

The Anterior Thalamus is Critical for Overcoming Interference in a Context-Dependent Odor Discrimination Task

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The anterior thalamus (AT) is anatomically interconnected with the hippocampus and other structures known to be involved in memory, and the AT is involved in many of the same learning and memory functions as the hippocampus. For example, like the hippocampus, the AT is involved in spatial cognition and episodic memory. The hippocampus also has a well-documented role in contextual memory processes, but it is not known whether the AT is similarly involved in contextual memory. In the present study, we assessed the role of the AT in contextual memory processes by temporarily inactivating the AT and training rats on a recently developed context-based olfactory list learning task, which was designed to assess the use of contextual information to resolve interference. Rats were trained on one list of odor discrimination problems, followed by training on a second list in either the same context or a different context. In order to induce interference, some of the odors appeared on both lists with their predictive value reversed. Control rats that learned the two lists in different contexts performed significantly better than rats that learned the two lists in the same context. However, AT lesions completely abolished this contextual learning advantage, a result that is very similar to the effects of hippocampal inactivation. These findings demonstrate that the AT, like the hippocampus, is involved in contextual memory and suggest that the hippocampus and AT are part of a functional circuit involved in contextual memory.

Keywords: anterior thalamus, learning, memory, interference, context

The anterior thalamus (AT) plays a critical role in learning and memory and shares many functions with the hippocampus. For example, the AT has a well-known role in spatial cognition, as indicated by the presence of head direction cells, which fire whenever the subject faces a particular direction regardless of position in the environment (Taube, 1995), and numerous findings of spatial memory deficits following AT lesions (e.g., Aggleton, Hunt, Nagle, & Neave, 1996; Byatt & Dalrymple-Alford, 1996; Sziklas & Petrides, 1999; Warburton & Aggleton, 1999; Warburton, Baird, & Aggleton, 1997). Also like the hippocampus, the AT has been implicated in episodic memory. AT damage is associated with severe amnesia in Wernike-Korsakoff syndrome (e.g., Harding, Halliday, Caine, & Kril, 2000; Kopelman, 1995; Mair, Warrington, & Weiskrantz, 1979) and other forms of amnesia (e.g., Cipolotti et al., 2008; Graff-Radford, Tranel, Van Hoesen, & Brandt, 1990). Recent studies of animal models of memory, such as the odor sequence memory task, have also shown an involvement of the AT (Wolff, Gibb, & Dalrymple-Alford, 2006).

The AT includes the anterior dorsal, anterior ventral, and anterior medial nuclei. The lateral dorsal nucleus has similar functions (e.g., head direction neurons, Mizumori & Williams, 1993) and is sometimes considered part of the anterior nuclear group (Saunders, Mishkin, & Aggleton, 2005; van Groen, Kadish, & Wyss, 2002;

Wright, Erichsen, Vann, O'Mara, & Aggleton, 2010). The AT is a major subcortical projection target of the hippocampal system, specifically the subiculum, with direct fornix projections and indirect projections via the mammillary bodies (Ishizuka, 2001; Meibach & Siegel, 1975; Nadel, Willner, & Kurz, 1985; Saunders et al., 2005; Shibata, 1992; Wright et al., 2010). The AT projects back to the hippocampal system directly and indirectly via the retrosplenial cortex (e.g., Shibata, 1993a; van Groen, Vogt, & Wyss, 1993; van Groen & Wyss, 1990a, 1990b, 1995), which is also involved in spatial cognition and memory (Cho & Sharp, 2001; Valenstein et al., 1987). These anatomical and behavioral observations have led several authors to propose that these structures are part of a functional circuit that supports learning and memory processes (for review see, Aggleton & Brown, 1999; Gabriel, 1993; Mizumori, Cooper, Leutgeb, & Pratt, 2000).

In addition to its role in spatial cognition and episodic memory, the hippocampus has a well-documented role in contextual memory (for review see, Bouton, 1993; Hirsh, 1974; Smith, 2008). For example, hippocampal neurons exhibit context-specific firing patterns (Anderson & Jeffery, 2003; Nadel et al., 1985; Smith & Mizumori, 2006b) and lesions impair conditioned responses to contextual cues (Kim & Fanselow, 1992; Phillips & LeDoux, 1992). Another component of this circuit, the retrosplenial cortex, has also been implicated in contextual memory (Keene & Bucci, 2008). Although no studies have directly tested the involvement of the AT in contextual learning, indirect evidence suggests an AT role in context. Studies of instrumental discrimination learning have identified patterns of neuronal activity in the AT and the retrosplenial cortex that are specific to a particular context and depend on how well the subjects have learned the task, suggesting that the firing patterns may reflect the association of the learned

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behavior with the learning context (Freeman, Cuppernell, Flanery, & Gabriel, 1996). Consistent with this idea, fornix lesions, which disconnect the hippocampus from the AT, disrupt these firing patterns and impair the ability to learn different discriminations in separate contexts (Smith, Wakeman, Patel, & Gabriel, 2004). Additionally, studies of immediate early gene expression indicate that AT neurons respond when subjects are exposed to a novel environment or reexposed to a context where they had received a shock (Jenkins, Dias, Amin, Brown, & Aggleton, 2002; Yasoshima, Scott, & Yamamoto, 2007).

