Impaired Allocentric Spatial Working Memory and Intact Retrograde Memory After Thalamic Damage Caused by Thiamine Deficiency in Rats

Dave G. Mumby, Luisa Cameli, and Melissa J. Glenn
Concordia University

Rats were tested on an allocentric-spatial working-memory task—delayed matching-to-place (DMTP) in a water maze—before and after either pyrithiamine-induced thiamine deficiency (PTD) or electrolytic lesions of the lateral internal medullary laminae (IML), an area damaged by PTD. DMTP trials consisted of paired swims, with the escape platform in a new location on each trial. PTD rats were impaired at retention delays of 300 s, but not at delays of 4 or 60 s. Rats with IML lesions performed normally at all delays. Both groups displayed normal retention of object-discrimination problems that they had learned at different intervals before treatment (5 weeks, 3 weeks, and 1 week). The results suggest that PTD causes delay-dependent deficits of allocentric spatial working memory and that damage outside the IML is probably responsible. Neither PTD-induced diencephalic damage nor restricted IML lesions appear to produce a global retrograde amnesia.

Thiamine deficiency is the primary etiological factor in Korsakoff’s disease, an amnesic syndrome associated with damage to midline diencephalic structures (Victor, Adams, & Collins, 1971). In rats, daily administration of the thiamine antagonist pyrithiamine produces diencephalic lesions and learning and memory deficits. Accordingly, pyrithiamine-induced thiamine deficiency (PTD) in rats is used to model the etiology, diencephalic neuropathology, and memory deficits of Korsakoff’s amnesia.

Rats recovered from PTD are impaired on tests of spatial memory, including delayed alternation (Mair, Anderson, Langlais, & McEntee, 1985), spatial matching- and nonmatching-to-sample (Mair, Anderson, Langlais, & McEntee, 1988; Mair, Otto, Knoth, Rabchenuk, & Langlais, 1991; Robinson & Mair, 1992), and acquisition of a water maze place-navigation task (Langlais, Mandel, & Mair, 1992). Rats with PTD are also impaired on olfactory- and auditory-based learning tasks (e.g., Mair, Knoth, Rabchenuk, & Langlais, 1991) and on tests of object-recognition memory (Mumby, Mana, Pinel, Banks, & David, 1995), indicating that the impairment extends across sensory modalities and includes nonspatial as well as spatial information. Moreover, PTD-induced deficits are observed on both appetitively and aversively motivated tasks (Langlais et al., 1992; Mair et al., 1985; Mair, Otto, Knoth, Rabchenuk, & Langlais, 1991).

Despite these diverse deficits, many learning and memory abilities are relatively intact in PTD rats, including object discrimination (Mumby et al., 1995), light–dark discrimination, and single-reversal learning (Mair et al., 1988), and transfer of serial-reversal learning across different modalities (Mair, Knoth, et al., 1991).

Although behavioral studies have made considerable progress in characterizing learning and memory deficits in PTD rats, some important questions about the model remain to be answered. One question concerns the locus or loci of PTD-induced damage underlying the memory impairment. It is widely assumed that some aspect of the diencephalic damage is responsible, and early PTD studies implicated the mediodorsal nucleus (e.g., Mair et al., 1985, 1988), a hypothesis that was compelling because it paralleled the dominant view that lesions of the mediodorsal nucleus make a critical contribution to the memory deficits of Korsakoff patients (Mair, Warrington, & Weiskrantz, 1979; Victor et al., 1971). But it has been difficult to establish with certainty the critical damage underlying PTD-induced deficits because several thalamic nuclei, fiber pathways, and the mammillary nuclei are damaged by PTD. Complicating matters even further, the extent of damage varies across different studies, mostly because of differences in the stage of neuropathological progression at which the PTD treatment is reversed (Zhang et al., 1995). Recent studies have revealed pathology in areas outside the diencephalon of PTD rats, including in parietal and frontal cortex and the corpus callosum (Langlais & Savage, 1995). Given the evidence that PTD-induced brain damage is widespread, and the popular belief that there are multiple memory systems in the mammalian brain that differ in terms of their anatomy and the kinds of information they deal with, it is reasonable to...
THIAMINE DEFICIENCY AND SPATIAL MEMORY

expect that different aspects of the PTD-induced memory impairment may be due to damage in different areas.

