# SURFACE LOCATION HAS PRIORITY OVER DISTAL AND LOCAL CUES FOR PLACE LEARNING IN TRANSLATIONAL PROBLEMS IN THE RAT: A BEHAVIOURAL AND NEUROBIOLOGICAL ASESSMENT

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# Surface Location Has Priority Over Distal and Local Cues for Place Learning in Translational Problems in the Rat: A Behavioural and Neurobiological Assessment

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# Abstract

A cognitive map is considered to be a representation of relationships between distal cues in the environment. Support for the cognitive map theory has come from behavioural, lesion, and electrophysiological studies. Recently place field data have suggested that place cells are more closely tied to local, apparatus cues, than to distal cues. This was shown in a series of studies in which an apparatus was translated 33-120 cm. Earlier translational place studies, of which there are very few, are consistent with these place cell recording studies. The present thesis extends the examination of place learning on a moveable apparatus in a larger environment to better understand the interaction between location on an apparatus and location in a room, highlighting which conditions are necessary for an animal to shift from a surface dominated strategy to a strategy based on distal cues. In the present thesis, success and failure on the translational place problem was observed. The only difference between success and failure was the presence of multiple discriminable start points when rats were successful. It is suggested that multiple start points provide positional information that allows the rats to notice different directions to the goal, and therefore shift from a surface dominated strategy to a distal cue dominated strategy. Qualitative changes in surface texture did not facilitate this shift from a surface to a distal cue strategy. Hippocampal and sham lesioned rats were trained on the same translational place problem in the presence of multiple start positions. Lesions of the hippocampus disrupted place learning on this problem suggesting that simpler orientation mechanisms were not involved. Theoretical models and future directions are discussed.

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## Chapter 1 – General Introduction

An organism can use multiple strategies to navigate within its environment. Which particular strategy is used may depend on situational factors (e.g., time of day) and the availability of cues (Restle, 1957). The navigational strategies that have been observed in the laboratory include: cue/response learning (i.e., learning to approach a beacon, such as a light) (Redhead, Roberts, Good, & Pearce, 1997; Restle, 1957); path integration (Etienne, Teroni, Maurer, Portenier & Saucy, 1985; Whishaw, 1998); direction learning (Blodgett, McCutchen & Mathews, 1949); the use of room or maze geometry (Cheng, 1986; Gallistel, 1990; Margules & Gallistel, 1988); and the use of relations between multiple cues in the environment (O'Keefe & Nadel, 1978; Tolman, 1948). The latter has perhaps received the most attention in the last 50 years.

### 1.1. Cognitive Map Hypothesis

The notion that rats develop a cognitive representation of the relationship between cues in the environment arose from work by Tolman in the 1940's. A crucial aspect of Tolman's idea was that it proposed that learning about space relied on the construction of maps, and not on associations of movements. Hull, a contemporary of Tolman's, suggested an explanation of a habit-family hierarchy (Hull, 1934a; Hull, 1934b). Hull's theory was in strict contrast to Tolman's view. Hull proposed that rats traversed a maze, starting in one position, and ending in the goal position, in a stimulus-response (S-R) fashion. According to Woodworth (1938), since response chaining, or motor pattern (i.e., S-R associations) could not adequately explain rats behaviour in mazes, Hull's habit-family hierarchy theory was rejected, while Tolman's idea that rats develop a cognitive representation of the relationships between cues in the environment was accepted.

In a novel set of experiments, Tolman, Ritchie, and Kalish (1946a) trained rats to find a food location by following a specific route, which lead to a goal box that was defined by a lamp light (i.e., a distal cue). Subsequently, after the rats had learned that task, the rats were placed on a sunburst maze in which the original route was blocked and the rat had access to 18 radiating arms. They observed that 36% of the rats chose the arm that lead directly to the food box, and concluded that this showed evidence that the rats used a place disposition, in other words a cognitive representation of the environment, to solve the problem. In their second set of experiments, Tolman, Ritchie, and Kalish (1946b) trained rats on a plus maze. The place group was trained from two start positions (180° apart) to find the goal box that was defined by distal cues. For example, when the rat was placed at one start point, the rat was required to make a right turn to find the goal box. Conversely, when placed at the opposite start point, the rat was required to make a left turn. Response rats had to make a right turn regardless of start location. It was concluded that while place and response dispositions were acquired by rats, place learning was more easily acquired and therefore was considered simpler and more primitive.

