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Conditional Motor Learning in the Nonspatial Domain: Effects of Errorless Learning and the Contribution of the Fornix to One-Trial Learning

Peter J. Brasted, Timothy J. Bussey, Elisabeth A. Murray, and Steven P. Wise
National Institute of Mental Health

Conditional motor learning contributes importantly to behavioral flexibility. In previous work, the authors found that fornix transections impaired the ability of macaque monkeys (*Macaca mulatta*) to learn conditional motor associations between the nonspatial features of visual stimuli and nonspatially differentiated responses. In the present study, they found that significant 1-trial learning of such associations also depended on the fornix. Furthermore, removal of the hippocampus, subiculum, and subjacent parahippocampal cortex, added to fornix transection, had no effect, thus demonstrating that fornix transections eliminated the contribution of the hippocampal system. In addition, the authors examined the effect of errorless learning and found, in control monkeys, that errors made prior to the 1st correct response retarded 1-trial learning.

Keywords: associative learning, arbitrary mapping, learning curve, hippocampus, medial temporal lobe

The hippocampal system (HS) includes several cortical fields, specifically CA1–CA4, the dentate gyrus, presubiculum, parasubiculum, subiculum, and prosubiculum, as well as the fibers of the fornix and fimbria, which provide afferents to and efferents from these areas. Conditional motor learning, which requires the formation of arbitrary associations between stimuli and responses and plays a major part in the ability to respond flexibly to changes in response contingencies, depends on the HS, at least for the fastest learning of this type. In a previous study, we showed that HS damage in the form of a fornix transection caused a persistent deficit in the ability of monkeys to acquire arbitrary associations, as evidenced by slowed learning rates on a nonspatial version of the conditional motor learning task (Brasted, Bussey, Murray, & Wise, 2002; 2003b). In this task, modeled after one devised by Gaffan and his colleagues (Gaffan & Harrison, 1989), monkeys learned to associate nonspatially differentiated visual cues with nonspatially differentiated responses. Throughout the experiment, monkeys made three such responses: tapping a touchscreen eight times (the *tap* response), maintaining steady contact with the touchscreen for 2–4 s (the *short-hold* response), and maintaining steady contact with the touchscreen for more than 4 s (the *long-hold* response). Their task was to learn conditional motor associations of the following type: "if object A, then tap"; "if object B, then short-hold"; "if object C, then long-hold." After considerable training, monkeys in an unoperated control group learned new associations of this type quickly. Monkeys with fornix transections continued to learn new conditional motor associations after their operation, but not as quickly as did the controls. Because the visual stimuli always appeared at the center of the monitor screen and the monkeys made responses to the same location, we considered this to be an example of the contribution of the fornix to associative learning outside the spatial domain.

The present study addressed four follow-up questions arising from that work: (a) Does fornix transection cause a deficit in one-trial learning, a hallmark of episodic memory? (b) Given the suggestion that errorless learning enhances associative learning in both amnesic patients and control participants, can errorless learning improve performance in fornix-transected monkeys or their controls? (c) Does the residual ability of fornix-transected monkeys to learn conditional motor associations depend on the remainder of the HS, which could mediate such learning through other pathways? (d) Do the effects of fornix transection depend on disrupting a contribution of the hippocampus per se (as opposed to the broader HS, which includes the subicular complex and the fornix)?

The concept of *errorless learning* deserves a few introductory comments. This concept refers to situations in which the participant has no experience with making an incorrect response prior to the first instances of making a correct one (see, e.g., Grandmaison & Simard, 2003; Kessels & de Haan, 2003; Kixmiller, 2002; McClelland, 2001). The absence of prior error expedites learning. In studies with human participants, this situation can be established by deciding, in advance, that the first response will be designated correct in one group and incorrect in another, regardless of the response. In the present study in monkeys, we selected errorless exemplars that arose by chance and compared learning rates when

Peter J. Brasted and Steven P. Wise, Laboratory of Systems Neuroscience, National Institute of Mental Health, Bethesda, Maryland; Timothy J. Bussey and Elisabeth A. Murray, Laboratory of Neuropsychology, National Institute of Mental Health.

Timothy J. Bussey is now at the Department of Experimental Psychology, University of Cambridge, Cambridge, United Kingdom.

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Correspondence concerning this article should be addressed to Steven P. Wise, Laboratory of Systems Neuroscience, National Institute of Mental Health, National Institutes of Health, 49 Convent Drive, Building 49, Room B1EE17, MSC 4401, Bethesda, MD 20892-4401. E-mail: stevenwise@mail.nih.gov

prior errors had not been made with learning rates when they had been.

Experiment 1 answered the first two questions listed above, and Experiment 2 resolved the third. Experiment 3, however, failed to provide a conclusive answer to the fourth question. The present results supersede those previously reported in abstract form (Brasted et al., 2003a).

General Method

Subjects

We studied the same eight experienced male rhesus monkeys (*Macaca mulatta*) as in our previous report (Brasted et al., 2003b). They ranged in weight from 5.4 to 8.1 kg and in age from 8 to 9 years old at the end of the study. The fornix-transection group comprised 4 monkeys, as did the unoperated control group. The monkeys lived in social housing and ate a diet of Purina Primate Chow (Purina Mills, St. Louis, MO) supplemented with fruit, with water available ad libitum. The food provided to the monkeys maintained their weight between 85 and 95% of their weight prior to the study. All procedures complied with the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 1996) and with an institutionally approved animal study proposal.

Apparatus

The monkeys were seated in a primate chair and placed in front of a 13-in. (33-cm) video monitor fitted with a touchscreen. The entire ensemble was enclosed in a test chamber. Correct responses were rewarded with 190-mg banana-flavored pellets (P. J. Noyes, Lancaster, NH), which a computer-controlled dispenser delivered to a food cup just below the monitor.

Testing Procedure

Brasted et al. (2003b) describe the initial training of the monkeys and the task requirements in detail. Here we present a truncated account of the testing procedure. On each trial, a visual stimulus appeared at the center of a video monitor, and the monkeys had to make one of three nonspatially differentiated responses at its location: a tap response, a short-hold response, or a long-hold response. Visual stimuli consisted of two superimposed ASCII characters, typically of different colors, with approximate heights of 5 cm and 3 cm, respectively. The tap response required eight successive cycles in which the monkeys touched the screen with their hand and then withdrew their hand to break screen contact. The requirement set by the computer for a tap allowed each individual contact to persist up to 2 s, but in practice the monkeys made all eight contacts within that time span. The monkeys completed the eight-tap response in a group mean of 1.2 s ($\pm$ 0.3 s *SD*). The short-hold response required the monkeys to touch the screen and maintain steady contact for a period of not less than 2 s, but not more than 4 s (mean [$\pm$ SD] contact time = 2.9 $\pm$ 0.4 s). The long-hold response required the monkeys to touch and maintain steady contact with the screen for greater than 4 s (mean [$\pm$ SD] contact time, 6.8 $\pm$ 1.5 s). In initial training and testing, the computer registered the long-hold response either (a) when the monkeys removed their hands from the touchscreen after 4 s or (b) when the continuous contact time reached 8 s. Because of some individual variability in how the monkeys made this response, we subsequently amended this procedure to require the maintenance of screen contact for 8 s. This new requirement did not impair performance or affect the learning impairment in operated monkeys, and we implemented it at the same time in the testing schedule for all monkeys (see Brasted et al., 2003b).

A *problem set* usually consisted of three visual stimuli. Each stimulus required a different response, one stimulus per response. The computer pseudorandomly selected one of those stimuli for presentation on each trial. The monkeys learned, by trial and error, which of the three responses each stimulus instructed. The stimulus remained on the screen until the computer registered a response, after which the stimulus disappeared and the screen remained blank for an intertrial interval of 3–8 s. Correct responses resulted in the delivery of a food pellet; incorrect responses resulted in a correction procedure. In the correction procedure, the same stimulus appeared in repeated, consecutive trials—separated by the intertrial interval—until the monkeys made the correct response. We termed each of these presentations a *correction trial*.

In Experiment 1, we presented each problem set for 50 trials, excluding correction trials. Only one problem set of this type was presented each day. In Experiments 2 and 3, in which the monkeys learned to a criterion level of 90 correct responses in a 100-trial session, sessions comprised 100 trials, also excluding correction trials. The monkeys typically performed 2–3 such sessions each day.

Experiment 1

The data presented in Experiment 1 provide a more detailed analysis of 30 testing sessions originally described in Brasted et al. (2003b, Table 1, row 9). These sessions began with novel problem sets, and the monkeys had solved more than 100 similar problem sets before we collected the data described here.