There is evidence that PTD-induced deficits of spatial memory are associated with lesions of the lateral internal medullary laminae (IML). PTD rats that have IML damage are impaired in acquisition of delayed matching- and nonmatching-to-position tasks in a T maze, whereas PTD rats without IML damage perform normally on both tasks (Langlais & Savage, 1995). There is a similar correlation between the presence of IML damage and PTD-induced deficits on a spatial delayed nonmatching-to-sample (DNMS) task in an operant chamber (Mair & Lacourse, 1992; Robinson & Mair, 1992). Also, extensive radiofrequency lesions of the IML produce similar DNMS deficits in nutrient-replete rats (Mair, Robinson, Koger, Fox, & Zhang, 1992). Like rats recovered from PTD treatment, untreated rats with radiofrequency lesions of the IML are impaired on a water maze place-navigation task (Savage, Sweet, Castillo, & Langlais, 1997).

The T-maze and operant-chamber tasks used in the abovementioned studies required working memory, but they could be solved using either egocentric spatial or allocentric spatial (i.e., place) response strategies. The water maze place-navigation task required allocentric spatial memory (i.e., the relation among multiple Extramaze cues and the hidden platform) and reference memory because the hidden escape platform was in the same location on all trials. Thus, it is still not clear whether PTD-induced diencephalic damage or restricted IML lesions impair allocentric spatial working memory.

There are also unanswered questions about the status of retrograde memory in PTD rats. Korsakoff amnesics display temporally graded retrograde amnesia (Albert, Butters, & Levin, 1979; Seltzer & Benson, 1974), but most studies in PTD rats have focused on anterograde memory. In one of the few studies to assess retrograde memory, PTD rats displayed normal retention of a hidden-platform water maze task that was initially learned over a 2-week period ending just before the commencement of PTD treatment (i.e., approximately 14 days before the onset of diencephalic damage), with retention testing conducted 5 weeks after the end of training (Langlais et al., 1992). In another study, PTD rats displayed normal retention of a single trial of a passive avoidance task that was conducted a few days before the occurrence of brain damage (Langlais & Savage, 1995). Although these findings suggest that PTD does not cause global retrograde amnesia, the interval between when learning occurred and when PTD-induced brain damage occurred was not varied in either study. It is possible, therefore, that retrograde memory loss would have been apparent with different learning-lesion intervals or on a task that required memory for a different type of information.

This study aimed to further characterize the effects of PTD on spatial working memory and retrograde memory for nonspatial information and to explore the role of IML damage. PTD rats and rats with restricted electrolytic lesions of the lateral IML were tested on a delayed matching-to-place (DMTP) task in a water maze. The DMTP task required rats to find an escape platform in a new target location on each trial and to remember this location across a variable retention delay. The rats could not see the platform, so they had to learn its location relative to extramaze cues. The DMTP task thus required allocentric spatial working memory. We gave our rats extensive DMTP training before their treatment or surgery to facilitate interpretation of the results, by ruling out any deficits caused by impaired learning of the procedural aspects of the task. Retrograde memory was evaluated by assessing the rats' posttreatment retention of three object-discrimination problems, each of which was learned at a different time period before treatment.

Method

Subjects

The subjects were 18 experimentally naive, male Long-Evans rats (Charles River, Quebec, Canada), approximately 10 weeks old at the start of the experiment. They were housed individually with continuous access to water under a 12-hr light-dark cycle, with light onset at 8 a.m. Before commencement of behavioral training, the rats' body weights were reduced to approximately 85% of free-feeding levels by giving them daily rations of Rat Chow (Ralston-Purina, St. Louis, MO). The rats received 20 to 30 g of chow per day during the pretreatment and posttreatment testing phases.

Apparatuses

DMTP testing was conducted in a water maze (Morris, 1981), 137 cm in diameter, that was filled with water to a depth of approximately 22 cm. The water (23 °C) was made opaque by adding instant skim milk powder. A moveable Plexiglas platform (20.5 cm high × 13 cm²) was hidden approximately 1.5 cm below the surface of the water. There were no visible cues within the pool that the rats could use to locate the hidden platform; thus they were required to learn its location relative to distal room cues.

The apparatus used for the object-discrimination problems has been described in detail elsewhere (Mumbly et al., 1990). Briefly, it consisted of an elevated runway, which was separated from identical goal areas at each end by opaque guillotine doors. Each goal area contained two food wells into which food pellets (45 mg; Bio-Serve, Frenchtown, NJ) could be delivered by hand through plastic tubes. The discriminanda were eight objects of various shapes, sizes, textures, and colors, and all were made of similar plastic materials. Each object was large enough to cover a food well but small enough and light enough to be easily displaced by a rat. The objects were washed with water after every session and with a solution of chlorine bleach at the end of each day to remove any extraneous scents that might have been acquired during displacement by the rats or handling by the experimenter.

