Localization of a “passive avoidance memory system” in the white rat

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Adult rats, previously trained to refrain from entering a small dark compartment from a large illuminated compartment, sustained lesions to 1 of 53 different brain sites and were subsequently tested for retention. Retention losses were associated with lesions to the neocortex, most elements of the limbic forebrain and basal ganglia, medial portions of the thalamus and hypothalamus, colliculi, median raphe, and cerebellum. Most of these structures were also found to be critical for retention of an active avoidance habit. It was hypothesized that avoidance habits depend upon the activities of four functional blocks of the brain: the first block (basal ganglia) is concerned with sensorimotor integration, the second block (dorsal midbrain, posterior thalamus, amygdala, nucleus accumbens, and frontal cortex) plays a role in fear-initiated responses, the third block (cerebellum, anterior and ventromedial thalamus, and parietal cortex) has somatosensory functions, and the fourth block (occipital cortex, hippocampal complex, and mamillary bodies) is involved with cognitive mapping. These functional blocks require the engagement of an inhibitory mechanism (medial hypothalamus and median raphe) or an excitatory mechanism (brainstem reticular formation and anterior cingulate cortex) in order to support passive and active avoidance habits, respectively.

This study represents another in a series of experiments aimed at identifying those pathways of the brain that are necessary for the memory (expression) of learned responses in the rat. The general procedure involves placing lesions in many different cortical and subcortical areas (using different subjects for different lesion placements) and then testing the subject's retention of a previously learned response. The distribution of individual lesions found to induce serious amnesic effects would delineate those pathways that are critical (either directly or indirectly) for the normal expression of that learned response.

For convenience, the resulting map of critical cortical and subcortical structures has been termed a “memory system.” As might be expected, the memory system corresponding to one type of learned response will be different from that corresponding to another type of learned response. This is indeed what has been found in comparing, for example, a “visual discrimination” memory system (Thompson, 1976) with a “vestibulo-kinesthetic discrimination” memory system (Thompson, Arabie, & Sisk, 1976) or with a “maze” memory system (Thompson, 1974).

The purpose of the present experiment was to map the brain of the rat for a “passive avoidance” memory system and to compare this map with one corresponding to an “active avoidance” memory system. The specific passive avoidance response chosen for study required the

rat, under threat of footshock, to refrain from entering a small dark compartment from a large illuminated compartment. Retention measures included the occurrence (or nonoccurrence) of the previously punished response as well as the presence (or absence) of a vacillatory response as the animal approached the dark compartment for the first time. It should be noted that strict adherence to latency scores in this experiment would pose problems of interpretation, because certain groups of brain-damaged rats are apt to differ markedly from controls in the initiation of locomotor behavior, independent of any prior punishment within the test situation (see Thompson & LeDoux, 1975).

Data on the active avoidance response have been published elsewhere (Thompson, 1978). In this situation, the rat was required to jump onto the ledge of a box within 10 sec in order to avoid footshock. The retention measure involved comparing the number of trials prior to the first appearance of an avoidance response in the retention test with the number of trials prior to the first appearance of an avoidance response in the original learning period.

METHOD

Subjects

Adult male albino rats ($n = 366$) of the Wistar strain were studied, their weights ranging from 400 to 650 g. All animals were maintained on a 12-h light-dark cycle and were tested only during the light phase.

Prior to original learning, each rat was handled periodically and checked for eye disease and middle-ear infection. Preoper-

This research was supported in part by a grant from the Graduate Council on Research, Louisiana State University.

actively, the animals were usually housed (two per cage) in medium-size wire cages containing a constant supply of food pellets and water. Postoperatively, each rat was allowed to recover in a separate cage, but was subsequently paired with another operated (or control) rat at least 1 week prior to the retention test.

Apparatus

The apparatus consisted of a two-compartment box having a grid floor (see Figure 1). The walls were 20.5 cm high and painted flat white. The large illuminated compartment was covered by a transparent Plexiglas lid while the small dark compartment was covered by a Plexiglas lid painted black on the outside. An opening at one end of the illuminated compartment gave access to the dark compartment. A guillotine door could be lowered to block entrance to the dark compartment. The grid floor of the dark compartment was connected to a Variac, which delivered footshocks with an average intensity of 3.5 mA.

The entire apparatus was located in a sound-attenuated room illuminated by conventional ceiling fluorescent lights. During testing, an opaque white screen with a small aperture for viewing was secured to one wall of the apparatus.

Procedure

Preparatory to the first trial, the rat was placed into the illuminated compartment at Section A or Section B (see Figure 1). (On subsequent trials, the rat was placed at Section C or Section D.) A trial was initiated with the raising of the guillotine door separating the dark compartment from the illuminated compartment. When the rat made an error by entering the dark compartment—all four feet being within the threshold—individual footshocks were administered at a rate of about one every 2 sec until the animal returned to the illuminated compartment (all four feet being outside of the threshold). No further footshocks were administered unless the animal reentered the dark compartment, thus committing a second error. The trial was terminated when the animal remained within the illuminated compartment for 10 min after receipt of its last experience with footshock. The guillotine door was then lowered and the rat returned to its home cage.

