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Involvement of Lactate Transport in Two Object Recognition Tasks That Require Either the Hippocampus or Striatum

Donna L. Korol,
Department of Biology, Syracuse University.

Robert S. Gardner,
Department of Biology, Syracuse University.

Tumay Tunur, and
Department of Biology, Syracuse University.

Department of Kinesiology, California State University San Marcos.

Paul E. Gold
Department of Biology, Syracuse University.

Abstract

Growing evidence indicates that hippocampal lactate, released from astrocytes, is an important regulator of learning and memory processing. This study evaluated the selective involvement of hippocampal and striatal lactate in two object recognition tasks. The tasks tested recognition memory after a change in location of two target objects (double object location; dOL) or after replacement of familiar targets with two new objects set in the original locations (double object replacement; dOR). Rats received three study sessions across which exploration times decreased. The recognition index was the change in exploration time of both objects on a test trial from the exploration times on the final study trial. We first verified a double dissociation between hippocampus and striatum across these tasks. The sodium channel blocker, lidocaine, was infused into one of the two brain regions after the study sessions and before the test trial. To test the role of neuronal lactate in recognition memory, an inhibitor of the neuronal lactate transporter, α-cyano-4-hydroxycinnamate (4-CIN), was similarly infused. For both drugs, infusions into the hippocampus but not the striatum impaired recognition in the dOL, whereas infusions into the striatum but not hippocampus impaired recognition in the dOR. The findings obtained with 4-CIN demonstrate for the first time the importance of neuronal lactate uptake in the hippocampus and the striatum for object recognition memory processing.

Keywords

object recognition; lactate; astrocytes; 4-CIN; multiple memory systems

Correspondence concerning this article should be addressed to Donna L. Korol, Department of Biology, Syracuse University, Life Sciences Complex, Syracuse, NY 13244. dlkorol@syr.edu.

Epinephrine, released into blood from the adrenal medulla, enhances learning and memory across a wide range of conditions (Gold, 1995; Gold & Korol, 2012). Epinephrine does not itself readily cross from blood to brain (Weil-Malherbe, Axelrod, & Tomchick, 1959), but appears to exert its actions on cognitive functions by increasing blood glucose levels (Gold, 2014; Gold & Korol, 2014) via activation of hepatic adrenergic receptors (Sutherland & Rall, 1960). Conditions that increase circulating glucose also enhance learning and memory across a range of tasks, species, and ages (Gold, 2001; Gold & Korol, 2012; Korol, 2002; Korol & Gold, 2007; Messier, 2004; Messier, Desrochers, & Gagnon, 1999; Morris & Gold, 2013; Smith, Riby, Eekelen, & Foster, 2011; van der Zwaluw, van de Rest, Kessels, & de Groot, 2015). Direct infusions of glucose into certain brain regions improve learning and memory (McNay & Gold, 1998; Morris & Gold, 2013; Ragozzino, Pal, Unick, Stefani, & Gold, 1998; Schr-oeder & Packard, 2003; Stefani & Gold, 2001; Stefani, Nicholson, & Gold, 1999) on tasks that rely on intact functioning of those neural systems. Morever, extracellular levels of glucose in brain are not uniformly saturated but instead respond dynamically to training and memory testing with extracellular depletion seen during early phases of testing followed thereafter by return to and elevations above baseline (McNay, Fries, & Gold, 2000; McNay & Gold, 2001; McNay, McCarty, & Gold, 2001; Newman, Korol, & Gold, 2011).

In the brain, glucose might act on learning and memory as a substrate for energy metabolism by uptake into neurons (Lund-gaard et al., 2015). However, glucose may also act through astrocytic uptake and conversion to lactate, which is subsequently used by neurons under conditions of high metabolic demand such as during cognitive processing (Alberini, Cruz, Descalzi, Bessieres, & Gao, 2018; Newman et al., 2011; Steinman, Gao, & Alberini, 2016; Suzuki et al., 2011). Astrocytic production of lactate as a downstream mediator of glucose actions to enhance learning and memory is supported by findings that, like glucose, direct infusions of lactate into the hippocampus enhance memory in spatial working memory tasks (Newman et al., 2011) and for inhibitory avoidance training (Suzuki et al., 2011). Blockade of lactate transport into neurons by pharmacological administration of α-cyano-4-hydroxycinnamate (4-CIN; Newman et al., 2011), a drug that blocks the monocarboxylate 2 (MCT2) transporters on neurons (e.g., Bergersen, 2007; Brooks, 2009), or manipulations of gene expression of the MCT2 transporter (Suzuki et al., 2011) impairs memory. Interference with the MCT2 transporter attenuates the ability not only of lactate but also of glucose to enhance memory. Taken together, the results suggest that lactate uptake into neurons through MCT2 mechanisms is a necessary step in the enhancement of cognition by glucose.

Like other forms of cognition, systemic administration of glucose enhances object recognition (Messier, 1997), implicating brain lactate as a potential modulator of recognition memory. The present experiments were designed to test the importance of lactate in regulating learning and memory for object recognition tasks across multiple memory systems. Distinct brain systems are important for processing information involved in learning tasks that have different attributes, such as egocentric (response) or allocen-tric (spatial or place) properties that rely on dorsal striatum and hippocampus functions, respectively (cf. Gold, Newman, Scav- uzzo, & Korol, 2013; Kesner, Bolland, & Dakis, 1993; Korol, Gold, & Scavuzzo, 2013; Packard & Goodman, 2012, 2013; White & McDonald, 2002). Supporting this view, hippocampal lesions impair stimulus-stimulus

associations and place-based learning while striatal lesions impair cued- and stimulus-response-based learning (Compton, 2004; McDonald & White, 1993). In addition, direct injections of drugs that impair the functions of these brain areas, for example, lidocaine or muscimol, also impair learning of the respective cognitive attributes (Chang & Gold, 2003a, 2004; McElroy & Korol, 2005; cf. Packard, 2009; Packard & McGaugh, 1996), whereas injections of drugs that augment function of these brain areas, for example, glutamate or glucose, enhance the classes of learning associated with each brain area (Canal, Stutz, & Gold, 2005; Packard, 1999). Furthermore, several biological measures in the hippocampus and striatum show differential responses to training, in a task by brain area manner (e.g., Colombo, 2004; Gardner et al., 2016; Gold, 2016; Gold et al., 2013; Newman, Scavuzzo, Gold, & Korol, 2017; Teather, Packard, Smith, Ellis-Behnke, & Bazan, 2005; Yagi, Chow, Lieblich, & Galea, 2016). These and other findings point to the hippocampus and striatum, among other brain areas, as parallel memory systems that process specific forms of learning and memory (Gold & Korol, 2017; White, Packard, & McDonald, 2013; Zurkovsky, Brown, Boyd, Fell, & Korol, 2007).