Method

Surgical procedures. Four monkeys underwent bilateral transection of the fornix, and the other 4 served as unoperated controls, with group allocation based on preoperative performance. Details of the bilateral fornix-transection procedure appear elsewhere (Brasted et al., 2003b; Murray, Davidson, Gaffan, Olton, & Suomi, 1989). Briefly, monkeys were immobilized with ketamine hydrochloride (10 mg/kg) and anesthetized with isoflurane (1.0–3.0%, to effect). During surgery, all monkeys received an intravenous drip of isotonic fluids containing an antibiotic (Cefazolin). Heart rate, respiration rate, body temperature, blood pressure, and expired CO_2 were monitored throughout the procedure. Surgery was carried out using aseptic procedures. After the skin and galea had been retracted, a small unilateral bone flap extending just over the midline was taken. One hemisphere was retracted slightly, the corpus callosum sectioned for a short distance, and the descending columns of the fornix were identified and transected with a small-gauge aspirator and cautery. The surgery concluded with reopposing the cut edges of the dura mater; replacing the bone flap; and closing the wound in anatomical layers, by means of Vicryl (Ethicon, Somerville, NJ) for the dura and either Vicryl or surgical steel staples for the skin. Before being removed from gas anesthesia, monkeys received ketoprofen (10–15 mg) for analgesia. For 1 day before surgery and 1 week after, the monkeys received a treatment regimen of dexamethasone sodium phosphate (0.4 mg/kg im) and Cefazolin to reduce inflammation and to protect against infection, respectively. Ketoprofen (10–15 mg, b.i.d.) was administered for 2 days, and acetaminophen (10 mg/kg, b.i.d.) for 5 additional days.

Assessment of the fornix transection. We initially assessed the completeness of the fornix transection with magnetic resonance (MR) imaging. Sixty coronal images (at 1-mm intervals) and 60 sagittal MR images (at 1.5-mm intervals) were derived from T1-weighted structural MR scans by means of a 1.5 Tesla whole body scanner (Signa, General Electric Medical Systems, U.S.A.). These MR images showed the transection of the fornix to be complete in all 4 operated monkeys. As well as the intended minor damage to the corpus callosum, slight unilateral damage to the cingulate gyrus occurred in Monkeys F2 and F4. We confirmed these observations with microscopic examination of a series of Nissl-stained sections (see Figure 1). Note, however, that this histological analysis occurred only after the fornix-transected monkeys had received additional aspiration lesions of

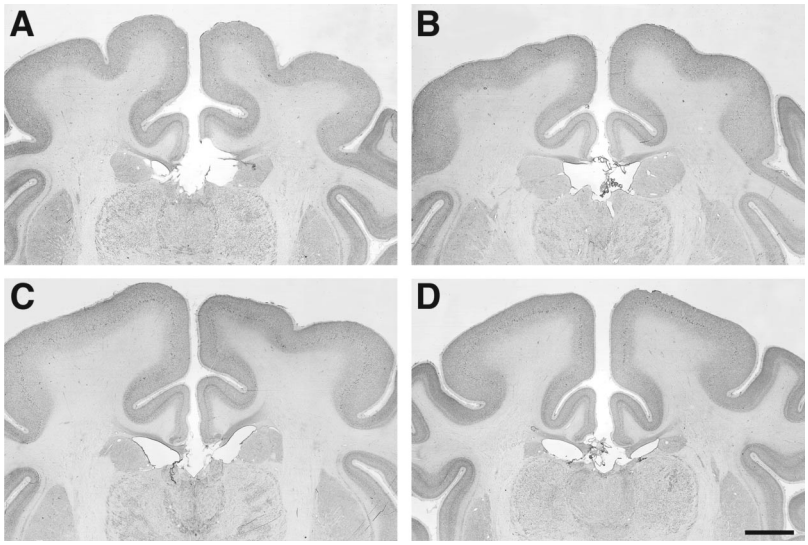

Figure 1. Histological demonstration of bilateral fornix transections. Taken from Monkeys F1–F4 (A–D, respectively) after the addition of bilateral aspiration lesions of the hippocampal system. Scale bar in D = 5 mm.

the hippocampus and subjacent cortex (see Experiment 2), an operation carried out approximately 2 years after the fornix transection. Thus, the MR analysis made prior to these aspiration lesions documents the fornix transection prior to that later surgery. One of the fornix-transection group, designated here as Monkey F4, had a preexisting bilateral aspiration lesion of the dorsolateral prefrontal cortex, but the previous study showed this lesion to be without effect on any aspect of this task (Brasted et al., 2003b). Nevertheless, we performed all statistical tests both with and without Monkey F4, and, except for the one instance noted below, no result changed because of exclusion of this monkey from the analysis. In addition, all paired comparisons were performed with both nonparametric and parametric methods.

Results

In Experiment 1, we assessed one-trial learning in two ways. First, we examined learning during the first three trials of a 50-trial session, which began with a novel problem set. Second, we examined the monkeys' response to the second presentation of a stimulus, regardless of when it occurred during a session.

In our description of these results, the word *trial* has two senses. In its usual sense, a trial consists of a single presentation of a stimulus together with the ensuing response. When we use the phrase *correction trial*, we mean trial in that sense. In a different sense, used often in this report, a "trial" consists of an initial stimulus presentation, the monkey's initial response, and all the correction trials. A trial—so defined—always ended with a correct response. Note, however, that a monkey's performance on correction trials never contributed to its score.

One-trial learning during the first three trials of a session. In this task, although the stimulus presented on Trial 1 of a 50-trial session was always novel, the stimuli appearing on Trials 2 and 3 were of two different types: repeat trials and change trials. On *repeat trials*, the stimulus was the same as that on the previous trial; on *change trials*, the stimulus was different from that on the previous trial. We made this distinction because previous work showed that some monkeys adopt a strategy that allows high levels of performance without (or prior to) learning conditional motor associations, especially for repeat trials (Wise & Murray, 1999). The monkeys in the present study did not consistently adopt these strategies but appeared to use them to some extent. Accordingly, the analysis presented in Figure 2 excludes repeat trials.

Each session lasted 50 trials and began with a novel problem set. One of the three stimuli in the set, selected pseudorandomly, appeared on Trial 1. Figure 2 shows the group mean scores for 30 problem sets (excluding correction trials), along with the mean scores of the individual monkeys. The monkeys had never previously seen the stimuli presented on Trial 1, and, accordingly, they performed near the chance level of 33% correct. Mean scores were 40.4 ± 4.6% (*SEM*) correct and 41.8 ± 3.9% correct for the control- and fornix-transection groups, respectively, neither of which differed significantly from chance: *t* test, control vs. chance, $t(3) = -1.59$, $p > .10$; fornix transection vs. chance, $t(3) = -2.23$, $p > .05$.

Next, we measured performance on the third trial of the session (Trial 3), averaged over the 30 problem sets, with repeat trials eliminated. Elimination of repeat trials ensured that the stimulus on Trial 3 could never have been the same as that on Trial 2. Thus, if the stimulus presented on Trial 3 also differed from that on Trial 1 (denoted as $S_{T1} \neq S_{T3}$ in Figure 2), then it was the first time that the monkey had ever seen that stimulus. If, however, the stimulus on Trial 3 was the same as that on Trial 1 (denoted as $S_{T1} = S_{T3}$ in Figure 2), then it was the second presentation of that stimulus, excluding correction trials. Thus, when $S_{T1} = S_{T3}$, the monkey had experienced one and only one correct response (on Trial 1), followed by reinforcement and an intervening trial with a different stimulus and response. With that one trial of experience, the control group performed significantly above chance ($M = 74.5 \pm 3.0\%$ correct), $t(3) = 13.78$, $p < .001$ (double asterisks in Figure 2), but the fornix-transection group did not ($M = 26.7 \pm 15.9\%$ correct), $t(3) = -0.40$, $p > .60$. When a novel stimulus appeared on Trial 3 ($S_{T1} \neq S_{T3}$), the control and fornix-transection groups

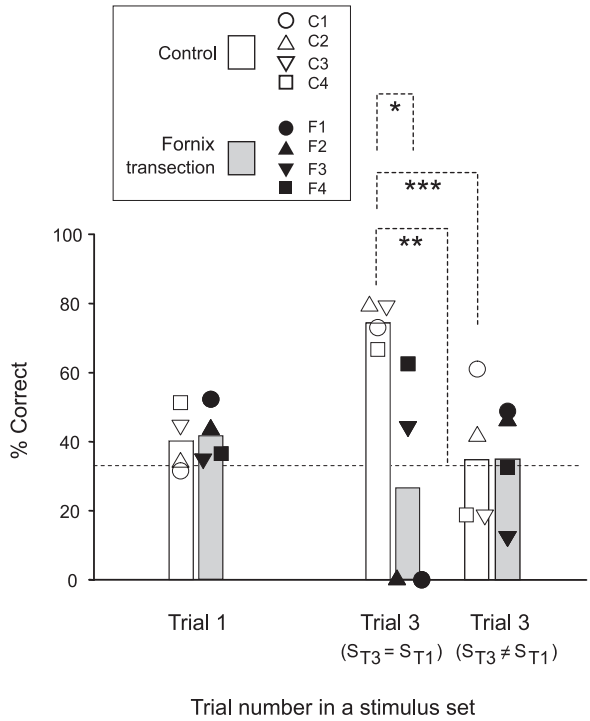

Figure 2. One-trial learning in the control group, but not the fornix-transection group. Trial 1 gives the average correct-response percentage for the stimulus presented on the first trial, as the monkeys began solving a set of three concurrent conditional motor problems. The plot excludes trials in which the stimulus was repeated from the previous trial. Accordingly, when the stimulus presented on Trial 3 (S_{T3}) was the same as that on Trial 1 (S_{T1}), it was the second presentation of that stimulus, but when it differed, it was the first presentation of that stimulus. Dashed horizontal line indicates chance level of performance. S = stimulus; T = trial. *p = .036; **$p < .001$; ***p = .031.

performed at 35.0 ± 10.2% and 34.9 ± 8.3% correct, respectively, which did not differ from chance: control versus chance, $t(3) = 0.20$, $p > .50$; fornix transection versus chance, $t(3) = 0.24$, $p > .40$. The two groups differed significantly from each other (asterisks in Figure 2) on Trial 3 when $S_{T1} = S_{T3}$, $t(3) = -2.73$, $p = .036$ (one-tailed), but not on Trial 1, $t(3) = 0.17$, $p > .40$, or on Trial 3 when $S_{T1} \neq S_{T3}$, $t(3) = -0.01$, $p > .40$. The control group performed significantly better on Trial 3 when $S_{T1} = S_{T3}$ than when $S_{T1} \neq S_{T3}$, $t(3) = -3.84$, $p = .031$ (triple asterisks in Figure 2). All of these results were confirmed with nonparametric statistics (Mann–Whitney U test).

