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The role of the dorsal and ventral hippocampus in olfactory working memory

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ABSTRACT

Olfactory working memory and pattern separation for odor information was assessed in male rats using a matching-to-sample for odors paradigm. The odor set consisted of a five aliphatic acids with unbranched carbon chains that varied from two- to six-carbons in length. Each trial consisted of a sample phase followed by a choice phase. During the sample phase, rats would receive one of five different odors. Fifteen seconds later during the choice phase one of the previous odors was presented simultaneously side by side with a different odor that was based on the number of aliphatic acids that varied in the carbon chains from two- to six-carbons in length and rats were allowed to choose between the two odors. The rule to be learned in order to receive a food reward was to always choose the odor that occurred during the study phase. Odor separations of 1, 2, 3 or 4 were selected for each choice phase and represented the carbon chain difference between the study phase odor and the test phase odor. Once an animal reached a criterion of 80–90% correct across all temporal separations based on 40 trials, rats received a control, dorsal hippocampal, or ventral hippocampal lesion and were retested on the task. On postoperative trials, only the ventral hippocampal lesion group was impaired relative to both control and dorsal hippocampal groups groups. There were no effects on odor pattern separation. All groups of rats could discriminate between the odors. The data suggest that the ventral hippocampus, but not dorsal hippocampus, supports working memory for odor information.

1. Introduction

There has been a recent surge in research concerning the differential roles of the dorsal and ventral portions of the hippocampus. The hypotheses driving this research are based on differences in intrinsic and extrinsic connectivity and molecular differences along the dorsal–ventral axis of the hippocampus (Amaral & Witter, 1989; Fanselow & Dong, 2010; Risold & Swanson, 1996). Theories encompassing ventral hippocampal function include a role in mediating anxiety (Bannerman et al., 2004; Barkus et al., 2010), hyponeophagia (Bannerman et al., 2002), retrieval of contextual and stimulus specific information during trace and delay fear conditioning (cf. Rogers, Hunsaker, & Kesner, 2006; Rudy & Matus-Amat, 2005; Yoon & Otto, 2007), and behavioral inhibition (cf. Gray & McNaughton, 1983, 2001; McDonald, Jones, Richards, & Hong, 2006). The dorsal hippocampus has been proposed as the neurological substrate underlying spatio-temporal processing (O'Keefe & Nadel, 1978; Rolls & Kesner, 2006).

On the basis of these hypotheses, numerous labs have effectively dissociated the dorsal and ventral halves of the hippocampus across spatial and nonspatial information processing (Bannerman et al., 1999; Moser & Moser, 1998). Despite the aforementioned dissociations, there is evidence that the ventral hippocampus may support spatial memory and assist in performance of spatial and nonspatial tasks primarily dependent upon the dorsal hippocampus if the animal is trained properly (DeHoz, Knox, & Morris, 2003; McDonald et al., 2006). In contrast, the ventral, but not dorsal, hippocampus may be more important for mnemonic processing of olfactory information. Support for this idea comes from a series of fMRI studies showing that processing of odor information resulted in greater activation of the ventral compared to the dorsal hippocampus in mice and anterior compared to posterior hippocampus in humans (Cerf-Ducastel & Murphy, 2001; Kent, Hess, Tonegawa, & Small, 2007). Thus, there is a good possibility that the ventral hippocampus supports processing of odor information (Cerf-Ducastel & Murphy, 2001; Kent et al., 2007; Pentkowski, Blanchard, Lever, Litvin, & Blanchard, 2006), whereas the dorsal hippocampus supports processing for spatial information (Moser & Moser, 1998; Rolls & Kesner, 2006). Whether working memory for odor information is a function of the ventral or dorsal hippocampus is not known. Thus, the purpose of the present study is to examine the role of the dorsal and ventral hippocampus in a working memory task for odors that consist of a series of aliphatic acids with unbranched carbon chains that varied from two- to

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six-carbons in length (see Cleland, Morse, Yue, & Linster, 2002). The odors were selected in order to assess whether the dorsal or ventral hippocampal lesions would also produce an odor pattern separation effect. A pattern separation function can be seen when there is poor performance for odors that are close together in terms of carbon chain lengths followed by improved performance as the distance in terms of carbon chain lengths increases. A separation function for odors could be based on perceptual-based similarity or memory -based similarity. In the present study the emphasis will be on memory-based similarity.

