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Improved acquisition of left–right response differentiation in the rat following section of the corpus callosum

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Split-brained rats learned a left–right response differentiation in a water maze significantly faster than rats with sham surgery. It is unlikely that this superiority resulted from improvement in performance variables since callosotomized rats did not differ significantly from sham operated in speed of acquisition of a brightness discrimination in the same apparatus. Additionally, callosotomy likewise had no effect on the acquisition of a water-maze task requiring consistent unilateral responses. The superiority of the callosotomized animals in forming the left–right response differentiation supports a hypothesis implicating the forebrain commissures in left–right confusion.

INTRODUCTION

An animal can be deemed capable of telling left from right if either of two conditions can be met⁸. Left–right stimulus discrimination (LRSD) is demonstrated if the animal can consistently generate non-mirror-image responses differentially to mirror-image stimuli. Left–right response differentiation (LRRD) is demonstrated if the animal can differentially generate mirror-image responses to stimuli which themselves convey no left–right information. Non-human animals, young humans, and occasional human adults, have difficulty with both types of task, and hence are often described as left–right confused. Our goal in the present study was to examine the role played by the forebrain commissures in such confusion.

Two alternative views of commissural transmission can be counterposited^{8,18}. The first supposes that the commissures contribute to a left–right mirror equivalence (and hence confusability) of sensory-motor events, this contribution perhaps being underlain by homotopic interconnections of the hemispheres. The second supposes that the commissures, perhaps via their heterotopic components, maintain left- and right-

specific events as distinct. Despite an abundance of reports dealing with the effects of split-brain procedures on information flow between the hemispheres, the literature addressed specifically to the effects of commissural section on behavioral left–right equivalence is remarkably scant. Indeed, we know of only three lines of relevant evidence.

Experimental investigations of the role of the commissures in left–right confusion were included in the studies of classical conditioning in dogs in Pavlov's laboratory. Krasnogorski, Bykov (both cited in ref. 7, p. 47), and Koupalov¹¹ reported that a conditioned response established to somesthetic stimulation at a locus on one side of the body was elicitable by stimulation of the homologous contralateral locus. Anrep² found that such responses generalized to test stimulations of other loci, the vigor of the response decreasing with increasing distance of the test locus from the conditioned one, and that this generalization gradient was bilaterally symmetrical: stimulation of a locus on the side contralateral to training elicited responses almost identical in vigor to those following stimulation of the homologous locus on the trained side. The left–right equivalence displayed by these dogs evidently resulted from callosal interconnections: Bykov and Speranski⁷ and Bykov⁶ reported that conditioned responses to stimulation on the one forelimb could not be elicited by stimulation of the other

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forelimb in dogs whose corpora callosa had been sectioned; the animals with separated hemispheres appeared not to 'confuse' their left and right body sides. In callosotomized dogs, but not intact ones, it was possible to establish a differentiation between homologous body parts by pairing the food with stimulation on one side and withholding it when the contralateral locus was stimulated.

Likewise, the avian tectal commissure appears to mediate an equivalence (and hence confusability) of left-right mirror-image stimuli. Pigeons trained to peck at an oblique line later pecked preferentially not only at the trained line but also at its mirror image¹⁹. This effect likely derives from a cross-hemispheric reversal: Mello¹² found that birds trained monocularly to peck for food at a 45-deg line pecked most frequently at a 135-deg line when tested with the untrained eye^{cf. 5}. Furthermore, pigeons whose tectal commissures had been severed pecked preferentially only to the trained-line orientation⁴.

The anterior commissure may also make a contribution. After re-analyzing Noble's¹⁴ data on the effects of sectioning various commissures on the ability of chiasm-sectioned monkeys to discriminate mirror images, Achim and Corballis¹ concluded that transmission across the anterior commissure evidently contributes to the special difficulty of left-right discrimination: for monkeys in which the severing of the anterior commissure was included in the split-brain procedure, the discrimination of left and right was no more difficult than that of up and down.

These lines of evidence are consistent in showing that commissurotomy reduced or eliminated a left-right equivalence, and so support the first view mentioned above. Nevertheless, our understanding of the relationship between commissural integrity and left-right confusion is far from complete. For one thing, the relevant studies all focused on left-right stimulus equivalence; none compared animals with intact and severed commissures on the ability to differentiate left and right responses. Furthermore, the only work of which we are aware that specifically assessed the effect of section of the corpus callosum on behavioral left-right confusion was the Anrep/Bykov research, which was carried out on only one species, the dog.