Procedure

The general procedures were as follows: The rats received water maze pretraining and DMTP training during the 5-week period preceding the initiation of PTD treatment. They were also trained on three object-discrimination problems over that same period, one of them 5 weeks before, another one 3 weeks before, and the remaining problem during the week before initiation of PTD treatment. Following recovery, the rats were first trained on a new object-discrimination problem, next they were tested for retention
of the pretreatment discrimination problems, and finally they were retested on the DMTP task.

The DMTP task. Four equally spaced points along the perimeter of the pool were designated as cardinal compass orientations (N, S, E, W) and served as release points for placing the rats into the pool. Each DMTP trial consisted of paired swims, separated by a retention delay. For the first swim of a trial, the rat was placed into the water, facing the pool wall, at one of the release points and allowed to search for the hidden platform. After finding the platform and climbing onto it, the rat was allowed to remain there for 10 s before the experimenter removed it. If a rat failed to find the platform and climb onto it within 60 s, the experimenter guided it there by hand. The retention delay began when the rat was removed from the platform and ended when the rat was placed into the pool again for the second swim of the trial. For the second swim (i.e., the retention test), the rat was again placed into the pool at the same release point and allowed to search for the platform, which remained in the same location. The main dependent measures used to gauge retention of the hidden-platform location on each trial were the escape latency and swim speed on both the first and second swim.

The platform was moved to a new location on successive trials, within and across sessions, cycling repeatedly through the sequence of 10 locations shown in Figure 1. This sequence included a similar number of platform locations near the edge of the pool, near the center of a quadrant, and near the center of the pool, which were chosen to prevent the rats from adopting successful strategies that obviated the need to use allocentric spatial relations, such as preferentially searching in a particular area of the pool, or along the pool wall, or at some fixed distance from the wall. Each release point was used approximately the same number of times for each of the 10 platform locations.

There were three DMTP trials per session, with an intertrial interval of approximately 10 min. Rats spent the intertrial intervals in the stainless steel, wire mesh cages and the retention delays in an opaque, plastic shoebox cage atop the transport cart. The retention delays used in the present experiment were 4, 60, and 300 s (see procedural details below), and it was not possible to return the shoebox cage to the cart during trials with a 4-s retention delay. On those trials the rats were removed from the platform following the first swim and carried to the release point for the second swim inside the shoebox cage.

Water maze pretraining. A 4-day pretraining phase familiarized the rats with several features of the DMTP test situation, including the spatial layout of the room, the presence of a hidden platform onto which a rat could escape from the cool water, and changing platform locations. Each rat received four paired swims (i.e., trials) per day. On the first day, the hidden platform remained in one location for all four trials (i.e., the rat found the platform in the same location a total of eight times). On the second day, the platform was moved to a new location, where it again remained for all four trials. On both the 3rd and 4th days, the session began with the platform in a new location and it was moved again after two trials.

Pretreatment DMTP training. After completion of pretraining, each rat was trained to its asymptotic performance level on the DMTP task with a 4-s retention delay between the first and second swim of each trial. Rats were determined to have reached an asymptote when their mean second-swim escape latencies did not vary significantly across three consecutive sessions, assessed by three t tests comparing performance on these sessions with α = .20. After reaching asymptote, each rat received an additional five sessions of DMTP with a 4-s delay. The delay was subsequently increased to 60 s for five sessions, and then to 300 s for an additional five sessions.

Retention curves were obtained during a final phase of pretreatment training. Each rat received 12 mixed-delay sessions, which consisted of three trials, one at each of the three delays (i.e., 4, 60, and 300 s). The order of delays used within a mixed-delay session was randomly determined.

Pretreatment object-discrimination training. Six weeks before initiation of PTD treatment, the rats were habituated to the apparatus and shaped to retrieve food pellets from the food wells (see Mumby et al., 1990). Subsequently, a different object-discrimination problem was learned at each of three different time intervals before treatment—Problem 1 was learned during the 5th week before PTD treatment, Problem 2 was learned during the 3rd week before treatment, and Problem 3 was learned during the week preceding initiation of treatment. Six objects were divided into three pairs, which served as the discriminanda for object-discrimination Problems 1, 2, and 3. One of the objects in each pair was designated S+ (rewarded) and the other one was designated S− (not rewarded). For each problem, one of the objects was S+ for half of the rats in each group, and the other object was S+ for the remaining rats.