2. Material and methods

2.1. Subjects

Nineteen male Long Evans rats (260–350 g) were housed independently in standard plastic rodent cages and maintained on a 12-h light/dark cycle. All testing was conducted in the light proportion of the light/dark cycle. Each rat was initially food-deprived to approximately 85–90% of their free-feeding weight, but was allowed free access to water throughout testing. All surgical and experimental protocols conformed to University of Utah IACUC and AAALAC protocols and regulations. The health of the animals was assessed weekly by an IACUC veterinarian.

2.2. Apparatus

The test apparatus (the same used by Kesner, Gilbert, & Barua, 2002) consisted of a box 84 cm long and 27 cm wide with four 30.5 cm high red Plexiglas walls. One removable guillotine door, also constructed of red Plexiglas, was placed 25 cm from one end of the box. The door divided the box into two separate compartments: a 27 × 25 cm start chamber and a 27 × 59 cm choice chamber. The floor of the maze consisted of wood that was painted black. On the back wall of the choice chamber, a spring was attached to the floor that secured one or two cup holders to the floor that were used to stabilize digging cups during testing.

2.3. Odor set

The odor set consisted of a series of aliphatic acids with unbranched carbon chains that varied from two- to six-carbons in length. All odorants were diluted with mineral oil before application with a Q-tip to a small plastic up containing sand. The following odors and volumes were used based on Cleland et al. (2002): 0.0140 acetic acid with two carbons (CH_3COOH), 0.0690 proprionic acid with three carbons (CH_3CH_2COOH), 0.2140 butyric acid with four carbons ($CH_3CH_2CH_2COOH$), 2.3260 valeric acid with five carbons ($CH_3CH_2CH_2CH_2COOH$), and 12.8660 caproic acid with six carbons ($CH_3CH_2CH_2CH_2CH_2COOH$).

2.4. Shaping

During the first week of training, each animal was handled for ~0.25 h daily and was then allowed to individually explore the test apparatus for 0.25 h. During the exploration period, ~10 pieces of Froot Loop cereal were spread out across the floor of the choice chamber and the guillotine door to the start chamber remained open. During the first week each rat was shaped in its home cage to dig in a small clear plastic cup (6 cm diameter × 6 cm tall) filled with sand to retrieve a food reward (Froot Loop cereal). Shaping continued by placing a reward on top of the sand and allowing the animal to find the reward. Across subsequent shaping trial presentations, the food reward was buried, partially at first and then deeper in the sand, until the rat dug in the sand even when the reward was not visible. Once an animal consistently dug in the sand, the rat was shaped to dig in a cup in the choice chamber of the test apparatus. The cup was placed in a cup holder that was mounted to the floor with a spring so that the rat could not spill the contents of the cup or displace the cup from its position. On each shaping trial, the rat was placed in the start chamber, the door was opened, and the rat was allowed to approach the cup and dig in the sand to retrieve the food reward. This procedure was followed 12 times each day. Once an animal consistently dug in the sand, the animal began preoperative training.

2.5. Preoperative training

Each subject was given eight trials daily in a matching-to-sample for odor information task. Each trial consisted of a sample phase followed by a choice phase. During the sample phase, a rat was placed in the start chamber of the box with the door to the choice chamber closed. In the choice chamber a small plastic digging cup (6 cm high, 6 cm diameter) filled with sand mixed with one of the five different odors was positioned centrally along the back edge of the choice chamber. A food reward (Froot Loops cereal) was buried in the sand. The door to the choice chamber was then opened and the animal was allowed to run to the cup, dig in the sand, and retrieve the reward. The rat then returned to the start chamber and the door to the choice chamber was closed. Fifteen seconds later during the choice phase one of the previous odors was presented simultaneously side by side with a different odor that was based on the number of aliphatic acids that varied in the carbon chains from two- to six-carbons in length and the animal was allowed to choose between the two odors. The rule to be learned in order to receive a food reward was to dig into the cup that contained the odor that occurred during the study phase (matching to sample). Odor separations of 1, 2, 3 or 4 carbons were selected for each choice phase and represented the carbon chain difference between the study phase odor and the test phase odor. The position of the correct odor varied from trial to trial such that the correct odor was equally presented on the right and the left. Five sets of each different odor were used in the study so that specific odors could be used on each consecutive trial to reduce interference. Once an animal reached a criterion of 80–90% correct across all odor separations based on 40 trials, the animal was scheduled for surgery. Ten sample phases for each of the odor separations were presented across a block of 40 trials. The intertrial interval was 60 s.

