Fornix Transection Impairs Conditional Visuomotor Learning in Tasks Involving Nonspatially Differentiated Responses

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Brasted, Peter J., Timothy J. Bussey, Elisabeth A. Murray, and Steven P. Wise. Fornix transection impairs conditional visuomotor learning in tasks involving nonspatially differentiated responses. *J Neurophysiol* 87: 631–633, 2002; 10.1152/jn.00656.2001. Rhesus monkeys learned a series of conditional visuomotor associations involving two-dimensional "objects" that instructed one of three responses: tapping a touch screen, steady contact with the screen for a brief period, or steady contact for a longer period. Relative to controls, fornix-transected monkeys were impaired in the acquisition of new associations and in the retention of preoperatively learned ones. These findings challenge the view that the hippocampal system participates in associative learning only when spatial information is relevant to either the stimulus or the response.

INTRODUCTION

The hippocampal system (HS) consists of CA1-CA4, the dentate gyrus, the subicular complex, and fibers in the fimbria and fornix. Considerable behavioral research, in both rodents (Jarrard 1995; Nadel 1991; O'Keefe 1999) and nonhuman primates (Gaffan 1998; Mahut and Moss 1986; Parkinson et al. 1988), suggests that the HS functions primarily in spatial localization or navigation. This view finds support in the lack of HS–lesion effects on tasks without relevant spatial contingencies (Gaffan et al. 1984; Murray and Mishkin 1998; Murray et al. 1993; Teng et al. 2000). Other neuropsychological evidence, however, indicates that the HS also functions in "nonspatial" tasks, e.g., those involving relational (Bunsey and Eichenbaum 1995), declarative (Squire and Zola 1997), and episodic (Gaffan 1994) memory.

Conditional visuomotor learning tasks, which involve the arbitrary association of a visual stimulus with a response, can be used to probe these two views of HS function. In such tasks, the stimulus is usually nonspatial in that its shape and color, but not its location, instruct the action to be performed. The response can also be nonspatial; for example, temporal rather than spatial features can differentiate responses. Reports that fornix transection disrupts conditional visuomotor learning in tasks involving spatial responses (Rupniak and Gaffan 1987), but not nonspatial ones (Gaffan and Harrison 1988), accord with the view that the HS functions primarily in the processing of spatial information. However, possible alternative interpretations of those data (Wise and Murray 1999) led us to re-examine the issue.

METHODS

Eight male rhesus monkeys (*Macaca mulatta*), 5.4 to 8.1 kg, were housed socially and were fed a restricted diet of Purina Primate Chow (Purina Mills Inc., St. Louis, MO) supplemented with fruit. We used an automated test apparatus in which visual stimuli were presented on a video monitor fitted with a touch-sensitive screen. An automated reward dispenser was used to deliver 190 mg food pellets (Noyes, Lancaster, NH) to a food cup beneath the touch screen.

The task required monkeys to solve a *problem set* that involved three novel stimuli, one instructing a *tap* response (8 touches to the touch screen, each <2 s), another instructing a *short-hold* response (steady contact of the touch screen for 2–4 s), and the third a *long-hold* response (steady contact for 4–8 s). Each visual stimulus consisted of two differently colored ASCII characters, superimposed, approximately 5 and 3.5 cm in height, respectively. On each trial, one stimulus, pseudorandomly selected from the current problem set, was presented until one of the three responses had been registered. Then, the stimulus was removed from the screen. If the response was the arbitrarily designated associate of that stimulus, a food pellet was delivered immediately. Any other response was followed by a correction trial, i.e., another presentation of the same stimulus, until the correct response was made. Sessions typically contained 100 trials, not including correction trials, with 8 s between each trial.

Preoperatively, monkeys were presented with a given problem set for several sessions, across days, until they attained the criterion of ≥90 correct responses, not including correction trials, in a 100-trial session. The monkeys learned seven problems sets, serially, the last five of which were analyzed as the preoperative performance baseline.[1] Two groups of four monkeys were then designated and balanced for errors to criterion. For the lesion group, the fornix was surgically transected as described elsewhere (Murray et al. 1989). After a mean postoperative recuperation period of 28 days, and an equivalent rest period for the controls, each monkey received a retention test: the last stimulus set learned preoperatively was presented again using identical procedures. Each subject then learned five novel problem sets (postop1), and, approximately 6–8 mo later, another five novel problem sets (postop2). Nonparametric paired comparisons were used to test between-group, within-subject differences in errors to criterion for

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[1] One fornix-transected monkey had a preexisting bilateral removal of the periprincipal frontal cortex, which caused no deficit on the task. This monkey had solved 12 problems sets prior to fornix transection rather than seven. Removal of this monkey's scores did not affect the statistical significance of any result presented here.

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preoperative versus postoperative performance (Wilcoxon rank-sum test).

Lesions were assessed using magnetic resonance (MR) imaging techniques (T1-weighted, 1.5 T, Signa, General Electric Medical Systems). Coronal images at 1-mm intervals (Fig. 1) and sagittal images at 1.5-mm intervals showed that, as intended, all animals in the lesion group had complete transections of the fornix along with minor damage to the corpus callosum. In addition, two monkeys sustained slight inadvertent damage to the cingulate gyrus in one hemisphere, which extended approximately 3 mm above the corpus callosum in one monkey and <2 mm in the other.

RESULTS

Monkeys with fornix transections were impaired relative to controls in both new learning (Fig. 2A, postop1) and retention (Fig. 2B). Relative to their own preoperative scores, controls made fewer errors to criterion, whereas fornix-transected monkeys made more errors postoperatively in both learning (control, -51 errors; lesion $+74$ errors; $P < 0.05$) and retention (control, -95; lesion $+75$; $P < 0.05$). There was no apparent relationship between the occurrence or extent of damage to the cingulate cortex and magnitude of impairment.