One trial was given daily, and the criterion of learning consisted of 2 consecutive errorless days.

From 4 to 24 h after learning, the majority of animals sustained brain damage. Five animals served as normal controls, and an additional 10 served as sham-operated controls. The latter underwent anesthesia, placement into the stereotaxic headholder, exposure of the skull, and suturing without further treatment. Half of the sham-operated animals underwent the foregoing surgical procedure only once, while the remaining animals underwent the surgical procedure twice, with an interoperative period of 7-10 days. (The latter subgroup served as a control for brain-damaged animals that sustained two-stage lesions.)

Following a 10-20-day recovery (or rest) period, each rat was required to relearn the passive avoidance habit to the criterion of 2 consecutive errorless days. The procedure was identical to that followed in original learning.

Measures of Performance

The number of errors along with the latencies to enter the dark compartment were recorded. Vacillatory responses were also recorded and were of three types. Type I vacillatory response occurred when the rat partially entered the dark compartment (forelegs inside of threshold, but hindlegs outside of threshold) and then fully retreated to the illuminated compartment. Type II vacillatory response occurred when the rat only slightly entered the dark compartment (any part of the head region inside the threshold, but all four legs outside of threshold) and then fully retreated to the illuminated compartment. Type III vacillatory response was usually observed when the rat occupied Section C or Section D, but could also be observed when the rat occupied

Figure 1. Floor plan of the apparatus showing the small dark box, large illuminated box (divided into four equal sections—A, B, C, and D), and the placements of the guillotine door and screen (heavy solid lines).

Section A or Section B: the rat would stretch its head and body in the direction of the dark compartment, but would not proceed toward the threshold. Type III vacillatory responses, however, were not included in any of the statistical analyses of this paper (except when specified) for two reasons. First, it was not clear that the animal was orienting toward the dark compartment specifically or toward some area adjacent to the dark compartment. Second, those animals exhibiting a Type III vacillatory response almost invariably exhibited Type I and/or Type II vacillatory responses.

Statistical Analysis

For each group, three measures of retention performance were calculated. One measure consisted of the percentage of rats that committed at least one error during the retention test. The second measure consisted of the percentage of rats that committed at least one error on the first day of the retention test. The third measure consisted of the percentage of rats that exhibited at least one vacillatory response (Type I or Type II) either prior to entry into the dark compartment for the first time or prior to the termination of the retention test, whichever came first.

The significance of the differences in these percentages (proportions) between each brain-damaged group and the controls were computed by the Fisher exact probability test.

Surgery and Histology

Bilateral lesions were customarily carried out in one stage under deep chloral hydrate anesthesia. For neocortical lesions and lesions to certain other areas (olfactory bulb, cingulate cortex, and cerebellum), the suction method was used. Subcortical lesions were made stereotaxically with reference to a modified version of the Massopust atlas (Thompson, 1978). Depending on the area to be destroyed, a constant anodal current, ranging from 1.5 to 5.0 mA for a duration of 5-15 sec, was passed through an implanted stainless steel electrode with 1.0-2.0 mm of the tip exposed. Lesions to the caudate nucleus and globus pallidus were invariably carried out in two stages, with an interoperative period of 7-10 days. In some cases, two-stage procedures were used to damage the paramedial portions of the mesencephalic and metencephalic

reticular formation. Details concerning the surgical procedures have been reported elsewhere (Thompson, 1971).

At the conclusion of postoperative testing, each brain-damaged rat was killed with an overdose of Nembutal, its vascular system perfused with normal saline followed by 10% Formalin, and the brain removed and stored in 10% Formalin for 2-5 days. For cortical injuries, the lesions were reconstructed on Lashley-type brain diagrams prior to sectioning. Each brain was then blocked and sectioned frontally at 90 microns with the use of a freezing microtome. Every third section through the lesion was photographed by using the section as a negative film in an enlarger (see Thompson, 1971).

The size and locus of the lesions to different brain sites were generally found to be comparable to those reported in earlier studies which also canvassed many different cortical and sub-cortical areas with lesions (see Thompson, 1978).

RESULTS

Preoperative Performance

Considering all 319 rats that completed preoperative and postoperative training in this experiment,¹ the mean

number of errors to learn the passive avoidance response was 1.8, with a range of 1-5 errors. The mean latency to enter the dark compartment for the first time was 44.4 sec, with a range of 3-650 sec.

It is important to note that 95.1% of the rats exhibited no vacillatory responses of any kind (Types I, II, or III) prior to entry into the dark compartment for the first time. (Hesitation or slow entrance into the dark compartment was occasionally observed, but this behavior was not scored as a vacillatory response.) Most of the animals, however, did exhibit at least one vacillatory response in the period between committing an error and reaching the criterion of learning.

