13

Long-term memory

The hippocampal syndrome derives from two sources: (1) the loss of those functions depending upon the locale system; (2) the forced dependence upon taxon mechanisms. The former contributes a specific deficit in place learning and exploration, the latter a bias towards persistence and stereotyped behaviour. In considering the lesion data as reflecting these two factors we have limited our remarks to the learning (or extinction) of various behavioural tasks and have not explicitly discussed the question of the long-term storage of place information. Several experimental approaches address this question, which we can now take up in the final chapter of this section; this will form an introduction to the final section of the book, which is concerned with the functions of the hippocampus in humans.

The suggestion that the hippocampus is involved in long-term memory storage derives primarily from work with humans, but it has also been forwarded as an explanation for considerable work with infra-humans. As we have seen, both electrical and chemical stimulation studies have implicated the hippocampus in memory processes, though there are problems with the interpretation of many of these studies. In this chapter we shall consider several types of lesion experiment which provide clues to the hippocampal role in long-term memory storage.

13.1. Long-term memory storage in the locale system

The study of memory function in the hippocampus (and many other brain structures) has often proceeded under the implicit assumption that memory is a unitary phenomenon. While few investigators would state this assumption explicitly, it is none the less present, often specifying certain cortical areas as the site of permanent memory. Rather fewer researchers hold the other traditional view, associated with Lashley, that memory cannot be localized in this way. The trend of much recent research indicates that neither the non-localization nor the limited localization theories are completely acceptable. Instead, it appears that there are different types of memory, relating perhaps to different kinds of information, and that these are localized in many, possibly most, neural systems.

We have hinted at this view by emphasizing the notion that behaviour, viewed at the molar level, consists of the use of particular hypotheses, each type resting on a different form of information. The memory for these would be stored in different neural areas, corresponding perhaps to those areas responsible for specific forms of information processing.

Under this assumption there is no such thing as *the* memory area. Rather, there are memory areas, each responsible for a different form of information storage. The hippocampus, for instance, both constructs and stores cognitive maps. Behaviour which is based on place hypotheses should require hippocampal participation during initial learning as well as during subsequent retention. Behaviour which does not utilize place hypotheses can be learned in the absence of the hippocampus, and it should not be surprising to find that experiments involving the removal of the hippocampus after such learning fail to interfere with retention. These assumptions can only be tested by using tasks whose behavioural basis (in intact animals) is well understood. To demonstrate that hippocampal lesions fail to interfere with the retention of, for instance, a simultaneous visual discrimination task says nothing about the long-term memory for places.

In the course of evaluating the possibility that the hippocampus has a long-term memory function we can also briefly discuss the related issue of *recovery* of *function.* As we noted earlier (see p. 235), serially produced lesions sometimes fail to have the same effects as lesions produced in a single operation. We suggested that this phenomenon partially resided in the fact that serial lesions did not produce some of the non-specific effects, such as surgical trauma, which accompanied single-stage lesions. It was also noted that this attenuation could result either from a *substitution* or *restitution* process. The latter would involve a genuine *take over* of function, such that learning would proceed in the same way as before the lesion, that is, utilizing the same hypothesis. The former, substitution, process would involve the solution of the task by a different hypothesis, thus using different neural systems *in their normal way.* We shall argue that any take over of function after hippocampal lesions results from substitution, not restitution. Such take over should be impossible when purely place-learning tasks are involved.

13.1.1. RETENTION STUDIES

Table A30 presents the results of studies concerned with the retention of tasks trained prior to the placement of hippocampal lesions. These studies provide a mixed picture: the retention of some tasks is affected, that of others is not. Generally, tasks demanding locale function, e.g. maze learning, elicit retention deficits, while tasks not requiring locale function, e.g. simultaneous visual discrimination, are retained normally. However, this neat classification, which strongly supports the suppositions made above concerning multiple memory storage sites, does not account for all the studies listed. We can consider the exceptions in more detail.