To examine the role of brain metabolism in different attributes of learning and memory using a multiple memory system approach, it would be useful to identify complementary hippocampus- and striatum-sensitive tasks that rely on endogenous motivators without confounds of aversive and appetitive rewards. Object recognition tasks may be particularly beneficial in this context because they circumvent the need for experimentally derived motivators; rodents explore objects in arenas spontaneously. Many neurobiological studies of object recognition tasks focus on the hippocampus as the site of action (e.g., Barker & Warburton, 2011; Cohen et al., 2013; Cohen & Stackman, 2015; Mumby, Wood, & Pinel, 1992; Steckler, Drinkenburg, Sahgal, & Aggleton, 1998a), with findings corroborating the hormonal, molecular, and pharmacological interactions with memory found using other hippocampus-dependent learning and memory tasks (e.g., Kim & Frick, 2017; Korol, 2004, 2018; Korol & Kolo, 2002; Korol & Pisani, 2015; Korol & Wang, 2018; Luine, Jacome, & Maclusky, 2003; Pisani, Neese, Katzenellenbogen, Schantz, & Korol, 2016; Sheppard, Koss, Frick, & Choleris, 2017; Walf, Rhodes, & Frye, 2006; Xu, Chen, Zhu, Shen, & Luo, 2005). However, evidence for striatum-sensitive involvement in object recognition tasks or clear dissociations of task by these two brain areas is lacking.

Here we describe double dissociations of the hippocampus and striatum in two object recognition tasks, basing differences in object recognition training procedures on past reports that showed hippocampal and nonhippocampal involvement. We first established task procedures that revealed a double dissociation of hippocampus and striatum using intrahippocampal or intrastriatal infusions of lidocaine. Lidocaine, a local anesthetic that blocks sodium channels, is often used to inactivate brain areas in many contexts, including assessments of the contributions of brain systems to learning and memory (Chang & Gold, 2003a, 2004; Gold, 2016). Subsequently, we tested the efficacy of MCT-2 blockade by 4-CIN to impair recognition memory in these hippocampus- and striatum-sensitive tasks according to the memory system involved. Thus, the second experiment tested the necessity of lactate delivery to neurons for memory enhancement across tasks and brain regions.

Method

Subjects

Three-month-old male Long-Evans rats were obtained from Harlan Laboratories (Oregon, WI). Throughout the experiment, the rats had free access to food and water and were maintained on a 12:12 hr light:dark cycle. Each rat was handled for several minutes each day for at least 4 days prior to behavioral testing. All procedures were approved by the Syracuse University Institutional Animal Care and Use Committee and were consistent with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Cannula Implantation

For cannula implantations, rats were anesthetized with 2% to 4% isoflurane and placed in a stereotaxic apparatus that contained a nosepiece adapted to provide continuous isoflurane delivery throughout surgery (SomnoSuite, Kent Scientific, Torrington, CT). Rats received 100,000 U penicillin (I.M.) and 5 mg/kg Rimadyl (carprofen) preoperatively. Using standard procedures and coordinates for cranial surgery (based on Paxinos & Watson, 2005; for details see Chang & Gold, 2003a, 2004; Zurkovsky et al., 2007), guide cannulae (6 mm long, 22 gauge; Plastics One, Roanoke, VA) were positioned bilaterally into the dorsal hippocampus (coordinates: –3.6 mm from bregma; ±2.2 mm lateral; 4.0 mm ventral from skull) or dorsal striatum (coordinates: +0.3 mm from bregma; ±3.7 mm lateral; 4.0 mm ventral from skull). After surgery, rats received injections of sterile saline (10 ml, s.c.) for hydration and ibuprofen (Children's Motrin) in drinking water (47 mg in 500 mL water bottles) for analgesic support after surgery. Rat health was monitored daily for the week after surgery.

Double Object Location and Object Replacement Recognition Tasks

At least 1 week after surgery, rats underwent object recognition training and testing within a single day. For study Sessions 1, 2, and 3 (S1, S2, and S3), rats were placed in a square, black Plexiglas arena (70 cm × 70 cm × 50 cm) with two objects, each approximately 7 cm tall, and were allowed to explore the arena. The objects were placed 40 cm apart and centered in the vertical orientation. Each study session was 5 min in duration with 3 min between sessions during which rats were returned to their holding cage. A test session was administered 30 min after S3. For the double object location task (dOL), the distance between the objects was decreased to 10 cm during the test session, as shown in Figure 1. On the test session for the double object replacement test (dOR), both objects were replaced with novel objects but kept in the same spatial locations and configuration (see Figure 1).

For each trial, the time spent exploring both objects and the total arena were recorded using videocameras and scored off-line by hand using ClickCounter (compliments of G. Dohanich). Object exploration was defined as any explicit interaction with the objects, such as whisking and sniffing. Sitting on, climbing on, or simply looking toward an object was not considered exploration unless the rat was actively engaged with the object. To reduce odor cues, objects were wiped clean with EtOH between all sessions. The configuration and testing procedures during study sessions were the same across the two tasks. Note that this recognition testing procedure involved changes in both objects and thus total time spent

exploring both objects was used as the dependent measure for study and test trials. General exploratory activity was reflected in arena exploration times independent of time spent with the objects.