To begin each session, the rat was placed into the center of the apparatus and allowed to explore for approximately 1 min. To begin the first trial, one of the guillotine doors was closed, and the experimenter positioned S+ and S− over the food wells on the other side of the door from the rat. The experimenter opened the door, and the rat approached and displaced one of the objects. If it displaced S+, a food pellet was delivered to that food well; if it displaced S−, no food pellet was delivered. A rat was considered to have made a choice if the object was displaced enough to expose the food well. The experimenter then closed the far door and positioned S+ and S− over the food wells on the other side of it, in preparation for the next trial. The intertrial interval was approximately 15 s. There were 25 trials per session, and the location of S+ (i.e., left or right well) varied pseudorandomly across trials. The rats were allowed to correct their errors on the first session of Problem 1, but not thereafter—if the rat displaced S− on these initial correction trials, it was allowed to then displace S+ to obtain a reward before the experimenter removed the objects. Training on each object-discrimination problem continued for a rat until it

Figure 1. The sequence of 10 platform locations that were used for the delayed matching-to-place (DMTP) task. The platform was moved to the next location in the sequence on successive trials within and between sessions.
reached a criterion of at least 20 correct trials of 25 (i.e., 80%) on two consecutive sessions; however, each rat received a minimum of three sessions (i.e., 75 trials) and a maximum of seven sessions (i.e., 175 trials) per problem.

**IML surgery and PTD treatment.** The 18 rats were divided into three groups of 6 rats each, matched for performance on the object-discrimination problems and on the DMTP task. There were no significant differences among the groups before treatment, either in the number of trials-to-criterion on object-discrimination Problems 1, 2, or 3, or in their mean second-swim latencies at any of the three delays on the final pretreatment DMTP mixed-delay session (ps > .10). One group received bilateral IML lesions (Group IML), another group received PTD treatment (Group PTD), and the third group received control treatment (Group CONT).

The PTD treatment was the same as that of most previous studies in rats (see Mair et al., 1988). The PTD rats' normal laboratory chow was replaced by ad-lib quantities of a thiamine-deficient diet (Teklad Mills, Madison, WI), and they received daily injections of pyrithiamine (0.5 mg/kg ip; Sigma Chemical, St. Louis, MO). Control rats received normal chow throughout the experiment and daily injections of saline (1.0 ml ip) during the period over which the PTD rats received pyrithiamine. The progression of neurological symptoms in the PTD rats followed previous descriptions (e.g., Troncoso, Johnston, Hess, Griffin, & Price, 1981): hypophagia, aphagia, dystnesia, ataxia, intermittent seizures, and opisthotonus. The PTD treatment was reversed by administration of thiamine (100 mg/kg ip) within 4 hr of the onset of opisphotonus or as soon as it was observed that placing the rat on its side induced overt seizures. Treatment was reversed on Day 12 or 13 for all PTD rats. Within 12 hr of receiving the thiamine supplement, acute neurological symptoms disappeared and the rats were fed a meal of wet mash made from normal lab chow. The thiamine-free diet was replaced with ordinary lab chow for the remainder of the experiment. With additional assisted feedings, all PTD rats recovered their ability to self-feed within 36 hr. The PTD and CONT rats were allowed 20 days to recover before behavioral training recommenced.

The 6 rats in the IML group received surgery on the day corresponding to Day 12 of treatment for the PTD group. This was assumed to correspond roughly to the onset of irreversible thalamic pathology in the PTD rats (Zhang et al., 1995). Surgery was conducted under pentobarbital anesthesia (65 mg/kg ip). The lesions were made with a stainless steel bipolar electrode, which was insulated with Teflon except for approximately 1.5 mm at its tip. With the incisor bar positioned 3.3 mm below the interaural line, the electrode was lowered into the lateral IML of each hemisphere at the following coordinates, relative to bregma: 1.1 mm from the midline, –2.3 mm and –3.0 mm posterior, and 6.2 mm ventral to the skull surface. A current of 0.8 mA was passed for 10 s. Three of the rats in Group CONT received sham lesions—the electrode was left in position for 20 s, but no current was passed through it. The rats were allowed to recover for 20 days before behavioral testing recommenced. The experimenter who collected the behavioral data was blind to the group assignment of individual rats.

**Posttreatment object discrimination testing.** Following recovery, the rats were first trained on a new object-discrimination problem (i.e., Problem 4), using procedures identical to those used during pretreatment object-discrimination training. One of the objects was S+ for half of the rats in each group and the other object was S+ for the remaining rats. The rats were trained on the new problem until they reached the criterion of 20 correct of 25 trials on two consecutive sessions.