In the present study, we assessed the role of the AT in contextual memory processes by temporarily inactivating the AT and training rats on a recently developed context-based list learning task (Butterly, Petroccione, & Smith, 2012), which was adapted from classic studies of human memory showing that learning two lists of items in separate contexts produces less interference and better recall than learning the two lists in the same context (Bilodeau & Schlosberg, 1951). In our task, rats are trained on one list of odor discrimination problems, followed by training on a second list in either the same context or a different context. In order to induce interference, the two lists contain overlapping items with reversed predictive values. In our previous study (Butterly et al., 2012), we showed that, as with human subjects, control rats that learned the two lists in separate contexts performed better than rats that learned the two lists in the same context. However, temporary lesions of the hippocampus completely and selectively abolished this contextual learning advantage. Instead, rats with hippocampal lesions performed as if they had learned the two lists in the same context, indicating that the hippocampus is needed when subjects must use contextual information to overcome interference. In the present study, we examine the effects of temporary AT lesions on this same task. A finding of a lesion induced deficit would be the first demonstration of an AT role in contextual learning and memory processes.

Method

Subjects, Surgical Procedures, and Microinfusions

The subjects were 36 adult male Long Evans rats (Charles River Laboratories, Wilmington, MA) weighing 300–350 g at the time of surgery. Guide cannula (Plastics One, Roanoke, VA) were stereotaxically positioned just above the target location so that the infusion cannula, which protruded 1.0 mm beyond the tip of the guide, would be positioned bilaterally in the AT (1.8 mm posterior from bregma, 1.5 mm lateral to bregma, and 3.8 mm ventral to the cortical surface, Paxinos & Watson, 1998). The rats were given an antibiotic (5 mg/kg Baytril) and an analgesic (5 mg/kg ketoprofen). All procedures complied with guidelines established by the Cornell University Animal Care and Use Committee. After one week for recovery from surgery, the rats were placed on a restricted feeding regimen (80–85% of free feeding weight) and they began training.

Temporary lesions were induced with the GABA_A agonist muscimol. Thirty minutes prior to relevant training sessions, muscimol or saline was infused bilaterally. The cannulas were left in place for one minute after the infusions. A commonly used muscimol concentration (1 μg/μl, Butterly et al., 2012) produced general impairments in behavioral responding, exploration, and so forth, even when minimal volume (0.2–0.3 μl) was injected into the

anterior thalamus. We titrated the dose in pilot animals by decreasing the concentration until the maximum concentration was found that reliably allowed rats to perform the task with no observable suppression of behavioral responding and that dose (0.2–0.3 μl of a solution containing 0.118 μg/μl of muscimol, infused over the course of 1 min) was used for all subjects.

In the present study, we specifically targeted the anterior dorsal, anterior ventral nuclei, and lateral dorsal nuclei because these nuclei are an integral part of the hippocampal-retrosplenial-anterior thalamic circuit of interest here (Aggleton et al., 2010; Saunders et al., 2005). The anterior medial nucleus is also interconnected with the anterior cingulate and prefrontal cortices (Shibata, 1993a, 1993b; Shibata & Kato, 1993; van Groen, Kadish, & Wyss, 1999), the latter of which plays a different, noncontextual role in this task (G. Peters, unpublished raw data). For this reason, the anterior medial nucleus was not specifically targeted and inactivation was likely minimal.

Apparatus and General Training Procedures

The training made use of a well-known digging task used to study olfactory memory (Eichenbaum, 1998), in which rats are trained to dig in cups of odorized bedding material to retrieve buried food rewards (45 mg sucrose pellets, Bioserve, Frenchtown, NJ). All of the rats were first trained on one list of odor discrimination problems. They were then given either muscimol or saline infusions and training on a second list of odors either in the same context or a different context. Thus, the experimental manipulations took place during training on the second list in a 2 × 2 design with lesion condition (saline or muscimol) and context condition (same or different) as factors.

The details of the apparatus, stimuli, and training procedures have been published previously (Butterly et al., 2012). Briefly, the two contexts differed along the following dimensions: color of the chamber (white or black), color of the curtains surrounding the training area (black or white), substrate in the chamber (uncovered Plexiglas floor or a black rubber mat), the 65 dB continuous background masking noise (white noise or pink noise) and the ambient odor left by wiping out the chamber with baby wipes prior to each training session (unscented or scented, Rite Aid, Inc.). Additionally, the rats were transported in covered cages to the experimental area by different methods in the two contexts (via a cart or carried by hand).