The concept of cognitive mapping encompasses the idea that an animal creates a stored representation of the relationships between cues in the environment, and can access these representations or maps. The cognitive map is said to show flexibility in that if the spatial environment is altered (e.g., by removing a subset of distal landmarks), the cognitive representation can be updated, and this removal of cues does not disrupt navigation based on the cognitive map. With this stored representation of the environment, an animal can navigate through and locate itself within its environment. The cognitive map allows rats to make goal-directed trajectories, and take novel paths to find a goal (Morris, 1981; O'Keefe & Nadel, 1978; Tolman, 1948; Tolman, Ritchie & Kalish, 1946a; Tolman, Ritchie & Kalish, 1946b).

O'Keefe and Nadel (1978) extended Tolman's notion that animals form cognitive representations of the relationships between cues in that environment and formulated the cognitive map hypothesis. O'Keefe and Nadel (1978) divided navigational strategies, or spatial learning, into two major categories: the taxon and locale systems of navigation. The former can be further divided into a guidance and an orientation system. The taxon system is more of a local cue strategy system that includes strategies such as beacon learning (i.e., the guidance system) and response learning (i.e., the orientation system). The cognitive map hypothesis is based on the locale navigational strategy and the rat's ability to use distal cues to navigate through its environment. O'Keefe and Nadel (1978) also suggested that the hippocampus was the neural basis of the cognitive map. This map generates the information on which place learning is based, and can be stored in the hippocampal system on the basis of a single experience. Support for the cognitive map theory is widespread, spanning across species. Cognitive mapping has been demonstrated in humans (e.g., Garling, Book, Lindberg & Arce, 1990; Herman, Miller & Shiraki, 1987; Peruch, Giraudo & Garling, 1989; Tolman, 1948), chimpanzees (e.g., Menzel, 1973), rats (Morris, 1981; O'Keefe & Nadel, 1978; Tolman, 1948), birds (e.g., Gould, 1982), reptiles (Lopez, Gomez, Rodriguez, Broglio, Vargus, & Salas, 2001; Lopez, Rodriguez, Gomez, Vargus, Broglio, & Salas, 2000; Rodriguez, Lopez, Vargus, Gomez, Broglio, Salas, 2002), fish (Lopez, Broglio, Rodriguez, Thinus-Blanc, & Salas, 1999; Lopez, Vargus, Gomez, Broglio, Salas, 2002; Rodriguez, Duran, Vargus, Torres, & Salas, 1994), and insects (e.g., Gould, 1986). Evidence supporting the cognitive map hypothesis came from a variety of sources, including behavioural (Morris, 1981; Sutherland & Dyck, 1984), lesion (Jarrard, 1995; Morris, Garrud, Rawlins & O'Keefe, 1982; Olton, Walker & Gage, 1978; Parron, Poucet, & Save, 2004), and electrophysiological studies (O'Keefe, 1976; O'Keefe & Dostrovsky, 1971).

### 1.2. Behavioural Evidence

The most prominent behavioural study that provided evidence of cognitive maps was done by Morris (1981). He placed rats in a circular pool with a hidden platform that remained in the same place with respect to distal cues. Over a number of trials, the rats learned to locate the platform by following a straight route from variable start points. During probe trials in which the platform was removed, the rats spent the majority of their time in the quadrant at which the platform was located on previous trials. Morris provided evidence for the cognitive map theory by systematically ruling out alternative strategies. When the platform was hidden in a different place with respect to distal cues on every trial, the rat failed to locate the platform suggesting that the rat was not using a guidance system of navigation. In another experiment, Morris (1981) positioned the hidden platform in a different place with respect to distal cues on every trial, but kept the angular relationship between the start location and the platform constant. Rats failed this task, ruling out the possibility that the rats were using an orientation system of navigation. It was concluded that the rats were using distal cues to navigate and were taking straight novel paths to the submerged platform, suggesting the presence of a cognitive map.

