
