We know of no study which directly examined the role of interhemispheric communication in behavioral left-right confusion in the rat. Yet, there is reason to suspect that the rat may be organized differently from the dog with respect to left-right equivalence. An effort to produce bilateral somesthetic generalization gradients in rats similar to those found in Anrep's dogs failed. Using an operant-conditioning paradigm (bar-

press for water), Axelrod and Kankolenski³ trained intact rats to discriminate between periods during which pulsatile stimulation was presented to a locus on one side of the body, and periods during which no stimulation was presented. Although subsequent test stimulation of other loci revealed systematic generalization gradients on the side ipsilateral to the conditioned locus in each of three rats, response rates to test stimulation of contralateral loci were markedly reduced, and there was only a suggestion of contralateral gradients; i.e. left-right equivalence could not be unambiguously elicited with this procedure.

Accordingly, in the present work we tested whether the effects of commissurotomy on left-right response differentiation in the rat would parallel those found for left-right stimulus discrimination in the dog, monkey and pigeon. We expected that callosotomy would improve the animal's ability to behaviorally differentiate left- and right-going responses. To test whether any obtained effects of commissurotomy could be accounted for by extraneous performance variables, we also measured the same subjects' performance on a brightness-discrimination task. Additionally, we report an experiment which explored the generality of the effects of callosotomy by assessing its effect on another learned lateralized behavior, namely, the rats' ability to generate consistently unilateral responses.

PROCEDURE AND RESULTS

Water maze. We employed two water mazes¹⁵, which were T-shaped plexiglass tanks, 46 cm deep (Fig. 1). Each maze arm was 15 cm wide extending for 30 cm laterally and then turned 90° back, so that the escape ramp was out of sight to a rat at the choice point. Water entered continuously (6.3 liter/min at 24 °C) at the floor of the starting box, and flowed out at the floor at the ends of both arms, being maintained at a depth of 25 cm. The reinforcement was escape from the water, accomplished by climbing up a ramp, which extended down into the water at the end of the appropriate arm. A 'dummy' ramp, which extended down only to 15 cm above the water surface and thus could not be used for escape, was placed in the opposite arm so that the escape ramp location could not be determined by a view from outside the tank.

The walls of the maze were white and could be back-illuminated. When not back-illuminated, the walls as viewed from within the maze appeared to the human observer as uniform and dark. When back-illuminated, alternating dark and light 3 cm-wide vertical stripes appeared.

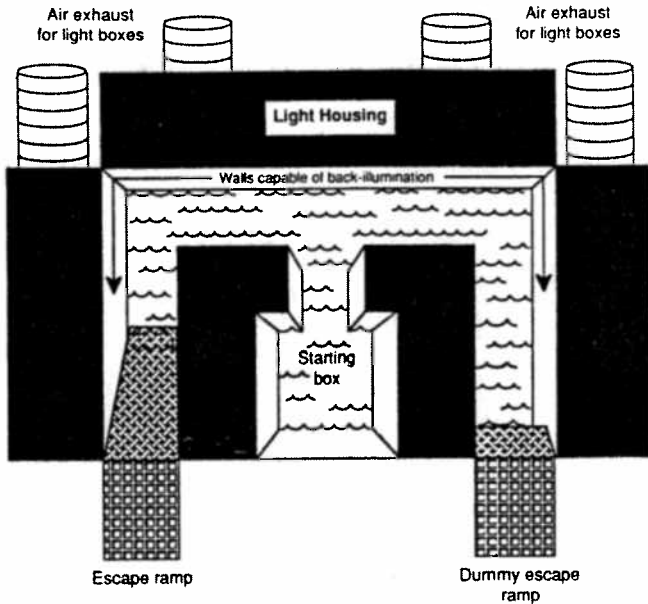


Fig. 1. The water maze.

All animal handling and data collection were carried out by observers blind to the surgical status of the rats (callosotomy or sham), and recorded on videotapes which were then reviewed by a second blind observer. In this and related projects, we have also conducted a number of checks to confirm that our subjects' scores were not functions of confounding variables: when testing was continued beyond criterion, but by different handlers/observers, in different mazes, in different rooms, and when oriented differently with respect to compass heading, the subjects continued to demonstrate reliable LRRD.