Drug Infusions

Drugs, purchased from Millipore Sigma (then SigmaAldrich, St. Louis, MO), were administered to the hippocampus or striatum between the last study session and the recognition test on either the object relocation or object replacement task, that is, 20 min after S3 and 10 min prior to T. Rats were assigned to one of two treatments: lidocaine hydrochloride (1%) or its vehicle (artificial cerebrospinal fluid [aCSF]) for Experiment 1, and 4-CIN (30 pmol) or its vehicle (0.9% saline [sal]) for Experiment 2. Drug or vehicle was infused bilaterally into either the hippocampus or striatum at a rate of 0.5 μl/min for 2 min. The lidocaine concentration is one used before to produce functional inactivation of the hippocampus and striatum (e.g., Chang & Gold, 2003a, 2004; Packard & McGaugh, 1996). The injection needle was left in place for 1 min after infusion to allow diffusion away from the injection needle anticipated to be ~1 mm based on previous reports (Edeline, Hars, Hennevin, & Cotillon, 2002; Myers, 1966; Walker & Gold, 1992). Except for removal during injections, each rat remained in its holding cage for the duration of the S3-test interval.

Rats were randomly assigned to one of 16 experimental groups. For each drug condition there were eight experimental groups representing two tasks (dOL, dOR), two brain sites (hippocampus, striatum), and two treatments (vehicle, drug; $N = 91$). Sample sizes for each group are noted in Figures 2 and 3.

Histology

Shortly after training and testing were complete, some rats received a pentobarbital overdose (50 mg/rat Fatal-Plus, Vortech Pharmaceuticals, Dearborn, MI) and were perfused transcardially with saline followed by paraformaldehyde. Other rats were decapitated, their brains rapidly extracted and frozen to be used for biochemical analysis in a subsequent experiment. Unfortunately, the biochemical assay failed and the data for these measures were not available. Perfused brains were removed, sectioned (40 μm) through the cannula placement site and stained with cresyl violet. Sections were examined with light microscopy to confirm accurate cannula placements and tissue integrity. During dissection and collection of flash frozen samples, brains were visually inspected to determine health of tissue and to verify cannula tracks in target structures, both of which were recorded.

Data Analysis and Statistics

Habituation to the objects across study sessions was defined as a decrease in total object exploration from S1 to S3. Four rats did not explore the arena during the study sessions, one rat failed to explore the objects, and another rat failed to show a decline in object exploration during the study phase; these rats were excluded from data analyses. The difference in object exploration times between the final study session and the test session (T-S3) was used as the index of recognition. For both tasks, this difference reflects a change in exploratory activity from the familiar condition of S3 to the novel condition of the test session. Similar

discrimination indices between familiar and novel objects are often used in other object tasks to operationalize recognition memory (Cohen & Stackman, 2015).

The statistical analyses were constructed to support three main aims of this study to show (1) a double dissociation of treatment effects across task and structure (three-way analysis of variance [ANOVA]), (2) treatment effects within structure and task (pairwise planned contrasts), and (3) recognition memory within each group (paired *t* tests).

To identify significant interactions of Task (dOL vs. dOR) × Brain Area (hippocampus vs. striatum) × Treatment (drug or vehicle), a three-way ANOVA was performed on the recognition index values (T-S3) within each experiment, that is, lidocaine and 4-CIN. The ANOVAs were followed by nonoverlapping, planned pairwise contrasts (Field, 2009) of treatment effects within task and brain region; the Bonferroni method was used to correct for multiple comparisons ($\alpha = .0125$).

The strength of recognition memory within groups was also examined. In this context, recognition memory was evaluated with paired *t* tests using within-subject comparisons of exploration times during S3 and test. A significant decrease in exploration from S3 to test was interpreted as continued habituation without recognition, whereas a significant increase in exploration was taken as evidence of detection of the change in object locations or new objects, that is, recognition memory as suggested by others (Goodrich-Hunsaker, Hunsaker, & Kesner, 2008).

Results

Experiment 1: Lidocaine

The results obtained using the recognition index, T-S3, are shown in Figure 2A. A double dissociation using lidocaine was confirmed with a 2 × 2 × 2 ANOVA showing a significant three-way interaction of drug treatment across brain area and task, $F(1,45) = 20.9$, $p < .0001$. Infusions of lidocaine into the hippocampus, but not striatum, impaired dOL recognition (hippocampal lidocaine vs. aCSF, $t[10] = 6.09$, $p < .0005$; striatal lidocaine vs. aCSF, $t[7] = 0.67$, $p > .5$). Conversely, infusions of lidocaine into the striatum, but not hippocampus, impaired dOR recognition (striatal lidocaine vs. aCSF, $t[9] = 6.05$, $p < .0002$; hippocampal lidocaine vs. aCSF, $t[11] = 0.43$, $p > .6$).

As shown in Figure 2B and 2C, there was a steady decrease in object exploration values during the study trials, S1 through S3, administered prior to drug treatment. Groups exhibited mean object exploration times of 35 to 45 s on S1 and ended with times of 5 to 8 s on S3. General exploratory activity was consistent across sessions and treatment groups. There were no significant effects of treatment in either task or brain region on total (Arena + Objects) exploration times (data not shown). All groups exhibited mean total exploration of the arena and objects ranging from 194 to 231 s of the 300-s test session (all $ps > .25$). Thus, group differences shown in Figure 2A reflect shifts in how the rats allocated their exploration time between objects and the arena on the test trial and not changes in general exploratory activity.

Strong recognition memory was demonstrated by all control, aCSF-treated rats in both dOL and dOR tasks regardless of site of infusion, as indicated by the significantly greater time spent exploring the objects during the test session than during S3 (Figure 2A; all *ps* < .05). Moreover, significant recognition memory was also observed in rats receiving lidocaine into the hippocampus for the dOR task and in those treated with striatal lidocaine for dOL (all *ps* < .05). However, lidocaine into the hippocampus for dOL and striatum for dOR prevented significant recognition, and in fact produced continued habituation in the dOL task for rats with hippocampal inactivation (see Figure 2A).

