Central Nervous System: Recovery of Function

Abstract. *Rats with one- or two-stage lesions in the hippocampus, amygdala, or frontal cortex were tested on a variety of tasks. Even though locus and amount of tissue damage were very similar in the two groups, animals with one-stage lesions were impaired as judged by performance on all problems, while animals with two-stage lesions were not.*

Although Lashley (*1*) considered the problem of equipotentiality of brain function 38 years ago, current research on brain-behavior relationships has tended to emphasize relatively strict localization of function. According to this later work, a particular area of the brain is necessary for the control of a behavior sequence, and its removal should impair or prevent the occurrence of that sequence. However, several studies have shown that successive two-stage cortical lesions have no effect upon retention of a learned discrimination under certain conditions, whereas bilateral, single-stage removal produced marked deficit in performance (*2*).

In view of the importance of these findings for general theories of brain function, we explored the possibility of obtaining similar results by testing acquisition as well as retention and by successively removing cortical as well as subcortical structures. Such data would indicate that, although a particular structure of the central nervous system may be involved in the mediation of certain behavior, its absence would not be a necessary condition for the elimination of that behavior. In addition, it would be difficult to claim that a specific behavioral function was localized in that structure. To test our hypothesis, we studied the effects of lesions in the frontal, hippocampal, and amygdaloid areas of the rat brain; it has been demonstrated that, in the rat, bilateral, single-stage damage in any of these zones produces a specific and highly replicable syndrome (*3*).

Our subjects were 72 male albino rats (approximately 275 to 300 g). Seven rats were randomly assigned to each of the following six groups, named for the treatment given: one-stage hippocampal lesions (1-HC), two-stage hippocampal lesions (2-HC), one-stage amygdaloid lesions (1-Am), two-stage amygdaloid lesions (2-Am), one-stage sham operation (1-S), or two-stage sham operation (2-S). Ten rats were assigned to each of the following three groups: one-stage orbitofrontal lesions (1-OF), two-stage orbitofrontal lesions (2-OF), or unoperated control (UC). Surgery was performed under general anesthesia with a stereotaxic device for the placement of the stainless steel, epoxy-coated electrode. A Grass radiofrequency device (used for the radiofrequency subcortical lesions) was used to deliver a 65-ma current for 20 or 30 seconds to either the hippocampus or amygdala, respectively. The orbitofrontal lesions were produced by subpial aspiration.

In the groups receiving one-stage surgical lesions (called one-stage groups or animals), bilateral damage was effected in a single operation. In the groups receiving two-stage lesions (called two-stage groups or animals), lesions were first made in either the right or the left hemisphere and then, 30 days later, in the same structure on the contralateral side. Animals that underwent a sham operation were treated like either the one- or two-stage animals except that the electrode never penetrated the brain. To minimize age differences between groups, all one-stage surgery was completed within 4 days after the two-stage groups received their second lesion. All the rats were handled each day during the 30-day recovery period of the two-stage groups. Testing began 2 weeks after surgery on a given group. The animals were maintained on a 23-hour, 45-minute water-deprivation schedule during all test periods.

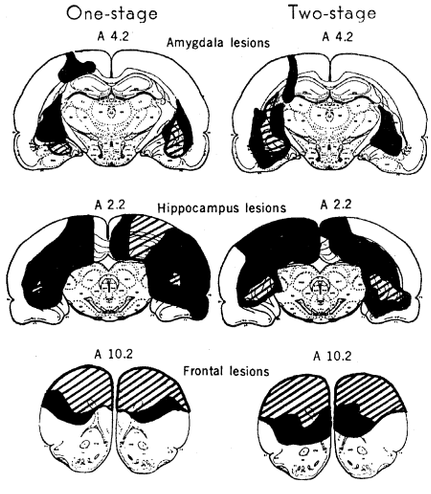

Fig. 1. Representative sections of the maximum and minimum extent of damage in the three structures. The hatched portions of the sections represent the minimum amount of damage indicated, and the solid portions represent the maximum damage located by the coordinate shown.