Surgery. The split-brain preparation was carried out by a procedure developed in our own lab. Our procedure utilizes a Z-shaped callosotomy knife (Fig. 2), made by modifying a dental amalgam-plugger. The knife was maneuvered under the meninges at a point lateral to the superior sagittal sinus and then through a

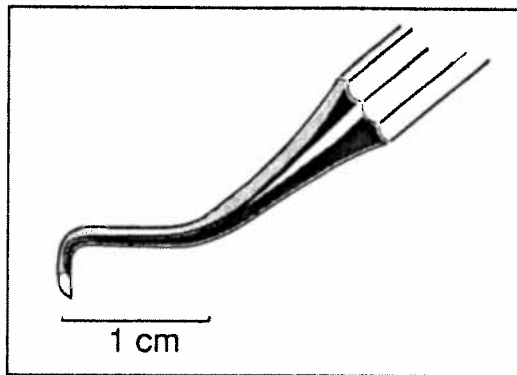


Fig. 2. The callosotomy knife.

sequence of pivots illustrated in Fig. 3 so that its leading edge could enter the longitudinal fissure to transect the commissure.

The anesthetized rat (ketamine (Ketaset) 52 mg/kg combined with xylazine (Rompun) 2.6 mg/kg) was placed for stability in the head holder of a stereotaxic apparatus. A midline scalp incision was made and the underlying periosteum retracted. With a variable-speed drill, the skull was thinned over an area extending from 4 mm anterior to the coronal suture to 2 mm anterior to lambda. The thinned area was approximately 6 mm wide anteriorly and 3 mm posteriorly, as illustrated in Fig. 4A and B. We counterbalanced the side of this cranial window and subsequent surgical approach across sex and surgical treatment.

The rat was then approached from the front (i.e. the rat and surgeon were positioned face to face). Using a microknife, a puncture wound through the adherent osteo-dural tissue was created approximately 2 mm anterior to the coronal suture and 2 mm lateral to the sagittal suture, care being taken to avoid any obvious blood vessels (Fig. 4C). A small hook was then used to lift the osteo-dural tissue at the puncture wound site. The callosotomy knife, held with its plane parallel to the surface of the brain, was slipped through the puncture wound between the dura and the pial surface (Fig. 4D), and maneuvered until its leading segment (a-b in Fig. 3(1)) lay directly under, and parallel to, the sinus (Fig. 4E). The knife was then rotated along the long axis of its middle segment (b-c in Fig. 3) so that the leading segment slid between the cerebral hemispheres down into the callosal tissue (Fig. 4E and F). The knife was then pivoted along the axis of the leading segment (a-b) so that the knife came to lie in the mid-sagittal plane (Fig. 4G). This pivot pressed the middle segment of the knife against the side of the puncture wound and caused stretching and distortion of adherent osteo-dural tissues, and a lateral displacement of the sinus. The knife was then slid posteriorly in the longitudinal fissure to the coronal suture (Fig. 4H). It was then slid anteriorly along the same path and dropped ventrally approximately 1 mm as it passed the coronal suture in an attempt to ensure full sectioning of the genu. When the leading segment of the knife came to lie directly under the puncture wound, which in its stretched state lay directly above the longitudinal fissure anteriorly, the probe was withdrawn directly upward (dorsally).

It was rare for more than a few drops of blood to well up during the knife's entire maneuvers. When the bleeding was stopped, and the skull was cleaned of any residual bonechip debris, the scalp was closed using 11 mm wound clips. The entire surgical procedure, from