One-trial learning on the second presentation of a stimulus. In a different assessment of one-trial learning, presented in Figures 3 and 4, we measured performance on the second presentation of each stimulus, regardless of when during the session that occurred. For example, the first presentation of a given stimulus might have occurred on the fourth trial of the session and the second presentation (neglecting correction trials) three trials later. In order to study the effects of errorless learning and intervening trials, we grouped these second presentations into four classes based on the combinations of two factors: (a) whether the monkeys had made errors prior to the first correct response to that stimulus and (b) whether they had responded to other stimuli between the first and second presentations of a stimulus. Recall that in order to complete each "trial", the monkeys had to perform correction trials until they responded correctly. Thus, at the time of the second presentation of each stimulus, the monkeys had performed and experienced only one correct, reinforced response to that stimulus. The combinations of these two factors produced the four classes of second-presentation trials illustrated in Figure 3.

Figure 3 confirms the finding of significant one-trial learning in the control group. A three-way analysis of variance (ANOVA) with factors group (control vs. fornix transection), prior errors (errorless vs. prior errors), and intervening stimuli (no intervening stimuli vs. intervening stimuli) showed main effects of group, $F(1, 7) = 21.0$, $p < .0001$; prior errors, $F(1, 7) = 46.1$, $p < .0001$; and intervening stimuli, $F(1, 7) = 20.3$, $p < .0001$, as well as a significant three-way interaction, $F(1, 7) = 5.1$, $p < .033$, and a Prior Errors × Intervening Stimuli interaction, $F(1, 7) = 9.3$, $p < .005$. (Exclusion of Monkey F4 changed the three-way interaction

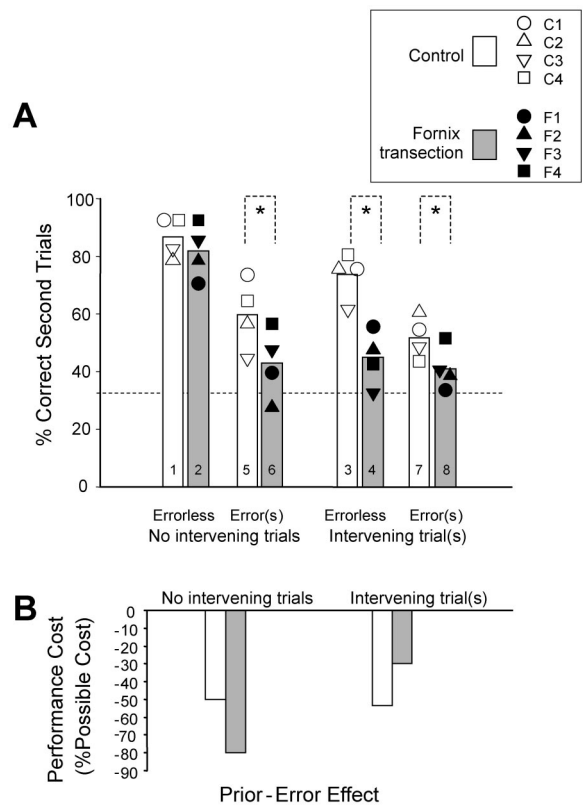

Figure 3. One-trial learning in the control group, but not the fornix-transection group. A: Average correct-response percentage for the second presentation of a given stimulus, regardless of when it occurred in the session. Second presentations occurred in four classes, depending on combinations of two factors: (a) whether the monkeys made one or more errors prior to the first correct response and (b) whether other stimuli appeared between the first and second presentation of a stimulus. The numbers at the base of each bar are referenced in the text. The dashed horizontal line indicates a chance level of performance. B: The performance cost of prior errors, calculated as the difference in response accuracy between the errorless and error conditions shown in Figure 3A, as a percentage loss relative to chance performance.

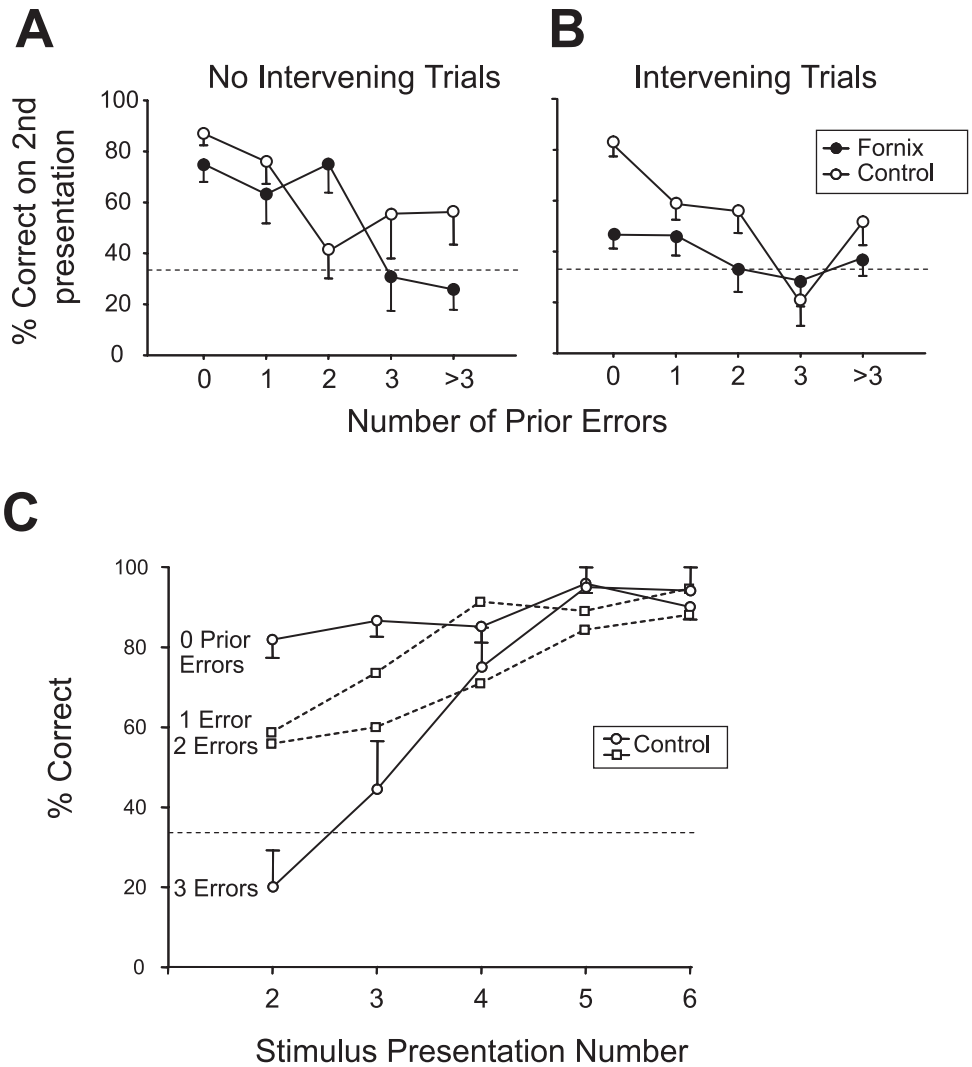

Figure 4. Effect of the number of prior errors. A: Mean (± *SEM*) percent correct performance on second presentations when no stimuli or responses intervened between the first correct response to a given stimulus and its second presentation. Regressions (where > 3 errors = 4): for the fornix-transection group, $y = -13.1x + 80.1$, $R^2 = .74$; for the controls, $y = -8.2x + 79.6$, $R^2 = .50$. B: Mean (± *SEM*) percent correct performance on second presentations in which some number of other stimuli intervened between the first correct response and the second presentation of a given stimulus. Regressions: for the fornix-transection group, $y = -3.6x + 45.7$, $R^2 = .51$; for the controls, $y = -9.9x + 73.5$, $R^2 = .50$. C: Mean (± *SEM*) percent correct performance (control group only) on the second through sixth presentation of each stimulus, for each number of errors made prior to the first correct response, if any. Circles and squares are arbitrary.

to $F[1, 7] = 4.0$, $p = .06$.) Post hoc (Newman–Keuls) analysis revealed no group difference when there were no prior errors and no intervening stimuli (bar 1 vs. bar 2 in Figure 3A). By contrast, we observed significant between-groups differences (asterisks in Figure 3) for all of the remaining classes of second presentations (i.e., bar 3 vs. 4, bar 5 vs. 6, and bar 7 vs. 8 in Figure 3A). The good performance of the fornix-transection group when there were no errors or intervening trials (bar 2 in Figure 3A) contrasted with that group's performance on the other classes of second presentations (bars 4, 6, and 8 in Figure 3A), which did not differ significantly from chance level. Within-group comparisons for the control group revealed that both prior errors and intervening stimuli contributed to significantly lower performance. Figure 3B shows a cost index, which measures the effect of prior errors, by group, for second presentations, both with (right) and without (left) intervening trials. This index shows the extent to which prior errors decreased scores to chance level. An index of –100% would indicate that the monkeys' group score decreased to chance level; 0% would indicate no effect.