Next, retention of the three pretreatment object-discrimination problems (i.e., Problems 1, 2, and 3) was assessed. Each retention session consisted of three blocks of five trials, and each block of trials constituted a different object-discrimination problem. Trial blocks were separated by a 30-s interblock interval. The order in which the three problems were presented varied in a balanced fashion across sessions, and different orders of presentation on each session were also counterbalanced among the subjects in each group. Training continued for each rat until it reached the criterion of at least 20 correct of 25 consecutive trials on all three problems; thus, each rat received a minimum of five retention sessions. All three problems continued to be administered each day, even if a rat reached the criterion on one or two of the problems.

**Posttreatment DMTP testing.** Retesting on the DMTP task began after all rats had completed the object-discrimination retention testing. The general procedures were similar to those used for the pretreatment training. There were three trials per session. The rats first received six DMTP sessions during which all 18 trials were at the 4-s delay, and then they each received 12 mixed-delay sessions using procedures identical to the pretreatment mixed-delay sessions.

**Histology.** Upon completion of behavioral testing the rats received an overdose of sodium pentobarbital and were perfused transcardially with saline, followed by 10% neutral buffered formalin. The brains were removed and stored in 10% formalin before being frozen and sectioned along the coronal plane at a thickness of 30 μm. Every third section through the thalamus was mounted on a glass slide, stained with Cresyl violet, and examined for cell loss and gliosis.

### Results

#### Behavioral Findings

**DMTP.** Figure 2 shows the mean second-swim escape latencies during the six reacquisition sessions at the 4-s retention delay. By the end of these six sessions, every rat had reached an asymptote in their mean second-swim latency, as determined in the same manner as during pretreatment training. There were no significant differences among the groups in the mean number of posttreatment trials required to reach asymptote on DMTP at a 4-s delay, $F(2, 15) < 1$. However, there was a significant group effect in the level of asymptotic performance that was reached, $F(2, 15) = 17.23, p < .001$, with significantly longer second-swim latencies in the PTD group than in either the CONT...
group or the IML group \((p < .05;\) Tukey honestly significant difference [HSD]) \). The CONT and IML groups did not differ significantly \((p > .05).\)

Figure 3 shows the mean first-swim and second-swim escape latencies at each delay during mixed-delay sessions. The groups were not significantly different on first swims, \(F(2, 15) < 1,\) but they were significantly different on second swims, \(F(2, 15) = 6.197, \ p = .01.\) There was a significant main effect of delay on second swims, \(F(2, 30) = 7.686, \ p < .01,\) but a nonsignificant Group \(\times\) Delay interaction, \(F(4, 30) = 1.637, \ p > .10.\) Post hoc comparisons (Tukey HSD) of the groups at each delay indicated that the PTD rats had significantly higher second-swim escape latencies at the 300-s delay than did CONT rats or IML rats \((p < .05),\) whereas the IML rats and CONT rats did not differ significantly \((p > .05).\) There were no significant differences among the three groups at the 4- or 60-s retention delays. Thus, the deficit that PTD rats had displayed at the 4-s delay during DMTP reacquisition was no longer apparent during mixed-delay testing. The longer second-swim escape latencies in the PTD rats at the 300-s delay cannot be attributed to a slower swimming speed, because the only significant difference among the groups in swimming speed at any delay was slower swimming by the CONT rats than the IML rats at the 300-s delay \((p < .05;\) data not shown).

**Object discrimination.** Figure 4 shows the mean number of posttreatment trials-to-criterion on the object-discrimination problems. There were no significant differences among the groups in acquisition of the new posttreatment problem \(\text{i.e., Problem 4), for both errors- and trials-to-criterion, } F(2, 15) < 1.\) Similarly, there were no significant differences among the groups in trials- or errors-to-criterion during retention testing on the three problems that had been learned before treatment: trials, \(F(2, 45) = 1.89, \ p > .05;\) errors, \(F(2, 45) = 1.84, \ p > .05.\) As shown in Figure 4, there was a floor effect on Problem 3 because all rats reached criterion on that problem within the minimum number of trials. The data from Problem 3, therefore, add unwarranted noise to the statistical analyses. Accordingly, we conducted a separate analysis of variance (ANOVA) without Problem 3, but this still failed to reveal a significant group difference in the number of trials-to-criterion on Problems 1 and 2, \(F(2, 15) < 1.\)