Experiment 2: 4-CIN

As shown in Figure 3A, the results seen in the recognition indices obtained with 4-CIN infusions were remarkably similar to those seen with lidocaine. The three-way ANOVA in the 4-CIN experiment revealed a significant interaction of Drug × Task × Brain Area, $F(1, 44) = 4.6$, $p < .05$. Infusions of 4-CIN into the hippocampus, but not striatum, impaired dOL recognition (hippocampal 4-CIN vs. sal, $t[11] = 4.26$, $p < .002$; striatal 4-CIN vs. sal, $t[8] = 0.62$, $p > .5$). The opposite pattern of results was seen on the dOR task. Infusions of 4-CIN into the striatum, but not hippocampus, significantly impaired dOR recognition (striatal 4-CIN vs. sal, $t[7] = 3.97$, $p < .01$; hippocampal 4-CIN vs. sal, $t[12] = 0.51$, $p > .5$).

For rats that received 4-CIN or saline infusions, the object exploration times decreased from ~25 to 40 s during S1 to 5 to 10 s during S3, that is, prior to treatments (see Figures 3A and 3B). As with lidocaine described in the preceding text, there were no significant effects of 4-CIN on total (Arena + Objects) exploration times for either the hippocampus ($p > .8$) or striatum ($p > .1$). The range of total exploration times across groups was 166 to 273 s during the 300-s test trial.

In this experiment, rats receiving saline infusions showed significant recognition memory (all *ps* < .05) except for rats with striatal infusions tested on dOL ($p = .28$; see Figure 3A). However, as described above, dOL recognition measures in these rats with striatal saline did not differ from those with striatal infusions of 4-CIN (see Figure 3A through 3C). As with lidocaine, rats with infusions of 4-CIN into hippocampus and striatum showed strong recognition memory on dOR and dOL, respectively (*p*s < .05), whereas those with 4-CIN infusions into the canonical structures, that is, hippocampus for dOL ($p = .16$) and striatum for dOR ($p = .25$) did not (see Figure 3A).

Histology

Complete histological assessment of cannula location was conducted in approximately one half of the rats from Experiment 1 (seven of 25 brains for hippocampal implants and 15 of 20 brains for striatal cannulae). We found 100% of the cannula placements were accurately positioned in the target structure based on light microscopic evaluation (see Figure 4). Brain samples from all rats in Experiment 2 were flash-frozen for biochemical assessment (not included). Thus, we lacked fine histological verification of cannulae for rats treated with 4-CIN. However, visual inspections of cannula tracks were recorded during brain dissections and revealed a 100% hit rate for gross placement in the target structure. Therefore, given the confirmed 100% placement rate in our samples with full histology as well as the samples

using visual observations at the time of dissection, the behavioral data for all rats, even those without microscopic evaluation, were included in the final analyses. Historically, our hit rates using similar coordinates for cannula placement in hippocampus and striatum have been 95% accurate (408 hits from 428 rats total; compiled from Chang & Gold, 2004; Chang, Savage, & Gold, 2006; McNay, Canal, Sherwin, & Gold, 2006; Morris et al., 2013; Newman & Gold, 2016; Newman et al., 2011, 2017; Pych, Chang, Colon-Rivera, & Gold, 2005a; Pych, Chang, Colon-Rivera, Haag, & Gold, 2005b; Pych, Kim, & Gold, 2006; Zurkovsky, Serio, & Korol, 2011), and thus we feel confident that our findings reflect processes specific to the structures of interest.

Discussion

We demonstrated that lidocaine and 4-CIN significantly impaired recognition memory for objects or their relative location but only when administered to the brain region believed to be necessary for that specific type of recognition. Thus, using two treatments with very different modes of action, that is, one that blocks neural activity and one that prevents lactate entry into neurons, we found a task by brain region double dissociation of recognition tasks that differed only in the type of change enacted during the recognition test, that is, change in positions versus new objects. Interference with hippocampal function disrupted dOL recognition, whereas interference with striatal function prevented dOR recognition regardless of treatment type, with the two experiments serving as an internal replication for these selective effects. It is important to note that both lidocaine and 4-CIN treatment effects were statistically significant despite the relatively small numbers of rats in each group (*ns* = 4–7/group). Even with the smallest sample sizes (see Figure 2A and Figure 3A), significant differences were detected for treatments into the canonical structure but not for the noncanonical structures for which the results did not approach significance. Thus, low statistical power did not likely contribute to the double dissociation.

Processing of metric relationships, consisting of quantitative measures of distances and angles, is sensitive to lesions of the hippocampus (Gallistel, 1990; Goodrich-Hunsaker, Hunsaker, & Kesner, 2005, 2008; Kuipers & Levitt, 1988; Poucet, 1993; Poucet & Herrmann, 2001). Models of hippocampus function and disruption of function following lesions suggest that the dentate gyrus of the hippocampus is engaged particularly on tasks that require distinctions between very similar spatial stimuli (Gilbert, Kesner, & Lee, 2001; Kesner, 2013; Leutgeb, Leutgeb, Moser, & Moser, 2007; Morris, Churchwell, Kesner, & Gilbert, 2012; Nakashiba et al., 2012; Rolls & Kesner, 2006). Thus, it is likely that both lidocaine and 4-CIN in the hippocampus interfered with mechanisms involved in detecting metric changes in object location. Very little, is known about the role of striatum in pattern separation and object recognition tasks, however the site selectivity seen in our results suggest that striatum engagement is not necessary for detection of change in object configurations.

The results obtained with 4-CIN that blockade of lactate transport into neurons impaired dOL and dOR are consistent with the view that lactate is a potent modulator of learning and memory processing (Alberini et al., 2018; Gao et al., 2016; Gold, 2014; Newman et al., 2011, 2017; Steinman et al., 2016; Suzuki et al., 2011; Tadi, Allaman, Lengacher,

Grenningloh, & Magistretti, 2015). The impairments in learning and memory by interference with lactate transport out of astrocytes and into neurons have been found for hippocampus-sensitive abilities such as spatial working memory in spontaneous alternation tasks and memory retention in one-trial inhibitory avoidance tasks (Newman et al., 2011; Suzuki et al., 2011). However, our findings with 4-CIN in the striatum are new and suggest that provision of astrocytic lactate for neuronal use is important across multiple brain systems and different types of memory processing including recognition memory. Recently, we found that the magnitude of training-induced increases in extracellular lactate levels in the hippocampus and striatum was dissociated during place and response learning in a manner that also interacted with the nature of reward, food versus water (Newman et al., 2017). Given the striatum's known role in reward processing (Burton, Nakamura, & Roesch, 2015), it was not surprising that the lactate response in striatum was unique to water versus food and was different from the response in the hippocampus. However, the findings do highlight the importance of controlling for reward-related effects on outcome measures that may interact with and confound experimental interventions, especially when examining differences across memory systems. One advantage of the object recognition tasks as described here is that learning is assessed under conditions of low stress and arousal in the absence of extrinsic rewards and punishments and may thus be useful in tests of neural mechanisms of memory.