Figure 4 shows the effect of the number of prior errors (and intervening trials) on the earliest phase of learning, including one-trial learning. As described above, the number of errors prior to the first correct response corresponded to the number of correction trials, if any. For example, if a monkey needed two cor-

rection trials to respond correctly to a new stimulus, then the monkey had made two errors before scoring its first successful response to that stimulus. The data presented in Figure 4A and B show performance for the second presentation of a given stimulus, and at that time the monkeys had always made only one correct response to that stimulus. A two-way ANOVA, with factors group (control vs. fornix transection) and number of prior errors (0, 1, 2, 3 and >3) showed that when no other stimuli intervened between the first and second presentation of a stimulus (Figure 4A), the number of prior errors had a highly significant effect, $F(1, 4) = 9.7$, $p < .002$, which was the same in both groups (i.e., no group effect), $F(1, 4) = 2.6$, $p > .10$. When the monkeys had responded to another stimulus or other stimuli between the first and second presentation (Figure 4B), that is, when there were intervening trials, the number of prior errors also had a highly significant effect, $F(1, 4) = 6.4$, $p < .0001$, but only in the control group. Thus, for the data illustrated in Figure 4B, the ANOVA showed a group effect, $F(1, 4) = 19.8$, $p < .0001$, which reflected the lack of one-trial learning in the fornix-transection group. The number of trials intervening between the first and second presentation of a stimulus had no significant effect (not illustrated), either when errors had been made prior to the first correct response, $F(1, 4) = 1.2$, $p > .30$, or in the absence of such errors, $F(1, 4) = 2.1$, $p > .40$.

In Figure 4C, we explore in more detail the data presented in Figure 4B. The figure shows how many presentations (and their associated correct responses) it took to overcome the effects of errors made prior to the first correct response. These data come from the control group only, and only when some number of other stimuli intervened between the first and second presentation of a stimulus. We did not assess how many trials intervened between subsequent presentations. When the monkeys had made no errors prior to the first correct response, their performance on the second presentation of a stimulus approximated plateau levels, indicative of strong one-trial learning. When the monkeys had made some number of errors prior to the first correct response, they reached their behavioral plateau by the time of the fourth or fifth presentation of each stimulus.

Discussion

One-trial learning. The present results show that with sufficient experience, macaque monkeys achieve significant one-trial learning in a nonspatial version of the conditional motor learning task and that fornix transection eliminates this capability. This finding extends to fornix transections and to nonspatially differentiated response results previously reported for aspiration lesions of the hippocampus and spatially directed responses (Murray, Brasted, & Wise, 2002). Of course, we cannot rule out the possibility that with additional experience, the fornix-transection group might have achieved significant one-trial learning. We note, however, that they had more than 2 years of experience with this task and had solved more than 100 three-stimulus problem sets. Nevertheless, they remained at chance levels of performance for the second presentation of a given stimulus (Figures 2 and 3), except for one particular circumstance (bar 2 in Figure 3A), which appears to reflect a response strategy that depended both on short-term memory and on errorless experience with a given stimulus and response. We take up that exception to the general finding, below, in the discussion of errorless learning.

There have been several previous reports of one-trial learning by monkeys on associative tasks, and some have discussed a role for the hippocampus in this type of learning. For example, it was originally reported that large lesions including the hippocampus and other structures led to deficits in remembering, simultaneously, where two objects had been located, and these deficits were attributed to the hippocampus (Parkinson, Murray, & Mishkin, 1988). Subsequent experiments showed, however, that the behavioral deficits had actually been caused by damage to the parahippocampal cortex and not by damage to the hippocampus (Malkova & Mishkin, 2003). Monkeys can also learn about rewarded objects or places in one trial (Aigner & Mishkin, 1993; Spiegler & Mishkin, 1981). In an interesting finding, Gaffan et al. (1984) showed a significant effect of fornix transection on only one of two versions of a one-trial, object–reward associative learning task. In separate experiments, they trained monkeys to perform the standard version of this task based on a win–stay rule and a variant based on a win–shift rule. In both versions of the task, monkeys performed two acquisition trials in which one item, presented singly, was baited and another item, again presented singly, was unbaited. This series of events was followed by a retention test in which the two objects were presented as opposing choices. The win–shift rule (also called *incongruent recall*) dictated that whatever item had been unbaited in an acquisition trial was baited on the retention test. Conversely, the win–stay rule (also called *congruent recall*) dictated that whatever item had been baited in an acquisition trial was also baited on the retention test. Familiarity could not guide performance because both of the items presented for choice on the retention test were equally familiar, both having appeared once during the acquisition phase. Gaffan et al. reported that monkeys with fornix transection were impaired in performing according to the win–shift, but not the win–stay, rule. This finding is relevant to one-trial learning because in the former task, win–shift, the monkeys must use the information gained during single acquisition trials (about what items had appeared with food) to override the instrumental response that has been reinforced. (By contrast, in the latter task, win–stay, the correct choice at test is consistent with the instrumental response that has been reinforced.) Thus, the selective impairment on the win–shift rule after fornix transection might reflect an inability to recall the information presented on the acquisition trials, which would represent a form of one-trial learning. We think that it is important, however, to distinguish memory for the learned value of objects (or places) from the type of memory required in tasks such as conditional motor learning and paired associate learning, which require stimulus–response and stimulus–stimulus mappings, respectively. This type of learning is performed optimally by pattern-associator networks of the type theorized to depend on the hippocampus. We also take up that topic below, in the discussion of errorless learning. First, we address one-trial learning in the context of episodic memory.

Episodic memory. One-trial learning has some bearing on the concept of episodic memory, which has been proposed as a principal function of the HS. We refer readers to our previous discussion of this issue (Brasted et al., 2003b), which we will not repeat here. Most authorities accept the idea that the HS plays a central role in episodic memory, despite differences in opinion about how

to define episodic memory and the concepts underlying those definitions. One approach to studying the neural basis of episodic memory in nonhuman animals depends on the use of tasks aimed at capturing the essential features of episodic memory. Gaffan (1994) has used object-in-place and scene-memory tasks in an attempt to measure episodic memory and has argued for a role of the HS in that function. Recently, this approach has been extended to include temporal processing (Charles, Gaffan, & Buckley, 2004; Fortin, Agster, & Eichenbaum, 2002). A second concept of episodic memory involves "mental time travel," the ability to project oneself into the past or future (Tulving, 2001). According to proponents of this concept, episodic memory—properly construed—occurs only in humans and has a close relationship to both conscious awareness and self-awareness. The third concept of episodic memory, and the only one directly relevant to the present results, involves the conjunction of information about the time, place, and content of events on the basis of a single experience (Clayton, 1995). Recently, Clayton, Bussey, Emery, and Dickinson (2003, pp. 436–437) attempted to define operationally what they term "episodic-like" memory in terms of content (what happened, where did it happen, and when), "structure," "flexibility," and "integration." Quantifying concepts such as flexibility and integration will likely prove very challenging, however. Accordingly, in the present study we concentrated on one-trial learning, which can be quantified as the increase in performance that follows from a single exemplar of a correct response to a given stimulus.

We found that control monkeys showed significant one-trial learning but that fornix-transection monkeys did not. We note a possibly important difference, however, between episodic memory as it sometimes occurs in humans and what we observed. Episodic memories can, sometimes and at least in principle, become encoded completely with just one exposure. The monkeys in the present study performed significantly above the chance level of performance after one exposure, but they did not perform at criterion level or reach their performance asymptote until several trials later. The final classification of this learning as either an example of episodic memory or an example of particularly fast learning of some other type will require additional study. If the HS does indeed make a crucial contribution to episodic memory, then perhaps the lack of one-trial learning after fornix transection reflects the loss of a contribution by episodic memory to conditional motor learning. Episodic memory might contribute to learning conditional motor associations, in part, by encoding the unique contexts of events, such as the mere fact that a given response and the delivery of reward occurred in the context of a given stimulus. This context could contribute to recall even when both the association and its context remain only partially encoded or consolidated. Indeed, an animal's internal state could provide another crucial aspect of context. Along these lines, Kennedy and Shapiro (2004) have recently shown that both hippocampal damage and fornix transection impair the recall of an arbitrary association based on context. They trained rats on an association between one object and food and an association between another object and water. Control rats could choose which object to approach on the basis of whether they needed food or water, and they did so significantly better than rats with HS damage.