Suzuki, Augerinos, and Black (1980) studied the ability of distal stimuli to gain control over spatial behaviour in the rat on an 8-arm radial maze. In this study they surrounded an 8-arm radial with a black curtain. As in classic working memory experiments, all arms were baited, and a correct choice was recorded as entry in an arm that had not been previously visited (and therefore contained food). Also, at the end of seven arms, there were distinct stimulus objects, all of which remained associated with a particular arm during all transformations. After three forced choices, the rats were confined to the center platform. After a 2.5 minute delay, the rats were given a free choice period. All transformations occurred during the delay interval. The three transformations included: a control (nothing changed), a rotation (arms and objects were rotated 180° to see if the rats oriented themselves based on the objects, and only by those objects), and a transposition (arms and objects were randomly moved to new positions). Rats were impaired at the task in the transposition transformation, while they were relatively unaffected by the control and rotation transformations. Since the control and rotation transformations left the relationship between arms and distal cues unaffected, rats were not impaired. In contrast, the transposition altered the relationship between (or configuration of) distal cues. They concluded that rats use the configuration of distal cues and that these cues can control rats' behaviour suggesting the presence of a cognitive map based on distal stimuli.

As was seen with Suzuki, Augerinos, and Black (1980), many other studies showed that manipulating the topographical arrangement of cues, but not the number of distal cues, disrupted place learning (O'Keefe & Nadel, 1978). For example, Pico, Gerbrandt, Pondel, and Ivy (1985) trained rats in a radial arm maze with 4 distinct distal cues. Deletion of any one or two cues had no effect on the rat's place learning. However, when three cues were removed, essentially eliminating the strategy of using relations between multiple stimuli, rats were impaired during the place task. These results are consistent with Fenton, Arolfo, Nerad, and Bures (1994) who trained rats in a water maze with four distinct distal cues. When any two cues were removed, no disruption of spatial navigation was observed. Similarly, when rats were trained with two distal cues and two novel cues were added, little disruption occurred. However, when rats were trained with two distal cues and those two cues were replaced by two novel cues, a large disruption was observed. These behavioural data are consistent with place unit firing (O'Keefe & Conway, 1978) (See Subsection 1.4).

### 1.3. Lesion Studies

Neurobiological studies also provided evidence of cognitive maps. Evidence that the hippocampus is important for place learning came from lesion studies of rats (Jarrard, 1995; Morris, Garrud, Rawlins & O'Keefe, 1982; Olton, Walker & Gage, 1978; Parron, Poucet, & Save, 2004), birds (Fremouw, Jackson-Smith, & Kesner, 1997), and turtles (Lopez, Gomez, Rodriguez, Broglio, Vargus, & Salas, 2001; Lopez, Rodriguez, Gomez, Vargus, Broglio, & Salas, 2000). These studies show that hippocampal lesioned animals are impaired in their ability to use distal cues (i.e., distal localization), but not in using local cues (i.e., proximal localization) to locate a specific place. Morris, Garrud, Rawlins & O'Keefe (1982) trained rats on the Morris water maze task and discovered that hippocampal lesions disrupted place navigation based on distal cues. Rats failed to locate the hidden platform located in a fixed position relative to distal cues when the hippocampus was lesioned. Furthermore, McDonald and White (1993) provided evidence that the hippocampus is involved in encoding stimulus-stimulus relations using an 8-arm radial arm maze.

Temporary inactivation studies also suggest the hippocampus is the neural basis of cognitive maps. Packard and McGaugh (1996) trained rats on a place problem after temporary inactivation of the hippocampus with lidocaine. The rats that had lidocaine injected into the hippocampus were impaired on the place problem. Similarly, Chang, and Gold (2003), and Compton (2004) showed that inactivation of the hippocampus impaired place navigational strategies.