The trials-to-criterion measure reflects performance over several trials, and therefore the absence of an anterograde deficit in the experimental groups might have obscured the presence of a retention deficit. A better index of retention can be obtained by looking at performance on only the first few retention trials of the problems that were learned before treatment. Accordingly, Figure 5 shows the mean number of correct trials on the first block of five posttreatment trials for each object-discrimination problem. Mean scores on the new discrimination problem \(\text{Problem 4) were not significantly different from chance for any of the groups (one-sample } t \text{ tests, } p > .05, \text{ two-tailed), which suggests that five trials is not sufficient for new learning to become evident in performance of an object-discrimination task. This in turn suggests that complete forgetting of a pretreatment discrimination problem should be reflected in a score on the first five posttreatment trials that is not different from chance, and that retention of a pretreatment problem should be reflected in scores that are higher than chance. An ANOVA performed on scores from the three pretreatment problems, with problem as a within-subjects factor, revealed a significant problem effect, \(F(2, 45) = 3.45, \ p < .05;\) a nonsignificant group effect, \(F(2, 45) = 1.89, \ p > .05;\) and a nonsignificant Group \(\times\) Problem interaction, \(F(2, 45) < 1.\) Scores on all three of the pretreatment problems were significantly better than chance \(\text{(one-sample } t \text{ tests, all } p < .05, \text{ two-tailed), which suggests that most rats retained some information relevant to the accurate performance of each of those problems. Retention scores were highest for Problem 3, the last problem learned before treatment.}\)

**Histological Findings**

Figure 6 shows a photomicrograph of a representative PTD lesion, illustrating the location and extent of the thalamic damage. In general, the pattern of thalamic damage was similar in all six PTD rats and consistent with that
previously reported for rats subjected to similar PTD treatment (e.g., Mair, Knoth, et al., 1991). The lesions were bilateral and roughly symmetrical, and every case exhibited gliosis and tissue cavitation that included the IML; the midline and intralaminar nuclei, including the centromedian, centrolateral, paracentral, parafascicular, and ventrolateral nuclei; ventral portions of the mediodorsal nuclei; and anterior portions of posterior nuclei. Most of the variability was in the extent of damage to posterior and ventrolateral nuclei, but all PTD rats had some damage in these areas, and there were no obvious relationships between the extent of posterior or ventrolateral nuclei damage and the severity of a rat's DMTP deficits.

Gliosis and neuronal loss were evident in the medial mammillary nuclei of the PTD rats. There was no evidence of pathology within the hippocampal formation. We undertook no systematic histological analysis of other areas outside of the thalamus.

Figure 7 shows the location and extent of the smallest and largest lesions in the IML group. Each rat sustained nearly complete bilateral tissue loss in the intended anterior region of the IML, extending between approximately $-1.9$ mm and $-3.4$ mm relative to bregma in all rats, and as far posterior as $-3.6$ mm in two of them. The centrolateral and paracentral nuclei were thus severely damaged in all IML-lesioned rats. There was also variable and moderate gliosis and cell loss in the anteriomedial, centromedian, ventral and lateral mediodorsal, and ventrolateral nuclei of all rats. With the exception of minor damage to the anterior thalamus of three
MUMBY, CAMELI, AND GLENN

2.56 mm – 1.80 mm

Figure 7. Location and extent of the largest (grey) and smallest (black) lateral internal medullary laminae lesions at three coronal planes (distance from bregma shown in millimeters). Coronal drawings are based on the rat brain atlas of Paxinos and Watson (1986).

IML-lesioned rats, all thalamic areas affected by the electrolytic IML lesions were also damaged in the PTD rats. Unlike the PTD rats, however, none of the IML-lesioned rats sustained damage to posterior or parafascicular nuclei.

Discussion

There were three main findings: (a) PTD produced delay-dependent DMTP deficits in pretrained rats—reacquisition at the 4-s delay was slightly impaired in PTD rats, but subsequent mixed-delay performance was normal at the 4-s and 60-s delays, whereas performance was severely impaired at the 300-s delay; (b) electrolytic lesions of the IML, an area that was also damaged in the PTD rats, had no significant effects on DMTP performance; and (c) neither PTD nor electrolytic IML lesions affected retention of simple object-discrimination problems that had been learned before treatment or acquisition of a new object-discrimination problem learned following treatment.