Errorless learning. The topic of errorless learning has attracted increasing interest in several fields, including such diverse areas as animal learning theory, cognitive psychology, and rehabilitation medicine. We found that the number of errors made prior to the first correct response affected performance for the second presentation of a given stimulus, despite the fact that the monkeys had experienced only one exemplar of the correct stimulus–response mapping at that time. Given this one trial of experience, monkeys performed significantly worse when they had made one or more errors before their first correct response than when they had, by chance, not made any errors in response to that stimulus. Rupniak and Gaffan (1987) reported a similar result (see their Figure 4). Their learning curves, as displayed in 10-trial blocks, showed a persistent effect of whether the monkeys had made a correct first response or an incorrect one. However, the effects on the second through sixth stimulus presentations, as reported here, could not be determined from their report.

The effect of errors on one-trial learning is of theoretical importance. McClelland (2001) has proposed that the prior execution of erroneous responses to a given stimulus impairs associative learning. He hypothesized that when a particular response follows the presentation of a stimulus, connections between neurons participating in the representation of the stimulus and the response strengthen, leading to an increased likelihood of the stimulus eliciting the same response on a subsequent presentation. When, by chance, the presentation of a stimulus leads to an incorrect response, this mechanism tends to strengthen incorrect associations, simply because the neurons involved discharge together in producing the erroneous response. Even though the incorrect response is never reinforced, this Hebbian mechanism would slow the network's learning of the correct output after it has produced an erroneous response. According to McClelland's model, the same process contributes to strengthening a correct response.

The performance of the control group provides support for McClelland's (2001) idea. Prior errors eliminate about half of the performance benefit gained from the first correct response (Figure 3A), in accord with McClelland's hypothesis. As shown in Figure 4C, it takes three or four correct responses to overcome the effects of errors that occur prior to the first correct response, and the greater the number of prior errors, the greater effects on fast learning (Figure 4A–C).

Another aspect of McClelland's (2001) idea involves the role of the HS in overcoming this maladaptive Hebbian learning. He hypothesized that the conjunction of stimulus, response, and reinforcement eventually serves to train the network to respond accurately, overcoming the interference caused by Hebbian mechanisms. According to several contemporary theories of HS function (Alvarez & Squire, 1994; McClelland, McNaughton, & O'Reilly, 1995; O'Reilly & Rudy, 2000; Wallenstein, Eichenbaum, & Hasselmo, 1998; Wiltgen, 2004; Wise & Murray, 1999), the HS plays a central role in recording these conjunctions. Such considerations have led to the idea that amnesic patients should especially benefit from errorless learning. For example, a recent meta-analysis of errorless learning showed a large and significant effect in amnesic patients (Kessels & de Haan, 2003). Among primary reports, patients with mild Alzheimer's disease have been shown to benefit from errorless-learning procedures (Grandmaison & Simard, 2003; Kixmiller, 2002). Unfortunately, because of a floor effect in the present data, we were unable to assess this aspect of McClelland's theory. Figure 3A shows why this is the case. Note that intervening stimuli, alone, impaired the fornix-transection group to the extent

that they performed near chance levels. Statistically, their performance did not differ from chance. It seems that either prior errors, alone, or intervening stimuli, alone, led to chance performance in the fornix-transection group. One intervening stimulus sufficed to cause this effect. Thus, the left half of Figure 3A and B cannot be taken as a measure of long-term associative learning. We speculate that the fornix-transection group performed at approximately 80% correct (see bar 2 of Figure 3A) by using short-term memory in the service of some version of a win–stay strategy, which either an intervening stimulus or a prior error undermined. It is clear why an intervening trial would undermine a win–stay strategy, but we do not fully understand why a prior error would do so. Perhaps this influence results from the Hebbian mechanisms mentioned above, especially those involving short-term changes in synaptic weights (McClelland & Rumelhart, 1985). Strengthening of the "wrong" synapses could lead to an incorrect choice based on stimulus–response associations, and this influence might overcome a correct choice based on a win–stay strategy. According to this suggestion, in the absence of the maladaptive synaptic strengthening associated with the prior error, the win–stay strategy would prevail. This sort of competition might be especially likely when both processes, associative and strategic, are near the threshold for decision.

Comparison with spatial versions of the task. Figure 5 presents a comparison of the learning curves from the present study, which involved conditional motor learning in the nonspatial domain, with those obtained from a different group of monkeys, which learned conditional motor associations in the spatial domain (Murray & Wise, 1996; Wise & Murray, 1999). In the spatial version of the conditional motor learning task, monkeys learned to respond to visual stimuli by moving a joystick in one of three directions; in the present, nonspatial version of the task, the monkeys responded with nonspatially differentiated taps or holds. The two studies used very similar stimulus material, but the differences between them extended well beyond the nature of the response. First, assessment of HS function in the spatial version of the task involved bilateral aspiration lesions of the hippocampus and subjacent cortex, whereas the present task involved fornix transections. Second, the spatial study compared preoperative scores (filled circles in Figure 5) with postoperative scores (unfilled circles), whereas the present study compared control group performance (filled triangles) with fornix-transection group performance (unfilled triangles). Despite these important methodological differences, the two studies revealed a similar degree of impairment. Indeed, the impairments resemble each other so closely as to suggest that the HS contribution differs little for spatial versus nonspatial versions of the task and that fornix transection causes as much impairment as removal of the hippocampus and subjacent cortical areas. Experiment 2 tested the latter suggestion.

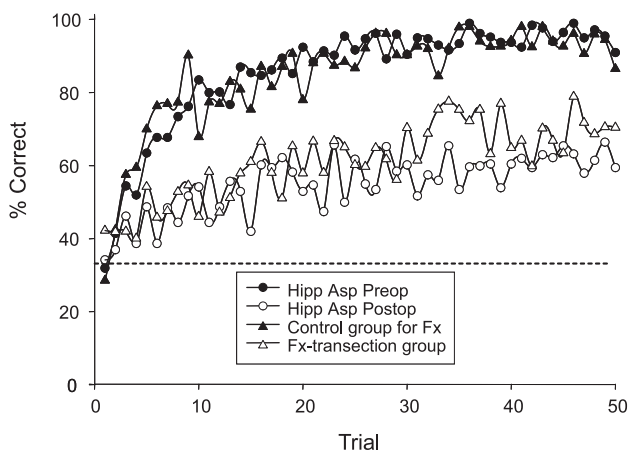

Figure 5. Learning curves for two kinds of conditional motor learning tasks. The present data (triangles) involved a comparison of the control group (filled triangles) with the fornix (Fx)-transection group (unfilled triangles) on a nonspatial version of the conditional motor learning task. The remaining data (circles) come from a spatial version of the task, published by Murray and Wise (1996), which used similar stimulus material and involved a comparison between preoperative (Preop; filled circles) and postoperative (Postop; unfilled circles) performance. The lesion was a bilateral aspiration lesion of the hippocampal system (Hipp Asp). Note that despite the differences in the nature of the response (nonspatial vs. spatial), the baseline for comparison (control group vs. preoperative performance), and the lesion (fornix transection vs. aspiration lesions of the hippocampal system), the baseline performance and the effects of hippocampal system damage resemble each other closely.

Experiment 2

Experiment 2 examined the effects of bilateral aspiration lesions of the HS on the residual learning capacity of monkeys with preexisting fornix transections. We reasoned that if, as suggested by Figure 5, the connections through the fornix conveyed the entire contribution of the HS to conditional motor learning, then removal of the hippocampus and subjacent cortex should cause no further deficits. Alternatively, the spared learning observed after fornix transections might have relied on the HS, as mediated through its other projections.

Method

Subjects. The subjects were members of the fornix-transection group of Experiment 1.

Surgery. The *Method* section for Experiment 1 described the general surgical procedures. The monkeys received one-stage, bilateral removal of the hippocampal formation plus the subjacent parahippocampal cortex by direct aspiration of the tissue with the aid of an operating microscope. The boundaries of the lesion consisted of the fundus of the occipitotemporal sulcus, ventrolaterally; the amygdala, rostrally; the brainstem, medially; and the roof of the ventricle, dorsally and laterally. The lesion thus included not only the HS (hippocampus proper, dentate gyrus, and subicular complex), but also the cortex of the parahippocampal gyrus and the posterior portion of the entorhinal cortex (see Figure 6).

For performance immediately prior to the aspiration lesion (here considered as preoperative data) and after the aspiration lesions (postoperative data), we measured learning rate as the number of trials to a criterion of 90% correct response for each problem set. In a relatively easy version of the task, problem sets consisted of three stimuli, which mapped uniquely to the tap, short-hold, and long-hold responses (termed *3:3 mappings*). In the relatively difficult version, problem sets consisted of 9 stimuli mapped onto the same three responses in a balanced manner, that is, three stimuli in the set mapped to each of the three responses (termed *9:3 mappings*). Note that because the fornix-transected monkeys did not show one-trial learning, we present no analysis of such rapid learning for Experiment 2.