Before discrimination training, rats with hippocampal or amygdaloid lesions and sham-operated rats were trained to run for water reward in an enclosed Y maze by being permitted a few sips of water upon entering either stem. Training on a light-dark discrimination problem began after each rat had learned to run regularly to water in the maze. Animals received a water reward in the left side of the maze when both arms of the Y were illuminated at the water spout and a reward in the right side of the maze when both arms were darkened. Testing was carried out under dim, red, room light. The intertrial interval was 30 seconds; during this period the rats were contained in the stem of the maze. Each animal received ten trials per day until it reached a criterion of nine correct responses in ten successive trials. The rats were then required to reverse their responses in the same apparatus to the same criterion used in the initial learning task.

Upon completion of reversal training, the rats were prepared for a passive-avoidance task; they received 100 water-reinforced trials (ten per day) in an enclosed straight alley marked off in squares. On day 11, the water spout was electrified, and the number of squares that the rats crossed and the number of shocks that they received were recorded. If an animal did not leave the starting area within 1 minute, trials for that day were terminated.

Because animals with frontal lesions are most impaired in spatial performance, we decided on a sequence of tasks sensitive to this deficit (*3*). Thus the rats with frontal lesions were tested for postoperative acquisition of (i) delayed spatial alteration, (ii) light-dark visual discrimination and reversal, and (iii) nonspatial, simultaneous visual discrimination. All these tasks involved water reward.

The first task was administered in a T maze with a 5-second intertrial interval. Subjects received 16 trials per day with either right or left response being rewarded on the first trial. On remaining trials, the rats were rewarded only when they switched from their last previously rewarded response.

Table 1. Number of trials to criterion and number of shocks given in tasks performed by rats with lesions of the hippocampus and amygdala. Groups with one-stage lesions are labeled 1-S; groups with two-stage lesions are labeled 2-S; LDD, light-dark discriminations; PA, passive avoidance.

Group	LDD (mean)	LDD reversal (mean)	PA (mean)
	Hippocampus		
1-S	120.0	168.6	16.9
2-S	51.7	91.7	5.7
	Amygdala		
1-S	94.3	120.0	11.3
2-S	84.3	92.9	5.7
	Sham-operated		
1-S	50.0	71.7	7.7
2-S	55.0	106.7	7.2

Training continued until the animals reached a criterion of 15 successive correct responses on a given day.

Upon completion of this task, the rats were trained on the same light-dark discrimination problem described earlier to a criterion of nine out of ten correct responses on a given day. This was followed by reversal training to the same criterion.

The final task required the animals to approach vertical and to avoid horizontal black-and-white stripes in a modified Grice-Thompson box (*5*). Animals received ten trials per day until they reached a criterion of nine correct responses on a given day.

We observed marked differences in performance among the groups (*4*). On acquisition of light-dark discrimination, 2-HC rats showed no deficit in comparison with the sham-operated groups, while 1-HC rats showed highly significant impairments in maze learning. Both 1-Am and 2-Am groups showed a deficit in acquisition; however, in neither case was it as severe as that observed in the 1-HC group.

Table 2. Number of trials to criterion in tasks performed by rats with lesions of the frontal cortex. Groups with one-stage lesions are labeled 1-S; groups with two-stage lesions are labeled 2-S; unoperated controls are labeled UC; DSA, delayed spatial alternation; LDD, light-dark discrimination; SD, simultaneous discrimination.

DSA	LDD (mean)	LDD reversal (mean)	SD (mean)
	Group 1-S		
300.0	278.5	313	120.0
	Group 2-S		
150.0	124.0	121	79.4
	Group UC		
104.6	148.0	132	73.0

In reversal learning, the 1-HC and 1-Am groups still showed marked disruption of performance, whereas the 2-HC and 2-Am subjects did not differ from the sham-operated controls.