Postoperative Performance

Table 1 summarizes the performance scores earned on the retention test for all groups. Since the normal and sham-operated rats were virtually indistinguishable from each other on the retention test, they were

Table 1
Percentage of Rats Committing At Least One Error on the Retention Test, Committing At Least One Error on the First Day of the Retention Test, and Showing At Least One Vacillatory Response Prior to Committing an Error or Prior to the Termination of the Retention Test, Whichever Came First

Group	N	Retention Error	First Day Error	Vacillatory Response
Control	15	26.7	0.0	100.0
Peripheral Blinding	5	60.0	40.0	100.0
Olfactory Bulb	5	40.0	40.0	80.0
Neocortex				
Frontal region	5	80.0	60.0*	40.0*
Parietal region	6	67.7	50.0*	67.7
Occipital region	4	100.0*	100.0*	0.0*
Other Telencephalic Areas				
Anterior cingulate cortex	5	60.0	40.0	80.0
Posterior cingulate cortex	4	50.0	25.0	100.0
Entorhino-subicular area	4	100.0*	100.0*	0.0*
Hippocampus (dorsal)	4	75.0	75.0*	50.0*
Septofornix area	5	100.0*	80.0*	40.0*
Septal area (rostral)	5	80.0	20.0	100.0
Amygdala	4	100.0*	100.0*	0.0*
Nucleus accumbens	5	80.0	80.0*	40.0*
Caudoputamen (rostral)	4	100.0*	100.0*	100.0
Caudoputamen (middle)	4	100.0*	100.0*	0.0*
Globus pallidus	4	100.0*	75.0*	0.0*
Entopenduncular area	4	100.0*	100.0*	50.0*
Thalamus				
Anterior area	5	100.0*	80.0*	40.0*
Ventromedial area	8	50.0	37.5*	62.5*
Dorsomedial area	6	100.0*	100.0*	50.0*
Lateral area	5	40.0	40.0	100.0
Ventral area	5	20.0	20.0	100.0
Nucleus posterior area	4	50.0	25.0	75.0
Parafascicular area	6	67.7	67.7*	83.3
Lateral geniculate nucleus	5	20.0	0.0	100.0
Hypothalamus				
Medial forebrain bundle (rostral)	7	71.4	42.9*	100.0
Medial forebrain bundle (caudal)	6	67.7	33.3	33.3*
Supraoptic area (medial)	6	83.3*	67.7*	50.0*
Ventromedial area	6	83.3*	83.3*	50.0*
Mammillary bodies	5	100.0*	100.0*	40.0*

Table 1 Continued

Subthalamus	6	67.7	67.7*	83.3
Pretectal Area	4	75.0	50.0*	50.0*
Brainstem Reticular Formation				
Mesodiencephalic region (medial)	4	50.0	25.0	100.0
Prerubral region	4	50.0	25.0	100.0
Suprarubral region	5	40.0	40.0	80.0
Supranigral region	7	71.4	57.1*	85.7
Postrubral region	4	50.0	25.0	100.0
Ventrolateral midbrain region	5	20.0	20.0	80.0
Pontomesencephalic region (medial)	4	75.0	75.0*	75.0
Pontine region (medial)	4	25.0	25.0	100.0
Other Brainstem Areas				
Superior colliculus	4	75.0	75.0*	50.0*
Inferior colliculus	4	100.0*	100.0*	25.0*
Subcollicular area	5	60.0	60.0*	80.0
Red nucleus	4	50.0	25.0	100.0
Substantia nigra	5	100.0*	100.0*	0.0*
Pedunculo-nigral area (lateral)	4	50.0	50.0*	75.0
Ventral tegmental area	6	67.7	50.0*	50.0*
Central gray	4	75.0	25.0	100.0
Interpenduncular nucleus	4	100.0*	100.0*	50.0*
Central tegmentum	4	100.0*	25.0	100.0
Raphe nuclei (median)	4	100.0*	100.0*	25.0*
Lemniscal midbrain area	5	60.0	60.0*	100.0
Cerebellum	6	67.7	33.3	50.0*

*Differed from the controls at least at the .05 level.

combined into one major control group for statistical purposes.

Retention Measures

One or more errors. Only 4 of the 15 control animals entered the dark compartment during the retention test. One was a normal control, 2 had one-stage sham operations, and 1 had a two-stage sham operation. No control animal committed more than one error on the retention test.

Based on the proportion of rats committing at least one error during the retention test, 18 of the 53 experimental groups showed a significant deficit in retention of the passive avoidance response (see Table 1).

Those groups showing the greatest disturbance in relearning the passive avoidance habit (averaging at least two errors before reaching the criterion) had lesions to either the entorhino-subicular area (Figure 2A), amygdala (Figure 2B), anterior thalamus (Figure 3A), dorsomedial thalamus (Figure 3B), substantia nigra (Figure 4A), or raphe nuclei (Figure 4B).

Error on first day. None of the control rats entered the dark compartment on the first day of the retention test.

Based on the proportion of rats committing at least one error on the first day of the retention test, 33 of the 53 experimental groups showed a significant loss in retention of the passive avoidance habit (see Table 1).

Vacillatory responses. The 11 control animals that failed to make an error in the retention test were observed to make at least one vacillatory response

(Type I or Type II) prior to the termination of the test. The four animals that did commit an error during the retention test were observed to make at least one vacillatory response prior to entering the dark compartment.