Furthermore, studies using immunohistochemical techniques show an increase in c-Fos (an immediate early gene expressed in most brain areas when that brain area is activated) and phosphoylated cAMP response element binding protein (pCREB) in the hippocampus one hour after performance on a place problem, suggesting that the hippocampus is activated during performance on a place task, and that it is involved in the possible formation of memory for space (Columbo, Brightwell & Countryman, 2003).

## 1.4. Electrophysiological Evidence

Some of the most compelling evidence for cognitive maps arises from electrophysiological studies on place cells within the hippocampus. When place cells were first observed in the freely moving rat (O'Keefe, 1976; O'Keefe & Dostrovsky, 1971), it was observed that these cells fired when the rat passed through a particular location (called a place field). These place cells were further investigated, and it was found that place fields were highly stable, were dependant upon controlled cues, and were not dependant upon motivational factors (O'Keefe & Conway, 1978), temporal factors (Jung & McNaughton, 1993; Muller, Kubie, & Ranck, 1983), or dwell time, defined as a preference for a certain region (Muller, Kubie, & Ranck, 1987). O'Keefe and Conway (1978) recorded place cell activity when no food was present on the maze, and found that the removal of food did not disrupt the ability of the cells to discriminate place. On the other hand, when a T-maze was surrounded by a black curtain, to limit the use of environmental cues, and four distinct cues were positioned within the curtain, seven of eight cells loss their ability to discriminate place when all these cues were removed. However, when only two cues were removed, place cell activity remained intact. Place cells also have different place fields within different contexts (suggesting the hippocampus is involved in context discrimination; Kubie & Ranck, 1983) and multiple place fields (Muller, Kubie, & Ranck, 1987). However, although place cells may appear to be controlled by distal cues, few studies suggest that place cell activity can be maintained in the absence of controlled visual cues and in complete darkness (O'Keefe & Speakman, 1987; Quirk, Muller, & Kubie, 1990). These studies suggest that place cells can be maintained using internally derived feedback from proprioceptive and vestibular signals and that place cells may be modulated by these signals.

Although electrophysiological studies on place cells have provided compelling evidence for the hippocampus as a substrate for the cognitive map, one of the major pitfalls to this line of thinking are the non-spatial correlates of place cell firing. According to Eichenbaum, Dudchenko, Wood, Shapiro, and Tanila (1999), most space must be represented by a set of place fields distributed uniformly throughout the environment. In other words, hippocampal spatial representations must be homogeneous in order for this theory to be plausible. We know from earlier work that hippocampal spatial representations are not homogeneous (Hetherington & Shapiro, 1997; O'Keefe & Burgess, 1996), with most place fields forming near walls with prominent local cues, and being controlled by distances between neighbouring stimuli (e.g., walls). These studies suggest the hippocampus is not involved in forming a holistic representation of every point in space, rather, as O'Keefe and Burgess (1996) suggested, place cells may identify environmental features such as walls and their directions from the rat, possibly derived from head direction cells.

Head direction cells (Ranck, 1984) are named for the fact that each cell fires rapidly only when the head of a freely moving rat points in a restricted range of angles in the horizontal plane. Head direction cells are quite abundant, and have been found in numerous brain regions, including the postsubiculum (Taube, Kesslak & Cotman, 1992; Taube, Muller & Ranck, 1990a; Taube, Muller & Ranck, 1990b), the striatum (Wiener, 1993), the lateral dorsal nucleus of the thalamus (Mizumori & Williams, 1993), the posterior cortex (Chen, Lin, Barnes & McNaughton, 1994), and the anterior thalamic nuclei (Taube, 1995). Like place cells, firing of head direction cells is dependant upon visual cues. By placing a salient cue, such as a white cue card, in the environment, that card becomes a reference for orientation. Support for this idea comes from cue rotation probes in which the cue card was rotated. An almost equal shift in the preferred firing direction of head direction cells was observed (Taube, 1995; Taube, Muller & Ranck, 1990b). Recently, head direction cells were found in the hippocampus (Leutgeb, Ragozzino, & Mizumori, 2000). This convergence of place and direction information in the hippocampus may indicate that both place and direction must be integrated to form a cohesive cognitive map.