The rats were trained in Plexiglas chambers (45 cm wide × 60 cm long × 40 cm deep) equipped with a removable divider, which separated the odor presentation area from an area where the rats waited during the intertrial interval. Odor cues were presented in ceramic dessert cups (8.25 cm in diameter, 4.5 cm deep) which fit into circular cutouts cemented to the floor of the chamber to discourage the rats from moving the cups or tipping them over. Thirty-two pure odorants served as cues. The amount of each odorant was calculated so that they produced an equivalent vapor phase partial pressure when mixed with 50 ml of mineral oil (Cleland, Morse, Yue, & Linster, 2002) and 10 ml of the resulting odorant solution was then mixed with 2 L of corncob bedding material and stored in airtight containers.

Prior to training, the rats were given two 15-min sessions of acclimation to each of the two contexts. The rats were then shaped to dig in cups of bedding for a sucrose reward. After the rats had

learned to reliably retrieve the rewards, they began training on the first list of odor discrimination problems. Each list contained eight odors pairs (16 different odors). Within each pair, one odor was rewarded and the other was not. The predictive value of the odors (rewarded or nonrewarded) was counterbalanced across subjects and their locations (left or right side of the chamber) were randomized. The daily training sessions consisted of 64 trials (eight trials with each odor pair, presented in an unpredictable sequence).

At the start of each trial, the experimenter placed the two cups containing the odorized bedding into the chamber and removed the divider so that the rat could approach the cups and dig until he retrieved the reward. A digging response was recorded if the rat displaced any of the bedding, except for incidental displacement (e.g., stepping into the cup while walking over it). After consuming the reward, the rat was returned to the waiting area for an intertrial interval of ~15 s while the experimenter prepared the cups for the next trial. The rats were given daily training sessions on List 1 until they reached a behavioral criterion of 90% correct choices on two consecutive sessions.

After reaching the criterion on List 1, rats were assigned to one of four groups for training on List 2. Rats were given training on List 2 in either the same context or a different context and they received AT infusions of either muscimol or saline (yielding four groups: saline—different context; muscimol—different context; saline—same context; and muscimol—same context). Infusions were given 30 min prior to each of the first three training sessions on List 2. The rats were then given two additional training sessions with no further infusions. To create maximal interference between items on the two lists, half the odors on List 1 were included on List 2, but their predictive value was reversed. Half of these repeated odors had been rewarded (+) previously and the other half were not previously rewarded (–). For example, if the first two odor pairs on List 1 were A+/B– and C+/D–, then the first two odor pairs on List 2 would be X+/A– and D+/Y–. This ensured that the rats could not adopt a simple strategy of avoiding more familiar odors or approaching novel odors.

The percentage of trials with a correct choice for each training session served as our dependent measure of performance. Analyses involving within-subjects variables were submitted to a linear mixed model analysis with Bonferroni correction for multiple pairwise comparisons following significant main effects (SPSS, IBM, Armonk, NY). In order to account for individual rat differences, rat ID was added as a random effect and was included in the overall error term. Analyses not involving within-subjects variables were submitted to standard ANOVA. All post hoc tests and planned comparisons were Bonferroni corrected.

Pellet Detection

Previous studies have indicated that rats cannot smell the buried rewards (Butterly et al., 2012). Nevertheless, most of the rats ($n = 22$) were tested to ensure that they could not directly detect the pellets. After the completion of training, the rats were given a session consisting of 64 trials (eight trials with each rewarded odor from List 2). On each trial, the rats were presented with two cups containing the same odor. However, only one of the cups was baited. If the rats could directly detect the pellets, they would be expected to perform better than chance (50%). The rats chose the baited cup $48.56 \pm 1.83\%$ (Mean \pm SEM) of the time, which did

not differ significantly from chance performance ($t_{(21)} = -0.79$, $p = .44$).

Histology

After completion of training, the rats were deeply anesthetized and transcardially perfused with 4% paraformaldehyde and their brains were removed, sectioned at 40 μm , mounted on slides and stained with cresyl violet. The stained sections were used to verify that the placement of the cannulas was within the AT. In addition to the Nissl stained tissue, five rats were given infusions of fluorescent muscimol (0.2–0.3 μl of a solution containing 1.0 μg of fluorescent muscimol in 1.0 μl of saline with 0.2 μl of DMSO to aid dissolution, infused at a rate of 0.1 $\mu\text{l}/\text{min}$, Molecular Probes, Carlsbad, CA) 30 min prior to perfusion in order to estimate the spread of the drug (Allen et al., 2008). For these brains, additional sections were collected and counterstained with ProLong Gold with DAPI (Molecular Probes, Carlsbad, CA). Placement of the infusion cannulas were verified in the Nissl stained tissue, and subjects with misplaced cannulas were excluded from the main analysis of the effects of lesions and were instead included in a “missed infusion” group that served as an additional control condition, as described below. Cannula locations and an estimate of the muscimol spread based on fluorescent muscimol are illustrated in Figure 1. These estimates suggested that the muscimol infusions were primarily confined to the AT.

