INTERACTIONS BETWEEN THE HIPPOCAMPUS, PREFRONTAL CORTEX AND THE VENTRAL STRIATUM DURING SPATIALLY-MEDIATED FORAGING BEHAVIOR IN THE RAT

by

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We accept this thesis as conforming
to the required standard

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ABSTRACT

Numerous studies have implicated the hippocampus in spatial learning and memory. The present series of experiments assessed the role of the ventral CA1/subiculum (vCA1/sub) region of the rat hippocampus in performance of a spatially-mediated radial-arm maze test battery. The role of this structure during foraging was assessed when rats either had, or did not have previous information about the location of food. In addition, the present study investigated the interactions between the vCA1/sub and either the nucleus accumbens (N.Acc.) region of the ventral striatum or the prelimbic (PL) region of the medial prefrontal cortex during performance of these different radial-arm maze tasks.

In Experiment 1, bilateral, transient, lidocaine-induced lesions of the vCA1/sub did not disrupt test-phase performance of a delayed spatial win-shift (SWSh) task, when lidocaine was administered prior to the training phase of this task. However, lidocaine infusions did impair foraging during the test phase of this task if lesions were administered prior to the test phase. Similarly, transient lesions of the vCA1/sub impaired performance during a random foraging (RF) task, which required rats to forage for four pellets placed randomly on an eight-arm maze.

In Experiment 2, interactions between the vCA1/sub and either the PL or the N.Acc. were examined, using a "disconnection procedure", involving a unilateral lesion of the vCA1/sub and a contralateral lesion of the PL or the N.Acc. prior to either the delayed SWSh task or the RF task. Disconnections between the PL and the vCA1/sub did not disrupt foraging during the RF task, but severely disrupted foraging during the test phase of the delayed SWSh task. Conversely, disconnections between the N.Acc. and the vCA1/sub impaired foraging behavior on the RF task, but not the delayed SWSh task.

The results of Experiment 1 suggest that the vCA1/sub region of the hippocampus is not involved in the acquisition of trial-unique spatial information, but is involved in the retrieval of

this information following a delay. This region is also involved in foraging on a radial arm maze, in situations in which an animal has no prior information about the location of food in an environment. Furthermore, the results of Experiment 2 support the theory that as the demands of different foraging task vary, the hippocampus interacts with different forebrain structures to guide foraging behavior. During foraging when the animal has no prior information about the location of food, the vCA1/sub appears to interact primarily with the N.Acc. and not the PL to guide this behavior. During delayed foraging, the vCA1/sub interacts primarily with the PL but not the N.Acc. to guide behavior. The present results support the hypothesis that different neural circuits are involved in different types of foraging behavior.

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Introduction

For the past 25 years, much of the research examining the neural substrates involved in learning and memory has focused on the role of the hippocampus. Over this period, a number of theories about hippocampal function have been proposed, including working memory (Olton & Papas, 1979), configural learning (Sutherland & Rudy, 1989), declarative memory (Squire, 1992) and spatial memory (Morris 1982;O'Keefe & Nadel, 1978). The role of the hippocampus in spatial memory has been supported by two main lines of evidence. First, electrophysiological recordings in freely-moving rats have shown that cells in different regions of the hippocampus demonstrate "place" specificity (O'Keefe & Nadel, 1978), showing a selective increase in activity when the animal is located in a specific region of space (Barnes, McNaughton, Mizumori, Leonard & Lin, 1990;Jung, Sidney, Wiener & McNaughton, 1994;Mizumori, McNaughton, Barnes & Fox, 1989;Poucet, Thinus-Blanc & Muller, 1995;Sharp & Green, 1994). Second, behavioural studies have demonstrated that 1) damage to the entire hippocampus, 2) selective damage to a number of hippocampal subregions, or 3) deafferentation of hippocampal outputs by sectioning the fornix/fimbria, all impair performance on tasks that require the processing of spatial information. These tasks include the Morris Water-Maze (Morris, 1981;Morris, Schenk, Tweedie & Jarrard, 1991;Sutherland, Wishaw & Kolb, 1983;Sutherland & Rodriguez, 1989), delayed matching-to-position in an operant chamber (Dunnet, 1990) and spatially-cued radial-arm maze foraging (Jarrard, 1978;Jarrard, 1986;Jarrard, 1993;McDonald & White, 1993;Olton & Papas, 1979;Packard, Hirsch & White, 1989;Poucet, Thinus-Blanc & Muller, 1994).

The ventral CA1/subiculum (vCA1/sub) subregion of the hippocampus is considered to be the main output region of the hippocampus (Groenewegen, Vermeulen-Van der Zee, Te Kortschot & Witter, 1987). Efferent projections of the vCA1/sub include the nucleus accumbens

(N.Acc.) and the prelimbic (PL) region of the medial prefrontal cortex, both of which have been demonstrated anatomically (Brog, Salyapongse, Deutch, & Zahm, 1993;Conde, Maire-Lepoivre, Audinat, & Crepel, 1995;Groenewegen et al., 1987;Groenewegen, Berendse, Meredith, Haber, Voorn, Wolters, & Lohman, 1991) and electrophysiologically (Gigg, Tan & Finch, 1994;Laroche, Jay & Thierry, 1990;Yang & Mogenson, 1985, 1987). During behaviours that require the processing of spatial information, hippocampal signals relaying this information may be routed to forebrain structures such as the N.Acc. or the PL for further processing or for integration into ongoing patterns of behaviour. If this is the case, lesions to either the N.Acc. or the PL would impair performance on tasks that are also sensitive to lesions of the hippocampus or the vCA1/sub.

The effects of lesions of the N.Acc. or the PL on spatially-mediated foraging behaviour

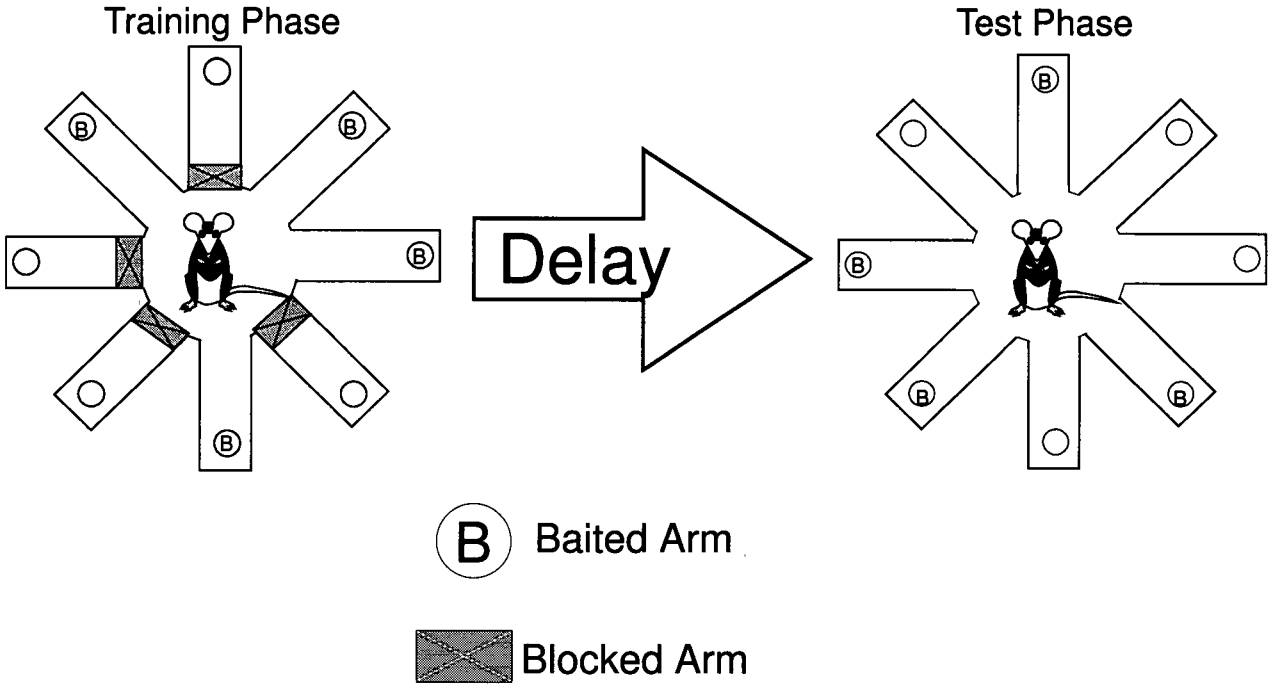
Recent research utilizing transient, lidocaine-induced lesions in rats has investigated the role of two of these efferent structures of the hippocampus, in the performance of two variants of the spatial win-shift (SWSh) radial-arm-maze task. In one version of the task, the animal acquired spatial information about the location of reward during a training phase, retained that information over a delay and used it to guide foraging behaviour during a test phase (for a description, see Fig 1A). Lidocaine infusions into regions of the N.Acc., which receive projections from the vCA1/sub region of the hippocampus, severely disrupted foraging during a delayed SWSh task (Seamans & Phillips, 1994). Similar disruptions of foraging behaviour were observed following lidocaine infusions into the N.Acc. prior to a random foraging (RF) task, in which rats had no previous information about the location of reward. In this task, four of eight arms were baited randomly, and the rat was required to forage in a non-repetitive manner (see Fig 1B). The pattern of errors observed on these radial-arm maze tasks following transient-

Figure 1. Diagrammatic representation of the delayed spatial win-shift (SWSh) and the random foraging (RF) eight arm radial-arm maze tasks.

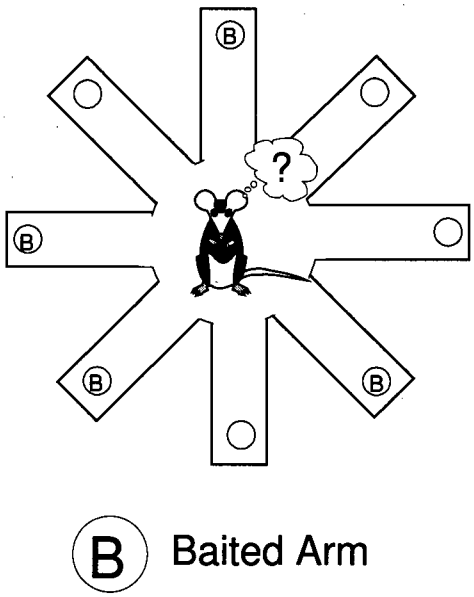
A) Delayed SWSh task. This task consists of a *training* and a *test* phase. During the training phase, 4 of 8 arms on a radial maze are randomly blocked, and the 4 remaining open arms are baited. Once the animal has retrieved the 4 pieces of food from the open arms, it is removed from the maze for a delay (ranging between 5 to 30 min). Following the delay, the animal is placed back onto the maze for the test phase. The arms that were previously blocked are now open and baited. The rat must remember which arms were previously blocked, and approach them in order to receive food reward.

B) Random Foraging task. This task consists of one phase. Four arms are randomly baited each day. Optimal foraging strategy requires the animal to enter arms in a non-repetitive manner. Unlike the test phase of the delayed SWSh task, the animal has no prior knowledge to the location of food.