The rats received extensive pretreatment training on the DMTP task, and therefore, the deficits displayed by PTD rats cannot be attributed to an impaired ability to learn the rules of performance (i.e., the matching principle) or procedural skills (e.g., attending to the appropriate cues, avoiding distraction). It is unclear whether the mild deficit displayed by the PTD rats during DMTP reacquisition was the result of a memory impairment or some transient nonmnemonic behavioral disruption. The latter explanation seems likely, considering that the PTD rats were not significantly different from the other groups at the 4- or 60-s delays during mixed-delay testing. Because the PTD rats were impaired only at the longest (i.e., 300-s) delay, their deficits cannot be attributed to motivational, attentional, or motor impairments, to an ability to navigate to a target location, or to an inability to suppress response biases such as searching in a particular part of the pool or along the pool wall. In light of these considerations, it is likely that the PTD rats’ DMTP deficits reflect an impairment of allocentric spatial working memory.

There was no evidence of retrograde amnesia for spatial information in either the PTD or IML-lesioned rats. All rats learned the spatial layout of the extramaze cues in the water maze room before treatment, and the rapid reacquisition of DMTP by all three groups suggests that the rats retained this cognitive map. This is consistent with the finding that PTD rats displayed normal retrograde memory for a fixed, hidden-platform, water maze task (Langlais et al., 1992). On the other hand, the DMTP deficits of our PTD rats at the 300-s delay contrast with evidence of normal long-term retention in PTD rats of a fixed, hidden-platform location over a 5-week period (Langlais et al., 1992). The different findings probably reflect differences in the tasks, the most obvious of which was that the platform was in the same location of every trial of the fixed-platform task employed by Langlais and his colleagues, whereas the present DMTP task assessed retention of a platform location that was relevant on only a single trial within a particular session.

The present DMTP findings make an important contribution to our understanding of PTD-induced spatial memory deficits. Previous studies have found deficits on spatial working memory tasks in PTD rats (Knoth & Mair, 1991; Langlais et al., 1992; Mair, Knoth, et al., 1991; Robinson & Mair, 1992), and in rats with radiofrequency IML lesions (Mair & Lacourse, 1992; Mair, Robinson, et al., 1992). The tasks used in those studies, however, could be solved using either egocentric or allocentric spatial response strategies. In other experiments, PTD rats were impaired in acquisition of an allocentric spatial reference-memory task in a water maze (Langlais et al., 1992; Mair & Lacourse, 1992). In contrast, the present DMTP task required the use of both allocentric spatial information and working memory because hidden-platform locations and release points changed from trial to trial.

The delay-dependent feature of the PTD-induced impairment is consistent with findings in PTD rats on an object-based DNMS task (Mumby et al., 1995). The PTD rats in that study had thalamic damage similar to that of our PTD rats, and the DNMS task paralleled our DMTP task in key respects, most notably in the use of trial-unique stimuli and a similar range of retention delays (15, 30, 60, and 120 s). PTD rats were severely impaired on the DNMS task at the 120-s retention delay and were moderately impaired at the 60-s delay, but they did not differ from controls at the 15-s or 30-s delays (Mumby et al., 1995). The most compelling similarity with our DMTP results is the lack of a significant DNMS deficit at retention delays shorter than 60-s. This
similarity in the pattern of PTD-induced deficits on two working-memory tasks that differ primarily in the type of information that must be remembered (i.e., an object vs. a place) is consistent with the hypothesis that PTD causes a general impairment of working memory (Langlais et al., 1992). This raises the question of whether PTD-induced anterograde memory deficits that have been observed on other spatial memory tasks (e.g., DNMS in a radial-arm maze, spontaneous alternation or delayed matching- or nonmatching-to-place in a T maze) reflect a deficit specifically in spatial-information processing or a more general disruption of working memory that affects both spatial and nonspatial information.

The findings of normal DMTP reacquisition and performance at all delays by rats with electrolytic IML lesions suggest that damage to the fiber pathways of the IML region does not impair allocentric spatial working memory. However, the location and extent of the IML lesions in the present study fall short of the criteria adopted by Mair and Lacourse (1992) for considering an IML lesion to be complete. They defined a complete IML lesion (as did Mair et al., 1992) as one with a total anterior–posterior length of 1.6 mm, extending between −2.0 and −3.6 mm relative to bregma. The posterior 0.2 mm of this range was spared in four of the six IML-lesioned rats of the present study, and this sparing of the posterior IML in a subset of rats may account for the normal DMTP performance of that group. Figure 7 indicates that the mediolateral and dorsoventral limits of the IML lesions in the present study were also somewhat less than those obtained by Mair and his colleagues, who have typically placed radiofrequency lesions at three anteroposterior (AP) locations and two depths, whereas we used only two AP locations and one depth so as to minimize damage to structures outside the IML region. Mair et al. (1992) found that lesions sparing either the anterior or posterior IML region did not impair performance of a DMTP task, whereas more complete IML lesions did produce a deficit. Thus, our conclusion that IML damage does not impair DMTP performance should be viewed as tentative pending confirmation from further experiments using more complete IML lesions.