Results

List 1 Performance

All of the rats were trained until they reached the behavioral criterion on List 1 before they began training on List 2. The rats took an average of 4.44 ± 0.12 (Mean \pm SEM) training sessions to reach the criterion. The average performance on the final day of training was $96.27 \pm 0.42\%$ correct and there were no performance differences between groups on the final day of List 1, $F(3, 32) = 0.977$, $p = .416$.

Effects of Temporary Anterior Thalamic Lesions

To assess the effects of the context manipulation and the temporary AT lesions, the average percentage of trials with a correct response for each session of List 2 was submitted to a linear mixed model (LMM) analysis with context condition (same or different) and lesion condition (saline or muscimol) as between subjects factors and training session (five sessions of List 2) as a within subjects factor (see Figure 2). The LMM revealed a significant main effect of context, $F(1, 32) = 11.05$, $p < .01$ and a main effect of lesion condition, $F(1, 32) = 10.65$, $p < .01$. The analysis also revealed a significant interaction of lesion and training session, $F(4, 128) = 7.98$, $p < .001$. This was likely attributable to the experimental design, which involved saline or muscimol infusions during the first three sessions but not during the last two sessions. Therefore, we decomposed this interaction by performing two additional LMM analyses, one to compare the performance of control and lesion subjects across the first three (infusion) sessions of List 2 and a second to compare performance during