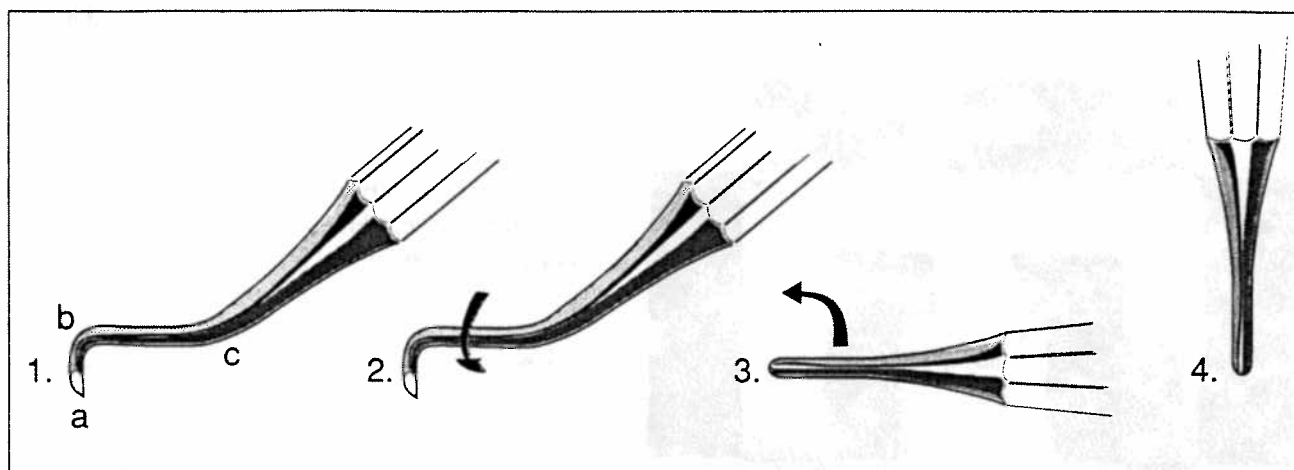


Fig. 3. The sequence of pivots used to maneuver under the superior sagittal sinus and sever the corpus callosum.

