VISUAL RECOGNITION IMPAIRMENT FOLLOWING MEDIAL THALAMIC LESIONS IN MONKEYS*

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Abstract—Monkeys with surgical lesions which removed the medial portions of the medial and anterior thalamic nuclei were markedly impaired on a test of object recognition. The same animals were able to learn visual pattern discriminations and a spatial delayed response task at a normal rate. These findings indicate that lesions in the medial thalamus produce a selective impairment in visual recognition memory in monkeys and, consequently, may provide an experimental model for human "diencephalic amnesia".

BILATERAL damage in either of two regions in man, the medial temporal lobe and the medial diencephalon [2, 5], may result in global amnesia. Our understanding of the neural basis of human "temporal-lobe amnesia" has been enhanced by the development of one-trial memory tests that have proved to be extremely sensitive to medial temporal lesions in nonhuman primates [19, 32, 34]. Such studies have shown that combined removal of the amygdala and hippocampus results in a severe, but selective, deficit in one-trial memory and hence provides an animal model of the global amnesia produced by medial temporal damage in man [19, 34]. In the present experiments we have used the same type of memory test to examine the effects of lesions involving the medial portions of the medial and anterior thalamic nuclei in the attempt to develop a model of "diencephalic amnesia" and help clarify the relationship of this syndrome to "temporal-lobe amnesia".

Descriptions of the neuropathology of diencephalic amnesia agree that one region that is frequently, if not invariably, necrotic is the medial part of the thalamus [2, 5]. Reports of amnesics with thalamic damage produced by ischemic infarcts [4, 16], traumatic injury [31], infections [6, 27], tumorous growths [12, 29], or as a result of Korsakoff's syndrome [2, 5, 14, 15, 33] have all contributed to this consensus. These neuropathological studies have variously suggested that damage in nucleus medialis dorsalis [5, 12, 31, 33], the anterior thalamic nuclei [4, 9], or the midline thalamic nuclei [14] may be responsible for diencephalic amnesia. Furthermore, neuroanatomical experiments in monkeys have demonstrated that the hippocampus and amygdala project to adjacent and overlapping cell groups within this same medial thalamic region. Specifically, the hippocampus projects to the anterior nuclei of the thalamus [25], the amygdala to the medial portion of nucleus medialis.

*A preliminary report of these data was presented at the 11th Annual Meeting of the Society for Neuroscience [1].
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dorsalis [21], and both to various midline thalamic nuclei [21, 25, 26]. These findings indicate the possibility that the medial temporal lobe and medial thalamic regions are both part of a neuroanatomical circuit essential for memory. We therefore studied the effects on a one-trial memory task of removing the target nuclei of the amygdala and hippocampus in the thalamus.

The memory test chosen, delayed non-matching-to-sample with trial-unique objects, is a task that assays the monkeys' ability to recognize novel objects presented a few seconds earlier [18]. To evaluate the selectivity of any behavioral losses on this task, we also tested the animals in visual pattern discrimination learning and spatial delayed response learning, two abilities known to be spared in the amnesia produced by medial temporal lesions in monkeys [23, 32].

**METHODS**

**Subjects**

Seven experimentally naive, male cynomolgus monkeys (Macaca fascicularis) weighing 4.0-8.6 kg were used in this study. The animals were housed individually and maintained on a diet of Purina Monkey Chow and fruit.

**Apparatus**

All experiments were carried out in a Wisconsin general testing apparatus (WGTA). The monkeys sat in an illuminated compartment separated from a three-well testing tray by an opaque sliding screen. Adjacent wells were 18 cm apart. The experimenter could observe the monkeys through a one-way window. Banana pellets (P. J. Noyes Co., 300 mg) or raisins served as rewards for correct choices.

**Surgery and histology**

Three of the seven monkeys received lesions in the medial portions of the thalamus (MT), three were unoperated (C), and one served as an operated control (Ct).