Lidocaine and 4-CIN blocked detection of change in objects or object locations when injected into the striatum or hippocampus, respectively; the drugs did not significantly affect recognition on the other task or on overall locomotor activity during the test trial. These findings are therefore consistent with an extensive literature showing that the hippocampus and striatum are important components of information processing for different attributes of learning and memory. Of note, lesions and drug manipulations that disrupt function of the hippocampus and striatum impair learning and memory based on allocentric (spatial or place) or egocentric (response, habit) task features (as reviewed by Gold et al., 2013; Korol et al., 2013; Packard & Goodman, 2012, 2013; White & McDonald, 2002). These dissociations of hippocampal and striatal functions in learning are also evident when monitoring functional correlates of activity during training on similar tasks (reviewed in Colombo, 2004; Gold, 2004, 2016; Gold et al., 2013). For example, differences between hippocampus and striatum in training- related release of lactate (Newman et al., 2017) and acetylcholine (Chang & Gold, 2003b; McIntyre, Marriott, & Gold, 2003; Pych, Chang, Colon-Rivera, & Gold, 2005a; Pych, Chang, Colon-Rivera, Haag, & Gold, 2005b), and in training-related changes in levels of choline acetyltransferase (Hawley, Witty, Daniel, & Dohanich, 2015), activation of CREB, and expression of c-Fos (Colombo, 2004; Colombo, Brightwell, & Countryman, 2003), c-Jun (Teather et al., 2005), and Arc (Gardner et al., 2016) depend on whether animals used place or response strategies to solve the task. The findings of the present experiment therefore position these object recognition tasks into the broader framework of multiple memory systems, in particular compared to place versus response maze learning (Gold et al., 2013; Korol, 2018; Korol et al., 2013), win-stay versus win-shift learning (White et al., 2013), and cognitive versus habit learning (Packard & Goodman, 2013).

Although the distinction of the classes of tasks promoted by the hippocampus and striatum is clear, the application of the distinction to object recognition tasks has not always been evident. The effects of hippocampal damage on spatial and nonspatial recognition tasks are mixed (Cohen & Stackman, 2015; Steckler, Drinken- burg, Sahgal, & Aggleton, 1998b). Caudate lesions also impair spatial object recognition learning without affecting nonspatial recognition, though tests of striatal contributions to nonspatial recognition are relatively lacking (Steckler et al., 1998b). It is perhaps the mix of specific methods used, for example, delays between training and testing, time between lesions and training, mazes versus open arenas, stimulus cues, and so forth, that contribute to the considerable overlap in the neural systems involved in recognition learning (Cohen & Stackman, 2015). The present experiments attempted to minimize these differences by using the same objects and test conditions and by including habituation trials to the objects on three study sessions thereby establishing baselines from which to evaluate recognition during the test session. On the test trial for dOL task, the position of both objects and the distance between them was changed, creating a new spatial configuration. On the test for the dOR task, both objects were replaced with novel objects that were similar in many respects, that is, general size, composition, location. In this manner, the tasks differ from more common paradigms that use a single study session (Ennaceur, 2010) and that focus on exploration of the new object or position, or comparison across old and new stimuli, as the main measure of recognition.

The magnitude of change in total object exploration from study to test phases was used as the operational measure of recognition. Because the 30-min delay between S3 and test was longer than the 3-min delays used between study sessions, the increase in object exploration during test may also reflect forgetting of the previous objects or configurations. However, we found that rats continue to show habituated responses to a fourth study session where no changes are made to the objects even when given 30 min after S3 (Tunur & Korol, 2015). Thus, increases in object exploration during the test most likely reflects recognition memory that allows pattern separation and not loss of the memory for the familiar conditions.

The present design involved administration of drugs given 20 min after the last study trial and 10 min before the test trials. Therefore, the results do not distinguish between retrograde effects on memory, that is, modulation of the prior experience versus anterograde effects on memory, including actions on retrieval or other performance variables during recognition testing (Steckler et al., 1998a). Of note, however, potential anterograde effects were not evident on total arena exploration times on the test trial but were restricted to object exploration times, suggesting that the inactivated structures were independently involved in novelty detection of each attribute, object location configuration versus object replacement. Additional experiments are needed to identify more selectively the phases of recognition memory underlying the drug impairments noted here.

Our findings suggest that lactate uptake into neurons via the MCT2 transporter is a key process modulating memory in two object recognition tasks that independently engage two different neural systems, the hippocampus and striatum, involved in different types of memory processing (Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007; Etchamendy & Bohbot, 2007; Gold & Korol, 2017; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; McDonald & White, 1993; Packard, 2009; Packard & Goodman, 2012, 2013). These tasks

can be administered in a single session (as short as 25 to 30 min), and avoid experimentally derived motivation, and thus are useful for assessing underlying molecular and cellular mechanisms of learning and memory without confounding effects of food restriction or aversive stimuli. As such, they are particularly useful for identifying the role of regulators of cellular metabolism, such as lactate as seen here. The tasks diverge from more commonly used recognition tasks in that both acquisition and recognition measured during the habituation phase can be evaluated, making them useful for assessments of both learning and memory.

These two objectrecognition tasks allow formechanistic tests of cognitive dysfunction and function in many human health contexts. From a multiple memory systems perspective, a shift from one style of problem solving to another can produce both deficiencies and sparing or enhancements in function (Korol, 2018). For example, aged rats exhibit impairments on a range of hippocampus-sensitive tasks, including the dOL task, but maintained or enhanced learning of striatum-sensitive tasks, including the dOR task (Gardner et al., 2019). These findings are remarkably similar to results seen in humans, who exhibit a shift across the life span from spatial to response strategies to solve virtual mazes (Bohbot et al., 2012). The results also fit well with growing evidence revealing that losses of functions on some cognitive attributes are often accompanied by shifts to maintained brain area functions, with preserved cognitive attributes accompanying aging, menopause, neurodegenerative states including Alzheimer's and Parkinson's disease, and amnesia syndromes (e.g., Bohbot et al., 2012; Foerde & Shohamy, 2011; Korol & Wang, 2018; Myers et al., 2003; Poldrack et al., 2001).