A The Delayed Spatial Win-Shift Paradigm



B The Random Foraging Paradigm



lesions of the N.Acc. suggested that this nucleus may be involved in integrating spatial and motivationally-relevant stimuli in order to initiate or guide goal-directed behaviours. To this end, the N.Acc. may utilize inputs from the hippocampus and other cortical and limbic structures to guide foraging behaviour. Place- and movement-correlated firing by N.Acc. neurons has been observed during foraging on a radial-arm maze (Lavioe & Mizumori, 1994), and similar findings were reported in the vCA1/sub region of the hippocampus(Barnes et al., 1990). Together, these finding are consistent with the hypothesis that the N.Acc. integrates spatial information from the vCA1/sub and other relevant stimuli in order to initiate and/or guide ongoing behaviour.

Related experiments have shown that transient lesions of the PL region of the prefrontal cortex produced selective impairments on a similar radial-arm maze test battery (Seamans, Floresco & Phillips, 1995). Specifically, animals receiving lidocaine injections into the PL prior to the test phase of a delayed SWSh task responded randomly, revisiting arms baited during the training phase and the test phase with equal frequency. However, similar lesions to the PL did not disrupt foraging during the RF task, when there was no delay component, and required animals to forage "on-line" (Seamans et al, 1995). This pattern of results, along with data from other investigations of medial prefrontal cortex function (Fuster, 1991;Grannon & Poucet, 1995;Kesner & DiMattia, 1987), supported the conclusion that the PL is essential for utilizing previously acquired information in order to forage efficiently at a later time. Thus, when an animal has obtained previous information about the spatial locations of food (as in the delayed SWSh task), the PL appears to be a cortical region that uses this information to formulate and execute a series of responses following a delay in order to forage efficiently. Conversely, the PL is not involved when an animal forages without any prior information about the location of food, and must process information "on-line" (as in the RF task).

Interactions between the Hippocampus, the N.Acc. and the PL during spatially-mediated foraging

As mentioned previously, lesions to the hippocampus or its output pathways produce impairments on radial-arm-maze performance (Jarrard, 1978;Jarrard, 1986;Jarrard, 1993;McDonald & White, 1993;Olton et al., 1979;Packard et al., 1989;Poucet et al., 1994). Similarly, lesions to either the N.Acc. (Seamans & Phillips, 1994) or the PL (Seamans et al., 1995) produced different effects on two variants of spatially-cued radial arm maze tasks described above. The fact that both of these forebrain regions receive projections from the vCA1/sub (Brog et al., 1993;Conde et al., 1995;Groenewegen et al., 1987;Groenewegen et al., 1991), raises the distinct possibility of separate functional interactions between the hippocampus, the N.Acc. and/or the PL during different foraging strategies. The following series of experiments were designed to test this hypothesis.

The "disconnection" procedure is particularly useful for investigating the route of serial information transfer between different brain regions in both rats (Everitt, Morris, O'Brien, Burns & Robbins, 1991) and primates (Gaffan & Harrison, 1987;Gaffan, Gaffan & Harrison, 1988, 1989). This technique utilizes a unilateral lesion of a primary structure in combination with a contralateral lesion of another brain region that receives direct projections from the first area. A diagrammatic representation of this procedure is shown in Fig 2. This procedure assumes that information is transferred serially from structure "A" to a second structure, "B" in parallel on both sides of the brain (Fig 2A). A unilateral lesion in structure "A" and a contralateral lesion in structure "B", could disconnect the pathway between these two regions on both sides of the brain (Fig 2B).

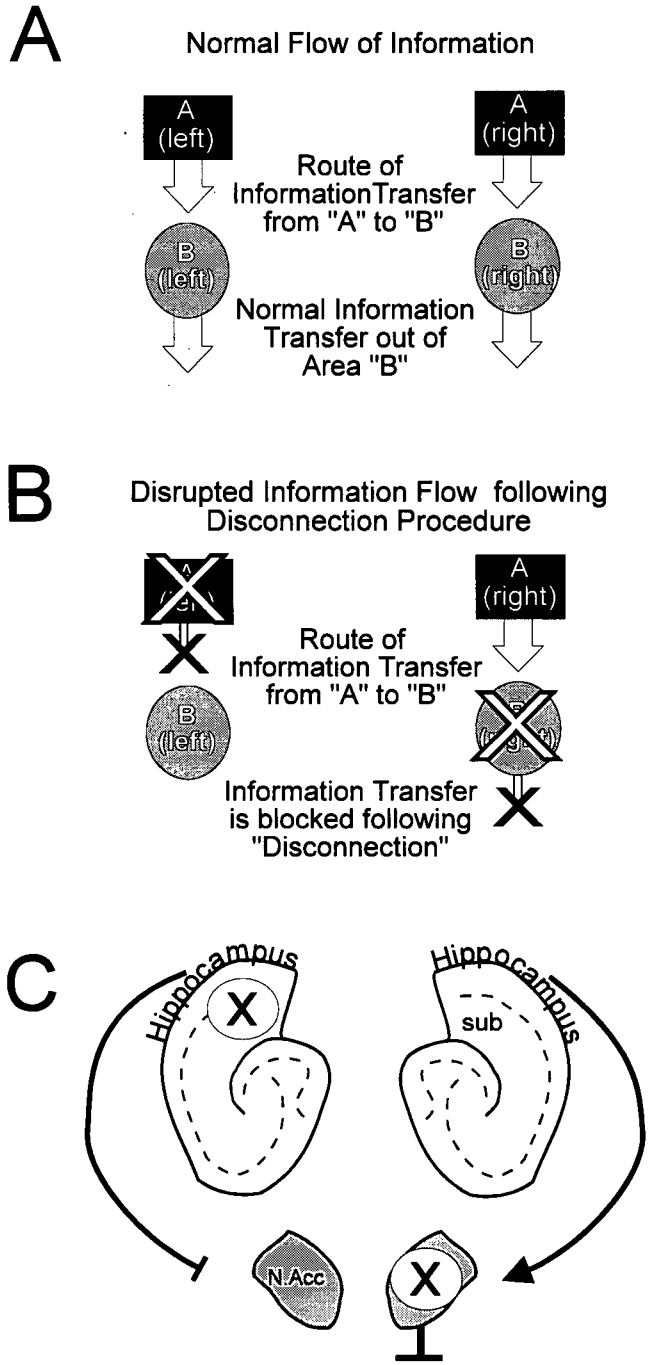


Figure 2. Schematic representation of a disconnection procedure.
A) Representation of the normal flow of information from left and right sides of structure "A", downstream to structure "B".

B) Following a disconnection, information from the left "A" is disrupted by a unilateral lesion, blocking the flow of information to the left "B". A contralateral lesion to the right "B" blocks further information transfer, and the disconnection is complete.

C) Application of a disconnection. A unilateral lesion of the vCA1/sub and a contralateral lesion of the N.Acc. would theoretically disconnection the route of signal transfer between these two areas.

For example, if one chooses to investigate the possibility of serial information transfer from the hippocampus to the N.Acc., a disconnection of this pathway could be produced following a unilateral lesion of the left vCA1/sub and a contralateral lesion of the N.Acc. (Fig 2C). This technique is one of the most direct and powerful means of assessing the routes of information processing in the brain during different types of behaviours. Accordingly, the following experiments utilized unilateral lesions of the vCA1/sub in combination with a contralateral lesion of either the N.Acc. or the PL prior to the test phase of the delayed SWSh task or prior to the RF task, to clarify the pathways of information transfer from the vCA1/sub to the forebrain during different types of foraging.

Most of the previous studies investigating the role of the hippocampus on radial-arm maze performance utilized permanent lesions, making it difficult to determine whether the deficits were due to an impairment in the encoding or retrieval of spatial information. Impairments following permanent lesions of the hippocampus may have been caused by a disruption in the initial encoding or consolidation of spatial information, or may have been the result of impaired recall of spatial information needed to forage efficiently. Thus, before undertaking the experiments utilizing disconnection lesions of the vCA1/sub and the N.Acc. or the PL, a first series of experiments assessed the effect of transient, lidocaine-induced lesions of the vCA1/sub on performance on the radial-arm maze test battery described above. Transient lesions administered prior to the training or test phase of the delayed SWSh or prior to the RF task permitted an assessment of the role of the this region of the hippocampus in the processing of trial-unique, spatial information during different foraging situations. The use of the same lesion technique and behavioural testing protocols used in previous studies of N.Acc. and PL function (Seamans & Phillips, 1994;Seamans et al, 1995) allowed for a direct comparison between these forebrain regions and the vCA1/sub.

Experiment 1: The effect of transient, lidocaine induced lesions of the ventral CA1/subiculum region of the hippocampus on a radial-arm maze test battery

Transient lidocaine-induced lesions in conjunction with a radial-arm maze test battery have been used to dissociate the roles of the N.Acc. (Seamans & Phillips, 1994) and two subregions of the medial prefrontal cortex (Seamans et al., 1995) in spatially-mediated foraging behaviour. The test battery used in these studies assessed the type of errors made on these tasks, which permitted a detailed analysis of the nature of the deficits produced by lesions to these structures. Comparisons of the number of across-phase (entering an arm previously entered during the training phase) versus within-phase (re-entering an arm entered during the test phase) errors made following lidocaine infusions prior to the test phase of the delayed SWSh task can suggest a disruption of either working memory (greater number of across-phase versus within-phase errors), or a global disruption in foraging strategy (same number of across-phase versus within-phase errors.). During the RF task, a greater number of re-entries to baited arms relative to non-baited arms may indicate an impairment in behavioural flexibility, whereas observing the same number of re-entries into both baited and non-baited arms may suggest a disruption of working or spatial memory processes. By comparing the type of impairments in foraging behaviour on each of the three tasks used in this test battery following selective transient lesions, a greater understanding of the functions of the vCA1/sub (as well as the N.Acc. and PL) in spatially-based foraging behaviour may be achieved.

In Experiment 1, three separate groups of well-trained rats with bilateral cannulae implanted into the vCA1/sub received infusions of saline or lidocaine on separate days, prior to the training phase or the test phase of the delayed SWSh task, or prior to the RF task.

Method

Subjects

The subjects were male Long Evans rats weighing between 300-450g prior to surgery. All rats were given free access to water and were maintained at 85% of their free feeding-weight by providing approximately 25-30 g of Purina lab chow pellets once daily. Rats were tested 5 to 7 days a week. A different group of rats was used for each part of Experiment 1.

Surgery

Rats were anesthetized with 100mg/kg of ketamine hydrochloride and 7mg/kg xylazine. Twenty three gauge stainless steel guide cannulae were implanted into the brain regions of interest using standard stereotaxic techniques. The stereotaxic coordinates (flat skull), were derived from, Brog et al., (1993), Conde et al., (1995) Groenewegen et al., (1987) and Paxinos and Watson (1986). Bilateral cannulae were implanted into the vCA1/sub region of the hippocampus : AP = -6.0 mm from bregma, ML = +/- 5.5 mm from midline and DV = -5.3 +/- 0.3 mm from dura. Thirty gauge obdurators flush with the end of the guide cannulae remained in place until the injections were made. Each rat was given at least 7 days to recover from surgery prior to behavioural testing.