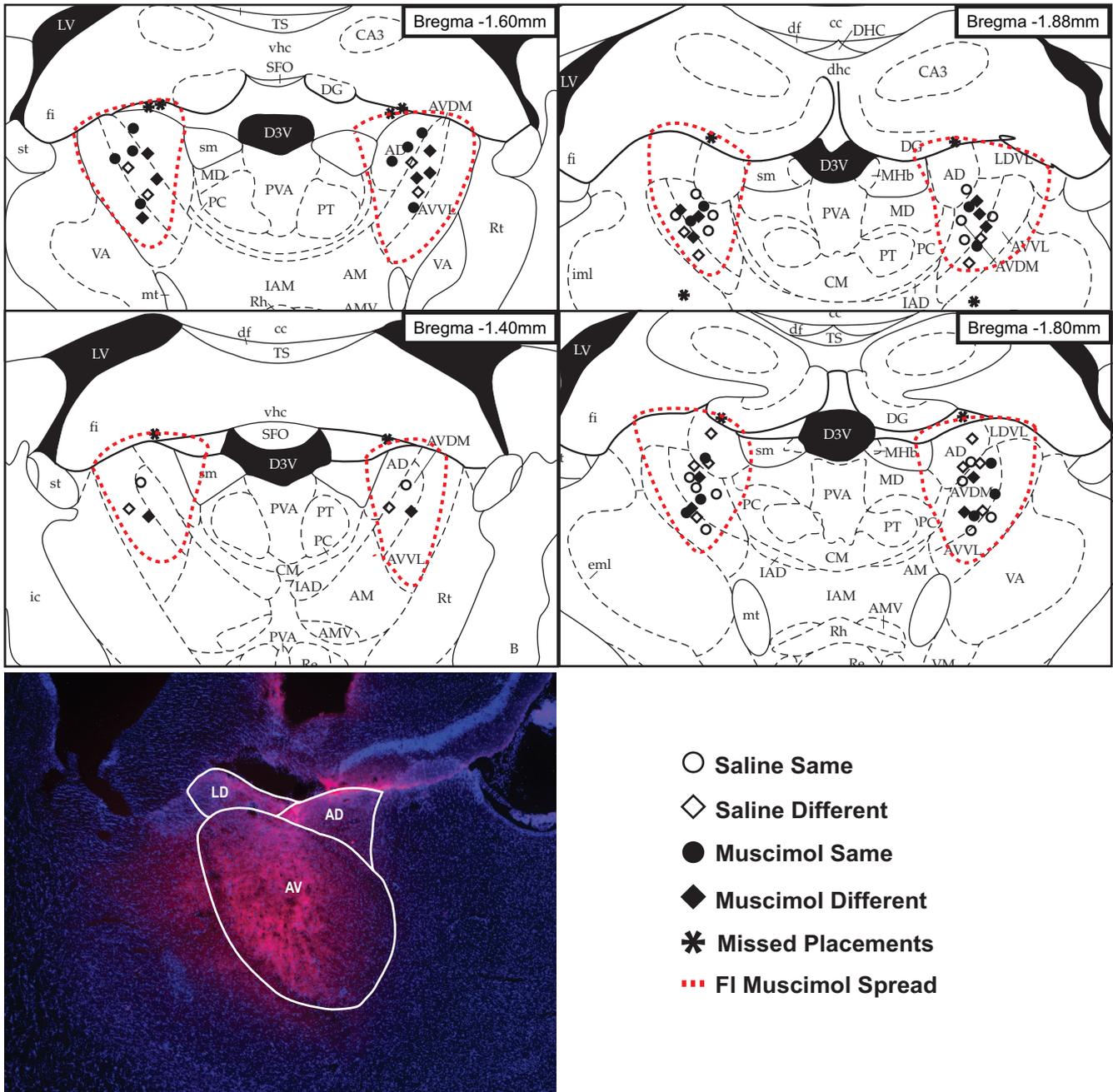


Figure 1. Infusion sites for subjects in the four experimental groups and the location of the misplaced infusions (see key) are shown on figures adapted from Paxinos and Watson (1998). Coordinates, in mm from bregma, are indicated for each panel and estimated spread of the infusions based on fluorescent muscimol infusions is indicated by the red dashed line. An example of fluorescent muscimol spread is also shown, with the anterior dorsal (AD), anterior ventral (AV), and lateral dorsal (LD) nuclei indicated. From The Rat Brain in Stereotaxic Coordinates (4th ed.), Figures 24–27, by G. Paxinos & C. Watson, 1998, New York, NY: Academic Press. Copyright 1998 by Elsevier Academic Press. Adapted with permission.

the final two (no infusion) sessions. The analysis of the infusion sessions again revealed a main effect of the context condition, $F(1, 32) = 7.46, p < .01$ and a main effect of the lesion condition, $F(1, 32) = 16.64, p < .001$. The interaction of the context and lesions factors did not achieve significance, $F(1,$

$32) = 3.16, p = .085$. Although rats given muscimol lesions were significantly impaired during the infusion sessions, their performance caught up to that of the control rats when infusions were no longer given (effect of lesion condition during the final two sessions: $F(1, 32) = 0.14, p = .713$).

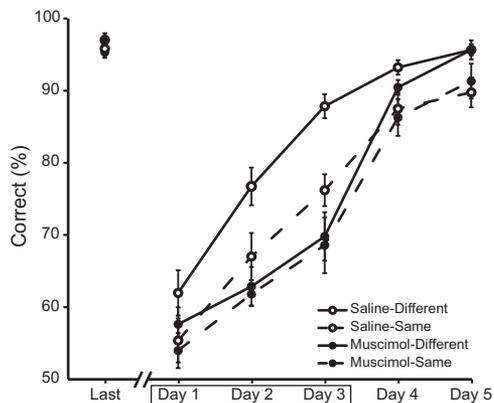


Figure 2. Average percent correct choices are shown for saline control rats (open circles) and muscimol rats (filled circles) and for the different context (solid lines) and same context conditions (dashed lines). Performance data are shown for the final session of List 1 training (Last) and the five training sessions of List 2. Muscimol or saline infusions were given prior to the first three training sessions of List 2, indicated by the box.

Our previous study showed that control rats performed significantly better when they learned the two lists in different contexts, but rats with hippocampal lesions did not benefit from learning in different contexts (Butterly et al., 2012). A major goal of the present study was to determine whether AT lesions would have a similar effect. Planned comparisons confirmed that control rats that learned List 2 in a different context performed significantly better than rats that learned the two lists in the same context ($t_{(16)} = 4.42$, Bonferroni corrected $p < .05$). However, rats with temporary AT lesions showed no advantage of learning the two lists in separate contexts, compared to rats that learned the lists in the same context ($t_{(16)} = 0.786$, $p = .443$).

Several muscimol subjects ($N = 8$) were excluded from the above analyses due to misplacement of the infusion cannulas (see Figure 1). However, since the placement of these cannulas was outside of the AT, they provide a good control for the possible effects of muscimol infusions extending beyond the AT. An ANOVA of performance during the infusion sessions revealed no difference between the saline group and the misplaced muscimol infusion group, $F(1, 32) = 2.62$, $p = .13$, Figure 3, suggesting that the spread of muscimol outside of the AT was not likely responsible for the effects seen in our experimental groups.