2.6. Surgery

Rats were randomly assigned to a surgery group. Rats were anesthetized and maintained using isoflurane (2–4% in 2 L/min medical air) and given atropine sulfate (0.2 mg/kg i.m.) as a prophylactic. Rats that received a lesion of the ventral hippocampus were given 0.75 mL of diazepam (2 mg/mL i.p.) 10 min prior to surgery to prevent any seizure activity that may result from the excitotoxic lesion. Rats that received a lesion of the dorsal hippocampus subregion were not given a diazepam injection, because, based on at least a hundred dorsal hippocampus lesioned rats, behavioral seizures had never been observed. Each rat was placed in a stereotaxic apparatus (David Kopf Instruments, Tunjana, CA) with its head level. The scalp was incised and retracted to expose bregma and lambda which were adjusted into the same horizontal plane by moving the incisor bar dorso-ventrally. Dorsal hippocampus lesions ($n = 5$) were made using ibotenic acid (Biosearch Technologies, Inc., San Rafael, CA, 8 mg/mL), infused using a micro infusion pump (Cole-Parmer; Vernon Hills, IL) and a 10 μL Hamilton syringe (Hamilton; Reno, NV) at a rate of 6 μL/h and a volume of 0.10 or 0.15 μL depending on the site, bilaterally

into three sites. After infusion, the cannula remained in each site for at least 1 min to allow diffusion of the injected excitotoxin. The coordinates for dorsal hippocampus lesions based on the Paxinos and Watson atlas (1997) were 3.6 mm posterior to bregma, 1.0 mm lateral to the midline, 2.4 mm ventral to dura (0.1 μL of ibotenic acid injected); 3.6 mm posterior to bregma, 2.0 mm lateral to the midline, 2.1 mm ventral to dura (0.1 μL); 3.6 mm posterior to bregma, 3.0 mm lateral to the midline, 2.3 mm ventral to dura (0.15 μL). Ventral hippocampus lesions ($n = 6$) were also made using ibotenic acid, infused following the same procedures as dorsal hippocampal lesions, into three sites within the ventral hippocampus located 5.3 mm posterior to bregma, 3.0 mm lateral to the midline, 2.8 mm ventral to dura (0.1 μL); 5.3 mm posterior to bregma, 5.2 mm lateral to the midline, 4.0 mm ventral to dura (0.1 μL); 5.3 mm posterior to bregma, 5.8 mm lateral to the midline, 6.2 mm ventral to dura (0.15 μL). Vehicle control lesions (dorsal hippocampus vehicle $n = 4$ and ventral hippocampus vehicle $n = 4$) were made using the same coordinates and procedures as the dorsal and ventral hippocampal lesioned groups; however, physiological saline was infused. Following surgery, the incision was sutured, 1.5 mL of saline was injected into each hip subcutaneously to hydrate the animal and assist in expelling the anesthetic, and the rats were allowed to recover on a heating pad for 30 min before returning to their home cage. In addition, rats received acetaminophen (Children's Tylenol; 200 mg/100 mL of water) as an analgesic and crushed food for 3 days following surgery. The behavior of all animals was monitored for epileptiform activity for 7 days post-surgery. No behavioral seizures were observed. Each animal was given a 7–10 day recovery period before postoperative testing.

2.7. Postoperative testing

Following recovery from surgery, each subject was again tested on the task following the same procedure used during preoperative training for one block of 40 trials.

2.8. Discrimination task

Following postoperative testing, a discrimination task was conducted to assess the ability of dorsal hippocampal lesioned ($n = 5$), ventral hipocampal lesioned ($n = 6$) and control ($n = 8$) rats to perceptually discriminate between two simultaneously presented odors. Each rat was given 10 trials each day. For the discrimination task, two odors that were far apart in terms of carboxyl chain length, namely acetic acid and caproic acid, were selected. One odor was designated as the rewarded odor and the other was designated as the nonrewarded odor. The rewarded odor varied across animals. To receive a reward the rat was required to dig in the cup containing the rewarded odor. The position of the rewarded odor was randomly determined for each trial. Each animal was tested until an 80% correct criterion across 10 consecutive trials was achieved.