Micro-infusion Procedure

Each rat received a 0.5 μl infusion of 20 μg of lidocaine or isotonic saline on separate days, in a counterbalanced order (see below). On injection days, the obdurators were removed and 30 gauge stainless steel injection cannulae that protruded 0.8 mm beyond the tip of the guide cannulae were inserted. Lidocaine or saline injections were delivered at a rate of 0.5 μl /1.2 min by a Sage Instruments Model 341 syringe pump. Injection cannulae were left in place for an

additional 1 min following the injections to allow for diffusion. Each rat remained in its home cage for an additional 3 min prior to being placed on the maze.

There are different estimates of the functional spread of lidocaine within the brain which appear to depend on the rate of infusion. Using an infusion rate of 1µl/min, Welsh and Harvey (1991) estimate that the functional spread is 1.4 mm in the cerebellum from the site of infusion. The functional spread of lidocaine in the occulomotor nucleus was estimated to be 0.5 mm with an infusion rate of 4 µl/15 min (Albert & Madryga, 1980). Furthermore, infusions of a 2% lidocaine solution at a rate of 1 µl / 2 min into either the PL or the anterior cingulate cortex of the rat produced distinctly different patterns of impairments (Seamans et al, 1995). These two regions of the rat medial prefrontal cortex are in close proximity to each other (1.5 mm in the dorsal/ventral plane). Based on these results, it is unlikely that the effective functional spread of lidocaine is greater than 1.5 mm. In the present study, an infusion rate of 0.5 µl/1.2 min, of 20 µg of lidocaine could be expected to produce an effective functional spread of approximately 0.75 ±0.5 mm.

Histology

After behavioural testing the rats were sacrificed in a carbon dioxide chamber. Brains were removed and fixed in a 10% formaline solution. The brains were frozen and sliced in 50 µm sections prior to being mounted and stained with Cresyl Violet. Placements were verified with reference to Brog et al. (1992), Conde et al. (1995), Groenewegen et al. (1987), and Paxinos and Watson (1986).

Apparatus

An eight-arm radial maze was used for all experiments. The maze had octagonal center platforms measuring 40 cm in diameter from which eight, equally spaced arms (measuring 50cm

x 9cm with a cylindrical food cup at the end) radiated out (see Fig 1). Removable pieces of white opaque plastic (9cm x 13cm) were used to block the arms of the maze. The maze was elevated 40cm off the floor and was surrounded with numerous extra maze cues (i.e., cupboards, posters, doors, the experimenter etc.). The maze was situated in a room 4 m x 5 m x 3 m, and was illuminated with overhead fluorescent light.

Foraging Tasks

The two foraging tasks that were used to assess the effect of lesions to the vCA1/sub were the Delayed Spatial Win-Shift (SWSh) task and the Random Foraging (RF) task.

The Delayed Spatial Win Shift task: This task was adapted from Packard et al.,(1990), and has been described in detail elsewhere (Seamans & Phillips, 1994;Seamans et al., 1995). On the first two days of testing, rats were habituated to the maze environment. Subsequent training trials were given once daily. These trials consisted of a Training phase and a Test phase, separated by a delay. Prior to the Training phase, a set of four arms chosen from a randomly generated list of numbers, were blocked. The arms that were blocked each day were chosen so that no more than two adjacent arms were blocked on any given daily trial. Bioserv™ food pellets (Frenchtown, NJ) were placed in the food cups of the four remaining open arms. During the Training phase, each rat was required to retrieve the pellets from the four open arms within 5 min, after which it was returned to its home cage for the delay period (see below). During the Test phase of each daily trial, all arms were open, but only the arms that were previously blocked contained food. Rats were allowed a maximum of 5 min to retrieve the four pellets during the Test phase.

The initial delay between Training and Test phases was 5 min. Upon achieving criterion performance of retrieval of all four pellets in five or fewer choices during the Test phase for two

consecutive days, the delay was extended to 30 min. The day after two consecutive days of criterion performance was attained at a 30 min delay, the first injection of lidocaine or saline was administered. Following the first test day, animals were retrained until they achieved a criterion of one error or less on either task for two consecutive days. On the day following criterion, a second, counterbalanced injection of lidocaine or saline into the vCA1/sub was administered. Two separate groups of rats received infusions of lidocaine and saline on separate days either prior to the *training phase* or the *test phase* of the delayed SWSh task.

On test days the number and order of arm entries were recorded. An arm entry was recorded when a rat moved down the entire length of an arm and reached the food cup at the end of the arm. Errors were scored as entries to unbaited arms, and further broken down into two error subtypes. An *across-phase* error was defined as any initial entry to an arm that was entered previously during the Training phase. A *within-phase* error was any re-entry into an arm that had been entered earlier during the Test phase. The latencies to reach the food cup of the first arm visited and to complete the phase were also recorded. This latter latency measure was divided by the total number of choices made during the phase to avoid confounding a larger number of errors with enhanced latencies.

Random Foraging: The RF task has also been described elsewhere (Seamans & Phillips, 1994;Seamans et al., 1995). Habituation to the maze during the first two days of training was identical to the delayed SWSh procedure described above. On subsequent daily trials animals were required to forage for four pellets placed randomly on the eight arms of the maze. The assignments of arms to be baited were taken from a list of randomly generated numbers. A novel set of arms was baited each day. Animals were trained to a criterion of one re-entry error or fewer per daily trial for 4 consecutive days. The day after criterion performance was achieved, the first injection of lidocaine or saline was administered into the vCA1/sub. Following the first

injection, animals were again trained to criterion for two consecutive days. On the following day, a second counterbalanced injection of either lidocaine or saline into the vCA1/sub was administered. Errors were scored as re-entries to arms entered previously within a trial. These errors were broken down further into re-entries to baited arms (arms that had been baited at the start of the trial) and re-entries to non-baited arms (arms that were not baited prior at the start of the trial). Subsequent re-entries to a baited arm following the first re-entry were still scored as errors to baited arms. The number of re-entries to arms (errors) made on each of the test days was recorded and used for data analysis. As with the delayed SWSh paradigm, the latencies to reach the first food cup (either baited or non-baited) after being placed on the maze and the average time to make subsequent arm choices were also recorded.

Results

Overall performance during training: Rats in all three groups showed rapid learning of the tasks. Rats receiving delayed SWSh training made an average of 2.94 (+/- 0.30) errors on the first day of training, and those receiving RF training made an average of 2.13 (+/- 0.69) errors on the first day of training. The average number of trials to reach criterion for delayed SWSh-trained animals was 11.8 (+/- 0.80), and for RF-trained animals was 11.4 (+/- 1.8)

Delayed SWSh, Pretraining injections: On separate days, eight animals in total received infusions of lidocaine and saline into the vCA1/sub prior to the training phase of the delayed SWSh task. The number and type of errors made during the test phase of the delayed SWSh task on the day prior to the first injection, and on lidocaine and saline test days were analyzed using a three-way, between/within, mixed analysis of variance (ANOVA) with the Order of injections (lidocaine or saline first) as a between-subjects factor, and Treatment-day and Error-type as two within-subjects factors. In addition, the number of errors made during the training phase by

animals on the day prior to the first injection, and on saline and lidocaine test days were also analyzed, using a one-way repeated measures ANOVA. There were no significant differences on the number of errors made on either the test phase ($F(2,12)=2.449$. n.s.; see Fig3A) or the training phase ($F(2,12)=0.325$, n.s.; see Fig 3A inset) during the day prior to the first injection and on saline and lidocaine test days. There were no significant effects of Order of injections or Order x Treatment interactions (all F's <2.0, n.s.).

The latency to reach the first food cup on test days was analyzed one-way repeated measures ANOVA. The average time per subsequent choice were calculated using the formula:

[(Time to complete trial-time to initiate trial) ÷ (number of choices made during trial) **].**

For example, if on a given test day, a rat took 10 s to reach the first food cup, and made 5 choices in a total of 70 s, the average time per subsequent choice would be (70 s - 10 s) ÷ 5 = 12 s per subsequent choice. These data were analyzed in a similar manner to the initiation latency data. There were no significant differences on latencies to reach the first food cup or the average time per subsequent choice on both the test and training phases (all F's < 1.3, n.s.)

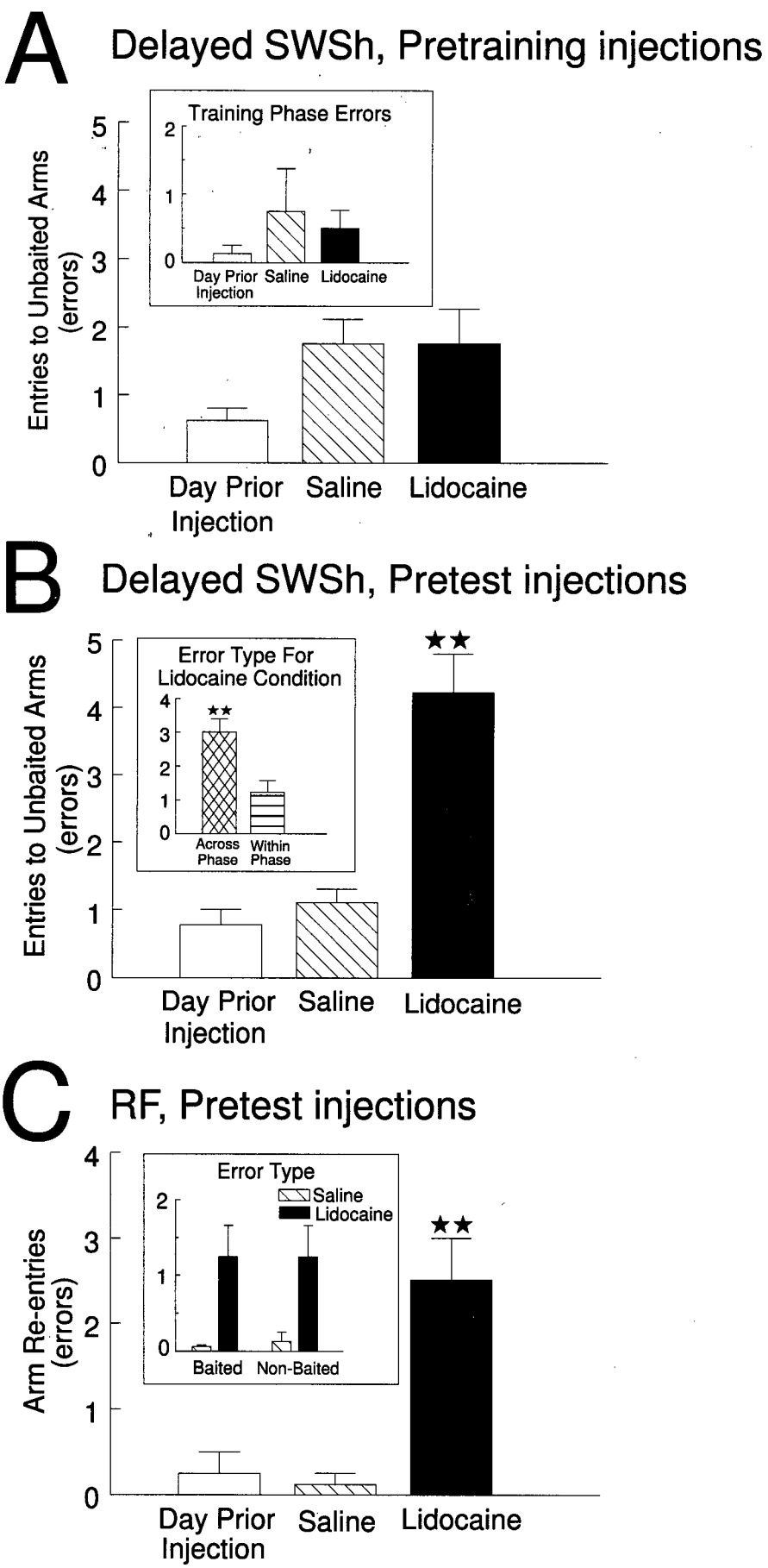
Delayed SWSh, Pretest injections: On separate days, nine rats received infusions of lidocaine and saline into the vCA1/sub prior to the test phase of the delayed SWSh task. The number and type of errors made during the test phase on the day prior to the first injection and on saline and lidocaine test days were analyzed in an identical manner as described above. Analysis of the number of errors made on the day prior to the first injection, and on saline and lidocaine test days revealed a significant main effect of Treatment ($F(2,14)=25.053$, $p<0.001$) (see Fig. 3B). Tukey's *post hoc* analysis for repeated measures showed that animals made significantly more errors on lidocaine test days relative to both the day prior the first injection and saline test days ($p<0.001$). Subsequent planned comparisons on the type of errors made on lidocaine test days

Figure 3: Results from Experiment 1.