Assessment of Interference in Each Condition

The experimental design allowed for a direct comparison of the effects of interference in each condition. If proactive interference occurred, performance should decline when subjects had to learn a second list of conflicting items after learning the first list. If no interference occurred, then performance on List 2 should be just as good as, or better than, performance on List 1. We computed an interference index for each subject by subtracting the average percent correct on List 1 from the average percent correct on List 2. These difference scores reflect the change in performance from List 1 to List 2, with positive numbers indicating facilitation and negative numbers indicating interference (see Figure 4). The scores were submitted to a two way ANOVA with lesion condition

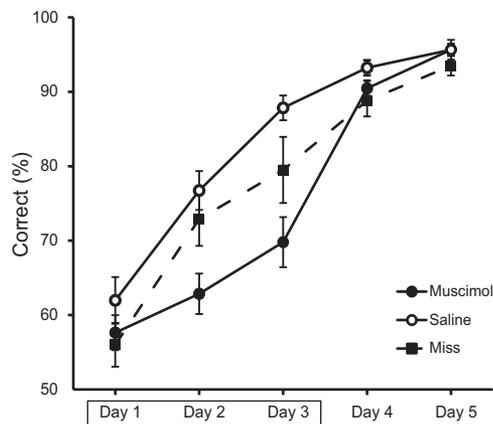


Figure 3. Average percent correct choices are shown for saline control rats (open circles) and muscimol rats (filled circles) and rats with misplaced infusions (black squares). Performance data are shown for the five training sessions of List 2. Muscimol or saline infusions were given prior to the first three training sessions of List 2, indicated by the box.

(control or muscimol) and context condition (same or different) as between subject's factors. This analysis revealed a significant interaction of the lesion and context conditions, $F(1, 32) = 6.53$, $p < .05$. Consistent with the above analysis of the percent correct data, post hoc comparisons showed that control rats experienced significantly less interference when they learned the two lists in different contexts, compared to learning the two lists in the same context ($t_{(15)} = 2.79$, Bonferroni corrected $p < .05$) but rats with temporary AT lesions showed equivalent amounts of interference regardless of whether they learned the lists in different contexts or the same context ($t_{(15)} = -1.118$, $p = .28$).

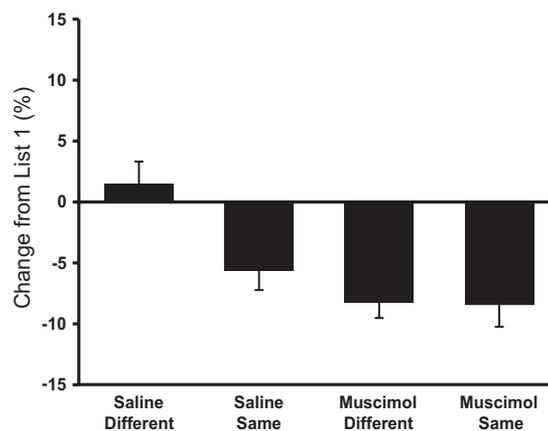


Figure 4. The change in performance from List 1 to List 2, computed as the average percent correct on List 2 minus the average percent correct on List 1, is shown for each of the experimental groups. Facilitation is indicated by better performance on List 2 than on List 1 (positive values) while interference is indicated by worse performance on List 2 (negative values).

Comparison of Anterior Thalamic and Hippocampal Inactivation

Previously we showed that the hippocampus is critical for using contextual information to facilitate learning in this task (Butterly et al., 2012). As described above, there is substantial evidence that the AT and the hippocampus are part of a functional circuit and these two regions may have similar functional roles. Thus, we expected lesions in the two regions to have similar effects. However, inspection of the current data suggested that the AT lesions may have produced a more severe deficit than the dorsal hippocampal lesions of the previous study. To formally examine this possibility, a LMM analysis was used with lesion location (AT or hippocampus, from the previous study: a single injection of 0.5 μ l of 1 μ g/ μ l muscimol infused into the dorsal hippocampus of each hemisphere, 3.6 mm posterior and 2.6 mm lateral to Bregma, 2.2 mm ventral to the cortical surface) as the between subjects factor and training session (the three muscimol infusion sessions of List 2 training) as the within subjects factor. The analysis showed no main effect of lesion location, $F(1, 32) = 2.69, p = .111$ but did reveal a significant main effect of training session, $F(1, 32) = 51.38, p < .001$ and a significant lesion location by training session interaction, $F(2, 64) = 3.97, p < .05$, Figure 5. Simple effects tests revealed a performance difference that just failed to reach significance on the second infusion day (Bonferroni corrected $p = .06$) and a significant difference on the third day (Bonferroni corrected $p < .05$) where the hippocampal lesion groups performed better than the AT lesion group. Comparisons involving data collected during different experiments can be problematic due to the possibility of systematic changes in uncontrolled variables. However, these concerns are somewhat mitigated here since the data were collected in the same laboratory using the same procedures, materials, and apparatus.