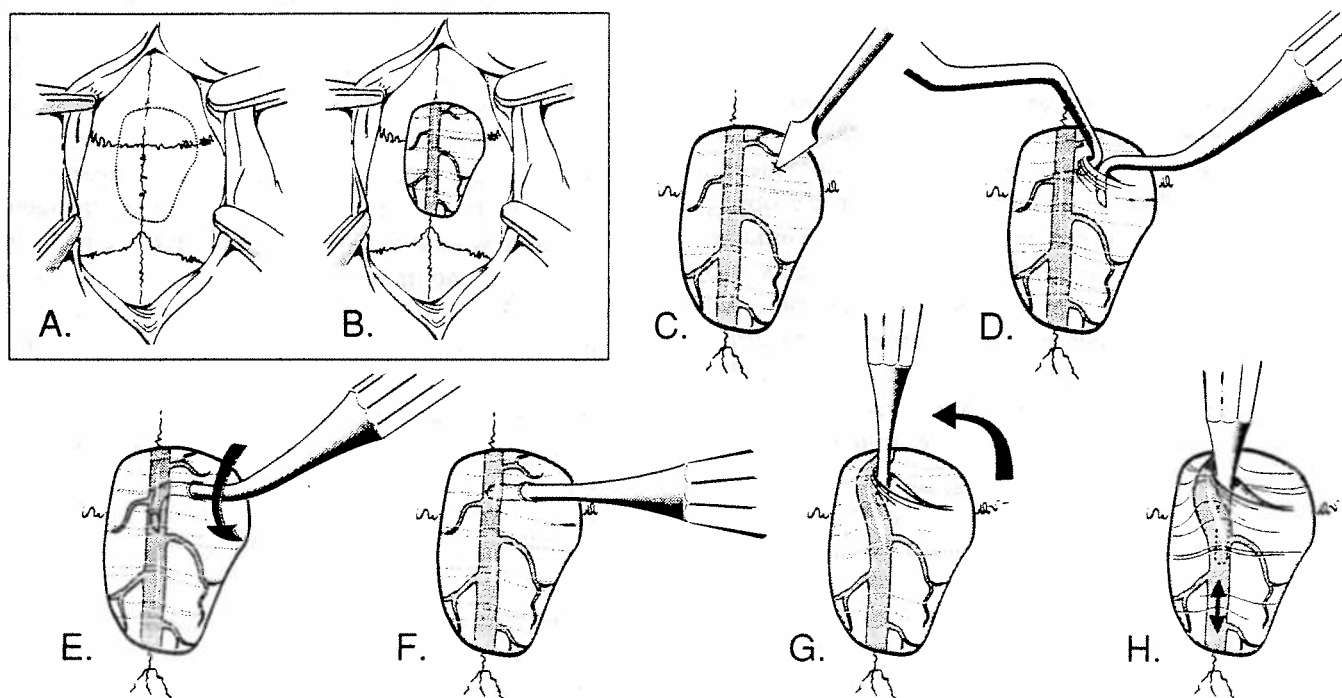


Fig. 4. The callosotomy surgical procedure. (A) The area of bone to be thinned; (B) the craniotomy with a thin and transparent osteo-meningeal membrane remaining; (C) a puncture wound being created with a microknife; (D) elevation of the adherent membranes and insertion of the callosotomy knife; (E) positioning the knife under and, parallel to, the superior sagittal sinus, and commencing the pivot of the blade down into the corpus callosum; (F) the position of the knife at the end of the first pivot; (G) the second pivot to align the knife along the mid-sagittal plane; (H) the cutting excursion of the knife posteriorly and its withdrawal anteriorly.

scalp incision to closure, lasted approximately 15 min per rat.

As a sham surgical treatment in the preparation of control subjects, we carried out an identical procedure using an instrument with a shortened leading segment. This probe slid under the sinus and within the longitudinal fissure, but above the corpus callosum.

Post-operatively, the subjects displayed no obvious behavioral deficits, maintaining normal weight, and demonstrating normal locomotion and reactivity. A minimum of six weeks postsurgical recovery was provided before beginning behavioral testing, and in the week preceding testing each rat was handled twice daily in order to habituate it to human contact.

Histology. Following behavioral testing, the rats were perfused intracardially with saline followed by formalin. The brains were sectioned at 8 μ m, and every 20th section was stained with Cresyl violet.

EXPERIMENT ONE

Subjects. Male and female hooded (Long-Evans) rats were obtained from Blue-Spruce (Harlan-Sprague-Dawley) at 35 days of age, and housed singly thereafter. They were randomly assigned to undergo either callosotomy or sham-surgery at approximately 100 days of age, and they underwent LRRD testing at 150 days of age. The rats were housed singly and maintained on an alternating 12:12 h white/red light cycle, with all testing occurring during the red phase. Room temperature was held at 26 °C.

1-A. Left-right response differentiation (LRRD)

Procedure. In this test¹⁵, when both arms of the maze were lit, the escape ramp was placed in the right arm, and when the maze was entirely unlit the ramp was in the left arm. Pseudorandomly sequenced trials (maze-illuminated/maze-unilluminated) were presented at 4-min inter-trial intervals. On each trial the rat was placed in the starting box and allowed to swim until it found the ramp; it was then returned to its home cage until the next trial. Each rat was tested for 25 trials per day until it reached the criterion of 10 successive correct first turns at the choice point (or for a maximum of five successive days). The number of trials taken to reach this criterion served as the index of left-right confusion^{cf. 15}.

Results. Callosotomy produced a striking (24.6%) and significant superiority over the control treatment,

the callosotomized subjects ($n = 28$) requiring a mean of only 49.3 trials to reach criterion, compared with 65.4 trials for the sham-operated controls ($n = 28$); see Table I. The mean scores of the male and female rats were virtually identical.

1-B. Brightness discrimination (BD)

In an effort to assess whether the superiority of the callosotomized subjects on LRRD was due to variables which might have improved water-escape performance in general, we tested half of the same subjects using the same water-maze on a visual discrimination task whose solution did not depend on the left-right distinction.

Procedure. Three to five weeks following LRRD, the male rats only underwent a test in which on each trial, only one of the two arms of the maze was lit, and the other arm unlit. The escape ramp was always to be found in the lit arm, with the side being varied pseudorandomly from trial to trial. As before, the rats were tested for 25 trials a day for a maximum of five days or until the rat reached the criterion of ten successive correct first responses.

Results. The brightness-discrimination scores of the split-brained rats did not differ reliably from those of the sham operates (Table I).

Histology. Fig. 5A and B show representative sections of callosotomized subjects. Postmortem examination of the prepared brains revealed that, for the callosotomy group, the proportion of the corpus callosum sectioned, defined as the number of sections in which the callosum was severed divided by the total number of sections in which the callosum crossed or would have crossed the midline, averaged 0.73 (range 0.53–1.00). There was a greater tendency for splenial fibers to have been left intact (some fibers being present in 83% of the brains) than for genu fibers

TABLE I

Mean trials to criterion \pm S.D.