2.9. Histology

At the conclusion of all testing, each animal was deeply anesthetized with 1.5 mL sodium pentobarbital (60 mg/kg i.p.), and perfused intracardially with phosphate buffered saline followed by a 10% formalin solution. The brain was removed from the skull and stored in a 10% formalin/30% sucrose solution as a cryoprotectant for at least 72 h prior to sectioning. Each brain was frozen and cut at 24 μm sections starting at bregma and extending through the posterior region of the hippocampus using a cryostat. Every third section was mounted on a gelatin coated glass slide, stained with cresyl violet, and examined microscopically for histological verification of the lesion placement.

3. Results

3.1. Histology

Sections were photographed and the regions of interest were outlined using Image J. The ventral hippocampus comprised the ventral 50% of the hippocampus, including the ventral CA3 and CA1 pyramidal cell layers and the ventral dentate gyrus granule cell layer–the ventral subiculum was excluded. The dorsal hippocampus comprised the dorsal 50% of the hippocampus, including the dorsal CA3 and CA1 pyramidal cell layers and the dorsal dentate gyrus granule cell layer–the dorsal subiculum was excluded. This was performed on a series of every fifth section across the entire hippocampus. The number of pixels contained within the entire ROI was calculated. Similar methods have been used in the past to quantify dorsal and ventral hippocampal lesions (Hunsaker, Fieldsted, Rosenberg, & Kesner, 2008). In all cases efforts were made to be as conservative as possible so as to under as opposed to over-estimate lesion size.

To determine the extent of the lesions, the process was repeated, this time only tracing the spared hippocampal tissues. The number of pixels within the spared regions was calculated. As such, percent damage was calculated as 100 – (spared area/total ROI area). This had the advantage of under, as opposed to over estimating lesion size by quantifying the amount of tissue that remained after the lesion.

For the present analysis, the intermediate hippocampus was not analyzed separately, and as such the dorsal hippocampus included the dorsal aspect of the intermediate hippocampus and the ventral hippocampus included the ventral aspect of the intermediate hippocampus. The majority of spared tissue after the lesions was in this more intermediate area.

The values obtained from ImageJ were averaged across all sections and all animals. No animals were excluded from statistical analysis due to inaccurate lesion placement. Fig. 1 shows representative sections for the extent of dorsal hippocampus lesions (A) and the extent of ventral hippocampal lesions (B) with black representing the largest and gray representing the smallest lesion. Dorsal hippocampus lesioned animals had (mean ± standard error) 87 ± 11.2% damage to the septal or dorsal half of the hippocampus. The dorsal CA1 and dentate gyrus subregion ablations were virtually complete. The spared hippocampal tissue was most often in the dorsal CA3 pyramidal cells of the intermediate hippocampus. No damage beyond the injection cannula track were observed in the overlying cortex.

Ventral hippocampus lesioned animals had 72.4 ± 8.3% damage to the septal or ventral half of the hippocampus. The ventral CA3 and dentate gyrus subregion ablations were virtually complete. Most often, ventral CA1 was spared adjacent to the intermediate hippocampus as well as limited sparing of hippocampal tissue adjacent to the amygdala. No cortices lateral to the ventral hippocampus nor thalamic tissues were affected by the lesions. Control lesions animals had no damage beyond that caused by the cannula track in both dorsal and ventral vehicle control lesioned animals.

3.2. Olfactory working memory

Preoperative acquisition of the odor task was analyzed by grouping the data into blocks of 10 trials for each of the four carbonic chain (odor) separations. There were no differences between the two control groups and therefore they were combined into one group. The average number of trials required to reach the preoperative criterion was 96 (range = 76–120) for the control group, 86 (range 65–110) for the dorsal hippocampus group, and 88 (range 65–130) for the ventral hippocampus group. Fig. 2 shows the mean