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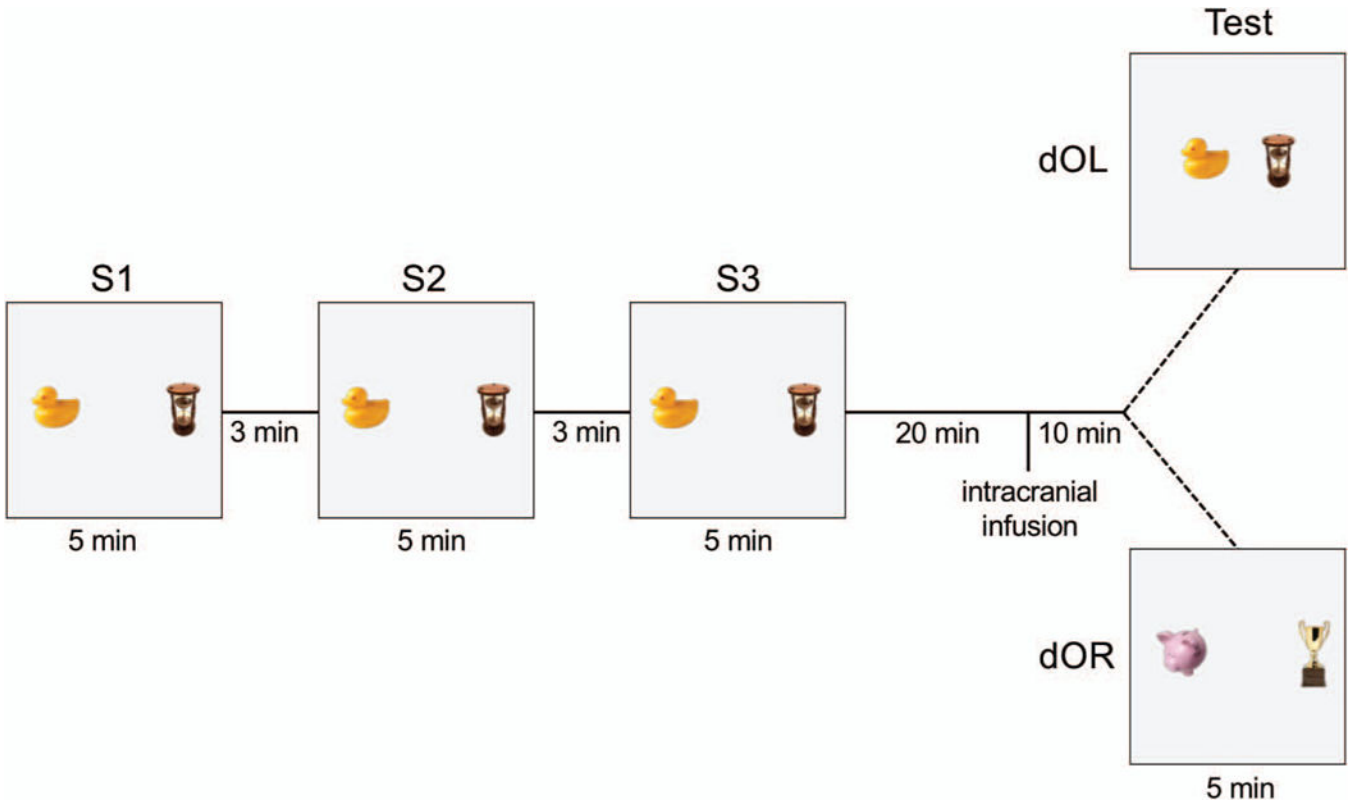

Figure 1.

Graphic representation of double object location (dOL) and double object replacement (dOR) recognition tasks. Two 3-dimensional objects are positioned 40 cm apart in a square Plexiglas arena. During each 5-min study session (S1, S2, S3), rats are placed into the arena and allowed to explore freely the field and the two objects anchored to the floor of the arena. Between each study session, rats are removed from the arena and placed in their holding cage for a 3-min interval. Twenty minutes after S3, rats received an infusion of lidocaine or 4-CIN into either the hippocampus or striatum. Ten minutes later, a 5-min test session for dOL or dOR recognition was conducted. For dOL, the two objects were repositioned horizontally to 10 cm apart. For dOR the old objects were replaced in the original locations by two new objects that were similar in size, but different in form, color, and material. See the online article for the color version of this figure.