Experiment	n	Treatment		F (df)	P
		Callosotomy	Sham surgery		
1A. Left-right response differentiation					
	56	49.3 \pm 18.7	65.4 \pm 22.3	8.55 (1,54)	0.005
1B. Brightness discrimination					
	26	60.9 \pm 32.2	58.7 \pm 23.4	0.04 (1,24)	NS
2. Consistent unilateral response					
Acquisition	47	15.1 \pm 4.6	15.5 \pm 5.9	0.07 (1,45)	NS
Retention	47	12.6 \pm 5.9	15.2 \pm 8.5	1.47 (1,45)	NS
Reversal	46	20.5 \pm 14.2	16.2 \pm 9.1	1.51 (1,44)	NS



Fig. 5. Representative brain sections. Left and center, callosotomized subjects; right, a sham-surgery subject.

(27%). Among these callosotomized subjects, neither the LRRD nor BD scores of rats with genu – or splenium – fibers remaining differed significantly from those without such fibers. There was a weak tendency ($r = -0.25$) for the proportion of callosal fibers cut to be associated with decreasing (improving) LRRD scores, but this relationship was not statistically reliable. Fig. 5C shows the brain of a representative control subject; none of the sham subjects showed any damage to callosal fibers.

A degree of unilateral damage caused by the cutting probe straying from the midline was observed in the septum in 66% of the brains (an example is presented in Fig. 5A), in the fimbria in 43%, in the hippocampus in 62% (an example is given in Fig. 5B), in the thalamus in 23%, and in the tectum in 37%; however, post-hoc ANOVA's revealed no reliable differences in LRRD or BD scores between callosotomized subjects with damage in these regions and those without such damage.

All of the callosotomized brains showed unilateral lesions of medial neocortex incident to the passage of the surgical knife into the longitudinal fissure. The brains of the sham subjects also sustained medial neocortical damage (see Fig. 5C), although somewhat less than that suffered by the callosotomy subjects.

Thus, the possibility cannot be ruled out that the differences in performance between our two groups was due to differences in extent of medial cortex damage. However, to assess this possibility, for each callosotomized subject we computed an index of the amount of medial-cortex damage by multiplying the depth of the lesion by the number of histological sections in which damage occurred; water-maze performance was not reliably correlated with this index of cortical damage, $r_{25} = -0.19$.

EXPERIMENT TWO

2. Consistent unilateral response test (CURT)

The question can be raised of the generality across tasks of the role of the corpus callosum in contributing to left-right confusion. To index rats' ability to distinguish left and right, Zimmerberg, Strumpf and Glick²¹ used a T-maze in which the animal escaped electric shock by entering one lateral arm. Over successive trials, the animal's entries into the unreinforced side were interpreted to reflect left-right confusion. We term such tasks Consistent Unilateral Response Tests (CURT). An improvement in CURT scores following

commissurotomy would suggest a degree of commonality across the two types of task in the callosal contribution to left-right confusion.

Subjects. The Long-Evans rats used in the preceding study were mated and their offspring were assigned as subjects in Experiment Two, randomly except that litter and sex were counterbalanced across treatments. The rats were housed singly from 28 days of age, and underwent surgery at approximately 65 days of age and water-maze testing at approximately 100 days. Again, we employed an alternating 12:12 h white/red light cycle, with all testing occurring during the red phase. Room temperature was held at 26 °C.

Procedure. In this test, the water maze was entirely unlit on every trial. On the first day (acquisition), no escape ramp was present when the animal was first placed into the water maze. Once the animal turned into one of the lateral arms, the escape ramp was placed into the opposite arm, with the rat being left to swim until it reached the ramp; thus, each rat had a similar experience of an 'incorrect' first choice. On subsequent trials the ramp was placed beforehand in the initially-reinforced arm. Trials were administered (inter-trial interval = 4 min) either until the rat reached the criterion of ten consecutive correct responses, or for a maximum of 50 trials. On the following day (retention), the rats were retested to the same criterion. They were then retrained on the third day (reversal), on a task in which the ramp was always placed in the arm opposite to the one which had been correct on the two previous days of testing.

Results. Callosotomy had no effect on CURT scores. On none of the three testing days did the callosotomized animals differ reliably from the controls (Table I). Male and female rat did not differ on either the acquisition or retention tests; however on day 3 (reversal), males took significantly fewer trials (14.7 ± 6.4) than females (21.8 ± 14.9 , $F_{1,44} = 4.32$, $P < 0.05$).