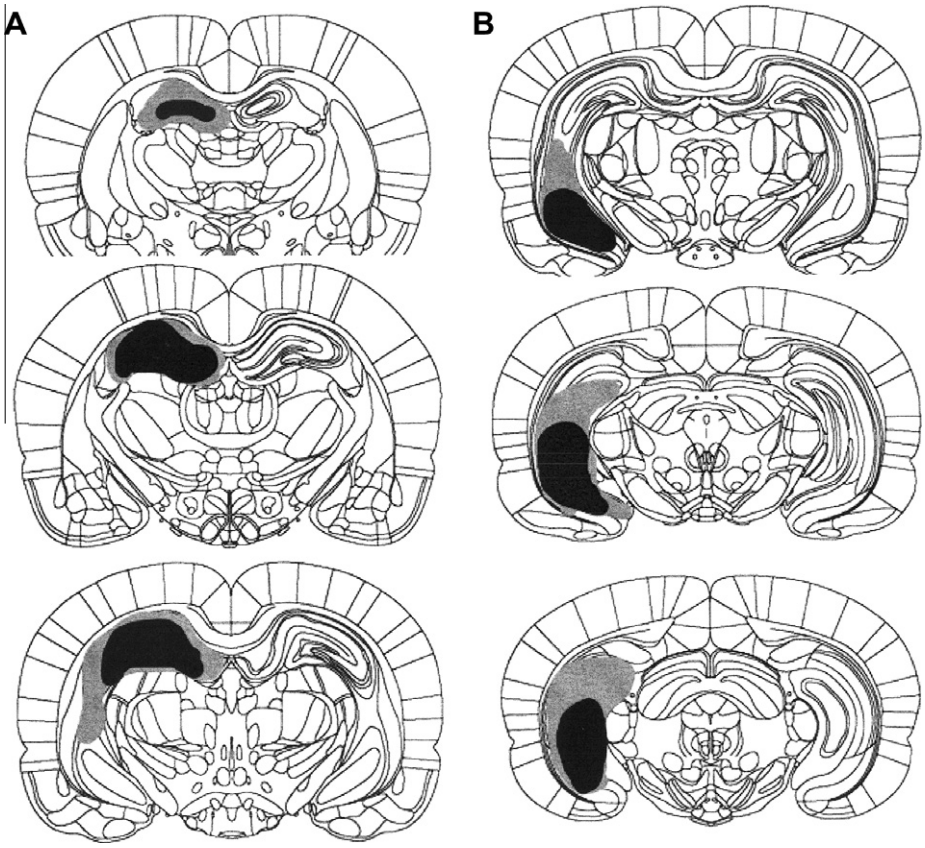

Fig. 1. Diagrammatic representation of the extent of dorsal hippocampus lesions (A) and the extent of ventral hippocampus lesions (B) with black representing the largest and gray representing the smallest lesion. Modified from Paxinos and Watson (1997) *The Rat Brain In Stereotaxic Coordinates*. (5th ed., Figs. 50, 60, 70 and 80), Elsevier Academic Press, San Diego, CA. Copyright 2005 by Elsevier Academic press. All lesions were bilateral, but maximal and minimal lesion extent were projected onto one hemisphere for the figure to allow for a more thorough analysis of lesion extent.

percent correct pre-surgery and post-surgery performance for the control, dorsal and ventral hippocampal lesioned groups as a function of the four carbonic chain (odor) separations. A repeated-measures 3-way analysis of variance with lesion (control, dorsal and hippocampus) as the between group factor and pre–post surgery and odor separation (1, 2, 3, and 4) as the within group factors revealed that there was a significant group effect $F(2, 127) = .11.17$, $p = .0001$, a significant pre–post effect $F(1, 127) = 56.6$, $p = .0001$, and a significant interaction between group and pre–post surgery $F(2, 127) = 28.14$, $p = .0001$, but there were no significant odor separation effect and there were no significant pre–post by odor separation, group by odor separation, and a three way interaction effects. A Newman-Keuls comparison test of the group and pre-post interaction indicated that during the post-surgery tests the ventral hippocampal lesioned group was significantly impaired relative to pre-surgery tests ($p < .01$) and relative to the post surgery control ($p < .01$) and post-surgery dorsal hippocampal lesioned tests ($p < .01$).