Figure 2. Unstained sections derived from two rats showing lesions of the entorhino-subicular area (A) and amygdala (B).

mental groups showed a significant retention deficit on the passive avoidance habit (see Table 1).

Size and Locus of the Lesions

As noted earlier, the lesions suffered by the various groups in this experiment were, on the whole, comparable in magnitude and locus to those reported in earlier studies, which likewise canvassed many different cortical and subcortical areas with lesions (see Thompson, 1978). The principal exception concerns those lesions to the inferior colliculus: in the present study, these lesions tended to be more medial than those in earlier studies (see Figure 5A). (Since these medial collicular lesions impaired retention of the passive avoidance task, it was necessary to examine the effects of similarly placed lesions on retention of the active avoidance task—see Figure 5B.)

SUMMARY

The Passive Avoidance Memory System

Considering the performance of the four controls that showed at least one vacillatory response prior to entry into the dark compartment, it can be argued that the presence (or absence) of a vacillatory response is a more sensitive measure of retention of the passive avoidance habit than is the presence (or absence) of the previously punished response—entry into the dark compartment. Thus, mapping the critical areas for the passive avoidance deficit (the composite of which will be termed

Figure 3. Unstained sections derived from two rats showing lesions of the anterior thalamus (A) and medial dorsal thalamus (B).

Figure 4. Unstained sections derived from two rats showing lesions of the substantia nigra (A) and median raphe (B).

Based on the proportion of rats exhibiting at least one vacillatory response prior to entry into the dark compartment or prior to the termination of the retention test (whichever came first), 25 of the 53 experi-

Figure 5. Unstained sections showing lesions of the inferior colliculus in a rat trained on the passive avoidance habit (A) and a rat trained on the active avoidance habit (B).

the "passive avoidance memory system") could be based on the distribution of lesions sustained by those subjects from groups showing a retention loss in terms of the vacillatory response measure. This procedure, however, was not followed for two reasons. First, since only one observer was involved in this experiment, the reliability of the observations concerning the presence or absence of a vacillatory response is open to question. Second, approximately 10% of the brain-damaged rats, when approaching the dark compartment for the first time, either showed hesitancy in entering the dark compartment or entered the dark compartment slowly. These behavioral patterns were not scored as vacillatory responses, but they could conceivably constitute an even more sensitive measure of retention of the passive avoidance habit than the vacillatory response.

Rather than choosing one retention measure over another as the best index of a passive avoidance deficit, it was decided to utilize all three retention measures. Thus, mapping the critical areas composing the passive avoidance memory system was based on the distribution of lesions sustained in those rats that came from groups that were significantly inferior to the controls on any one of the three retention measures. Figures 6, 7, and 8 depict these critical areas (shaded areas on the left side of each diagram or section). To emphasize possible focal points within the passive avoidance memory system, darkened areas indicate the distribution of lesions in those rats coming from groups that were significantly inferior to the controls on all three retention measures.²

Figure 6. Schematic drawings of the dorsal and lateral surfaces of the olfactory bulbs, cerebral cortex, and cerebellum (A, B, and C) and a parasagittal section of the rat brain (D). Stippled areas indicate composite lesion placements leading to moderate retention deficits, and blackened areas indicate composite lesion placements leading to severe retention deficits. Areas on the left side of each section or diagram refer to the passive avoidance data, while areas on the right side refer to the active avoidance data.

Figure 7. Frontal sections at successive levels of the brainstem are based upon a modified version of the Massopust stereotaxic atlas (Thompson, 1978). (See Figure 6 for description of stippled and blackened areas.) Abbreviations: AH = anterior hypothalamus; AMY = amygdala; CG = central gray; CP = caudoputamen; DRF = diencephalic reticular formation; gl = lateral geniculate nucleus; gm = medial geniculate nucleus; GP = globus pallidus; H = dorsal hippocampus; IC = inferior colliculus; L = lateral thalamus; LL = lateral lemniscal area; MRF = mesencephalic reticular formation; np = nucleus posterior; P = pons; PRF = pontine reticular formation; R = median raphe; r = red nucleus; S = septal area; SC = superior colliculus; V = ventral thalamus; vm = ventromedial hypothalamus.

For comparative purposes, the critical areas making up the "active avoidance memory system" (shaded areas on the right side of each diagram or section) are also presented. The latter areas were derived from an analysis of over 300 brain-damaged rats previously trained to jump onto the ledge of a box within 10 sec in order to avoid footshock (see Thompson, 1978). Again, to emphasize possible focal points within the active avoidance memory system, darkened areas indicate the distribution of lesions in those rats that failed to make a single avoidance response during the retention test.

DISCUSSION

General Findings

The passive avoidance habit studied in the current experiment was found to be highly susceptible to interference by discrete brain lesions; of the 53 brain sites chosen for study, 36 were associated with retention deficits. Critical areas included the frontal, parietal, and occipital portions of the neocortex, all major limbic forebrain areas except the olfactory bulbs, cingulate cortex, or rostral septal area, all structures lying along

the nigro-striate dopaminergic pathway, medial portions of the thalamus and hypothalamus, pretectum, colliculi, median raphe and interpeduncular nuclei, and cerebellum (see Figures 6, 7, and 8).