A) Number of errors (mean +/- S.E.M.) made by rats during the test phase on the day prior to the first injection (open bar) and following infusions of saline (hatched bar) and lidocaine (black bar) into the vCA1/sub prior to the training phase of the delayed spatial win-shift task. *Inset* shows number of errors made during the training phase on the day prior to the first injection (open bar) and on saline (hatched bar) and lidocaine (black bar) test days.

B) Number of errors (mean +/- S.E.M.) made by rats during the test phase on the day prior to the first injection (open bar) and following infusions of saline (hatched bar) and lidocaine (black bar) into the vCA1/sub prior to the test phase of the delayed spatial win-shift task. ** indicates significance at $p<0.001$ relative to saline and day prior. *Inset* shows number of across phase errors (cross-hatched bar) and within phase errors (stripped bar) made by rats on lidocaine test days. ** represents significance at $p<0.01$.

C) Number of errors (mean +/- S.E.M.) made by rats on the day prior to the first injection (open bar) and following infusions of saline (hatched bar) and lidocaine (black bar) into the vCA1/sub prior to the random foraging task. ** indicates significance at $p<0.001$ relative to saline and day prior. *Inset* shows number of revisits to baited arms and non-baited arms on saline (hatched bar) and lidocaine (black bar) test days.


A
Delayed SWSh, Pretraining injections
Training Phase Errors
Day Prior Injection
Saline
Lidocaine
Entries to Unbaited Arms (errors)
Day Prior Injection
Saline
Lidocaine
B
Delayed SWSh, Pretest injections
Error Type For Lidocaine Condition
Across Phase
Within Phase
Entries to Unbaited Arms (errors)
Day Prior Injection
Saline
Lidocaine
C
RF, Pretest injections
Error Type
Saline
Lidocaine
Baited
Non-Baited
Arm Re-entries (errors)
Day Prior Injection
Saline
Lidocaine

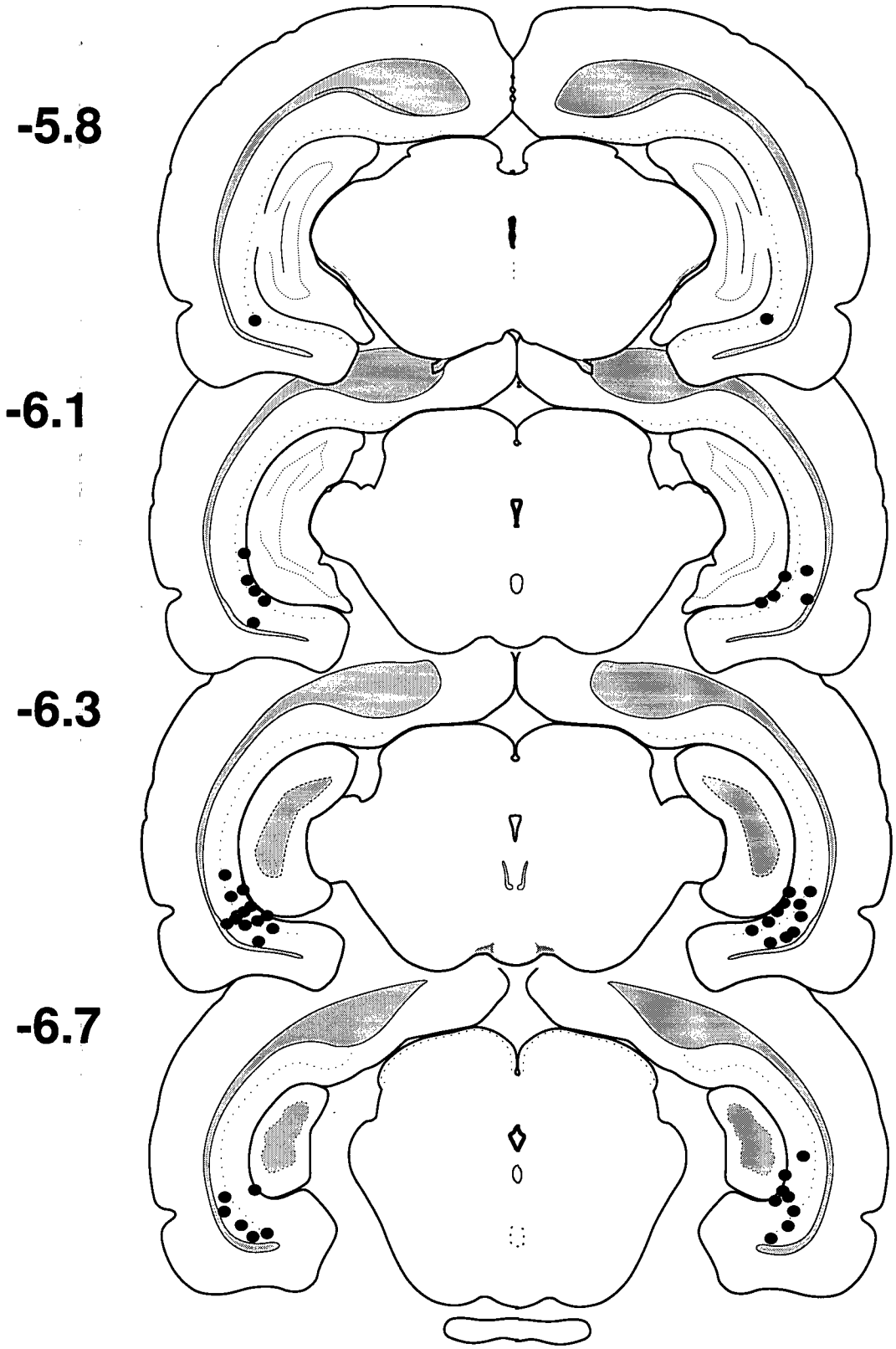
revealed that rats made significantly more across-phase errors than within-phase errors ($p<0.01$; see Fig 3B, inset). There were no significant effects Order of injections, or Treatment X Order interactions (all F's < 1, n.s.). Likewise, there were no significant differences between test days on the latency to reach the first food cup or on the average time per subsequent choice (all F's < 1.7, n.s.).

Random Foraging: On separate days, eight animals in total received infusions of lidocaine and saline into the vCA1/sub prior to the random foraging task. The number and type of errors made on the day prior to the first injection and on saline and lidocaine test days were analyzed in a similar manner to the delayed SWSh experiment described above. However, instead of dissociating between across and within phase errors, the error types were broken down into re-entries to baited and non-baited arms. Analysis revealed a significant main effect of Treatment ($F(2,12)=21.894$, $p<0.001$). Tukey's *post hoc* analysis showed that rats made significantly more errors on lidocaine test days relative to saline test days and to the days prior to the first injection ($p<0.001$; Fig3C). Subsequent analysis on the type of errors made on test days revealed that animals receiving lidocaine infusions made the same number of revisits to both baited and non-baited arms, ($F(1,7)=0.039$, n.s.; Fig 3C inset). There were no significant effects of Order of injection or Order x Treatment interactions (all F's < 1.2, n.s.). There were also no significant differences on the latencies to reach the first food cup or on the average time per subsequent choice on all 3 test days (all F's <2.2, n.s.).

Histology The location of the cannulae tips for all animals tested in Experiment 1 are diagrammatically represented in Fig 4. Some placements encroached slightly on the CA1/dentate gyrus border, but the behaviour of these animals did not differ from those whose placements were located exclusively in the vCA1/sub.

Figure 4. Histology from Experiment 1.

Diagrammatic representation of the location of cannulae tips (black circles) for all rats used for data analysis in Experiment 1. Plates are computer generated adaptations from Swanson (1992) that were modified to resemble those from Paxinos and Watson (1986). Numbers beside each slide correspond to mm from bregma.


-5.8
-6.1
-6.3
-6.7

Experiment 2: The effect of disconnection lesions between the ventral CA1/subiculum and either the nucleus accumbens or the prelimbic cortex on a radial-arm maze test battery

The results of Experiment 1 support the hypothesis that one role of the vCA1/sub is in the processing and retrieval of trial-unique spatial information whether or not a rat has previously-acquired information about the location of food. However, the functional significance of the connections between the vCA1/sub and the PL and N.Acc. is still unclear. Transient lesions of both N.Acc. and PL produced specific patterns of deficits on a radial-arm maze test battery identical to the one that will be used in the present study. Specifically, transient lesions of the N.Acc. in well-trained rats prior to the test phase of the delayed SWSh task or prior to the RF task severely disrupted foraging behaviour, whereas lesions prior to the training phase of the delayed SWSh task had no effect (Seamans & Phillips, 1994). However, lesions to the PL only disrupted foraging when administered prior to the test phase of the delayed SWSh task, but not prior to the RF task (Seamans et al., 1995). The purpose of Experiment 2 was to examine under what task demands are the functional connections between the vCA1/sub, the N.Acc. and/ or the PL crucial for efficient foraging behaviour.

"Disconnection" lesions have been used previously to examine the interactions between the amygdala and its connections during stimulus-reward mediated behaviours in both rats (Everitt et al., 1991) and primates (Gaffan & Harrison, 1987; Gaffan et al., 1988, 1989). The use of such a procedure relies on two assumptions. First, the anatomical connections between the two regions under investigation must be almost exclusively unilateral in each hemisphere, to allow for a near complete disconnection of this pathway. Anatomical studies have demonstrated this to be the case for both the vCA1/sub-N.Acc. pathway (Brog et al., 1993) and the vCA1/sub-

PL pathway (Conde et al., 1995). Second, it is assumed that an animal is still able to forage efficiently following a unilateral lesion to either the vCA1/sub, the N.Acc. or the PL. The following procedure controlled for this assumption by utilizing unilateral lesions of either the vCA1/sub, the N.Acc. or the PL on separate test days. In addition, a disconnection lesion consisting of a unilateral lesion of the vCA1/sub and a contralateral lesion of either the N.Acc. or the PL was administered prior to either the test phase of the delayed SWSh task or prior to the RF task.