None of the sham subjects evidenced any callosal damage. In the callosotomy group, the proportion of the corpus callosum sectioned averaged 0.94 (range 0.63–1.00). Some splenial fibers were left intact in 39% of the brains, and genu fibers in 4%; again the presence or absence of these fibers was not related to water-maze performance. Consequent to efforts to sever a greater proportion of callosal fibers than in Experiment 1, sub-callosal damage was more frequently observed: unilateral damage was evident in the septum in 91% of the brains, in the fimbria in 96%, in the hippocampus in 96%, in the thalamus in 22%, and in the tectum in 9%. Accordingly, to assess possible contributions of these incidental lesions to CURT performance, we compared the scores of those subjects

which evidenced no or slight damage to the septum, fimbria or hippocampus with those showing evidence of somewhat greater damage. No differences were found for the acquisition or retention tests. For the reversal test, although there was no relationship between trials-to-criterion and degree of hippocampal or septal damage, subjects with greater incidental damage to the fimbria were significantly better than those with lesser fimbria damage ($F_{1,19} = 4.36$, $P = 0.05$); we will offer no interpretation of this unanticipated and isolated result. No reliable differences were found in any CURT scores between callosotomized subjects with and without damage in the thalamic or tectal regions. Again, all of the callosotomized brains showed unilateral medial neocortical lesions, which were somewhat more extensive than those seen in the brains of sham operates, and whose size did not relate to water-maze performance.

DISCUSSION

The expected and most common result of damage to the central nervous system is of course a deficit in function: a compromised brain is as a rule less capable than an intact one of meeting the needs of the subject. Nevertheless, functional improvement can occasionally be shown to result from destructive processes ^{e.g. 13,17}, and in such instance, the paradox provides an opportunity for an elucidation of the relationship between the neural substrate and the demands of the task set for the subject.

We interpret the facilitation of LRRD performance by callosotomy to implicate callosal transmission in left-right confusion. The neurophysiological effects of either homotopic or heterotopic commissural fibers are still largely matters of speculation, as are their effects on the flow of information. At this stage, we can only conclude that whatever their numerous beneficial effects may be ^{see 9,10,16}, as a whole, the callosal connections, by allowing lateralized signals to intermix, evidently increase the difficulty of distinguishing between left and right. Our split-brained subjects, not experiencing the confusing intermixing of left and right information, were better able to differentially associate lateralized responses with the discriminative stimuli.

The inference of a contribution of the callosum to a process by which left- and right-specific neural events are equated can also be drawn from electrophysiological evidence. Electrical stimulation of the sensorimotor cortex of one hemisphere produces an evoked response in the contralateral sensorimotor cortex, a response which is abolished by midline sectioning of the corpus callosum²⁰.

The absence of a facilitatory effect of callosotomy on either the brightness discrimination or the CURT task, both depending upon water escape in the same maze used for LRRD, makes it unlikely that the facilitatory effect seen in the LRRD test was due to enhancement of extraneous performance variables (information processing capacity, swimming skill, escape motivation, arousal, attentiveness, etc.) not specific to the LRRD test itself.

The failure of the callosotomized subjects to achieve superior CURT scores when compared with controls might have been due to a 'floor effect'. That is, the task might simply have been too easy for intact animals for any relative improvement to have been demonstrable. On Day 1, for example, the overall mean trials-to-criterion score was 15.3, including the ten criterial trials. Nevertheless, it is worth noting that the relative ease our subjects experienced with this test matches that shown in similar studies⁸, pp. 38-42 in which non-contingent consistent unilateral responses were demanded. Thus CURT may be different in kind from LRSD and LRRD, which characteristically prove difficult. We wonder whether the neural operations underlying the process of response selection on the CURT task even need to take the left-right distinction under consideration; it may be possible for one unilateral response to be 'turned on' without the mirror homologous response even being considered. In any event, we cautiously conclude that callosal transmission makes no contribution to the processes involved in CURT performance.

In experiments now under way, we are asking whether the facilitatory effect of callosotomy on left-right response differentiation can be narrowed down to a specific anatomical division of the corpus callosum, and whether LRRD performance can be related to individual variation in callosal structure.

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