The removals were essentially as intended. Figure 6 illustrates the extent of the lesions in 2 representative monkeys. Histological analysis of the volume of removed hippocampus and subiculum showed a complete lesion in all 4 members of the group. Damage to the entorhinal cortex, which was

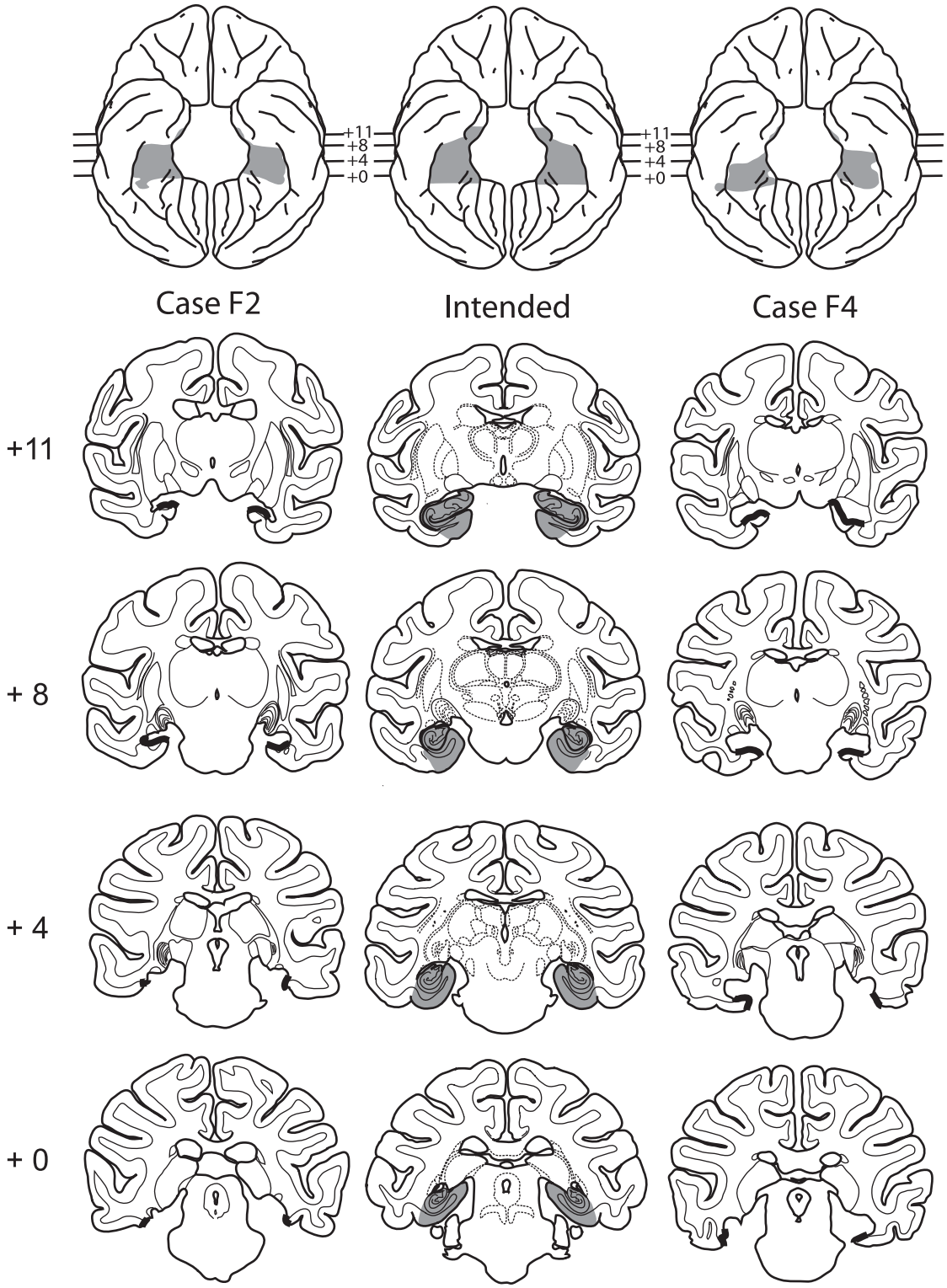

Figure 6. Histological documentation of the extent of the bilateral aspiration lesions of the hippocampal system in 2 representative monkeys. The central column shows the intended lesion on sections from an unpublished atlas. The left and right columns show reconstructions of the extent of the lesions (top) and coronal sections through the lesion (bottom) in each of 2 monkeys. Thick black lines indicate the line along which tissue was removed, that is, the edge of the lesion. Numerals indicate distance from the intra-aural plane.

slight, was limited to the most caudal and medial portions of this field; the extent of this damage in Monkeys F1 and F3 was similar to that shown in Figure 6 for Monkeys F2 and F4.

Results

Figure 7 shows that the aspiration lesions of the hippocampus plus the subjacent cortex, when added to fornix transection, did not significantly slow the rate of learning for either 3:3 mappings: preop versus postop, $t(3) = 0.86$, $p > .20$, or 9:3 mappings: preop versus postop, $t(3) = 0.17$, $p > .40$. For 3:3 mappings, the monkeys attained criterion performance in a mean ($\pm$ *SEM*) of 52.7 $\pm$ 15.7 trials preoperatively and 63.2 $\pm$ 22.3 trials postoperatively. For 9:3 mappings, they did so in 217.5 $\pm$ 61.5 trials preoperatively and 225.2 $\pm$ 63.2 trials postoperatively.

Discussion

The results show that structures other than the HS mediate the nonspatial conditional motor learning spared by fornix transection. Whatever the contribution of the fibers of the fornix to or from the HS, severing those fibers eliminates the entire contribution that the HS makes to this form of associative learning. This finding constrains the idea that the deficit in learning rate results from the elimination of the cholinergic input that the fornix supplies to the HS (Barefoot, Baker, & Ridley, 2000, 2002; Gaffan, 2002; Ridley, Aitken, & Baker, 1989). The present finding shows that this idea, if correct, applies only to the fastest learning and not to the slower learning spared by fornix transection. Cholinergic inputs to the HS are thought to play an important role in neuronal plasticity (Parent & Baxter, 2004), and, if that is so, then the loss of this plasticity eliminates the contribution of the HS in the present task entirely. The alternative, that the loss of cholinergic inputs to the HS merely slows the rate of encoding of the relevant information in the HS, can be ruled out by the present result.

The mechanism by which the HS accelerates the learning of conditional motor associations may be mediated by its output either to the mammillary bodies, emanating mostly from the subiculum, or to parts of the neocortex as relayed via the entorhinal cortex. The present results point to the importance of information conveyed by the fornix. In a series of experiments carried out by Gaffan and Parker, it was shown that the fornix and anatomically related sites, including the mammillary bodies and anterior-group nuclei of the thalamus, are necessary for efficient learning of object-in-place scenes (Parker & Gaffan, 1997a, 1997b). In this task, monkeys were rewarded for touching a particular object of a pair, which always occupied a particular position in a unique background (or scene). Although monkeys were not required to remember the spatial organization of the scenes in this task, memory for either the spatial layout or the content of the scenes could well have guided the responses, as in the present study, by providing a context for a particular action. In any event, transection of the fornix has been found to disrupt the fastest learning of both conditional visuomotor and object-in-place associations. A recent study by Sziklas and Petrides (2004), in rats, indicated that lesions of the hippocampus impaired the learning of conditional motor associations, but lesions of the mammillary nuclei and the anterior group of thalamic nuclei did not. Putting aside possible species differences for the sake of discussion, it is possible that outputs from the fornix directly to the mammillary nuclei and indirectly to the anterior thalamic nuclei contribute mainly to fast conditional visuomotor and object-in-scene learning. This account might explain why Sziklas and Petrides, who measured slow learning across days, failed to observe a deficit after their subcortical lesions.

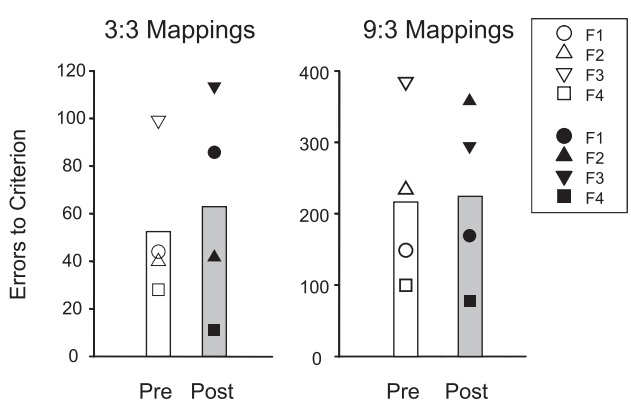

Figure 7. Learning rate after bilateral aspiration lesions of the hippocampal system in monkeys with longstanding fornix transections. Two kinds of problem sets were presented: those consisting of three stimuli (3:3 Mappings) and those consisting of nine stimuli (9:3 Mappings). The plots show the mean errors made (correction trials excluded) to a learning criterion of 90% correct responses, just before the addition of the aspiration lesion to the fornix transection (Pre, for preoperative) and after the aspiration lesion (Post, for postoperative). Unfilled symbols indicate monkeys with fornix transection; filled symbols, the same monkeys with fornix transection plus bilateral removal of the hippocampus proper, dentate gyrus, subicular complex, and subjacent parahippocampal cortex.