Method

Subjects

The subjects used for Experiment 2 were Long Evans rats housed identically to those used in Experiment 1.

Surgery

Two sets of bilateral cannulae were surgically implanted. One pair of cannulae were implanted into the vCA1/sub, as described in Experiment 1. A second pair of cannulae were implanted into either the PL region of the medial prefrontal cortex (PL: AP = +2.6 mm, ML =± 0.7 mm from bregma and DV = -3.0 mm from dura) or the medial shell region of the N.Acc. (AP = +1.6 mm from bregma, +/- 1.3 mm from midline and -6.0 mm from dura). All other surgical conditions were identical to Experiment 1

Procedure

The microinfusion protocol, the radial arm maze, and behavioural tasks used for Experiment 2 were identical to those used in Experiment 1

A within-subject design was used for all four parts of Experiment 2. A separate group of animals were used for each part. Two groups of animals implanted with two sets of bilateral

cannulae into both the vCA1/sub and the PL were trained on either the delayed SWSh task or the RF task, in the same manner to Experiment 1. Another two groups of animals with cannulae implanted into the vCA1/sub and the N.Acc. were also trained on both tasks.

Each animal in each part of Experiment 2 received four injection test days in total : 1) a disconnection lesion entailing a unilateral lesion of the vCA1/sub in combination with a contralateral lesion of either the N.Acc. or the PL ; 2) a unilateral lesion of the vCA1/sub in combination with a saline injection of the N.Acc. or PL ; 3) a unilateral lesion of the N.Acc. or PL in combination with a saline injection of the vCA1/sub and 4) an injection of saline into both the vCA1/sub and either the N.Acc. or the PL. The order of injections was counterbalanced between animal using a quasi-Latin square design. The counterbalancing was designed so that no injection in one order was in the same position as any other order. The hemisphere (left or right) of the first injection was also counterbalanced, and alternated between every injection.

After reaching the first criterion on either the delayed SWSh task or the RF task (see Experiment 1 method section), an animal received a first injection test day. Following this first test day, the animal was retrained until it returned to criterion performance. On the day following this second criterion, it received a second, counterbalanced injection. This procedure was repeated until the animal had received 4 injections. The data recorded during these test days was identical to those taken during the test days of Experiment 1.

Results

PL- vCA1/sub disconnections

Random Foraging: On separate days, eight rats with two sets of bilateral cannulae implanted into the PL and the vCA1/sub received the four injection protocol described above

Figure 5: Results of PL.-vCA1/sub disconnections in Experiment 2 .

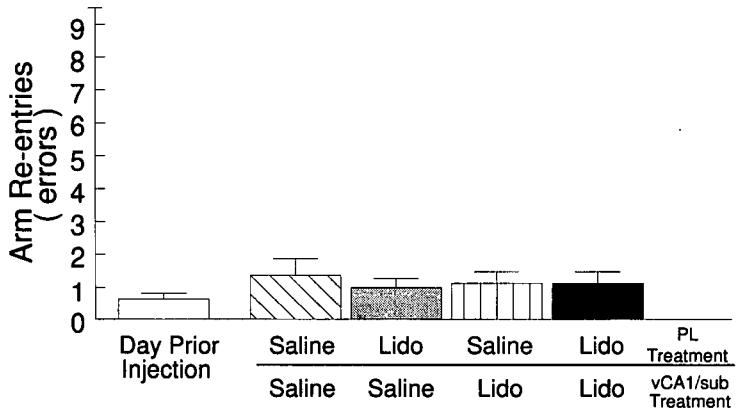
A) *Random foraging* Number of errors (mean +/- S.E.M.) made by rats on the day prior to the first injection (open bar), following unilateral infusions of saline into both the PL and the vCA1/sub (hatched bar), unilateral infusions of lidocaine (Lido) into the PL and contralateral saline in the vCA1/sub (grey bar), unilateral infusions of Lido into the vCA1/sub and contralateral saline into the PL (stripped bar) and unilateral Lido into the vCA1/sub and contralateral Lido into the PL (disconnection ; black bar) prior to the RF task.

B) *Delayed Spatial Win-Shift* Number of errors (mean +/- S.E.M.) made by rats on the day prior to the first injection (open bar), following unilateral infusions of saline into both the PL and the vCA1/sub (hatched bar), unilateral infusions of lidocaine (Lido) into the PL and contralateral saline in the vCA1/sub (grey bar), unilateral infusions of Lido into the vCA1/sub and contralateral saline into the PL (stripped bar) and unilateral Lido into the vCA1/sub and contralateral Lido into the PL (disconnection ; black bar) prior to the test phase of the delayed SWSh task. ** indicates significance at $p<0.001$ versus all other treatment conditions. *Inset* shows number of across-phase (cross-hatched bar) versus within-phase (horizontal-stripped bar) errors made by rats during Lido/Lido (disconnection) test days.

C) Diagrammatic representation of the location of cannulae tips (black circles) for all rats used for data analysis receiving PL-vCA1/sub disconnections prior to either the RF task or the delayed SWSh task. Plates are computer generated adaptations from Swanson (1992) that were modified to resemble those from Paxinos and Watson (1986). Numbers beside each slide correspond to mm from bregma. Note that figure is intended to represent the disconnection procedure. All animals received infusions of either lidocaine or saline in both hemispheres of each region. The figure represents location of cannulae tips on sides that received infusions on disconnection test days.

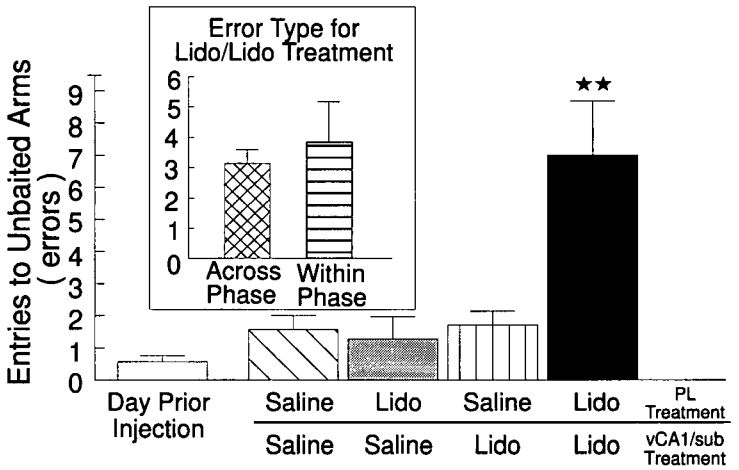
A

Random Foraging



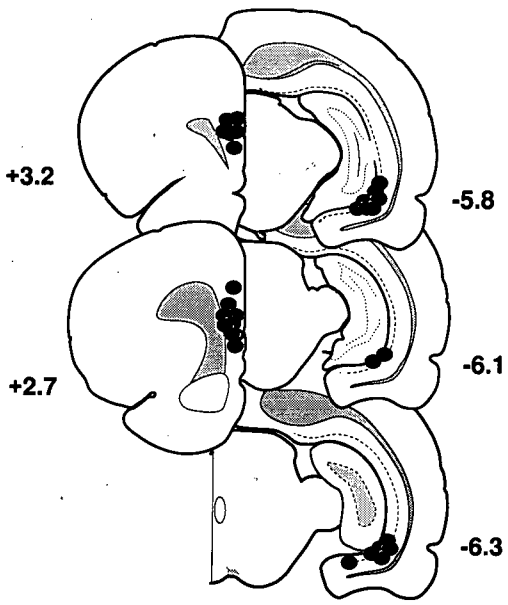
B

Delayed Spatial Win-Shift



C

Location of Cannulae Tips



prior to the RF task. These data were analyzed in a similar manner to those obtained in Experiment 1. The analysis revealed no main effect of Treatment ($F(4,16) = 0.67$, n.s.; see Fig 5A).Similarly, there were no main effects of Order of injections, Error type, or any significant interaction (all F's <1.2 , n.s.). Finally, a separate analysis confirmed that there were no significant differences between treatment condition on the latency to reach the first food cup or on the average time per subsequent choice (all F's <1.1, n.s.).

Delayed Spatial Win-Shift: On separate days, seven animals with two sets of bilateral cannulae implanted into the PL and the vCA1/sub received the four injection protocol described above prior to the test phase of the delayed SWSh task. The analysis revealed a highly significant main effect of Treatment ($F(4,12) = 10.99$, $p<0.001$). Tukey's *post hoc* analysis for repeated measures revealed that rats made significantly more errors on disconnection test days versus all other test days ($p<0.001$; see Fig 5B). There were no other significant differences in the number of errors made on any of the other test days. Subsequent planned comparisons on the type of errors made on disconnection test days showed no significant differences in the number of across versus within-phase errors made following PL-vCA1/sub disconnections ($F(1,6) = 0.517$, n.s.; see Fig 5B, inset). Furthermore, there were no significant effects of Order of injections, Error type, or any significant interactions (all F's <2.1, n.s.). A separate series of tests were conducted to assess any hemispheric biases on the number of errors made following unilateral vCA1/sub lesions, unilateral PL lesions and disconnection lesions. This analysis consisted of three, one-way ANOVA's with side of the vCA1/sub injection as a between-subjects factor. This analysis revealed no significant effects of the side of injection on the number of errors made by rats of the 3 test days (all F's <1.0, n.s.).

Analysis of the latency data revealed no significant differences in the latency to reach the first food cup on all test days ($F(4,24) = 0.098$, n.s.). In contrast, analysis of the average time per

subsequent choice data did show a significant effect of Treatment ($F(4,24) = 3.760, p<0.05$). Tukey's *post hoc* test for repeated measures revealed that animals took significantly longer ($p < 0.05$) on average for each choice (M= 38.1 s) following saline injections into both the PL and vCA1/sub versus latencies on unilateral PL lesion test days (M=23.3 s) and versus the day prior to the first injection (M=17.3 s). However, there were no differences in latencies between bilateral saline test days and disconnection test days (M=25.6 s), nor did the latencies on disconnection test days differ significantly from any other treatment condition. Given that animals receiving saline treatments in all other experiments of the present study did not differ in the this latency measure when compared to the day prior to the first injection, or to latencies on lidocaine test days, it appears that the present enhancement of latencies following saline/saline treatments in the PL and the vCA1/sub is a statistical anomaly.

Histology: The location of the cannulae tips for all animals receiving PL-vCA1/sub disconnections is represented in Fig 5C. Bilateral placements in the vCA1/sub were similar to those observed in Experiment 1. Similarly, bilateral placements in the PL were within the same regions of the prefrontal cortex as those observed by Seamans et al. (1995). Note that Fig 5C represents the disconnection lesions (see legend for details).