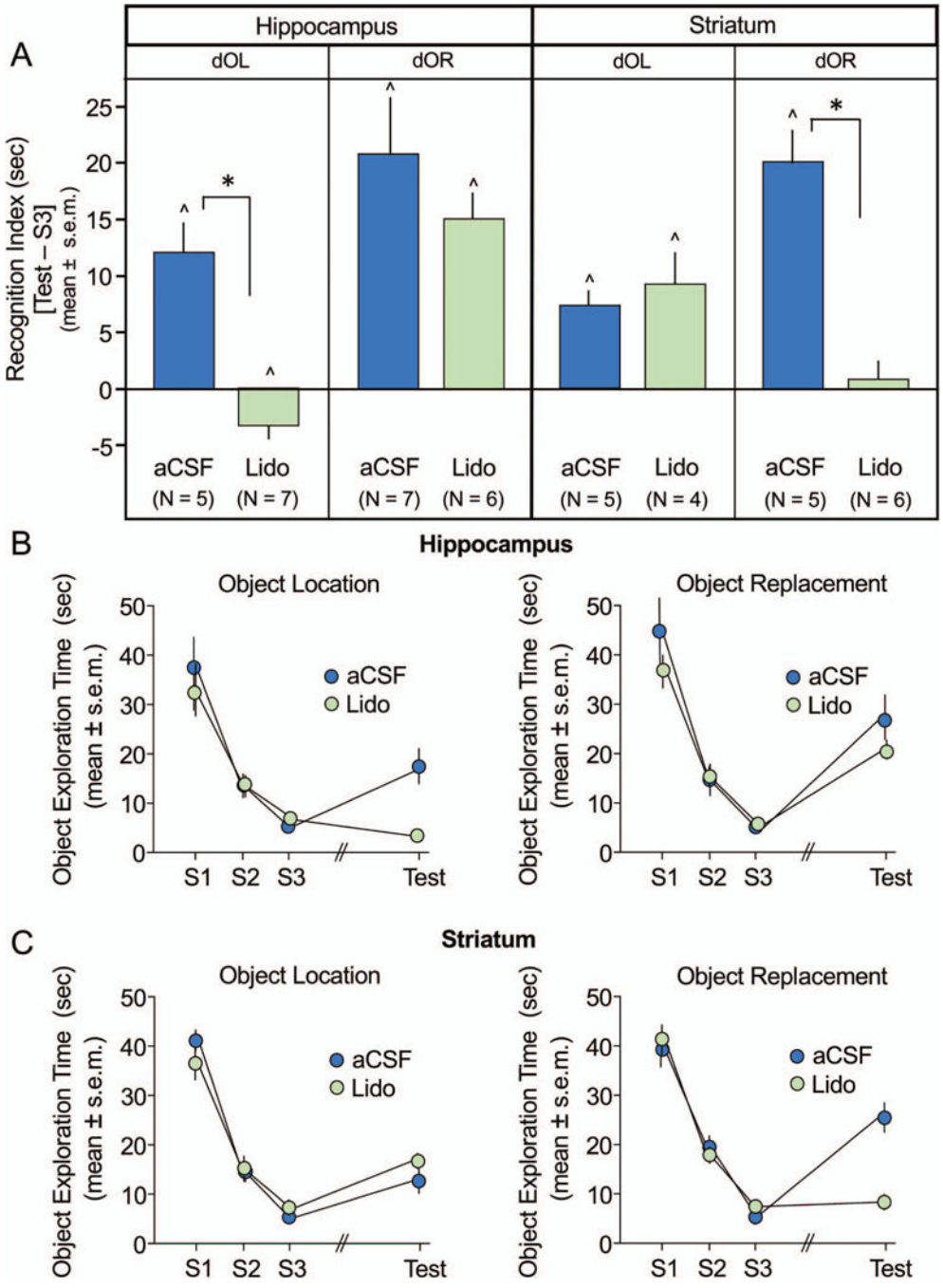

Figure 2.

Effects of lidocaine (Lido) infusions into the hippocampus and striatum on double object location (dOL) and double object replacement (dOR) tasks. A: Recognition index scores reflecting difference in time exploring objects during test (T) and study session (S)3 (T-S3) show that compared to artificial cerebral spinal fluid (aCSF), Lido infusions into hippocampus impaired recognition for dOL but not dOR recognition (left panel), while infusions into the striatum impaired dOR but not dOL recognition (right panel). All rats treated with aCSF demonstrated significant recognition from S3. B: Time exploring both

objects during S1, S2, S3, and test sessions following hippocampal infusions or striatal infusions (C). Object exploration curves reveal a decline in exploration across S1-S3. Rats that recognize change during test show increase in exploration compared to S3. * $p < .0125$ aCSF versus Lido; ^ $p < .05$ versus 0, within subjects. See the online article for the color version of this figure.