Discussion

In line with previous list learning studies in humans (Bilodeau & Schlosberg, 1951) and rodents (Butterly et al., 2012), rats that

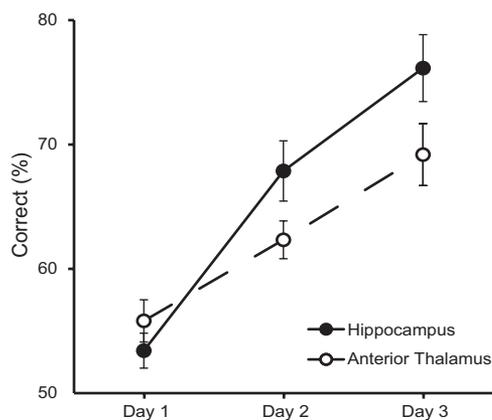


Figure 5. Average percent correct choices are shown for rats given muscimol infusions in the dorsal hippocampus (black circles, Butterly et al., 2012) and for rats given muscimol infusions in the AT (open circles). Performance data are shown for the three training sessions in which muscimol infusions were given on List 2.

learned the two lists with overlapping items in different contexts performed better than rats that learned the two lists in the same context. However, AT lesions completely abolished this contextual advantage. The lesions were also associated with increased susceptibility to interference in the different context condition. These results suggest that the AT, like the hippocampus, plays a critical role in the use of contextual information to overcome interference. Previous work has shown that the AT and hippocampus work together in the domains of spatial cognition and episodic memory (for a review see Aggleton & Brown, 1999; Aggleton et al., 2010; Mizumori et al., 2000). However, these results are the first demonstration of a critical role of the AT in contextual learning and memory processes.

The hippocampal role in processing contextual information has been appreciated since the 1970s (Hirsh, 1974) and many studies have shown that the hippocampus is needed for various forms of contextual memory (for reviews see, Bouton, 1993; Hirsh, 1974; Smith, 2008). More recently, we have suggested that hippocampal context coding is important because it provides a means of overcoming interference (Butterly et al., 2012; Smith & Mizumori, 2006b). Specifically, the hippocampus is thought to generate a new representation whenever the subject encounters a novel context and, through learning processes, these context representations become associated with the behaviors and memories that go with that context. Later, when the subject returns to the same context, the hippocampal representation is reexpressed, resulting in the priming of context-appropriate memories and behaviors, thereby minimizing interference caused by intrusions of memories relevant to other contexts. The present results suggest that the AT also plays a key role in this process and are the first demonstration that the AT is involved in the resolution of interference.

The fact that temporary lesions of the AT and the hippocampus (Butterly et al., 2012) both impair this task is consistent with the literature on spatial cognition and human amnesia, which suggest that these structures are part of a functional circuit that supports various cognitive processes. Context is an important point of convergence for theoretical accounts of spatial cognition and episodic memory, which are often treated as distinct functions. A number of authors have suggested that the spatially localized firing patterns (i.e., place fields) seen in the hippocampus can best be thought of as a neural representation of the spatial context (Anderson & Jeffery, 2003; Nadel et al., 1985; Smith & Mizumori, 2006a) and episodic memories necessarily include memory for the spatial and temporal context along with the events that occurred. Thus, episodic memory deficits could arise from deficits in context processing (Smith, 2008). Recent research suggests that remembering past episodes and imagining future episodes both involve a process of constructing a representation of the context and the events that occur in that context (Schacter, Addis, & Buckner, 2008). Consistent with this idea, amnesics show a striking deficit in the ability to mentally construct highly contextualized imaginary future episodes such as a trip to the beach or a birthday party (Hassabis, Kumaran, Vann, & Maguire, 2007). The present results suggest that the AT, like the hippocampus and retrosplenial cortex, plays a key role in processing the contextual information that is a critical component of spatial cognition and episodic memory.

Empirical evidence suggests that the AT and hippocampus are components of a functional memory circuit that supports various memory processes. Many studies have shown that lesions of either

structure produce similar impairments (Aggleton, Hunt, & Rawlins, 1986; Aggleton, Neave, Nagle, & Hunt, 1995; Anagnostaras, Gale, & Fanselow, 2001; Butterly et al., 2012; Celerier, Ognard, Decorte, & Beracochea, 2000; Fortin, Agster, & Eichenbaum, 2002; Wolff et al., 2006). As mentioned above, neurons in the AT and retrosplenial cortex exhibit context specific response patterns during instrumental discrimination learning and these firing patterns are degraded by fornix lesions (Smith et al., 2004). Other studies have shown that AT neurons fire in synchrony with the hippocampal theta rhythm (Tsanov et al., 2011; Tsanov et al., 2011; Tsanov et al., 2011) and direct hippocampal projections to the AT exhibit long term potentiation while indirect projections (via the mammillary bodies) exhibit long term depression (Tsanov et al., 2011). These interactions are bidirectional. AT neurons are thought to contribute directional information to hippocampal representations (Knierim, Kudrimoti, & McNaughton, 1995; Mizumori, Miya, & Ward, 1994; Muir & Taube, 2002). Lesions of the hippocampus cause hypoactivity in the AT during radial maze performance (Jenkins, Amin, Brown, & Aggleton, 2006) and, conversely, lesions of the AT cause hypoactivity in the dorsal hippocampus during exposure to a novel context (Jenkins et al., 2002) and deficits in many hippocampal dependent tasks (Aggleton et al., 1996; Byatt & Dalrymple-Alford, 1996; Gibb, Wolff, & Dalrymple-Alford, 2006; van Groen et al., 2002; Warburton, Baird, Morgan, Muir, & Aggleton, 2001; Wolff et al., 2006).