Similar results were obtained for passive avoidance; only the 1-HC and 1-Am animals were unable to avoid shock, and the 1-HC rats were even more disabled than the 1-Am rats. The impairment in light-dark discrimination appearing in the 2-Am animals was not observed in the performance of any subsequent task. (Table 1).

We found that group 1-OF took significantly longer to reach criterion than either group 2-OF or the unoperated controls on each of the tasks. In marked contrast to group 1-OF, group 2-OF did not differ significantly from unoperated controls on any of the tasks used in this experiment. There was no overlap in performance of the subjects in groups 1-OF and 2-OF on the first three tasks (Table 2).

When the tests were completed, the animals were killed by intracardial perfusion, and the brains of rats with lesions were removed and prepared for histological examination (*6*). In all cases, there was extensive bilateral damage in the hippocampus or amygdala. Most animals with amygdaloid lesions also suffered damage to the ventral hippocampus and to the claustrum. The rats with lesions in the hippocampus also suffered damage to the overlying neocortex. In four cases there was slight, unilateral damage to the lateral geniculate body. In all cases, orbitofrontal damage was confined to the frontal lobes. There was only one instance of slight damage to the anterodorsal caudate nucleus and this was in an animal with two-stage lesions. The extent of damage in animals with one- or two-stage lesions was not significantly different (*7*).

Our data indicate that in adult rats successive removal of approximately equal amounts of brain does not produce the same deficits as single-stage removal. In our experiments sequential removal of cortical and subcortical associative areas of the brain did not render the animal different from normal and sham-operated controls with respect to performance on a variety of tasks. In contrast, rats with one-stage lesions at the same loci showed marked and long-standing deficits on these tests of learning and performance. Since no training intervened between first and second stages of the operations in the two-stage groups, and since all animals were handled in the same manner, the apparently normal behavior of the two-stage animals must be due to some naturally occurring reorganization of activity of the central nervous system.

Recovery of function in the absence of specific training has been observed in very young animals (*8*), but similar plasticity in the absence of prior learning or rehabilitative training has not been as clearly demonstrated in mature organisms. Several hypotheses have been presented in an attempt to account for reorganization, but they fail to specify the responsible mechanisms. Lashley thought that compensation or vicarious function might be due to overlapping neuronal fields such that specific memory traces are scattered over a large area of the brain (*1*). Kennard suggested that other structures take over the function of tissue that has been removed but was unable to specify the particular pathways or mechanisms involved (*9*).

Since we did not observe regeneration of neural tissue in any of our brain-damaged groups, it is likely that the remaining tissue, unaffected by surgery, must be involved in the recovery of function. If this is true, then it becomes somewhat difficult to infer that particular portions or areas of the central nervous system are necessary or critical for the mediation of complex behavioral responses; the behavior is apparently normal even though the tissue presumed to be essential has been removed. Luria suggested that complex adaptive activity is a function of the dynamic integration of the whole central nervous system and that functional systems mediating complex behavior are not fixed in any one area of the brain (*10*). His position is similar to Lashley's notion of overlapping zones, but it cannot explain why two-stage lesions permit rapid recovery, while the same damage, performed in one stage, does not. At present the physiological mechanisms which underlie this phenomenon are not well known, but there is recovery of function in the absence of retraining in mature rats subjected to lesions in a number of different brain areas.

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Rapid Eye Movement Sleep: A Sleep-Dependent Process

Othmer *et al.* (*1*) reported that cyclic patterns of brain activity, similar to those that occur during sleep (*2*), also continue during daytime wakefulness. Their conclusions, if valid, would have fundamental implications for the function and nature of rapid eye movement (REM) sleep processes. However, they are based on measurements of only a single variable, REM itself, as representative of continuing cycles of brain activity throughout the 24-hour period. I take exception to their analysis for the following reasons:

1) Rapid eye movement is only one of a large constellation of physiological manifestations of REM sleep. To conclude that the periodic cerebral activity pattern of REM sleep continues during wakefulness by day on the basis of gross similarities of eye movement patterns alone is unjustified. That REM normally occurs during daytime wakefulness is axiomatic. Indeed, one of the characteristics used to define wakefulness is the presence of REM (*3*). It is well known that REM sleep occurs during daytime naps (*4–6*), so that REM sleep in normal individuals is contingent upon the prior occurrence of nonrapid eye movement (NREM) sleep, with the proportion of NREM sleep following a diurnal rhythm corresponding closely to that of body temperature (*4*).