Experiment 3

Experiment 3 examined the effect of excitotoxic lesions of the hippocampus on conditional motor learning. The finding that fornix transection impaired the ability of monkeys to learn a nonspatial version of the conditional motor task led us to explore whether that contribution depended on the hippocampus per se (i.e., CA1–CA4 and the dentate gyrus) or on adjacent areas such as the subicular complex and entorhinal cortex. The afferents to the HS that arrive via the fornix, such as cholinergic and GABAergic inputs from the basal forebrain, distribute terminals beyond the hippocampus to the subicular complex, entorhinal cortex, and other structures, and neuropsychological studies have explored the function of these afferents (Easton & Gaffan, 2001; Easton, Ridley, Baker, & Gaffan, 2002; Gaffan, 2002; Gaffan, Parker, & Easton, 2001). Further, the efferent projections from the HS conveyed by the fornix arise in large part from the subiculum, and only to a lesser extent from the hippocampus proper. Because of this anatomy and in view of the studies in rodents and primates showing differences in the effects of hippocampal lesions versus fornix transection (Cassel et al., 1998; Clark, Zola, & Squire, 2000; Whishaw & Jarrard, 1995), we examined the effect of selective excitotoxic lesions of the hippocampus proper on the same type of learning studied in Experiment 1.

Method

Subjects. The subjects were members of the control group of Experiment 1.

Surgery. The *Method* section of Experiment 1 described the general surgical procedures. In Experiment 3, however, lesions were made by injection of the excitotoxin *N*-methyl-D-aspartate (NMDA), rather than by aspiration or fiber-tract transection. Because ketamine hydrochloride blocks NMDA receptors and might therefore interfere with the neurotoxic action of NMDA, the monkeys were restrained with a combination of medetomidine (0.1 mg/kg; Domitor, Pfizer, New York, NY) and butorphanol (0.3 mg/kg) rather than ketamine. After intubation, surgical levels of anesthesia were maintained with isoflurane (1–3%, to effect) and then the effects of medetomidine were reversed with atipamezole (0.5 mg/kg; Antisedan, Pfizer). Two different stereotaxic approaches were used to make the NMDA injections. The first approach involved turning a large bone flap over the dorsal cranium and making 2–3 injections of NMDA in the uncus of each hemisphere. A 10-μl Hamilton (Reno, NV) syringe, held in a Kopf electrode manipulator (David Kopf Instruments, Tujunga, CA) and introduced via a dorsal approach, delivered the excitotoxin to the targeted tissue. At each site, 2.0 μl NMDA (0.2 M) was injected at a rate of 0.2 μl/minute, in one hemisphere at a time. The second approach involved injecting excitotoxin in the body of the hippocampus via one longitudinal needle penetration (see Hampton, Buckmaster, Anuszkiewicz-Lundgren, & Murray, 2004). This procedure required two bone openings of about 1 cm diameter over the occipital cortex, one in each hemisphere. The needles of two 25-μl Hamilton syringes, held in manipulators, were introduced through small slits in the dura and advanced from caudal to rostral until they reached the most rostral injection site. Then, 7–10 separate injections were made, at sites 2 mm apart, along the length of each hippocampus. At each site, 2.0 μl NMDA (0.2 M) was injected at a rate of 0.25 μl/minute, in both hemispheres simultaneously. A 3-min waiting period intervened between injections, after which the needle was withdrawn along its track, from one injection site to the next.

Lesion assessment. The NMDA injections affected from 42% to 67% of the volume of the hippocampus (see Table 1). Thus, although all 4 monkeys sustained substantial bilateral damage to the hippocampus (including the dentate gyrus), none of them received a complete lesion. As intended, the subiculum proper, presubiculum, parasubiculum, and entorhinal cortex were nearly completely intact in both hemispheres, except where indicated in Table 1. The prosubiculum suffered damage only rarely and never in both hemispheres at the same level. The most rostral 2–3 mm of the temporal poles of the hippocampus proper also remained intact, as did 2–3 mm of tissue in the lateral aspect of the hippocampus of at least one hemisphere in each monkey. There was no clear relationship between the extent of the lesion or its location within the hippocampus (temporal vs. intermediate vs. septal parts) and the performance of individual monkeys. Nevertheless, it may be of interest that C4, the only monkey that obtained somewhat lower scores after surgery, sustained extensive damage to the presubiculum in the right hemisphere, in addition to hippocampal damage. All other subdivisions of the subicular complex were largely spared.

Results

Figures 8–10 show that the excitotoxic lesions aimed at the hippocampus had no effect. These highly experienced monkeys learned novel conditional motor associations rapidly. For 3:3 mappings, they solved novel conditional motor problems in a mean of 14.0 ± 5.2 trials prior to the excitotoxic lesions and in 10.1 ± 2.7 trials postoperatively (Figure 8, left). For 9:3 mappings, they reached criterion in 65.9 ± 11.2 trials preoperatively and 74.4 ± 31.0 postoperatively (Figure 8, right). Neither difference reached statistical significance: for 3:3 mappings, $t(3) = 1.38$, $p > .10$; for 9:3 mappings, $t(3) = 0.32$, $p > .30$.

Figures 9 and 10 show the analysis of one-trial learning, repeating the same data from Figures 2 and 3 for the control group, now as preoperative data. After the excitotoxic hippocampal lesions, the monkeys continued to show significant one-trial learning, with some improvement, which failed to reach statistical significance, $t(3) = 1.10$, $p > .10$.

Discussion

Excitotoxic lesions aimed at the hippocampus proper neither slowed the monkeys' rate of learning new conditional motor associations nor disrupted one-trial learning. Indeed, a slight improvement occurred postoperatively for one-trial learning, probably because of the additional experience accrued. Because the hippocampal lesions were incomplete, we cannot rule out the possibility that complete lesions would have disrupted learning. We can only conclude that substantial amounts of damage to the hippocampus, ranging from ~40% of hippocampal volume in the least affected monkeys to ~67% in the most affected ones, did not cause a deficit in either one-trial learning or in the monkeys' overall learning rate.

A preliminary report on these data (Brasted et al., 2003a) stated that excitotoxic lesions of the hippocampus had no effect on

Table 1
Three Measures of Performance for Each Control Monkey, With the Extent of the Hippocampus and Subiculum Lesion for Each Hemisphere

	% hipp. damage (by volume)		% subiculum damage (by volume)		No prior errors with intervening trials, 2nd trial performance (% correct)			Prior errors with intervening trials, 2nd trial performance (% correct)			Learning rate for 9:3 mappings (errors to criterion)		
Monkey	L	R	L	R	Pre	Post	Diff	Pre	Post	Diff	Pre	Post	Diff
C1	66.8	66.6	2.5	0.0	76	91	+15	55	80	+25	92	62	+30
C2	67.2	57.6	21.2	14.5	76	92	+15	61	67	+6	52	40	+12
C3	64.6	48.8	10.6	58.9	62	88	+26	49	53	+5	43	30	+13
C4	46.0	42.0	6.5	21.0	81	50	−31	44	40	−4	77	165	−88

Note. hipp. = hippocampus proper; L = left hemisphere; R = right hemisphere; Pre = testing prior to the excitotoxin injection (preoperative); Post = testing after the excitotoxin injection; (postoperative); Diff = difference between the preoperative and postoperative scores (positive numbers indicate relative improvement postoperatively; negative differences indicate relative impairments).

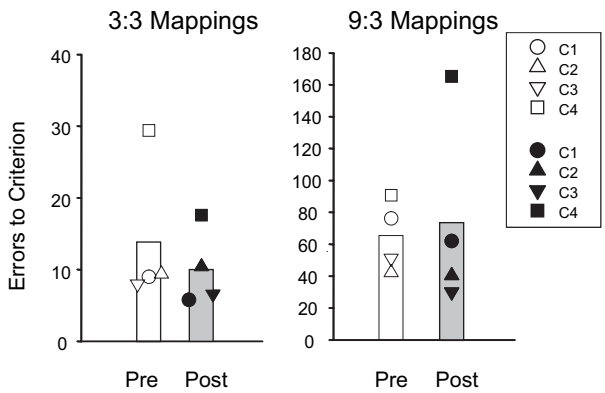

Figure 8. Learning rate after bilateral excitotoxic lesions of the hippocampus. Format as in Figure 7. Unfilled symbols indicate unoperated controls; filled symbols, the same monkeys after bilateral, selective excitotoxic lesions of the hippocampus. Pre = preoperative; Post = postoperative.

learning in this task. This conclusion applies only to lesions of the limited extent reported here. On the view that even such incomplete lesions of the hippocampus should produce a deficit if it contributes to this behavior—as has been reported for the present set of monkeys (Chudasama & Murray, 2004) and different monkeys (Baxter & Murray, 2001) trained on other tasks—these results might be taken to suggest that the hippocampus proper does not contribute importantly to the learning of new, nonspatial conditional motor associations. Such a conclusion would imply that this capacity instead depends on parts of the HS outside of the hippocampus proper, such as the subicular complex. We do not, however, rely on the incomplete lesions made in the present study to arrive at such a far-reaching conclusion.