One-stage bilateral thalamic lesions were performed aseptically while the animal was under Nembutal anesthesia (35 mg/kg). Dorsomedial bone and dural flaps were made to allow retraction of the medial wall of the left hemisphere. A slit was then made through the corpus callosum to expose the dorsal thalamus, after which the entire extent of the thalamic midline, or massa intermedia, was transected with a glass sucker. A parasagittal strip of tissue approximately 1 mm wide anteriorly and 2 mm wide posteriorly was removed from either side of the massa intermedia with a 22-gauge sucker. The third ventricle surrounding the massa intermedia served as the perimeter of the intended lesion.

The operated control monkey (Ct) received the same surgery as the MT animals except that no thalamic tissue was ablated after the thalamic midline was transected.

At the completion of the experiments the animals received a fatal dose of Nembutal and were perfused intracardially with a 10% solution of formol saline. The brains were removed, blocked, embedded in celloidin, and cut at 25 μm in the coronal plane. Every tenth section was stained with thionine.

In the three MT animals the following midline thalamic nuclei were removed completely: nuclei paraventricularis, centralis latocellularis, centralis densocellularis, alaris, rotundus, centralis superior, centralis intermedialis, and centralis inferior [22]. In addition, there was bilateral damage to most of nuclei anterior medialis, reuniens, and paratenialis, much of the magnocellular portion of nucleus medialis dorsalis, parts of nucleus centrum medianum and parafascicularis, and the mamillothalamic tract (Fig. 1). Other structures damaged, sometimes only unilaterally, were the cingulate gyrus, fornix, stria medullaris, and the remaining anterior thalamic nuclei. One monkey (MT 3) had, in addition, nearly complete destruction of the entire nucleus medialis dorsalis on one side as a consequence of ischemia. The mamillary bodies were not directly invaded in the surgery, but in all three monkeys the medial nuclei showed partial retrograde degeneration as evidenced by both gliosis and cell loss. This degeneration was presumably the result of direct damage both to the anterior thalamic nuclei and the mamillothalamic tract. The amygdaloid complex and the hippocampal formation appeared normal in all animals.

In the surgical control animal (Ct), all of the midline thalamic nuclei were damaged partially, the greatest damage occurring in nuclei centralis superior, intermedialis, and inferior, with nucleus centralis intermedialis almost completely removed. The thalamic transection, which was approximately 200-300 μm wide, produced only slight damage in nuclei paracentralis, centrum medianum, parafascicularis, and the magnocellular portion of medialis dorsalis. Only the most medial portion of the fornix was damaged in this animal.
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Delaying procedures

Delayed non-matching-to-sample. The animals were trained on this one-trial object recognition task preoperatively. Each trial consisted of two parts. First, the monkey pushed aside an object overlying the middle well of the three-well tray to uncover a food reward. The opaque screen of the WGTA was then lowered between the animal and the tray and raised again 10 sec later to display both the previously presented object and a novel object over the lateral wells. In this second part of the trial, the monkey was rewarded for displacing the novel object. Twenty trials
separated by 30-sec intervals were given daily, each trial with a new pair of unique, unmounted objects. A pool of 1300 objects was used so that no item was repeated within a month. This procedure ensured that correct choice depended on memory for the sample object gained from its single presentation 10 sec earlier. The monkeys were trained to a criterion of 90 correct choices in 100 trials and then received surgery.

Postoperative training began 2 weeks after surgery and the animals were tested until they reattained the preoperative criterion. The monkeys' recognition memory was then taxed further through progressive increases of the delay between sample presentation and choice test from the initial 10-sec delay to 30 sec, 60 sec, and finally, 120 sec. The animals received 100 trials at each delay interval.

**Visual pattern discrimination learning.** Approximately 7 months after surgery, all monkeys except the operated control (Ct) were trained on two visual discrimination tasks. The discriminations were between two-dimensional patterns, + vs □ and N vs W, formed from white paper strips set on 7.5 cm square cardboard plaques. The plaques, which were blue for the first discrimination and gray for the second, were placed over the outer food-wells according to a pseudorandom left-right sequence. The + and the N were the positive stimuli. The animals received either 20(+ vs□) or 30 (N vs W) trials a day until they achieved a criterion of 90%, correct responses on 2 successive days.