More recent work shows that while head direction cells are dependant on distal cues, place cells may be more closely tied to local or apparatus cues (Yoganarasimha & Knierim, 2005). This idea that place cells fire to non-spatial cues (e.g., local or apparatus cues) has been shown before. Place cell firing has been correlated with local apparatus cues (Gothard, Skaggs, & McNaughton, 1996; Knierim & McNaughton, 2001; Young, Fox, & Eichenbaum, 1994), as well as self motion cues (Save, Nerad, & Poucet, 2000; Sharp, Blair, Etkin, & Douglas, 1995; Stackman, Clark, & Taube, 2002; Zinyuk, Kubik, Fenton, & Bures, 2000).

### 1.5. Translation Versus Rotation

Recently, Knierim's laboratory has shown that firing of the majority of place cells was determined by the rats' location on an apparatus rather than by the rats' location in the room (Knierim & Rao, 2003; Siegel, Rao, Lee, & Knierim, 2005; Yoganarasimha &

Knierim, 2005). They showed this in experiments in which the apparatus location was translated by 33-120 cm, rather than rotated, relative to distal cues. When the distal landmarks were rotated, Knierim and colleagues showed, as previously seen, that place fields are correspondingly rotated, as are head direction cells (Knierim, Kudrimoti, & McNaughton, 1995; Yoganarasimha & Knierim, 2005). Knierim and colleagues suggest that the head direction cell system may modulate the firing of place cells tied to the track (i.e., local cues). As did O'Keefe and Nadel (1978) earlier, Knierim and Rao (2003) hypothesized that distal cues provide map orientation information, but that fine grained place information depends on path integration and location on the apparatus.

When the distal cues or a maze within a room with prominent visual cues is rotated, there is an almost equal shift in place fields. When the maze is translated, place cells remain tied to the rat's location on the apparatus. Much of the previous behavioural work on place learning was conducted using a stationary maze. In the few studies where the maze was moved, the manipulation was essentially a rotation. Tolman, Ritchie, and Kalish (1946b), Packard and McGaugh (1996), and Chang & Gold (2003a) trained rats from two start points positioned on the north and south arms of a plus maze, essentially a 180° rotation. One early exception was an experiment by Blodgett, McCutchan, and Mathews (1949). Blodgett, McCutchan, and Mathews (1949) trained rats on a translational version of the place problem in which the maze was translated 122 cm. Rats were required to make different responses and approach different directions from two start points to find the goal located in a consistent place as defined by distal cues. When the rats started on the south arm of a plus maze, they were required to turn right, and go east. After a translation of 122 cm to the right, the rats started on the same south arm, but were required to make a left turn, and go west to locate the food. Blodgett, McCutchan, and Mathews (1949) found that rats were impaired on the place task.

Similarly, Weisand *et al.* (1995) conducted an experiment that tested whether rats in the Morris water task were using distal landmarks to escape to the hidden platform, or the spatial geometry of the pool itself. Weisand *et al.* (1995) trained rats to escape to a hidden platform in the northeast quadrant of the pool. When the rats had reached asymptotic performance, the pool was shifted diagonally so the platform was now located in the southwest quadrant of the pool, but remained in the same place with respect to distal landmarks. If the rats were indeed using distal landmarks to locate the hidden platform, the rats would be expected to locate the platform since it still occupied the same place with respect to the distal cues. In fact, 100% of the rats navigated toward the northeast quadrant of the pool, supporting the idea of a local, surface boundary strategy with a small translation of the apparatus. Both of these studies are consistent with the idea that place cells are tied to the apparatus.