Despite differences in the relevant motive (the one underlying the response to be suppressed), the apparatus, and the retention measures, the results of the current study are generally in accord with earlier reports dealing with the effects of local brain damage on retention (and/or learning) of more conventional passive avoidance tasks. Correspondences were observed in connection with lesions to the frontal cortex (Kaada, Rasmussen, & Kveim, 1962), occipital cortex (Wilson & Vardaris, 1972), hippocampus (Kimura, 1958; Isaacson & Wickelgren, 1962; Wishart & Morgenson, 1970), septofornix area (deCastro & Hall, 1975; Thomas, 1972; Wishart & Morgenson, 1970), entorhino-subicular area (Entingh, 1971; Ross, Walsh, & Grossman, 1973), amygdala (Nagel & Kemble, 1976), medial hypothalamus (Kaada et al., 1962), medial forebrain bundle (Heybach & Coover, 1976; Kaada et al., 1962), anterior and/or medial thalamus (Gerbrandt, 1965; Kaada et al., 1962), interpeduncular nucleus (Wilson, Mitchell, & Van Hoesen, 1972), central tegmentum (Wilson et al., 1972), dorsal mesencephalon (Liebman, Mayer, & Liebeskind, 1970), caudoputamen (Kirkby & Kimble, 1969; Mitcham & Thomas, 1972; Prado-Alcalá, Grinberg-Zylberbaum, Arditti, Garcia, Prieto, & Brust-Carmona, 1975; Winocur, 1974), and substantia nigra (Mitcham & Thomas, 1972).

Some Preliminary Considerations

While the data of this experiment tend to agree with earlier findings, it still can be argued that the overall pattern of results obtained on the retention test may be confounded by lesion-induced alterations either in the relevant motive (light aversion), activity level, or probability of making a vacillatory response. An examination of these possibilities is given below.

Brain Lesions and Light Aversion

Since entrance into the dark compartment is based, at least in part, on the "light aversion" motive (see Whishaw, 1974), brain damage could conceivably have influenced performance on the retention test by altering the light aversion motive, independent of any effects on retention of the earlier experience with footshock. Destruction of certain brain regions might diminish the rat's aversion for light and, therefore, would diminish the rat's tendency to enter the dark compartment. On the other hand, damage to other brain sites might enhance the animal's aversion for light and, therefore, would increase the animal's tendency to enter the dark compartment.

Several lines of evidence suggest that lesion-induced alterations in the light aversion motive cannot adequately account for the results of this experiment. First of all,

Figure 8. Frontal sections at successive levels of the brainstem. (See Figures 6 and 7 for description.)

in a study dealing with the effects of discrete lesions to one of 37 different brain areas on the rat's preference for the dark (Thompson & LeDoux, 1976), only 11 lesion placements led to a significant reduction in the animal's aversion for light. The areas in question included the occipital cortex, cingulate cortex, dorsal hippocampus, anteromedial hypothalamus, dorsomedial thalamus, nucleus posterior thalami, interpeduncular nucleus, median raphe, mesodiencephalic reticular formation, dorsal midbrain reticular formation, and the pontine reticular formation. In view of these data, it would be expected that the rats of the current experiment having lesions to any one of the foregoing areas would show better retention of the passive avoidance habit than other brain-damaged rats because of a reduction in the light aversion motive. Yet, 6 of the 11 lesion placements led to defective retention of the passive avoidance habit. Second, in the study by Thompson and LeDoux (1976), not one of the 37 lesion placements significantly increased the rat's preference for the dark. Four brain-damaged groups (those with either mammillary body, ventral tegmental, prerubral, or cerebellar lesions) did show an unusually strong preference for the dark, spending 100% of the time in the dark compartment as compared to 93.3% shown by the control group, but this finding may be related to the animal's hypokinesia or lack of interest in a novel environment rather than to the animal's increased motive to avoid light (see Thompson & LeDoux, 1975). Finally, those brain-damaged groups of the current experiment that

showed repeated attempts to enter the dark compartment (committing at least two errors on the retention test) sustained lesions in brain areas that tended to be associated with an attenuated light aversion motive (Thompson & LeDoux, 1976).

Brain Lesions and Activity

Lesion-induced increases in activity level might be expected to interfere with retention of virtually any passive avoidance task, whereas lesion-induced decreases in activity level would be expected to facilitate retention of passive avoidance behavior. This is not, however, what was found in the current study. In fact, an opposite trend was observed if one considers those lesion placements that produce either hyperkinesia or hypokinesia during the first postoperative week (see Thompson, 1978). Of the 25 brain-damaged groups of the current experiment that might be expected to show hyperkinesia, only 14 exhibited retention losses on the passive avoidance habit. In contrast, of the 15 brain-damaged groups of this experiment that might be expected to show hypokinesia, 13 exhibited defective retention of the passive avoidance habit.