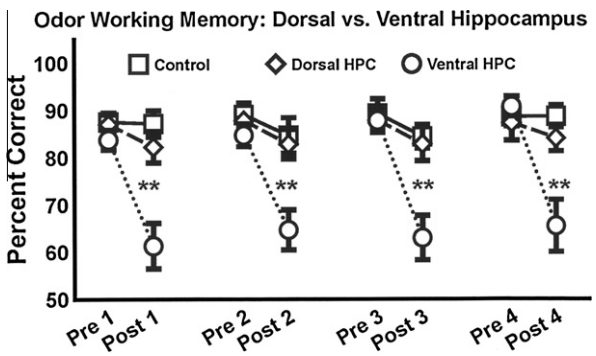

Fig. 2. Mean percent correct performance (±SEM) of control, dorsal and ventral hippocampal lesioned rats on pre- and post-operative trials. Note that post-operatively the ventral hippocampal group is significantly impaired relative to the control and dorsal hippocampal groups'.

3.3. Discrimination task

Fig. 3 shows the number of trials required by control, dorsal and hippocampal lesioned rats to reach an 80% correct criterion on the discrimination task based on ten consecutive trials. The number of trials required to reach an 80% correct criterion based on 10 consecutive trials was recorded for each animal. A one-way analysis of variance revealed no significant difference in trials to criterion between the dorsal, ventral and hippocampal lesions and control groups $F(2, 16) = .24$, $p = .79$. Since there were no significant differences in trials to criterion between the control and hippocampal lesioned rats, any deficit in performance of the olfactory working memory task is not likely due to an inability to perceptually discriminate the odors.

4. Discussion

The results indicate that the ventral, but not dorsal hippocampus, mediates working memory for odor information. It is important to note that the dorsal and ventral hippocampal lesioned groups did not have any difficulty in olfactory discrimination,

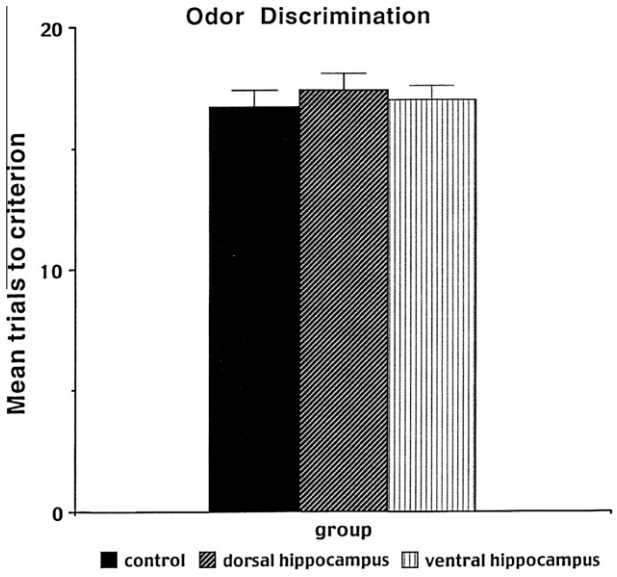

Fig. 3. Mean number of trials to criterion required by control, dorsal and ventral hippocampal lesioned rats to reach a 90% correct criterion on the discrimination task based on ten consecutive trials. Note that there are no differences between groups, suggesting intact olfactory perception.

suggesting intact olfactory perception. Additional data supporting a greater involvement of the ventral hippocampus compared to the dorsal hippocampus in processing odor information comes from the findings demonstrating that context conditioning to cat odor in rats resulted in decreased freezing following ventral, but not dorsal hippocampal lesions (Blanchard, Canteras, Markham, Pentkowski, & Blanchard, 2005; Pentkowski et al., 2006). As a control it was shown that exposure to a cat had no deleterious effects on freezing for either ventral or dorsal hippocampal lesioned rats (Pentkowski et al., 2006). In addition, blockade of muscarinic receptors in the ventral hippocampus impairs the retrieval of a socially transmitted food preference (Carballo-Marquez, Vale-Martinez, Guillazo-Blanch, & Marti-Nicolovius, 2009). In another study, Levita and Muzzio (2010) trained mice in a visuo-spatial and an olfactory task. In the visuo-spatial task mice had to associate a specific location with a reward independent of the odor associated with the reward. In the odor task mice had to associate a specific odor with the reward independent of location. Following dorsal hippocampal lesions, there were deficits only in the visuo-spatial task based on accuracy and latency to respond, but little effect on accuracy with an increased variability in latency to respond in the olfactory task. To explain the variability in latency it appeared that some mice had larger lesions that extended into the ventral hippocampus that resulted in an impairment in latency to respond in the olfactory task, but not the visuo-spatial task, suggesting ventral hippocampus involvement with learning of an olfactory task. Also, based on fMRI data for processing odor information, there was greater activation of the ventral compared to the dorsal hippocampus in mice and anterior compared to posterior hippocampus in humans (Cerf-Ducastel & Murphy, 2001; Kent et al., 2007). Thus, there is good evidence to support the idea that the ventral hippocampus supports processing of odor information (Cerf-Ducastel & Murphy, 2001; Kent et al., 2007; Pentkowski et al., 2006), whereas the dorsal hippocampus supports processing for spatial information (Moser & Moser, 1998; Rolls & Kesner, 2006).