N.Acc.-vCA1/sub disconnections

Random Foraging: On separate days, eight animals with two sets of bilateral cannulae implanted into the N.Acc. and the vCA1/sub received the four injection protocol described above prior to the RF task. Analysis of these data revealed a highly significant main effect of Treatment ($F(4,16) = 10.563, p<0.001$). Tukey's *post hoc* test for repeated measures revealed that rats made significantly more errors on disconnection test days versus all other test days ($p<0.001$), and no other test days differed significantly from each other (see Fig 6A). Subsequent planned comparisons on the type of errors made on bilateral saline and

disconnection test days revealed that rats made an equal number of re-entries into baited and non-baited arms, and that this pattern did not significantly from bilateral saline treatment($F(1,7) = 0.439$, n.s.; see Fig 6A inset). There were no main effects of Order of injections, Error type, or any significant interactions (all F's ≤1.6, n.s.). Similarly, there were no hemispheric biases on the number of errors made on either unilateral vCA1/sub lesion, unilateral N.Acc. lesion of disconnection test days (all F's <3.0, n.s.) In addition, there were no significant differences between all treatment conditions on the latencies to reach the first food cup or on the average time per subsequent choice (all F's <2.2, n.s.).

Delayed Spatial Win-Shift: On separate days, nine animals with two sets of bilateral cannulae implanted into the N.Acc. and the vCA1/sub received the four injection protocol described above prior to the test phase of the delayed SWSh task. Analysis of these data revealed no significant main effect of Treatment ($F(4, 20) = 0.816$, n.s.; see Fig 6B). There was a significant main effect of Error type ($F(1,5) = 15.053$, $p<0.05$), indicating that animals made significantly more across-phase errors than within-phase errors during all treatment conditions. There were no significant main effects of Order of injection, or any significant interactions (all F's < 1.0, n.s.). Similarly, there were no significant differences between treatment conditions on the latencies to reach the first food cup or on the average time per subsequent choice (all F's < 1.7, n.s.)

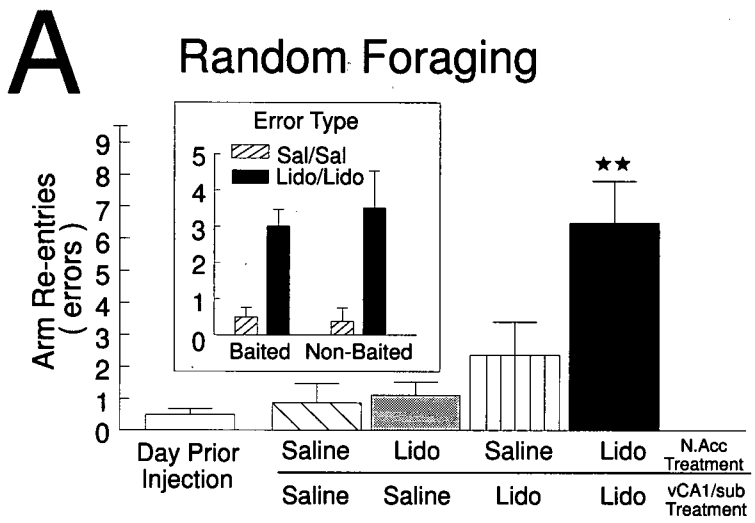
Histology The location of the cannulae tips for all animals receiving N.Acc.-vCA1/sub disconnections is represented in Fig 6C. Bilateral placements in the vCA1/sub were similar to those observed in Experiment 1. Similarly, bilateral placements in the N.Acc. were within the same regions of the ventral striatum as those observed by Seamans and Phillips (1994). Note that Fig 6C represents the disconnection lesions (see legend for details).

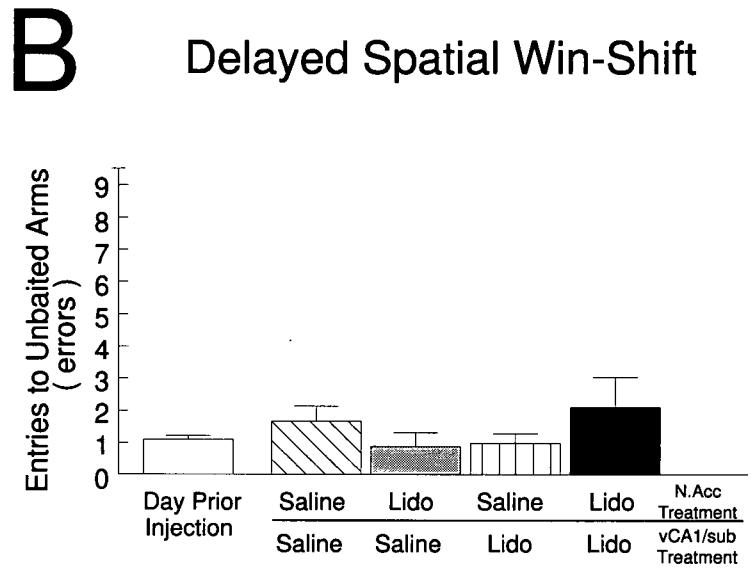
Figure 6: Results of N.Acc.-vCA1/sub disconnections in Experiment 2 .

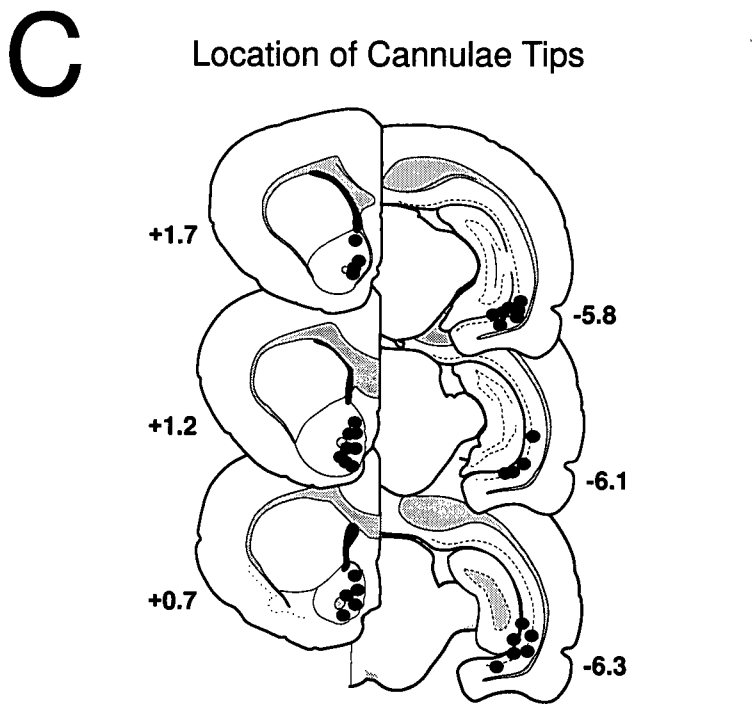
A) *Random foraging* Number of errors (mean +/- S.E.M.) made by rats on the day prior to the first injection (open bar), following unilateral infusions of saline into both the N.Acc. and the vCA1/sub (hatched bar) unilateral infusions of lidocaine (Lido) into the N.Acc. and contralateral saline in the vCA1/sub (grey bar) unilateral infusions of Lido into the vCA1/sub and contralateral saline into the N.Acc. (stripped bar) and unilateral Lido into the vCA1/sub and contralateral Lido into the N.Acc. (disconnection ; black bar) prior to the RF task. ** indicates significance at $p<0.001$ versus all other treatment conditions. *Inset* shows number of re-entries to baited arms and non-baited arms on saline/saline (hatched bar) and Lido/Lido disconnection (black bar) test days.

B) *Delayed Spatial Win-Shift* Number of errors (mean +/- S.E.M.) made by rats on the day prior to the first injection (open bar), following unilateral infusions of saline into both the N.Acc. and the vCA1/sub (hatched bar) unilateral infusions of lidocaine (Lido) into the N.Acc. and contralateral saline in the vCA1/sub (grey bar) unilateral infusions of Lido into the vCA1/sub and contralateral saline into the N.Acc. (stripped bar) and unilateral Lido into the vCA1/sub and contralateral Lido into the N.Acc. (disconnection ; black bar) prior to the delayed SWSh task.

C) Diagrammatic representation of the location of cannulae tips (black circles) for all rats used for data analysis receiving N.Acc.-vCA1/sub disconnections prior to either the RF task or the delayed SWSh task. Plates are computer generated adaptations from Swanson (1992) that were modified to resemble those from Paxinos and Watson (1986). Numbers beside each slide correspond to mm from bregma. Note that figure is intended to represent the disconnection procedure. All animals received infusions of either lidocaine or saline in both hemispheres of each region. The figure represents location of cannulae tips on sides that received infusions on disconnection test days.


A
Random Foraging
Error Type
Sal/Sal
Lido/Lido
Baited
Non-Baited
Arm Re-entries (errors)
★★
Day Prior Injection
Saline
Lido
Saline
Lido
N.Acc Treatment
Saline
Saline
Lido
Lido
vCA1/sub Treatment


B
Delayed Spatial Win-Shift
Entries to Unbaited Arms (errors)
Day Prior Injection
Saline
Lido
Saline
Lido
N.Acc Treatment
Saline
Saline
Lido
Lido
vCA1/sub Treatment


C
Location of Cannulae Tips
+1.7
+1.2
+0.7
-5.8
-6.1
-6.3

General Discussion

Experiment 1: the role of the vCA1/sub during performance of a radial-arm maze test battery.

Previous investigations have demonstrated that permanent lesions of hippocampal subregions or the fornix/fimbria produce severe deficits on radial arm maze performance (Jarrard, 1978;Jarrard et al., 1986;Jarrard, 1993;McDonald & White, 1993;Olton & Papas, 1979; Packard et al., 1989). The results of Experiment 1 confirmed these previous findings and provided new insight into the role of this region of the hippocampus for performance of tasks with different mnemonic demands.

Animals receiving infusions of lidocaine into the vCA1/sub prior to the training phase of the delayed SWSh were unimpaired relative to their performance after saline infusions on either the training phase or the test phase of the delayed SWSh task. These data are consistent with those obtained by Floresco, Seamans and Phillips (1996) which showed that similar, lidocaine-induced lesions to the vCA1/sub prior to the acquisition of a Morris water maze task did not disrupt performance during a retention phase, given 30 min later, after the anesthetic effects of lidocaine had dissipated. Similar findings were observed by Poucet, Herman and Buhot (1991), who reported that lidocaine infusions into the ventral hippocampus did not disrupt learning of a holeboard escape task. The results of these previous studies, in addition to those of Experiment 1 support the conclusion that the vCA1/sub region of the hippocampus is not involved in either the acquisition of trial-unique spatial information in different test environments, or storage of this information over a delay.

Transient lesions of the vCA1/sub also did not impair foraging on a 4-arm task during the training phase of the delayed SWSh task, suggesting that this region of the hippocampus is not required for simple foraging in a 4-arm maze environment. This conclusion is supported by the

observations that transient lesions of the vCA1/sub (Floresco et al, 1996) or excitotoxic lesions of the subiculum (Bohius et al, 1994) did not disrupt performance during a water maze task if rats had been given maze training prior to lesioning. Collectively, the results from these studies suggests that if a rat has been given access to an environment with a limited number of relevant location in space (i.e.: one platform in a water maze, or four arms on a radial maze), and is presumably allowed to form a spatial map of this environment with an intact hippocampus, subsequent foraging in this environment does not require an intact vCA1/sub.