Brain Lesions and Vacillatory Responses

It is conceivable that certain brain lesions might alter the probability of occurrence of vacillatory responses in the presence of a doorway leading from one compartment to another, independent of any prior experience with footshock. That this was probably not the case is suggested by two observations. First, all brain-damaged rats approaching the threshold of the dark compartment exhibited vacillatory responses during the course of the experiment (either before or after committing an error). Second, in the study examining the effects of 37 different lesion placements on the rat's preference for the dark (Thompson & LeDoux, 1976), it was rare for any brain-damaged (or control) animal to exhibit a vacillatory response prior to entering the dark compartment.

Passive Avoidance Memory System vs. Active Avoidance Memory System

The most informative comparison to be made in connection with the data on the passive avoidance memory system (PAMS) would be with those data on an active avoidance memory system (AAMS). The latter was derived from an earlier experiment examining the effects of lesions to 50 different cortical and subcortical structures on retention of a jumping avoidance response (see Thompson, 1978).³ While several methodological differences did exist between the study of the passive avoidance habit in the current experiment and the study of the active avoidance habit in the previous experiment, the experimental procedures overlapped at several significant points (the same observer, subjects of the same strain and of comparable age and previous experience,

lesions of comparable size and location, motive of avoidance of footshock, and one trial given daily in the original learning period as well as in the retention test). It is also important to note that the two problems were not remarkably different from each other in difficulty. While the passive avoidance habit was learned after an average of 1.8 shock experiences, the first appearance of the active avoidance response occurred after an average of 3.1 shock experiences. Furthermore, retentiveness of the two habits was virtually the same. With respect to the passive avoidance habit, 11 of the 15 control animals made no errors during the first 2 days of the retention test. This compares favorably with the active avoidance habit: 10 of the 15 control animals made no errors during the first 2 days of the retention test. And finally, neither habit appears to be dependent upon or guided by visual cues—peripheral blinding produced no deleterious effects on either habit.

In light of the foregoing similarities, the data charted in Figures 6, 7, and 8 have opened the way to at least a provisional examination of regional differences and similarities in the brain mechanisms underlying the performance of passive and active avoidance tasks. Obviously, conclusions based upon the comparison of the PAMS with the AAMS must be made with caution, especially when it is considered that contradictions and confusion generally surround the literature dealing with the significance of specific brain sites in the performance of avoidance habits (see, for example, the recent review article by Black, Nadel, and O'Keefe, 1977, on the hippocampus).

Similarities

More similarities than differences are present between the PAMS and the AAMS. Both embrace the cerebellum, and virtually all sectors of the cerebral cortex, including the occipital areas (see Figure 6). (This latter finding further emphasizes the nonvisual function of the occipital cortex—see Winer & Lubar, 1976.) Except for the olfactory bulbs, cingulate cortex, and rostral septal area, both the PAMS and the AAMS share major divisions of the limbic system, including the entorhino-subicular areas, amygdala, hippocampus, septofornix area, mammillary bodies, anterior thalamus, and interpeduncular nucleus. At brainstem levels, there is a relatively continuous overlap of critical areas extending from the caudate nucleus, through the medial forebrain bundle and medial thalamus, to the ventral tegmental area, substantia nigra, interpeduncular nucleus, and collicular areas of the midbrain (see Figures 7 and 8).

Clearly recognizable within the overlapping critical areas of the brainstem is the nigro-striate dopaminergic pathway (Ungerstedt, 1971) which originates within the nigra and adjacent tegmentum, passes through the ventral tegmental areas and lateral hypothalamus, enters the internal capsule in the vicinity of the entopeduncular nucleus, courses through the globus pallidus, and sub-

sequently ramifies within the caudoputamen. Since damage to any one of these subcortical structures was found to impair retention of both active and passive avoidance habits, the possibility must be considered that depletion of dopamine within the neostriatum is responsible, at least in part, for the observed deleterious effects. Although crucial evidence on this matter is lacking, the recent findings of Fibiger, Phillips, and Zis (1974) and Kelly, Alheid, McDermott, Halaris, and Grossman (1977) suggest that dopaminergic efferents to the neostriatum, while playing an important role in acquisition, may not be essential for retention of avoidance habits. The possibility exists, therefore, that non-dopaminergic nigro-striatal projections (Hedreen, 1971), caudato-pallido-nigral projections (Carter & Fibiger, 1978; Knook, 1965), or both may be significant for the expression of avoidance habits.

The functional significance of the nigro-striate complex in the performance of avoidance habits remains obscure. The notion that this complex may be concerned with sensorimotor integration (Levine & Schwartzbaum, 1973; Marshall, Richardson, & Teitelbaum, 1974) is in keeping with current neurophysiological views about the role of the basal ganglia in the control of movement (Kornhuber, 1974; Webster, 1975) and is likewise consistent with those studies implicating this complex in the performance of a wide variety of activities, such as skilled movements (Hore, Meyer-Lohmann, & Brooks, 1977; Levine & Schwartzbaum, 1973; Spiliotis & Thompson, 1973), orientation to environmental stimuli (Marshall et al., 1974), and spatial localization (Potegal, 1972). Whatever its function in learned performance, it cannot be confined to the execution of avoidance habits. Lesions placed virtually anywhere along the nigro-striate (or caudato-pallido-nigral) pathway have been reported to impair retention and/or acquisition of many different learned activities (Kelly et al., 1977; Thompson, 1978).