Additional data supporting the idea that the ventral hippocampus and especially ventral CA1 may also be critical for temporal processing of odor information comes from the findings of Hunsaker et al. (2008) who showed that when ventral and dorsal CA1 lesioned rats were tested on temporal ordering paradigms for different types of information based on exploratory behavior with olfactory stimuli or spatial locations. The rats with ventral CA1 lesions showed significant deficits for the temporal ordering of olfactory information relative to control and dorsal CA1 lesioned animals. In contrast, rats with dorsal CA1 lesions showed a significant deficit for the temporal ordering of spatial locations relative to control and ventral CA1 lesioned animals. These data suggest that both dorsal CA1 and ventral CA1 contribute to temporal ordering processes, but further suggest that dorsal CA1 and ventral CA1 are dissociable for temporal ordering based upon the nature of the information that is being processed. The data also suggest that ventral CA1 is capable of processing olfactory information into a temporal code that can be recalled, whereas dorsal CA1 is not critically involved for this processing (although dorsal CA1 does show some neural activity related to olfactory temporal ordering (Manns, Howard, & Eichenbaum, 2007).

This report supports previous anatomical models suggesting that the dorsolateral band of the entorhinal cortex, which primarily carries olfactory information from olfactory and perirhinal cortices, projects to the ventral hippocampus more robustly than to the dorsal hippocampus (Kerr, Agster, Furtak, & Burwell, 2007; Steffenach, Witter, Moser, & Moser, 2005; Witter, Wouterlood, Naber, & van Haeften, 2000). Also, the ventral hippocampus receives inputs from the periamygdaloid nucleus, the amygdala region that processes olfactory information (Majak & Pitkanan, 2003). Furthermore, the ventral CA1, but not the dorsal CA1, subregion of the hippocampus projects to the olfactory bulb (Gulyas, Toth, McBain, & Freund, 1998; van Groen & Wyss, 1990).

Yet, other studies have examined odor information and showed that the dorsal hippocampus can also play a role in odor processing. For example, Otto and Poon (2006) showed that dorsal hippocampal lesions disrupt the acquisition of odor mediated contextual fear conditioning. It is important to note that the involvement of the dorsal hippocampus is primarily related to the acquisition and consolidation of new learning experiences, whereas the current study emphasized the importance of olfactory working memory.

We selected the odors, so that it might be possible to detect an odor pattern separation function. The data, however, do not support the presence of an odor pattern separation function. This could be a function of the size of the lesion of the ventral hippocampus which included the dentate gyrus (DG), CA3, and CA1 subregions. With respect to pattern separation for spatial information, it is known that dorsal CA3 lesions similarly disrupt working memory across all spatial locations, but do not produce a pattern separation function for spatial information. In contrast, dorsal dentate gyrus lesions produce a significant impairment at short spatial separations with performance of the dorsal DG lesioned animals increasing as a function of increased spatial separation between the correct object and the foil on the choice phases. It is also the case that perceptual pattern separation for odors based on discrimination studies resides in the olfactory bulb (Barnes, Hofacer, Zaman, Rennaker, & Wilson 2008; Wilson & Stevenson, 2003), which could explain the lack of a pattern separation effect following ventral hippocampal lesions. However, there is another possibility based on the finding that ventral hippocampal lesions did not disrupt discrimination of odors, implying that the task used in this experiment is based primarily on olfactory working memory and thus ventral hippocampus could be involved in a memory-based pattern separation for odors. Support for this idea comes from preliminary findings that control rats display a pattern separation function for odors using a 1 min instead of a 15 s delay between the study and test phase.

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