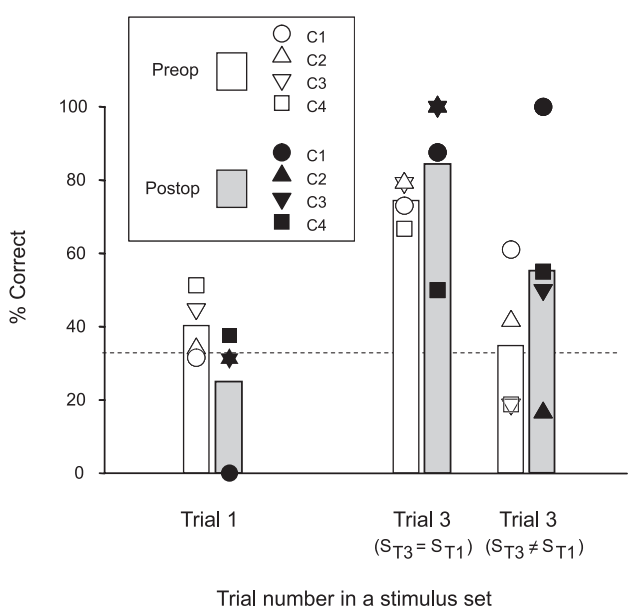

Figure 9. One-trial learning after bilateral excitotoxic lesions of the hippocampus. Format as in Figure 2. Unfilled symbols indicate unoperated controls; filled symbols, monkeys with bilateral, selective excitotoxic lesions of the hippocampus. Preop = preoperative; Postop = postoperative; S = stimulus; T = trial.

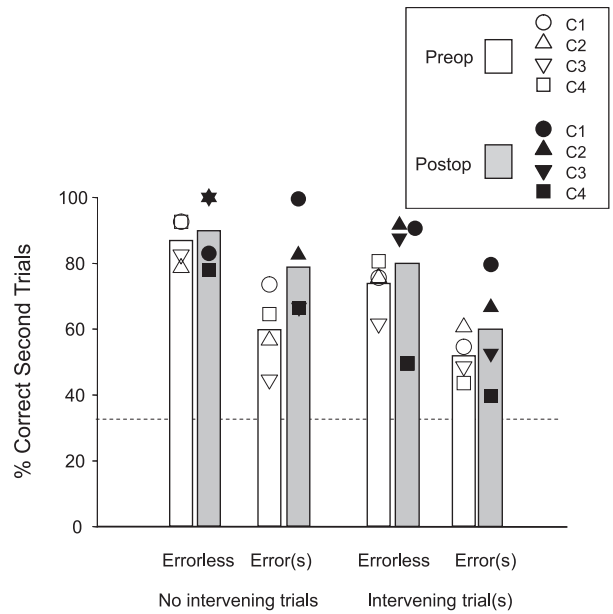

Figure 10. One-trial learning after bilateral excitotoxic lesions of the hippocampus. Format as in Figure 3. Unfilled symbols indicate unoperated controls; filled symbols, monkeys with bilateral, selective excitotoxic lesions of the hippocampus. Preop = preoperative; Postop = postoperative.

General Discussion

The present results lead to three conclusions. First, monkeys can learn conditional motor associations in a single trial, and this one-trial learning depends on the fornix. Second, errors made prior to the first correct response slow learning, in accord with theories predicting advantages for errorless learning. This conclusion supports the idea that Hebbian mechanisms underlie the learning of arbitrary associations. Third, fornix transection eliminates the contribution of the HS to nonspatial forms of conditional motor learning, and the data shown in Figure 5 suggest that fornix transection would also eliminate the contribution of the HS to spatial versions of this task.

Taken together, these data support a role for the HS, which in the present terminology includes the fornix, in the most rapid learning subserved by the brain's pattern-associator networks. We have previously discussed the question of whether the function of the HS is limited to information processing in the spatial domain (Brasted et al., 2002, 2003b), and we will not repeat that material here. In brief, there remain two seemingly disparate views of HS function, one emphasizing spatial and idiothetic information processing and another emphasizing domain generality. In Brasted et al. (2003b), we acknowledged the view that a spatial or ideothetic deficit of some kind might have accounted for all of the previously reported effects of HS lesions. We argued, however, that the present task is a genuinely nonspatial one, which established a role for the HS in associative functions beyond the spatial domain. To extend that discussion, we note two recent articles that support a

role for the HS of rats in nonspatial information processing (Broadbent, Squire, & Clark, 2004; Kennedy & Shapiro, 2004). For monkeys, in addition to the data cited previously (Brasted et al., 2003b), more recent work has shown that the fornix contributes to learning about the spatial configuration of tadpole-like objects (Buckley, Charles, Browning, & Gaffan, 2004), and in some ways its contribution in that task resembles that for conditional motor learning. Specifically, Buckley et al. (2004) found that fornix transection did not impair the recall of preoperatively learned spatial problems, but new learning was significantly impaired. Similarly, fornix transection impaired the learning of new conditional motor associations, but not the recall of previously learned ones (Brasted et al., 2003b). The same pattern of results followed aspiration lesions of the HS (Murray & Wise, 1996; Wise & Murray, 1999). Thus, the HS, taken to include the fornix and the subiculum, may function similarly for spatial and nonspatial problems. Recent evidence against the idea of such domain generality comes from the finding that incidental learning of stimulus–stimulus associations remained unaffected by fornix transections (Charles, Dickenson, & Gaffan, 2002), as well as other work on stimulus–stimulus associations reported by Gaffan and his colleagues and cited in Brasted et al. (2003b). In our view, however, a final conclusion on this issue requires further work.

In an attempt to reconcile the spatial and general purpose, pattern-associator views of HS function, Brasted et al. (2003b) suggested that the HS may play a role in supramodal information processing. *Supramodal* information, which involves both space and time, does not arise uniquely from any single sensory modality or through crossmodal association. Rather, various sensory transducers provide the basis for its computation, and the deficit reported here might involve a decreased ability to map nonspatial information onto the temporal information needed to dissociate the three tap and hold responses. Support for the supramodal processing idea comes from a study showing that fornix transections impair recency judgments in monkeys (Charles et al., 2004). Perhaps another way of reconciling the spatial and pattern-associator views of HS function involves the concept of spatial mediation. As in Brasted et al. (2003b), the responses in the present study depended on nonspatially differentiated tap and hold responses. Furthermore, a detailed analysis of the two different kinds of hold responses and several comparison conditions argued against any interpretation of the deficit in terms of spatial information processing. Nevertheless, spatial information could mediate two separate associations: one between a nonspatial stimulus and a place and another between the same place and a nonspatially differentiated response. The monkeys always directed their responses toward a certain place: the center of the video monitor, located at a specifiable coordinate within the monkeys' workspace. The HS and its connections via the fornix might contribute to nonspatial conditional motor learning by mediating two spatial–nonspatial associations, each involving that part of the workspace. Three such associations could be mediated by neuronal subpopulations with partially overlapping spatial fields, all of which include the center of the monitor. However, the finding that fornix transections impair recency judgments (Charles et al., 2004) indicates that one need not resort to a spatial-mediation account for the present results or those of Brasted et al. (2002, 2003b).

Despite the remaining uncertainty about the specificity of HS function to nonspatial versus spatial information processing, whatever contributions the HS makes to associative learning mainly involve the fastest phases of learning and not the recall of well-learned associations. This conclusion accords with recent neurophysiological results showing that neuronal activity changed relatively early in the hippocampus during the learning of conditional motor associations (Wirth et al., 2003). The HS results contrast with those that follow the crossed disconnection of the dorsal premotor cortex and the basal ganglia. Using this procedure, Nixon, McDonald, Gough, Alexander, and Passingham (2004) showed that intrahemispheric interaction between these two structures is necessary for normal recall of preoperatively learned conditional motor associations, but not for new learning. The idea that the dorsal premotor cortex and its striatal territory (the "premotor striatum") play a greater role in the consolidation and recall of conditional motor associations also accords with neurophysiological results (Brasted & Wise, 2004; Mitz, Godschalk, & Wise, 1991). Taken together with the finding that lesions of the ventral and orbital prefrontal cortex prevent fast learning (Bussey, Wise, & Murray, 2001), we suggest that the prefrontal cortex and its striatal territory (the "prefrontal striatum"), working in conjunction with the HS, subserve the fastest phases of learning, including one-trial learning. Additional evidence for an early involvement of the prefrontal striatum comes from neurophysiological results obtained during the learning of conditional motor associations (Pasupathy & Miller, 2005). A larger contribution of prefrontal striatum to new learning, with a larger contribution of premotor striatum to recall, has also been reported for sequence learning in monkeys (Miyachi, Hikosaka, & Lu, 2002).

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