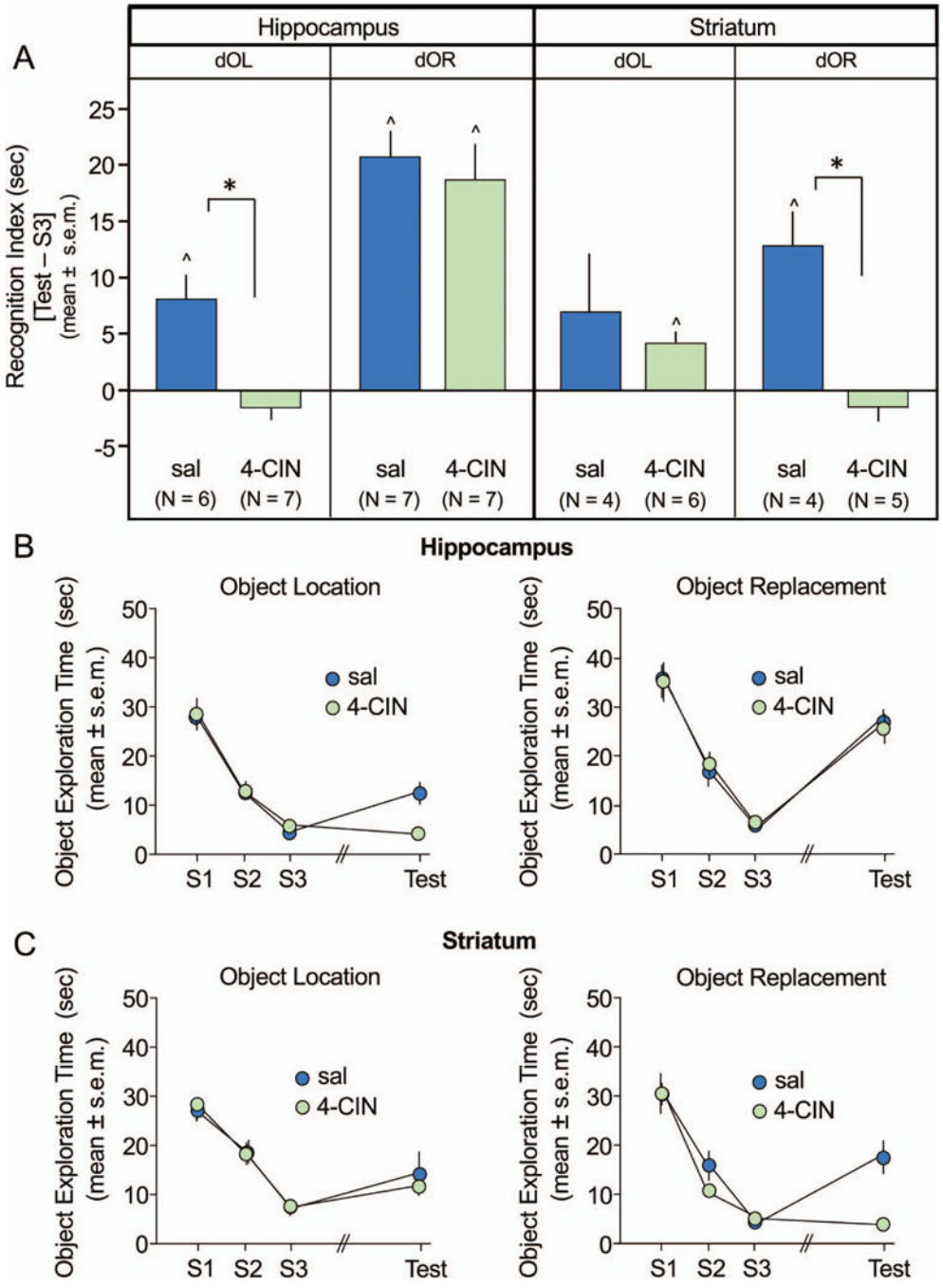

Figure 3.

Effects of 4-CIN infusions into the hippocampus and striatum on double object location (dOL) and double object replacement (dOR). A: Recognition index scores show that 4-CIN infusions into hippocampus impaired recognition for dOL but not dOR recognition (left panel). Conversely, infusions into the striatum impaired dOR but not dOL recognition (right panel). All saline (sal)-treated rats, except those with striatal infusions tested on dOL, showed recognition of changes in objects from study session (S)3. B: Time exploring both objects during S1, S2, S3, and test sessions following hippocampal infusions or striatal

infusions (C). Object exploration curves reveal a decline in exploration across S1 through S3. Rats that recognize a change during test show an increase in exploration compared to S3. * $p < .0125$ sal versus 4-CIN; ^ $p < .05$ versus 0, within subjects. See the online article for the color version of this figure.

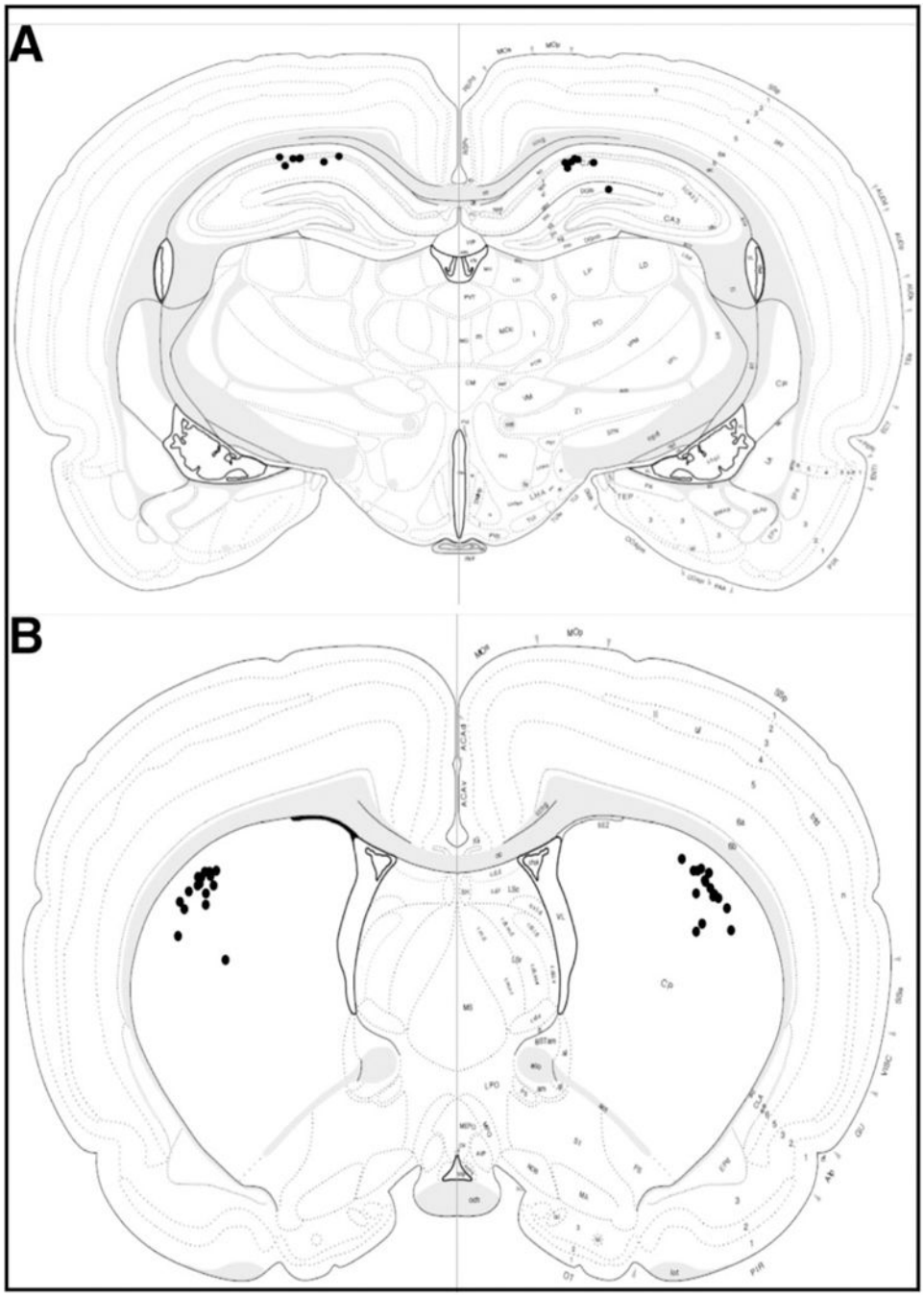

Figure 4.

Distribution of bilateral lidocaine infusion sites targeting (A) hippocampus and (B) striatum for rats in Experiment 1. Full histological assessment was completed for hippocampal placements in 7/25 rats and for striatal placements in 15/25 rats. Note that 100% of the placements were accurate.