Studies of the retention of one-way active avoidance have produced mixed results. As we have already seen (pp. 306-8), this task can be solved with either place or taxon hypotheses. Retention tests should reflect this fact. In Niki's (1962) study hippocampal rats were impaired neither in post-operative acquisition nor in the retention of pre-operative learning. In the study by Olton and Isaacson (1968a) hippocampal rats were impaired in both. This suggests that the two experimental situations were differentially loaded in favour of taxon and place hypotheses, respectively. It is significant that identical results were obtained in both acquisition and retention.

The possibility that the hippocampus is differentially involved in particular stages of the memory process has already been raised in discussing stimulation studies; these failed to produce any clear-cut conclusion. Several lesion studies have also approached this question, again with inconclusive results. Uretsky and McCleary (1969) and Glick and Greenstein (1973) both report that the interval between learning experience and lesion can influence the results of retention tests. In the first study combined lesions of the fornix and entorhinal area 3 h, but not 8 days, after learning induced deficits in active avoidance retention. In the second study impairments in retention of a passive avoidance task were only produced with immediate lesions, not when surgery was delayed for one hour after training. These studies were interpreted as indicating an involvement of the hippocampus in some form of short-term or temporary memory, but not in the long-term memory for the same material.*

Boast, Zornetzer, and Hamrick (1975) addressed the same issue in a different way and obtained markedly different results. Lesions were made prior to training on a passive avoidance task, but retention was tested either 15 min or 25 h after training. Lesions anywhere in the hippocampal system produced deficits at 24 h, while only lesions in the fascia dentata produced deficits at 15 min. These data are difficult to interpret and are complicated by several factors. Uretsky and McCleary (1969) only obtained deficits when the entorhinal cortex was damaged; Glick and Greenstein (1973) and Boast et al. (1975) used tasks which do not necessarily involve the hippocampus. It is not possible to say anything conclusive about a differential involvement of the hippocampus in short-term and long-term memory on the basis of this work.

One final type of experiment should be discussed in this context.

* The possible involvement of the hippocampus in short-term memory processes has been investigated with an interference paradigm in several studies. Rats were trained a task, and then an 'interfering' task was interpolated between successive trials of the first task (Walker and Means 1973, Alexander, Broome, and Means 1974, Jarrard 1975). The results of these studies were mixed; the first and last study showed abnormal interference effects, but the second did not.

Animals are taught an alley approach-avoidance task, and lesions are made at various stages of this training sequence. For instance, in Fried and Goddard (1967) the sequence consisted of approach, intermittent punishment, and then continuous punishment. Intact rats respond to this sequence in the following way: they slow down during the initial stages of intermittent punishment, then speed up again, then slow down drastically during continuous punishment. Hippocampal lesions were made either (1) before any training, (2) when the rats had slowed down during intermittent punishment, or (3) after intermittent punishment had been terminated, when the rats were running rapidly again but before continuous punishment had begun. Rats which received lesions at either the first or third stage showed poor avoidance when continuous punishment was introduced, which is in agreement with other studies of this type of passive avoidance. However, those rats which received lesions at the second stage did slow down when continuous punishment was introduced. The authors suggested that

'the dominant emotional state of the organism at the time of the lesion is of prime importance in determining the effect of that lesion on subsequent avoidance behaviour' (p. 329).

An alternative interpretation of these data is possible, one which brings them into line with our earlier discussions. The intermittent punishment used in these studies has many of the properties of intermittent reward (cf. Banks 1966), in that it produces persistent stereotyped behaviour. We can assume that this represents the action of variability upon the selection of behavioural strategies, leading to the substitution of taxon for place hypotheses. The slow running stage after the introduction of intermittent punishment would partly reflect the conflict between a place and a taxon hypothesis–running through a dangerous place to get reward in another place. The increase in running speed could then reflect the ascension of the running hypothesis and the abandonment of the conflicting place hypothesis. Continuous shock overcomes this taxon hypothesis and leads to the suppression of running. In the absence of a conflict between a place and a taxon hypothesis the recovery of running after the introduction of intermittent shock should be quite rapid, as Fried and Goddard report, but the strength of the ensuing taxon hypothesis might be less than in the case where a conflict existed. This could account for the better passive avoidance shown by those animals lesioned prior to conflict resolution. Our explanation here is quite speculative and not meant to suggest a final interpretation of these data. The results of these studies are quite variable, the task itself is particularly confusing, and it is perhaps best to leave such studies aside in any analysis of the hippocampal role in memory storage.