Skinner *et al.* (2003) explicitly compared the rotational and translational versions of the place task in the same study. In one group, the maze was rotated 90°, while in the other group the maze was translated 85 cm. The rotation group was successful at solving the place task, while the translation group was impaired. This, again, is consistent with place field data. It appears that place fields are stable in an apparatus with small translations, but place fields rotate with a clear change in direction relative to distal cues such as that produced by either a rotation or a large change in translational distance.

The present thesis extends the examination of place learning on a moveable apparatus in a larger environment to better understand the interaction between location on an apparatus and location in a room. The thesis presents evidence that place learning can occur with a translational version of the place problem, highlighting which conditions are necessary for an animal to use surface properties, and which kinds of manipulations will cause an animal to shift from a surface dominated strategy to a strategy based on distal cues.

# Chapter 2 – Surface Location Has Priority Over Distal and Local Cues for Place Learning in Translational Problems in the Rat

## 2.1. Introduction

A debate over whether rats use a local surface dominated strategy or a distal cue dominated strategy has been around for many years. Most experiments treat the use of local and distal cues to navigate as two mutually exclusive strategies. Typically, a black curtain surrounding the maze is used to control for distal cues and cleaning the maze surface/rotation of arms and disorientation procedures are used to control for possible informative local and idiothetic cues, respectively. Similarly, much research has been done when these two sets of cues (local and distal) are in conflict, with rats preferring one over the other depending on the types of cues available. Some research suggests beacon learning (a local strategy) dominates place learning when local and distal cues are in conflict (Redhead, Roberts, Good, & Pearce, 1997; Pearce, Ward-Robinson, Good, Fussell, & Aydin, 2001). Restle (1957) suggested that in cue rich rooms rats use distal cues. In cue poor rooms, local cues are used. We know rats can use local cues for proximal localization and distal cues for distal localization (Morris, 1981), but is there a shift from using a local surface strategy to a distal cue strategy in the formation of a cognitive map, and if so, what aspects of the environment necessitate this shift?

Earlier, O'Keefe and Nadel (1978) suggested that distal cues provide map orientation information, but path integration and location on the apparatus provide the rats with fine grained place information. When a maze is rotated 90°, the change in orientation (governed by distal cues) is drastically different, and rats can successfully solve a place problem (Skinner *et al.*, 2003). However, when a maze is translated a distance of ~33-120 cm, the change in orientation is not great enough to elicit a shift from a surface boundary dominated strategy to a distal cue dominated strategy, and rats fail this problem (Blodgett, McCutchen, & Mathews, 1949; Skinner *et al.*, 2003; Weisend *et al.*, 1995). Recent place field data are consistent with these results, suggesting that firing of place cells are determined by the rat's location on an apparatus rather than by the rat's location in the room (Knierim & Rao, 2003; Siegel, Rao, Lee, & Knierim, 2005; Yoganarasimha & Knierim, 2004).

Previous versions of the cognitive map theory suggested that rats use the relationship between distal cues to identify goal location. This is a simplistic characterization of O'Keefe and Nadel's (1978) original cognitive map theory in that it does not explain why rats fail a translational place problem (Blodgett, McCutchen, & Mathews, 1949; Skinner *et al.*, 2003; Weisend *et al.*, 1995). It is possible that rats use these distal cues to identify their start point, or at the least provide their initial orientation. The aim of the present chapter is to better understand the interaction between location on an apparatus and location in a room and to determine the conditions necessary for successful place learning on a translation problem.

## 2.2. Experiment 1

In Experiment 1, rats were tested with three place learning problems that varied the nature of the surface location information on an apparatus. In the first problem, a single plus maze was translated between two adjacent locations, as in the earlier experiments by Blodgett, McCutchan and Mathews (1949) and Skinner *et al.* (2003). For the rat on the start arm, its location with respect to the surface of the apparatus does not change, but its location with respect to distal cues does change. If the earlier experiments are replicated, the rats will have difficulty solving this problem. In the second problem, two adjacent plus mazes were provided so that the rats started from two different surface locations with respect to the apparatus. These locations were the same with respect to distal cues as for Problem 1. With differentiable and consistent surface and distal cue locations, the rats should be successful. The third problem provided multiple, but unreliable surface start locations, although the start locations were at the same two distal cue locations as for both of the previous problems. Rats were given two adjacent plus mazes with an additional plus maze added to either end in a variable pattern. Thus, the rats had two start locations with respect to the apparatus surface, but surface location itself was uninformative. Specifically, the rats' start locations with respect to the distal cues were the same as in the previous two problems, but on some trials it started from the last of three plus mazes, while on other trials it started from the second of three plus mazes (see Figure 2.1). If the rats rely only on surface location on the apparatus to solve the problem they will fail.