Several studies have noted a relationship between the presence of IML damage and the severity of PTD-induced memory deficits (Langlais & Savage, 1995; Langlais et al., 1992; Mair, Otto, et al., 1991; Robinson & Mair, 1992). Although there was no evidence of such a relationship in the present experiment, it should be noted that all of our PTD rats sustained IML damage, so there was no PTD subgroup with IML-sparing that would enable the most appropriate comparison. The rats with electrolytic IML lesions did not have the additional damage outside this area that was sustained by PTD rats, and the normal DMTP performance of the IML rats is consistent with the hypothesis that damage outside the IML region underlies the spatial working memory deficits displayed by PTD rats. But rather than suggesting that damage of the IML makes no contribution whatsoever to PTD-induced deficits on memory tasks, our results merely suggest that IML damage by itself cannot account for all of the deficits. It is possible that the critical damage in the PTD rat involves a combination of IML damage and damage in some other area. Moreover, IML damage may underlie PTD-induced deficits that have been observed on other spatial and nonspatial memory tasks.

The observation of normal acquisition of an object-discrimination task by PTD rats is consistent with a previous report (Mumby et al., 1995) and with other studies that have found normal acquisition of visual discriminations in PTD rats (Mair, Anderson, et al., 1988). As mentioned previously, there have been only a few studies of the effects of PTD on retrograde memory, and this was the first to assess retrograde memory for object discriminations. PTD and IML-lesioned rats performed as well as controls on the retention tests, which suggests that neither treatment caused a generalized retrograde amnesia. Further support for this hypothesis comes from previous reports that PTD rats with IML damage displayed normal retention of a hidden-platform water maze task (Langlais et al., 1992) and a one-trial passive avoidance task (Langlais & Savage, 1995) that were learned before treatment.

Thiamine deficiency in rats has been used as a model of Korsakoff amnesia, and several parallels have been noted in the pattern of memory deficits observed in Korsakoff patients and PTD rats. As mentioned earlier, our observation of delay-dependent deficits on the DMTP task fits well with other reports of delay-dependent anterograde memory deficits in PTD rats and also with similar findings in Korsakoff patients (e.g., Oscar-Berman & Bonner, 1989).

There appears to be less correspondence between PTD rats and Korsakoff patients in terms of retrograde memory. Retrograde amnesia in Korsakoff patients is difficult to assess because their neuropathology and cognitive impairments progress over a relatively long period, and thus the time of onset of both the brain damage and the amnesia are uncertain. Nevertheless, most Korsakoff amnesics display what appears to be a temporally graded retrograde amnesia (Albert et al., 1979; Seltzer & Benson, 1974). There is no evidence that PTD causes temporally graded or ungraded retrograde amnesia for any type of information, but because retrograde memory in this model has heretofore received relatively little investigation, it is possible that the types of information for which retrograde memory has been assessed in PTD rats or the intervals between learning and onset of brain damage simply do not correspond to the types of information or time periods for which Korsakoff patients display retrograde amnesia. As an anonymous reviewer emphasized, the types of information for which retrograde memory is typically assessed in amnesic patients (e.g., famous faces, public events) seem very different from that which underlies performance of the present object-discrimination task.

In sum, the present experiment was the first to demonstrate a delay-dependent deficit of allocentric spatial working memory in rats following an acute bout of thiamine deficiency. We conclude that damage to the IML pathways, or to the thalamic nuclei that were damaged in the IML-lesioned rats, cannot account for the deficits observed in our PTD rats. Instead, the PTD-induced deficits probably resulted either from damage outside the IML or from combined damage to the IML and some other area(s). Determina-
tion of the locus or loci of the PTD-induced deficits will require additional experiments that compare spatial memory abilities in PTD rats and rats with surgical lesions of discrete areas corresponding to those damaged by PTD. It is interesting to note a recent study in which damage to the posterior region of the thalamus (parafascicular and posterior nuclei), a region that was slightly damaged in our PTD rats, caused delay-dependent deficits on a spatial memory task (Savage et al., 1997).

We also conclude from the results on the object-discrimination task that neither PTD nor restricted IML lesions produces a global retrograde amnesia. Because there has been so little exploration of retrograde memory in PTD rats or in rats with restricted lesions of the IML region, the possibility remains that either or both treatments can produce retrograde amnesia for other types of information.

References