13.1.1(a). Conclusions. The general thrust of the data from retention studies is that the hippocampus is involved in at least the long-term storage of place information. Further, there does not appear to be any mechanism for replacing this function in the absence of the hippocampus. This suggests that `recovery of function' after hippocampal lesions, which we discuss in a moment, resides not in a direct take over of function, but rather in the finding of new solutions based on taxon hypotheses if possible.

The conclusion that the hippocampus is integral to the long-term storage of locale information gives this structure a central role in memory mechanisms. As such, it brings the animal data into line with data gathered in the clinic during studies on patients with known or putative hippocampal damage (see Chapter 15). The important point is that this is not a generalized long-term memory defect; it relates specifically to information stored in the locale system. This specificity might explain the failure of previous investigators in pinning down a memory function for the hippocampus. The particular type of information stored in the hippocampus must remain the central question. Our assumption that locale information is involved indicates that the hippocampal memory store would be critically important for both the detection of novelty and for the utilization of place hypotheses.

The notion that the same task can be solved in any of several ways underlines the need for extreme caution in both the planning of experiments and the interpretation of results. Too often, negative results have been taken as proof that the hippocampus had no role in long-term memory in animals. This conclusion was clearly unjustified, as later work has shown.

13.1.2. SERIAL VERSUS SINGLE-STAGE LESIONS

Additional data bearing on the problem of alternative solutions to behavioural tasks comes from those studies concerned with the `take over of function' problem. In its simplest form this area of research has been concerned with the long-term after effects of surgical procedures, making the assumption that animals suffering brain damage might, with time, acquire the ability to solve problems which were initially retarded by the operation. It has often been assumed that such recovery would reflect some reorganization of cerebral function, such that remaining brain areas were performing the function of excised areas.

Another approach to such recovery is suggested by the assumption that many behavioural tasks can be solved in more than one way. Take over of function might represent a change in the means of behavioural solution, rather than an actual reorganization of brain capacities. Such a shift would accord more comfortably with what is known of the specific anatomical and

physiological properties of most extra-cortical structures as we have already pointed out.*

Very little work has been reported concerning the recovery of function following hippocampal lesions. In one recent study Mahut and Zola (1973) report that two years after fornix section monkeys had improved their performance on certain discrimination tasks. Any conclusions regarding this form of recovery await further long-term research.

Somewhat more data are available from studies contrasting the effects of single-stage and serial lesions. Traditional views of functional recovery would suggest that serial lesions might attenuate expected deficits in that neural reorganization would proceed more steadily. Further, a psychological statement of the same order might argue that multi-stage lesions afford the animal an opportunity to transfer the learning from one structure to another. When the target structure is totally ablated, other structures will be capable of subserving retention. It is implicit in this argument that no brain structure has a unique capability which cannot be `taken over' by another.

On the other hand, a view which emphasizes the uniqueness of particular brain structures in conjunction with the possibility of alternative solutions to the same problems would state that serial lesions will only attenuate deficits in those cases where the lesioned structure is not essential to learning. That is, tasks demanding

* Another approach to the question of recovery of function is provided by the use of neonatal lesions. Here, it is possible that the brain can reorganize itself during development such that no specific deficits would be produced by the lesion. There has been little work to date on neonatal hippocampal lesion effects and what there is seems rather confusing (e.g. Isaacson et al. 1968, Nonneman and Isaacson 1973, Moorcroft 1971, Molino 1975). The first two reports, involving the testing of cats some time after neonatal lesions, suffer from the `filling in' of the lesion during development and from the fact that neocortical lesions had many of the same effects as did the aspiration hippocampal lesions. None the less, there were indications that neonatal lesions could affect a number of functions usually impaired by adult lesions, though some tasks, such as runway extinction, were unaffected by the early lesions.