The above discussion emphasizes the shared functional role of the hippocampal-AT circuitry. However, there is also evidence suggesting that these two regions make distinct contributions to memory. For example, the AT is critically involved in instrumental discriminative avoidance learning, including a simple (noncontextual) discrimination task (Gabriel et al., 1983). In contrast, lesions of the fornix or hippocampus have no effect on this kind of learning (Kang & Gabriel, 1998; Smith et al., 2004). Additional evidence comes from the domain of spatial navigation, where the primary spatial firing correlate of AT neurons is head direction (elevated firing when the subject is facing the preferred direction, regardless of location within the environment, Mizumori & Williams, 1993; Taube, 1995; Tsanov et al., 2011) while the primary spatial correlate of hippocampal neurons is the place field (O'Keefe & Nadel, 1978). Interestingly, neurons in both regions are sensitive to the context but the way that the neurons respond to context change differs. In the hippocampus, place fields in one context shift to new and unpredictable locations or disappear altogether in a new context (for review see, Colgin, Moser, & Moser, 2008). Indeed, hippocampal place cells may acquire entirely different correlates in a new context (e.g., nonspatial reward or odor responses, Eichenbaum, Kuperstein, Fagan, & Nagode, 1987). In contrast, AT head direction neurons may change their preferred direction in a new context, but all the neurons shift as a coherent unit, rather than remapping individually in an unpredictable manner, and they continue to exhibit directional firing rather than acquiring new correlates in the new context (Goodridge & Taube, 1995; Yoder et al., 2011). Thus, hippocampal representations of the spatial context are highly orthogonalized whereas AT representations, while they do differ from one context to another, may not be as distinct.

Attempts to disentangle potentially different contributions of the AT and hippocampus are complicated by the fact that in addition

to disrupting any intrinsic function of the region in question, the lesions also probably disrupt the dynamics of the entire circuit resulting in a variety of indirect effects. For example, AT lesions dampen activity in the hippocampus and retrosplenial cortex (Jenkins, Dias, Amin, & Aggleton, 2002; Jenkins et al., 2002). Additionally, although AT lesions do not directly affect ACh transmission in the hippocampus and do not alter baseline levels of ACh, AT lesions do cause a dramatic reduction in behaviorally induced ACh efflux in the hippocampus (Savage, Hall, & Vetreno, 2011). These effects may be partially mitigated by the use of temporary inactivation procedures, as in the present study, but even temporary removal of a key component of the circuit is likely to have widespread effects. Thus, in addition to understanding the functional contributions of each region to contextual memory, it will also be necessary to understand the relevant circuit dynamics. The neural reuse hypothesis suggests that a given region may participate in many different circuits and that the resulting cognitive functions depend more on the currently active circuit than the intrinsic cognitive function of individual regions (Anderson, 2010). This may be the case with the AT and the hippocampus, which may be two nodes that participate in overlapping, but not identical circuits. The AT participates in a circuit that supports discriminative avoidance learning (Gabriel et al., 1983) and another circuit that supports spatial, episodic, and contextual memory, whereas the hippocampus only participates in the latter circuit and is not needed for discriminative avoidance learning (Kang & Gabriel, 1998).

Recent studies have shown that another component of this circuitry, the retrosplenial cortex, is also critically involved in contextual learning and memory processes (Smith, Barredo, & Mizumori, 2011). The retrosplenial cortex is the major cortical projection target of the AT and is reciprocally interconnected with the hippocampus (e.g., Shibata, 1993a; van Groen et al., 1993; van Groen & Wyss, 1990a, 1990b, 1995). We have shown that hippocampal neurons exhibit several kinds of highly context specific response patterns, including spatial firing, reward related firing, and firing during the intertrial delay period. In contrast, retrosplenial neurons specifically differentiated the particular cues that uniquely identify the context (Smith et al., 2011). Thus, the hippocampus and retrosplenial cortex both play a role in contextual learning and memory processes, but neurophysiological data suggest that they may make somewhat different contributions. It remains for future experiments to determine whether the AT neurons also make a unique contribution to contextual memory.

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