Other ascending pathways that appear to be represented within the critical brainstem areas of the PAMS and AAMS are the spinomesencephalic and spinothalamic "pain" tracts. These tracts, according to Mehler's (1969) observations on the rat, terminate in or pass through the intercollicular nucleus, dorsal midbrain area, tegmentum medial to the medial geniculate nucleus, and the posterior thalamus (around the pretectal and parafascicular nuclei). It is conceivable that these sites constitute a "posterior" subsystem concerned with aversive motivational states. Other structures within the PAMS and AAMS that may also participate in this function include the frontal cortex (Tanaka, 1973), amygdala (Blanchard & Blanchard, 1972), and medial thalamus (Vanderwolf, 1971).

Interestingly, most of the remaining critical areas composing the PAMS and AAMS (parietal cortex, occipital cortex, cerebellum, entorhino-subicular area, hippocampus, septofornix area, mammillary bodies, anterior

thalamus, ventromedial thalamus, interpeduncular nucleus, and central tegmentum) are also critical for retention of a maze habit (see Thompson, 1974). Conceivably, the avoidance habits and the maze habit share certain features at the behavioral level which account for the overlapping critical brain areas. One of these features is probably related to the utilization of a cognitive map (see Black et al., 1977).

Differences

Some very striking differences are present between the composition of the PAMS and that of the AAMS. The latter, but not the former, includes the olfactory bulbs, anterior cingulate cortex, ventral thalamic nucleus, nucleus posterior thalami, and the paramedial portions of the brainstem reticular formation. By contrast, the former, but not the latter, includes the medial portions of the hypothalamus, the raphe nuclei, and the lateral lemniscal midbrain area. With only a few exceptions, it appears that the main difference between the PAMS and the AAMS lies in the extent to which each embraces the arousal (or sleep) mechanisms of the brain: the PAMS contains those structures concerned with sleep (preoptic and supraoptic hypothalamic regions and the raphe nuclei), while the AAMS contains those structures concerned with arousal (brainstem reticular formation). This finding is at least intuitively consistent with the notion that passive and active avoidance habits involve opposing central response mechanisms; namely, an inhibitory response mechanism and an excitatory (facilitatory) response mechanism, respectively (McCleary, 1961). Furthermore, this finding provides remarkable support for the view that serotonergic pathways (originating within the raphe nuclei) underlie passive avoidance behavior, while catecholaminergic pathways (originating within certain cell groups of the brainstem reticular formation) underlie active avoidance behavior (Allen, Allen, & Rake, 1974).

One of the most surprising outcomes of this study was the finding that the brainstem reticular formation is relatively unimportant for the preservation of the passive avoidance habit. Earlier studies have shown that lesions to the ventral parts of the brainstem reticular formation impair retention of such tasks as visual and nonvisual discrimination problems, a maze habit, an active avoidance response, and an assortment of latchbox problems (Spiliotis & Thompson, 1973; Thompson, 1978). This difference in the brain mechanisms underlying the passive avoidance task, as opposed to other laboratory tasks, indicates that the brainstem reticular formation may be primarily concerned with learned tasks that require action, response facilitation, and/or "goal-reaching" behavior rather than inaction, response inhibition, and/or "goal-forsaking" behavior. (The fact that the anteromedial hypothalamus is involved in retention of a passive avoidance task but is not involved in retention of other laboratory tasks (see Thompson,

On the strength of the preceding analysis, the expression of both passive and active avoidance habits may be dependent on the integrity of four "functional blocks" within the brain (see Figure 9).⁴

The second block (stippled areas) is conceived to play a role in fear-initiated responses. This block consists of a "posterior" division involving the dorsal midbrain and posterior thalamus and an "anterior" division involving the amygdala, medial thalamus, rostral parts of the medial forebrain bundle and caudoputamen, nucleus accumbens, and frontal cortex.

The third block (areas occupied by vertical lines) is assumed to constitute the most essential part of a sensory system that processes tactile, kinesthetic, vestibular, and proprioceptive signals necessary for guidance of responses (and the construction of a cognitive map) in nonvisual space. It consists of the cerebellum, parietal cortex, anterior thalamus, ventromedial thalamus, and interpedunculo-central tegmental area. As might be expected, lesions to any one of these components would severely compromise habits based on the discrimination of vestibulo-kinesthetic cues, such as a maze habit (Thompson, 1974) or an incline plane discrimination problem (Thompson et al., 1976), but would not disturb visually guided habits (Thompson, 1976).