To support their conclusions, Othmer *et al.* would have to demonstrate either that REM sleep occurs periodically during extended periods of wakefulness, or that during wakefulness there exist periods of REM accompanied by other activated physiological patterns of brain and body activity alternating with periods of relative ocular quiescence and reduced physiological activity. Neither of these alternatives was evident in their results.

2) Othmer *et al.* attempted to show that subjects exhibited periods of wakefulness accompanied by eye movements similar to those of REM sleep. As illustrations they presented two examples (their Fig. 2, IIIA and IIIB) of the polygraphic recordings during such periods which are ambiguous for scoring. As well as can be judged, the electroencephalogram (EEG) in these two examples is not one of unambiguous wakefulness characterized by predominant alpha rhythm, as shown in section IV of the same figure. Rather, the EEG more closely resembles that of stage 1 sleep, shown in section V, with slow rolling eye movements present and in sections I and II of REM sleep. Although alpha rhythms are evident, they appear to constitute less than 50 percent of the record. Taken together with the presence of REM's and absence of muscle tone, I would classify these samples as stage REM sleep (*3*).

It would seem most important to have shown examples of wakefulness without REM, which occurred for periods exceeding 2 hours as indicated in Fig. 1. Examples of transitions from such periods into wakefulness accompanied by REM would also have been more informative than an arbitrary example of an extreme form of waking voluntary eye movement (Fig. 2, IV). Periods of wakefulness as long as 2 hours unaccompanied by rapid eye movements must represent a remarkable phenomenon.

3) Othmer *et al.* conclude "that REM occurs at intervals throughout a 24-hour period and not solely during the usual periods of sleep." Even if one grants that the reported wakeful periods accompanied by REM were indeed genuine wakefulness, subject 1 failed to display such periods under three of the four conditions, subject 3 only once on each of three of the conditions and not at all under condition II, and subject 2 on only two occasions during conditions I and IV (Fig. 1).

4) The article contains insufficient description of the experimental methods and is replete with incongruous data. No description of the electrode placements for recording the EEG, electrooculogram (EOG), and electromyogram (EMG) was given, nor was there a description of the time constants used, which are especially important in the evaluation of the EOG. The speed of the recordings shown in Fig. 2 is indicated neither by a time marking nor in the text. Othmer *et al.* give no quantitative criteria for discriminating between single REM's and bursts of REM's, but merely present two ambiguous illustrations of the distinction (Fig. 2, IIIA and IIIB).

What were the instructions given to the subjects, and what were they told regarding the purpose of the experiment? It would seem crucial that the subjects be naive about the nature of the investigation? What exactly are "eye-rollers"? Why were two of the subjects studied after nights when they themselves reported lack of sleep? Clearly, sleep deprivation disrupts the normal patterns of sleep and wakefulness (*7*). Adaptation nights prior to the experimental sessions would have been desirable.

What was the rationale for the adoption of the different conditions and especially for waking subjects after 3 minutes of stage 2 sleep under condition (iv)? Figure 1 incomprehensibly shows that all subjects had at least as much if not more stage 2 under condition (iv) as under any of the other three conditions! Moreover, immediate transitions from stage W to stages 3 and 4 under this condition, as the authors describe in the text are not evident in a single instance in the same figure; in fact, it shows subject 2 to have had small amounts of stage 3, while subjects 1 and 3 had no stage 3 or 4 sleep at all.

The characteristics of the nighttime sleep bear little resemblance to those which have been almost universally reported by others. During the initial