Moorcroft's study does not shed much light on the recovery question, as his rats were tested only 3 days after lesions were made. For this very reason, however, these data provide information on the maturation of hippocampal functions. As we have pointed out already, there is considerable post-natal neurogenesis in the hippocampus, and the structure does not appear to be fully functional in the rat for about 3 weeks. Given this, it should be possible to demonstrate the developmental onset of locale system functions with growth. Moorcroft showed that the hyperactivity usually induced by hippocampal lesions only appears when lesions are made at 16 days or older and the rats tested at around 20 days. Of course, these data do not say much about the onset of locale function; it would be better to study normal rats at different ages in situations such as spontaneous alternation, exploration, and so on (see e.g. Douglas et al. 1973). Altman el al. (1973) have pointed out that neonatal rats bear a strong resemblance to adults with hippocampal lesions, a suggestion with which we concur, with certain reservations (see Nadel et al. 1975). Finally, Molino (1975) tested rats with either dorsal or ventral lesions made in infancy; he also observed some `filling in' of the lesion. Neither lesion affected the development of a CER, which was somewhat retarded by adult ventral lesions. Similarly, neither infant lesion facilitated two-way avoidance; only the adult ventral lesion had this effect. It should be noted that the different groups were all tested 60 days postoperatively, thus at quite different ages. The extent to which this procedure was responsible for the atypical adult data remains to be determined.

locale solutions should not benefit from serial lesions, while those which can be solved either through place or taxon hypotheses might benefit.

Five studies of recovery of function after serial lesions in hippocampus have been reported (Isaacson and Schmaltz 1968, Stein *et al.* 1969; LeVere and Weiss 1973, Dawson, Conrad, and Lynch 1973; Greene, Stauff, and Walters 1972). In two of these some recovery was seen, while in the other three serial lesions yielded the same results as did one-stage lesions. In the Stein *et al.* report the animals were tested on several tasks, in all cases after all surgical treatments had been effected. Included were tests of successive discrimination and passive avoidance, both examples of tasks in which either place or taxon hypotheses could conceivably be used. In these cases the authors report that two-stage lesions yield normal performance, while one-stage lesions yield deficits. In that the animals in this study were not given any training in the interval between the two operations, one cannot argue that the recovery of function depended upon an initial displaced learning which survived the second, and final, operation. As such, these data support the notion that serial lesions, without intervening training, are less deleterious than are single-stage lesions. Dawson *et al.* compared one-stage and two-stage lesions and provided an important control lacking in the Stein *et al.* study; their rats were tested at equivalent times after the completion of surgery. They concluded that

> `there are no distinguishable differences in the behavioural deficits produced by single-stage as compared with two-stage hippocampal lesions' (p. 275).

Thus, in their study, perseveration and hyperactivity were a constant feature of bilateral hippocampal damage, whether the lesions were made serially or in a single operation.

In the Greene *et al.* study the two-stage lesion group received some training between the two operations. Hippocampal animals with serial lesions were less impaired on a spatial alternation task than were one-stage animals. However, the serially lesioned rats were still significantly worse than were control animals. Thus, while serial lesions can overcome part of the deficit they apparently cannot eliminate it. Finally, LeVere and Weiss have provided the strongest evidence that the nature of the task and the particular brain structure involved put unique constraints on the extent of `recovery' following serial lesions. They used a task which almost inevitably produces deficits in hippocampal animals: spatial discrimination reversal. No difference was seen between animals receiving one-stage or two-stage lesions in this situation, both groups being impaired relative to controls.*

* Douglas (1975) reported on some hitherto unpublished work demonstrating that serially produced hippocampal lesions abolish spontaneous alternation.