Infusions of lidocaine into the vCA1/sub prior to the test phase of the delayed SWSh task disrupted performance during the test phase of this task. Rats receiving vCA1/sub lesions made more across-phase errors (M = 3.0) relative to within-phase errors (M = 1.22), re-entering arms which contained food during the training phase more frequently that those entered during the test phase. This pattern of errors could be interpreted as either a temporally-graded working memory deficit, or as a perseveration deficit. However, this latter interpretation is unlikely, given that infusions of lidocaine into the vCA1/sub did not result in perseverative behaviour during the RF task, but caused animals to re-enter baited and non-baited arms with equal frequency. Thus, one explanation for the pattern of results in Experiment 1 is that lidocaine infusions into the vCA1/sub disrupted the "online" processing and/or retrieval of spatial information. A similar conclusion was reached by Olton and Papas (1979), who found that lesions to the entire hippocampus disrupted foraging on a radial-arm maze task, causing rats to make "working memory" errors more frequently than "reference memory" errors.

Numerous behavioural and electrophysiological studies have suggested that the hippocampus is a neuroanatomical locus for the processing of spatial information (Barnes et al., 1990;Jung et al., 1994;Mizumori et al., 1989;O'Keefe & Nadel, 1978;Poucet et al., 1995;Sharp & Green, 1994). One of the main lines of evidence supporting this theory is the observation of

"place cells" in the hippocampus (i.e.; cells which show specific firing correlates when an animal is located in a certain region of space). The existence and behaviour of these hippocampal cells in freely moving animals led O'Keefe and Nadel (1978) to conclude that the hippocampus forms a "cognitive map" of a spatial environment, and that this map guides an animal's navigation through space. Place-cell activity has also been demonstrated in the vCA1/sub (Barnes et al., 1990;Jung et al., 1994), the main output area of the hippocampus (Groenewegen et al., 1987). Thus, an alternative (but not necessarily contradictory) explanation for the results of Experiment 1 is that transient lesions of the vCA1/sub disrupted the processing of spatial information by this brain region needed for efficient radial-arm maze foraging. Moreover, lesions to the vCA1/sub may have disrupted the transfer of this spatial information to other brain structures for subsequent processing and behavioural output. This hypothesis was tested directly in Experiment 2.

Experiment 2: The effect of disconnection lesions of the vCA1/sub and the N.Acc. or the PL during performance of a radial-arm maze test battery.

The results from Experiment 1, along with those from previous studies assessing the roles of the N.Acc. (Seamans & Phillips, 1994) and the PL (Seamans et al., 1995) in radial-arm maze foraging allow for speculation about the functions of each of these structures during spatially-mediated foraging behaviour. The present findings support the claim that the vCA1/sub is involved in the processing of *spatial information* about the relevant locations in space. The PL may play a specific role in *using previously acquired spatial information* to guide foraging behaviour at a later time *following a delay* (Kesner & DiMatta, 1987;Grannon & Poucet, 1995;Seamans et al., 1995). The N.Acc. appears to be a nucleus where signals from a

variety of limbic and cortical areas converge, resulting in the *initiation and guidance of ongoing goal-directed behaviours* (Mogenson et al., 1993;Seamans & Phillips, 1994).

The results of Experiment 2 provides new insight about the nature of interactions between these 3 regions during different kinds of foraging. A diagrammatic representation of the connections between the vCA1/sub the PL and the N.Acc. is represented in Figure 7A. The possible routes of information transfer between the vCA1/sub and the forebrain during different types of foraging are represented by Figure 7B-E.

PL-vCA1/sub disconnections: Disconnections between the PL and the vCA1/sub prior to the RF task did not significantly disrupt foraging relative to control treatments. This result suggests that a functional interaction between the PL and the vCA1/sub is not crucial for efficient performance on a task in which an animal has no prior information about the location of food. This finding is consistent with those of Seamans et al., (1995) who showed that bilateral lesions of the PL did not disrupt foraging when administered prior to the RF task. However, bilateral lesions of the vCA1/sub (Experiment 1) did impair foraging during the RF task. Given the present finding, it appears that during performance of a single-phase foraging task, spatial information exiting the vCA1/sub is not routed to the PL, but to another brain region. This region appears to be the N.Acc., as bilateral lesions of the N.Acc. severely disrupted RF performance (Seamans & Phillips, 1994). As such, a disconnection between the PL and the vCA1/sub may have not disrupted performance during the RF task because the functional pathway between the N.Acc. and the vCA1/sub was still intact (see Fig 7B).

In contrast, disconnections between the PL and the vCA1/sub prior to the test phase of the delayed SWSh task resulted in a severe disruption in foraging behaviour, suggesting that this functional pathway is crucial for the performance of this task. Thus, a unilateral lesion of the vCA1/sub in the present study could have disrupted the flow of spatial information from the

hippocampus to the PL. In addition, a contralateral lesion of the PL would have blocked subsequent processing of this information that was necessary to guide behaviour during the test phase of the delayed SWSh task. In combination, this disconnection would have ultimately resulted in both hemispheres of the brain lacking in crucial components of an efficient foraging strategy (i.e.; hippocampal-mediated spatial information and subsequent PL dependent processing), thereby leading to impaired performance (see Fig 7C). This theory is supported by other data that have shown that lesions to either the PL or the hippocampal system produce specific deficits on tasks that require the encoding, storage and retrieval of spatial information over a delay. These tasks include delayed matching-to-position in an operant chamber (Dunnet, 1990), and T-maze delayed alternation (Brito & Brito, 1990;Thompson, 1981). Similarly, Kesner and DiMatta (1987) reviewed data showing that lesions of either the prefrontal cortex (including the PL) or the hippocampus impaired prospective coding on a spatially-cued 12-arm radial maze task. Collectively, these previous studies, in addition the present findings, support the hypothesis that hippocampal inputs arising from the vCA1/sub and converging in the PL are essential for performance of tasks that require the utilization of previously acquired spatial information to guide foraging behaviour following a delay.

N.Acc.-vCA1/sub disconnections: Disconnections between the N.Acc. and the vCA1/sub disrupted foraging behaviour on the RF task, a finding consistent with previous studies (Experiment 1;Seamans & Phillips, 1994). The pattern of errors made by rats receiving N.Acc.-vCA1/sub disconnections was similar to those observed following bilateral lesions to either structure, when animals made an equal number of re-entries to both baited and non-baited arms. These data support the hypothesis proposed by Lavoie and Mizumori (1994) and Seamans and Phillips (1994), that the hippocampus may interact with the N.Acc. in order to guide foraging behaviour on a radial-arm maze. Moreover, the present findings, in conjunction with

Figure 7: Diagrammatic representation of the anatomical connections between the ventral CA1/subiculum (Hipp), the prelimbic cortex (PL) and the nucleus accumbens (N.Acc.). (X) represents the location of the unilateral lesions to the vCA1/sub and/or PL/N.Acc. for each task.
Solid arrows (⟶) represent intact pathways. Open arrows (⟶) represent pathways that are not anaesthetized, but do not carry the relevant information due to a lesion upstream of this pathway. Broken lines (⇢) represent pathways that are intact, but are not normally required for efficient performance on the task. Blunt arrows (⟶|) represent pathways that have been blocked.

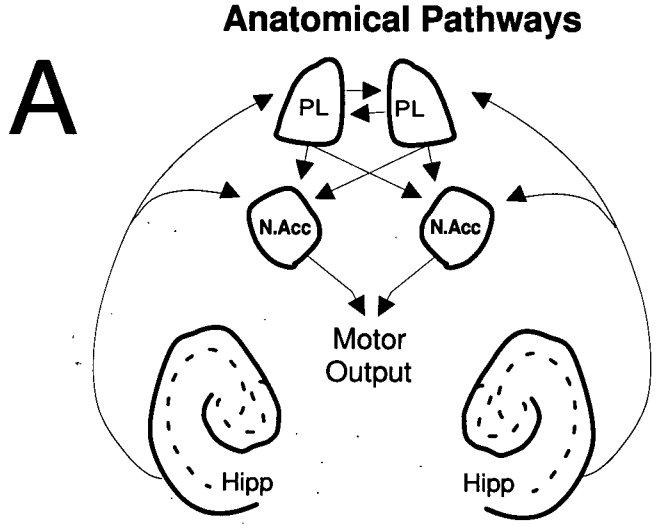
A) An overview of the ipsi- and contralateral connections between the 3 brain regions. Note the contralateral projections between the PL and its connections to the N.Acc.

B) Theoretical route of information transfer between the vCA1/sub and the PL during the RF task. By disconnecting the PL-vCA1/sub pathway, information is still able to go through the N.Acc., thereby allowing for appropriate output. (No impairment)

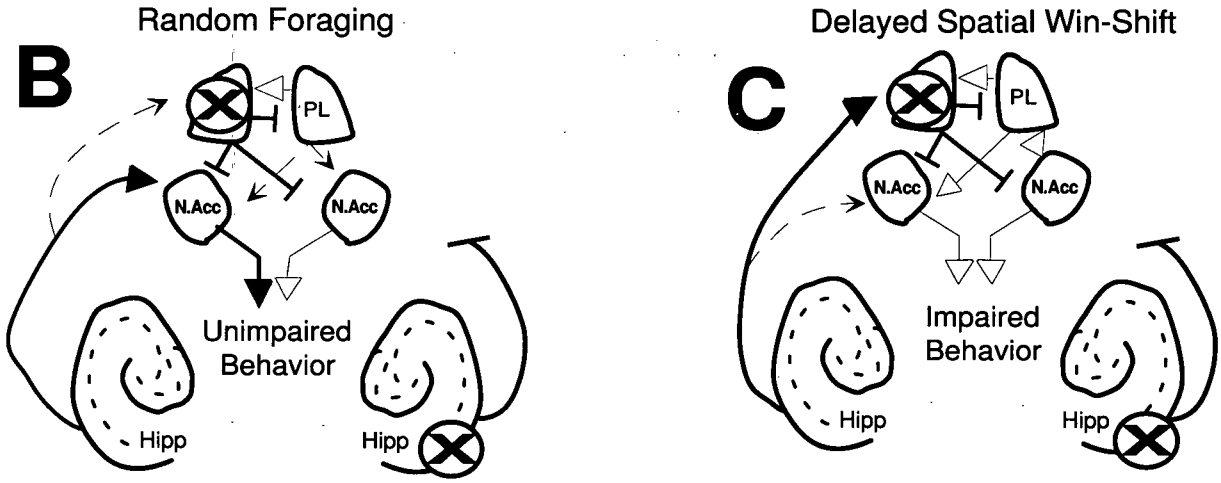
C) Theoretical route of information transfer between the a vCA1/sub and PL during the delayed SWSh task. By disconnecting the PL-vCA1/sub pathway, information cannot be processed by the PL to generate a planned response, thereby blocking appropriate output (Impairment)

D) Theoretical route of information transfer between the vCA1/sub and N.Acc. during the RF task. Disconnection of the N.Acc.-vCA1/sub pathway prevents the flow of information from the vCA1/sub through the N.Acc. to motor output centers (Impairment)