Group differences for the tap (control, -12; lesion, $+15$) and short-hold (control, -30; lesion, $+12$) responses were both significant ($P < 0.05$), although that for the long-hold response just failed to reach significance (control, -33; lesion, $+24$; $P < 0.1$). In learning five additional novel problem sets approximately 6–8 mo after postop1 (Fig. 2A, postop2), operated animals continued to make significantly more errors than controls (control, -96; lesion, $+1$; $P < 0.05$) relative to their own preoperative scores; however, both groups improved from postop1 to postop2 to a similar extent (control, -45; lesion, -73; n.s.). The five problem sets solved in postop1 were presented periodically throughout the study. Both groups showed stable performance on these familiar problem sets. Immediately prior to postop2, controls scored 94, 93, and 87% correct for tap, short-hold, and long-hold responses, respectively; fornix-transected monkeys scored 97, 86, and 81% correct.

DISCUSSION

Although previous reports have shown that HS damage causes deficits in conditional visuomotor tasks involving spatial components (Gaffan et al. 1984; Murray and Wise 1996; Rupniak and Gaffan 1987), the present results show that these impairments are not confined to the spatial domain. Fornix
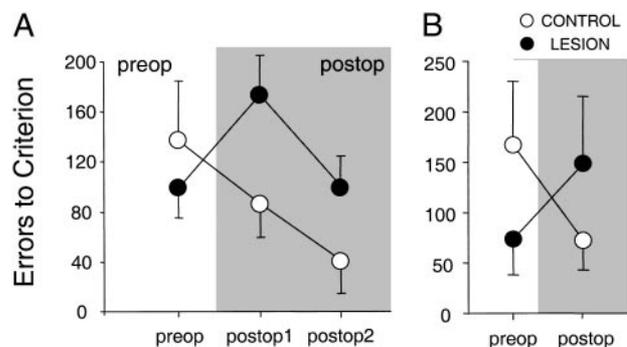
FIG. 2. A: acquisition test. Errors to criterion (mean ± SE), by group, for 5 novel problem sets in each of 3 testing periods. B: retention test. Scores for the last preoperative problem set on initial presentation (preop) and postoperative (postop) retesting. Note that although there was a large proportional difference in the number of errors to criterion preoperatively (leading to approximately 15% more preoperative trials for controls), both groups were trained to the same criterion (90% correct within one session).

transection induced a significant impairment in the ability of monkeys to learn and retain conditional visuomotor associations, even when both the instruction stimuli and the responses were nonspatially differentiated.

Alternative interpretations of the deficit can be ruled out. Fornix transection does not impair visual discrimination (Gaffan and Harrison 1989; Moss et al. 1981; Murray et al. 1989; Zola-Morgan et al. 1989), which rules out an account in terms of sensory deficits. Motor and timing deficits can also be excluded. Postoperatively, no monkey was impaired in executing any of the responses; each continued to perform three discrete responses. For example, in executing tap responses, all eight monkeys contacted the screen for considerably <2 s per touch. Also arguing against a motor deficit were the good scores, 97% correct on tap trials, attained by the operated monkeys on the familiar problem sets. In addition, although a timing deficit might be expected to produce impairments in associations involving the short-hold and long-hold responses, associations with tap responses were also impaired significantly and these had minimal timing constraints. Finally, although each response had a spatial component, in that each involved movements orthogonal to the screen, those components of the response were not relevant to the task. We conclude, therefore, that the impairment in fornix-transected monkeys can be ascribed to a disruption in their ability to associate nonspatial stimuli with nonspatial responses.

The current results appear to differ from those of Gaffan and Harrison (1988), who found that fornix transection had no significant effect on a similar task. The fact that the present task had three choices, whereas that of Gaffan and Harrison had two, might account for the discrepancy. Wise and Murray (1999) speculated that monkeys could perform a two-choice conditional visuomotor task by application of certain strategies, without learning the associations. However, given that the monkeys in the present study showed little evidence of those strategies, the present results do not support that idea. Alternatively, our monkeys learned many visuomotor associations preoperatively, whereas those studied by Gaffan and Harrison learned none. Perhaps substantial preoperative training, as was given in this and other studies (Murray and Wise 1996; Rupniak and Gaffan 1987), makes conditional visuomotor learning vulnerable to HS damage. It is conceivable that ex-
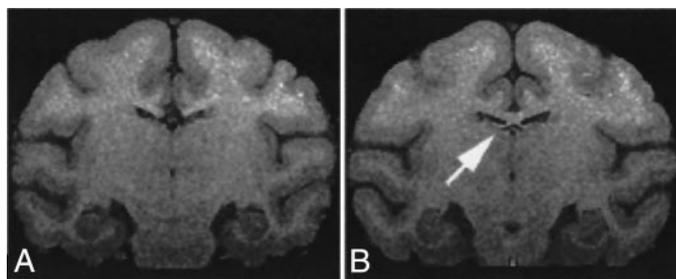
FIG. 1. A: coronal magnetic resonance (MR) image from a fornix-transected monkey showing a complete bilateral section. B: image from a control subject at a comparable rostrocaudal level. Arrow indicates intact fornix.

perimentally sophisticated monkeys solve associative learning problems differently than do experimentally naïve monkeys and that their task-specific experience renders them susceptible to HS lesions.

The impairment observed in the present study could reflect the interruption of any of the projections conveyed by the fornix, e.g., projections from the HS to the diencephalon or to the nucleus accumbens (Reading et al. 1991) or HS afferents such as those arising from cholinergic neurons (Ridley et al. 1989). Regardless of which disconnections cause the impairment, the present finding suggests that the HS plays a more general role in associative learning than commonly accepted.

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