The fourth block (blackened areas), which includes the occipital cortex, entorhino-subicular area, hippocampus, septofornix area, and mammillary bodies, is conceived to serve in those integrative activities related to the construction, storage, and utilization of a cognitive map. The evidence that the hippocampus may constitute the site where cognitive mapping takes place is impressive and has been summarized in papers by Nadel and O'Keefe (1974), Olton (1977), and Black et al. (1977). The decision to incorporate the occipital cortex and mammillary bodies into this block is based on the findings that these two structures, along with the

These four functional blocks may be viewed as making up the core of a neural system mediating avoidance habits. If the habit requires the animal to refrain from moving from one spatial location to another in order to avoid noxious stimuli, then an inhibitory mechanism (composed, in part, of the medial hypothalamus, median raphe, and lateral lemniscal midbrain area) must be coupled with this core in order to support the habit. If, on the other hand, the habit requires the animal to move from one spatial location to another in order to avoid noxious stimuli, then a facilitatory mechanism (composed, in part, of the brainstem reticular formation, nucleus posterior thalami, ventral thalamus, anterior cingulate cortex, and olfactory bulbs) must be coupled with this core in order to support the habit. It should be clear from the preceding discussion that the engagement of the inhibitory or facilitatory mechanism with the core must necessarily be made at the level of the first functional block (that block embracing the basal ganglia) which is presumed to participate in sensorimotor integration. The recent demonstrations of projections from the raphe nuclei to the substantia nigra (Reubi & Emson, 1978) and caudoputamen (Miller, Richardson, Fibiger, & McLennan, 1975) and from the brainstem reticular

Figure 9. Schematic drawing of a parasagittal section of the rat brain showing the four functional blocks necessary for the performance of avoidance habits: the first block (areas occupied by black dots) is concerned with sensorimotor integration, the second block (stippled areas) plays a role in fear-initiated responses, the third block (areas occupied by vertical lines) has somatosensory functions, and fourth block (blackened areas) is involved in cognitive mapping. Abbreviations: AMY = amygdala; AT = anterior thalamus; CB = cerebellum; CG = central gray; CMF = caudal medial forebrain bundle; CS = superior colliculus; CT = central tegmentum; DMT = dorsomedial thalamus; EP = entopeduncular nucleus; ESA = entorhino-subicular area; FC = frontal cortex; GP = globus pallidus; H = hippocampus; IC = inferior colliculus; IP = interpeduncular nucleus; MB = mammillary bodies; MC = middle caudoputamen; NAS = nucleus accumbens septi; OC = occipital cortex; P = prefrontal area; PC = parietal cortex; PF = parafascicular nucleus; RC = rostral medial forebrain bundle; SCA = subcollicular area; SF = septo-fornix area; SN = substantia nigra; SNA = supranigral area; ST = subthalamus; VMT = ventromedial thalamus; VTA = ventral tegmental area.

formation to the caudoputamen (Lynch, Smith, & Robertson, 1973; Robertson & Travers, 1975) provide possible pathways that may mediate, at least in part, inhibitory and facilitatory influences on passive and active avoidance habits, respectively.

Admittedly, the speculations presented in this section are in need of further specification. It must also be emphasized that the data upon which these speculations are based may themselves be intimately tied to the methodology used. This, of course, means that a "lesion survey" of the brain in connection with retention of a two-way active avoidance habit (as opposed to a one-way habit) or in connection with retention of a passive avoidance habit involving the suppression of a food-approach response (as opposed to a dark compartment-approach response) would probably yield results somewhat different from those of the present experiment. It is also likely that a study using subjects with two-stage lesions would generate a different pattern of results from one using subjects with one-stage lesions (see Stein, Rosen, & Butters, 1974).⁵ In all of the above cases, however, it is reasonable to assume that at least a major portion of each of the four functional blocks shown in Figure 9 (together with the corresponding inhibitory or facilitatory mechanisms) will be involved so long as the subject is tested under unrestrained, free-moving conditions, and does not utilize nonspatial cues in differentiating the area of safety from the area of danger. The most likely exception concerns the functional block containing the hippocampal complex. As pointed out by Black et al. (1977), the extent to which the hippocampal complex is implicated in avoidance performance seems to depend on the extent to which "place learning" contributes to the successful execution of an avoidance response.

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NOTES

1. Thirty-one rats were discarded from the experiment because their lesions were either too small, too large, or placed in regions not intended for study. An additional 16 rats received two-stage lesions to either the occipital cortex, entorhino-subicular area, amygdala, or substantia nigra. The data derived from these rats are mentioned in Footnote 5.
2. Obviously, the lesions of those rats showing "normal" retention that came from groups which were significantly inferior to the controls were not plotted in Figures 6, 7, or 8.
3. In order to achieve a closer correspondence in lesion placements between those animals studied on passive avoidance and those studied on active avoidance, it was necessary to run additional subjects on the active avoidance task. For this reason, the data presented elsewhere on active avoidance (Thompson, 1978) are not identical to those presented in the current paper.
4. It should be emphasized that this conceptualization does not imply that any given component within the four functional blocks has only one function. The occipital cortex is a case in point.
5. In order to determine if two-stage lesions would drastically alter the character of the PAMS, additional animals were trained on the passive avoidance habit and then were subjected to two-stage lesions of the occipital cortex, entorhino-subicular area, amygdala, or substantia nigra. The postoperative test disclosed that all groups, except the one with occipital damage, were significantly inferior to the controls on each of the three retention measures. The occipital group did not differ significantly from the controls on any one of the three retention measures.

(Received for publication February 14, 1978;
revision accepted May 23, 1978.)