**Spatial delayed response learning.** Nine months after surgery, all monkeys except the operated control were trained on a spatial delayed response task, which required the animal to remember the location of a food reward concealed in one of two food-wells for delays of up to 10 sec. The food reward was placed under one of two identical gray cardboard plaques, 7.5 cm square, and the plaques were set over the outer food-wells according to a pseudorandom sequence. The monkeys received 30 trials a day and were initially allowed to choose as soon as the wells were covered. After an animal succeeded on at least 27 trials in one session, an opaque screen was lowered between the monkey and the tray, imposing a delay before the animal could make its choice. This delay was gradually increased from 0 to 5 sec according to a titration procedure [8]. Finally, once the animal had achieved 90% correct responses in one session at 5-sec delays, it was tested at 10-sec delays to the same criterion.

**RESULTS**

**Delayed non-matching-to-sample**

The medial thalamic lesions had a profound effect on performance of the recognition task. Whereas the three normal and the one operated control monkey reattained the preoperative criterion within a maximum of 80 trials, the best monkey with a medial thalamic lesion (MT 1) needed 640 trials (Fig. 2). The other two monkeys in this group required over 1,000...
trials and then succeeded only when the sample object was presented twice prior to the recognition test. Under this condition the sample was baited on only one of its two presentations, in a balanced temporal order. Despite this extra exposure to the sample stimulus, the two monkeys (MT 2 and 3) still required an additional 140 and 720 trials, respectively, to reattain the criterion.

The imposition of longer delays between the sample presentation and choice test reinstated the deficit in the experimental animals. Whereas the scores of the three normal and the operated control monkeys remained about 90%, those of the experimental group fell to approximately 70% after the 120-sec delays (Fig. 2). This differential sensitivity to delays was confirmed by an analysis of variance which demonstrated not only a significant difference overall between the two groups \( F(1,5) = 151.2, P < 0.001 \) but also a significant interaction between the groups and the delay intervals \( F(3,15) = 21.3, P < 0.025 \).

**Visual pattern discrimination learning**

Figure 3 shows the learning scores of the monkeys on the two visual pattern discriminations. The animals with medial thalamic lesions behaved like the controls, requiring a comparable number of trials to reach criterion on each of the discriminations.

**Spatial delayed response learning**

The total number of trials and errors accumulated by each monkey over the various delays up to 10 sec are depicted in Fig. 4. Two of the monkeys with medial thalamic lesions performed normally on this task. The monkey with the ischemic infarct (MT 3), however, failed to attain criterion at delays over 1 sec; the animal’s testing was stopped after 1,000 trials on the titration procedure.

**DISCUSSION**

The present experiments demonstrate, for the first time in the monkey [1], that a limited lesion of the medial thalamic region (MT) may produce a striking impairment in a test of
visual object recognition and thus reproduce one of the core symptoms of 'diencephalic amnesia'. The lesion involved all of the thalamic midline and much of the medial sectors of the anterior and medial thalamic nuclei. The impairment was reflected both in the difficulty that the monkeys with MT lesions showed in relearning the original delayed non-matching-to-sample task and, following relearning, by the sharp decline in their performance with increasing delays. The reinstatement of the deficit with longer delays strongly suggests that the retardation in relearning was due not to any difficulty with the non-matching principle itself (e.g. a reduced preference for novel objects, or a difficulty in readopting the "win-shift" strategy) but rather to a genuine loss in recognition memory.

Except for one monkey on one test, the experimental animals performed normally on the control tests, demonstrating that the impairment on the recognition problem was not the consequence of alterations in such processes as perception, attention, motivation, or selection. The one monkey (MT 3) that failed to learn delayed response sustained an ischemic lesion of the entire nucleus medialis dorsalis on one side. Since it has been shown that extensive lesions of nucleus medialis dorsalis involving the parvocellular portion may indeed result in a delayed response impairment [11, 28], it is likely that the additional damage to the parvocellular portion of the nucleus in MT 3 was responsible for this animal's poor performance.