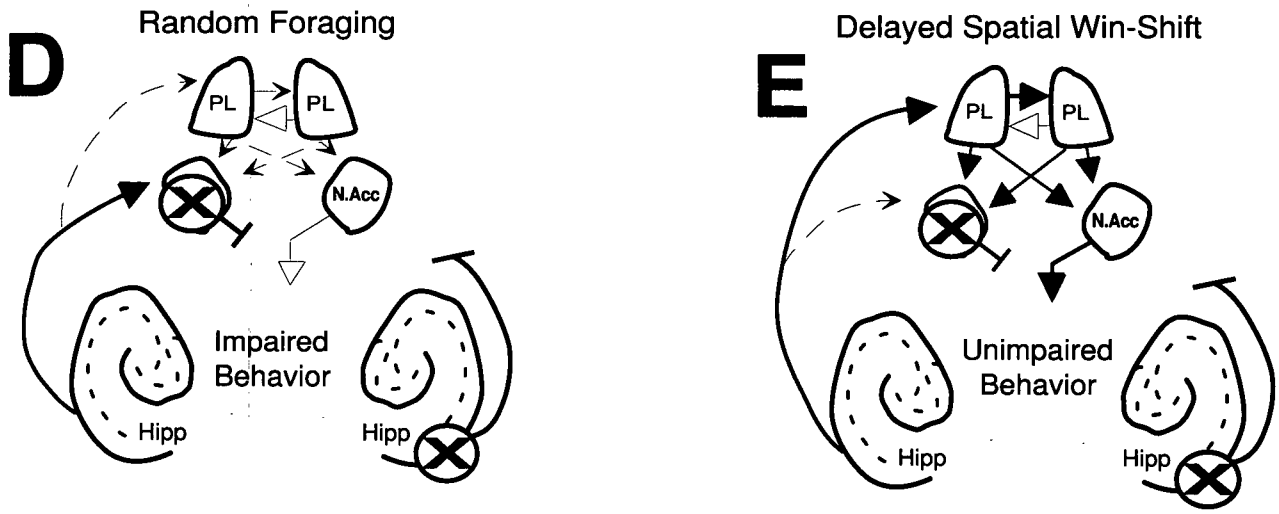
E) Theoretical route of information transfer between the vCA1/sub and N.Acc. during the delayed SWSh task. Information from the vCA1/sub may be routed primarily through the PL and subsequently to the N.Acc.. Thus, even though the pathway from the vCA1/sub to the N.Acc. is disconnected, spatial information may still be transferred from the unanaesthetized vCA1/sub to the ipsilateral PL and subsequently routed to the contralateral N.Acc., allowing for appropriate output. (No impairment).



Prelimbic Cortex-ventral CA1/subiculum Disconnections



Nucleus Accumbens-ventral CA1/subiculum Disconnections



the observation that similar disconnections between the PL and the vCA1/sub did not disrupt foraging behaviour on the RF task supports the premise that when an animal is foraging on a radial-arm maze with no previous information about the location of food, spatial information may be routed from the vCA1/sub, primarily to the N.Acc. and bypassing the PL in order to guide efficient "on-line" foraging. With regards to the present study, a unilateral lesion of the vCA1/sub may have deprived one hemisphere of the brain the necessary spatial information needed to guide behaviour during the RF task. A subsequent contralateral N.Acc. lesion may have prevented the integration of this information into appropriate motor responses, thereby leading to random responding and impaired foraging behaviour (see Fig7D).

Disconnections between the N.Acc. and the vCA1/sub prior to the test phase of the delayed SWSh did not significantly disrupt foraging during this task, suggesting that direct inputs from the hippocampus to the N.Acc. are not essential for efficient performance. This result may seem paradoxical, considering that bilateral lesions to either the vCA1/sub (Experiment 1) or the N.Acc. (Seamans & Phillips, 1994) severely disrupted test phase performance. A potential resolution of this paradox comes from an explanation of the anatomical connections between these 3 brain regions. The vCA1/sub sends almost exclusively unilateral projections to the forebrain, and contralateral connections between either sides of the vCA1/sub and forebrain are sparse (Brog et al., 1993;Conde et al., 1995;Groenewegen, et al., 1989;Groenewegen, et al., 1991 ; see Fig 7A). However there are dense *contralateral* connections between both sides PL and the N.Acc. (Brog et al., 1993;Sesack, Deutch, Roth, & Bunney, 1989). With reference to the present experiment, a unilateral vCA1/sub / contralateral N.Acc. lesion would have disconnected this pathway and prevented the processing of hippocampal signals by the N.Acc. Despite this manipulation, the pathway between the vCA1/sub and the PL would still be relatively intact. This detail is important, given that

disconnection of the PL-vCA1/sub pathway did impair test phase performance. In view of these considerations, an explanation for the finding that disconnections between the vCA1/sub and the N.Acc. did not impair delayed SWSh performance is as follows. During the test phase of the delayed SWSh task, spatial information from the unanaesthetized vCA1/sub may have been routed primarily to the intact PL. Subsequent processing of this spatial information may still have been able to access the unanaesthetized N.Acc., ipsilaterally and/or contralaterally (see Fig 7E). Since an intact N.Acc. is necessary for delayed SWSh behaviour (Seamans & Phillips, 1994) but hippocampal projections to the N.Acc. are not, the current data suggest that inputs to the N.Acc. from the PL, but not the vCA1/sub are critical for guidance of behaviour on this task.

A number of authors have speculated that interactions between the prefrontal cortex and the basal ganglia mediate the ability to plan, monitor and carry out a sequence of actions in a complex environment (Goldman-Rakic, Bates & Chafee, 1992;Robbins, 1990, 1991). In the rat this postulation is supported by the observations that bilateral lesions to either the N.Acc. or the PL result in produce similar impairments on delayed tasks, including delayed SWSh (Seamans & Phillips, 1994;Seamans et al, 1995) delayed non-matching to position (Dunnet, 1990) and T-maze delayed alternation (Annett, McGergor & Robbins, 1989;Brito & Brito, 1990). All of these tasks are also impaired by lesions to the hippocampal system (Experiment 1; Dunnet, 1990;Thopmson, 1981). In light of the fact that damage to either the hippocampus, the PL or the N.Acc. all can disrupt performance on spatially-mediated, delayed task, but that only disconnections between the PL-vCA1/sub (and not the N.Acc.-vCA1/sub pathway) impaired performance on the delayed SWSh task, it is suggestive that during performance of such a task, spatial information is transferred *in series* primarily from the vCA1/sub to the PL and then presumably to the N.Acc. for appropriate motor output.

Summary and Functional Implications

The results from Experiment 2, along with other studies investigating the roles of the hippocampus, the prefrontal cortex and the ventral striatum in spatial learning and memory provide the basis of a reformulation of the functions of the hippocampus and how it interacts with other brain regions to guide behaviour. As opposed to viewing performance of spatial tasks as a process solely mediated by the hippocampus, the present series of experiments suggest that an alternative view may lead to a better understanding of the underlying neural processes that mediate these behaviours. Specifically, the phenomenon known as " spatial processing" or "spatial memory" does not appear to be mediated by one fixed neural circuit. Rather, these data support the claim that different neural circuits come into play as the spatial and mnemonic demand of different tasks vary. The following model proposes a behavioural hierarchy of how spatial information originating in the hippocampus may be routed to different cortical and subcortical structures during different task demands.

The mnemonic demands of the Morris water maze are relatively small. The task requires the animal to remember one fixed location in space, that remains constant over training trials. Neurotoxic lesions to the hippocampus impair escape behaviour during a Morris water maze task whether or not an animal has received prior training before administration of the lesion (Bolhius et al., 1994;Morris et al., 1982;Morris et al., 1991;). However, neurotoxic or lidocaine-induced lesions to the subiculum only produce significant impairments in Morris water maze performance if lesions are administered prior to any experience in the maze (Floresco et al., 1996;Morris et al., 1991) while lesions to this region of the hippocampus following pre-lesion training have relatively little effects on efficient escape behaviour (Bolhius et al., 1994;Floresco et al., 1996). Furthermore, other studies have demonstrated that lesions to either the PL or the N.Acc. produce little or no impairments on a similar Morris water maze paradigm (Annett et al.,

1989;deBruin, Sànchez-Santed, Heinsbroek, Donker & Postmes, 1994; Floresco et al., 1996; Sutherland, 1985;Sutherland & Rodriguez, 1989).

Taken together, these studies investigating the neuroanatomical substrates involved in Morris water maze performances suggest that in such behavioural context that requires an animal to learn to find the location of a fixed point in space, the routing of spatial information may bypass both the N.Acc. and the PL. Instead, spatial information may be transferred from the hippocampus, through the vCA1/sub, to other cortical regions during the initial learning of this task. Some of these other cortical areas may include the entorhinal cortex (Schenk & Morris, 1985), the posterior parietal cortex (Kesner & DiMattia, 1987) or the retrosplenial cortex (Sutherland, Wishaw & Kolb, 1988). Furthermore, if an animal is permitted to learn this fixed location in space with an intact hippocampus, subsequent search behaviour for this location may no longer require the vCA1/sub (Bolhius et al, 1994;Floresco et al, 1996).

The RF task has considerably more mnemonic demands than the Morris water maze task. This task requires the rat to remember up to eight separate locations in space, and to monitor its actions during each training trial. Furthermore, the task uses trial-unique information, creating ambiguity about the locations of reward in the environment and requiring a rat to disregard any reward-related information it may have acquired during previous training trials. Efficient performance on this task requires both an intact N.Acc. (Seamans & Phillips, 1994) and a functional vCA1/sub (Experiment 1), but does not require inputs from the PL (Seamans et al., 1995). Given that the results from Experiment 2 showed that efficient performance on the RF task requires an intact serial transmission between the vCA1/sub and the N.Acc. but not the PL, it suggests the following; in an environment where there is ambiguity about the locations of reward and in which an animal must use spatial information to forage "on-line", essential spatial

information from the vCA1/sub may bypass the PL and be routed directly to the N.Acc. in order to guide foraging behaviour.

The delayed SWSh task has even greater memory demands that the RF task. Not only does this task require a rat to remember up to eight locations in space but it also require the animal to acquire reward-related spatial information, to hold that information in memory over a delay and subsequently use this information to formulate a correct response. This task is loosely analogous to the delayed response, or delayed non-matching to position task used with rats and primates. All of these tasks also share neuroanatomical specificity. Performance on these paradigms is impaired following lesions to either the hippocampus or its subregions (Experiment 1;Dunnet, 1990;McDonald & White, 1993;Packard et al., 1989), the PL (Dunnet, 1990;Seamans et al., 1995) or the N.Acc. (Dunnet, 1990;Seamans & Phillips, 1994). Furthermore, the data from Experiment 2 showed that effective performance on the delayed SWSh task required an intact vCA1/sub-PL pathway, but not a vCA1/sub-N.Acc. pathway. If this finding can be generalized to similar delay-type tasks, it would suggest that in behavioural situations that require an animal to use previously acquired spatial information to guide behaviour following a delay, spatial information be routed serially to the PL and then subsequently to the N.Acc. in order for efficient behavioural output.

Granted, the proposed model of these hippocampal- prefrontal cortical- ventral striatal interactions are highly speculative. The true test for this model will come from using similar disconnection procedures on other task that share similarities to the test battery used in the present series of experiments, in both rats and primates. Research focusing on interactions between these limbic, cortical and striatal areas should ultimately lead to a greater understanding of the underlying neural processes that mediate spatially learning and memory in the mammalian nervous system.

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