While these initial experiments indicate that lesions in the medial thalamus in monkeys can mimic some aspects of human diencephalic amnesia, additional studies are clearly needed to verify the model. First, the present experiments investigated visual recognition only, whereas human diencephalic amnesia is known to extend beyond vision and to involve associative memory as well. A wide variety of memory tests, including those that have now been found to yield impairments after combined removal of the amygdala and hippocampus in monkeys [19, 20, 32], must now also be applied to animals with medial thalamic lesions. Second, the permanence of the experimental amnesia has yet to be ascertained, although the poor performance of the MT monkeys was still evident 6 months after surgery.
A more difficult issue concerns specification of the damage responsible for the impairment. The normal performance of the operated control monkey (Ct) demonstrates that the deficit in the experimental group was not simply the result of splitting the massa intermedia. Further, it is unlikely that the variable damage to the fornix can explain the results. Although complete transection of the fornix may sometimes produce an impairment in recognition [7, 24; but also see 3, 13], the severity of the deficit found after these medial thalamic lesions, as measured by both the number of trials taken to reach criterion and the need for double presentation of the sample by two of the monkeys, was far greater than that reported after fornix transection alone. More importantly, the degree of damage to the fornix did not correlate with the magnitude of the impairment: the greatest damage occurred in the least impaired monkey (MT 1), whereas the damage was particularly slight in the animal that took the longest to relearn (MT 3). No evidence could be found of a correlation between the extent of damage in any particular nucleus and the severity of the postoperative deficit though both animals MT 2 and MT 3, who were most impaired, suffered slight unilateral damage in the cingulate cortex. These same two monkeys took longest to learn the object recognition task before surgery, however, and this may have influenced their postoperative performance.

All of the animals with medial thalamic lesions showed bilateral degeneration in the mamillary bodies. Whether or not this pathology contributed to the deficit in recognition memory remains to be determined. While the present study did not address this question, the results provide a baseline impairment against which to compare the effects of mamillary body lesions, as well as those of more selective thalamic lesions, comparisons that are essential to the further anatomical delineation of “diencephalic amnesia”.

The present results together with earlier data indicate that in the monkey, as in man, bilateral damage in either of two regions, the medial temporal lobe and the medial thalamus, may result in an anterograde amnesia. In both species the impairment is selective, affecting only certain cognitive abilities [23, 32]. These findings, coupled with the knowledge that the temporal and diencephalic regions are anatomically interconnected, support the notion that the hippocampus, amygdala, and medial thalamus are interlocked in a functional system essential for the formation of new memories [17]. The hypothesis that these several structures form an integrated memory system leaves open the possibility that each structure contributes to the system in a different way [10, 30].

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REFERENCES


Résultats

Des singes porteurs d'une ablation chirurgicale de la portion médiane des noyaux thalamiques médians et antérieurs ont présenté un déficit marqué dans un test de reconnaissance d'objet. Les mêmes animaux étaient capables d'apprendre normalement des discriminations de formes visuelles et des réponses spatiales retardées. Ces résultats indiquent que les lésions du thalamus médian produisent chez le singe une atteinte sélective de la mémoire de reconnaissance visuelle. Ils peuvent par conséquent servir de modèle expérimental pour l'"amnésie diencéphalique" chez l'homme.

Zusammenfassung:

Affen, bei denen chirurgisch der mediale Anteil der medialen und vorderen thalamischen Kerne entfernt worden waren, zeigten deutliche Leistungs- minderung bei einem Test für Objekterkennen. Dieselben Tiere waren imstande, die Unterscheidung von visuellen Mustern und eine räumliche Aufgabe mit verzögter Reaktion in normaler Geschwindigkeit zu lernen. Diese Befunde zeigen, daß Läsionen des mittleren Thalamus bei Affen eine selektive Störung im visuellen Wiedererkennen hervorrufen und deshalb als experimentelles Modell für die "dienzephale Amnesie" des Menschen dienen können.