### 2.2.1. Methods

*Subjects.* Nineteen naïve, male, Long Evans rats, obtained from the Charles River Company (St. Constant, Quebec, Canada), and weighing between 195 g – 212 g at the start of the experiment, were used. Rats were housed in clear plastic cages (45 x 25 x 21 cm) with secured metal lids and maintained on a 12-hr/12-hr light/dark cycle with lights on at 0700. Subjects were maintained on a food deprivation schedule by measured feedings of Purina Rat Chow, as to not allow their weights to drop below 85% of their ad libitum weight. All rats had continuous access to water in their home cages. Animal care and all procedures used in the present experiments were approved by Memorial University's Institutional Committee on Animal Care and followed the Canadian Council on Animal Care guidelines.

*Apparatus.* The training room (615 cm X 302 cm) was rich in extra-maze cues. On the north wall, there was a blue door and a poster (93 cm X 122 cm). On the east wall, there was a desk (152.4 cm X 61.0 cm) and two wooden chairs. There was also a computer terminal and a black counter with a sink (245.1 cm X 74.9 cm). The south wall consisted of windows with the blinds open for the duration of training. On the west wall, there were two posters (93 cm X 122 cm) and a blue door.

For the One Maze problem, a single plus maze was used (see Figure 2.1A). For the Two Maze problem, two adjacent plus mazes were used (see Figure 2.1B). For the Three Maze-Unreliable Start Location problem, two mazes formed the core problem and an additional single plus maze was placed either to the right or left of the two mazes (see Figure 2.1C) on a variable schedule. Each wooden plus maze had a square center (15.5 cm X 15.5 cm) with 4 arms (38.5 cm X 15.5 cm) radiating out at 90° angles. At the end of each arm, a circular depression in the wood (diameter = 2.6 cm) formed a food cup. The plus mazes were elevated on a wooden stool and were 61.3 cm from the floor. No walls were present on the arms of the mazes to allow the rat a clear view of room. Any two plus mazes touched at one arm, as shown in Figure 2.1B. A Froot Loop® half was placed in the food cup at the end of the correct arm as reinforcement.

*Training Groups.* Rats were assigned to one of three groups on the basis of body weight such that no significant differences were observed with respect to body weight between the groups: the One Maze group (n = 6), the Two Maze group (n = 6) and the Three Maze-Unreliable Start Location group (n = 7). All groups were trained to locate the food reward in a consistent place with respect to distal cues. For all groups there were two different start locations with respect to distal cues. These start locations were identical across groups. The One Maze group was trained using only one plus maze that was translated to two locations across trials. When the rat was placed on the start arm, its location with respect to the surface of the apparatus did not change across trials, but its location with respect to distal cues did change. The Two Maze and the Three Maze-Unreliable Start Location groups were trained on the double-plus maze. The only difference between the Two Maze and the Three Maze-Unreliable Start Location groups was that for the latter group, an additional plus maze was positioned on one side of the double-plus maze (on the left for half the trials and on the right for the other half; see Figure 2.1C). Within each group, half of the rats started on one of two arms (i.e., a & b) while the other half started on the other two arms (i.e., c & d).

*Procedure.* During pre-training, Froot Loops® halves were spread evenly on the table located in the animal's housing room. Each rat was placed on the table and allowed to explore for 2 minutes. Once the rats moved and ate on the table, they were moved to a single plus maze. Initially, all arms were baited (with the exception of the start arm) with 2 Froot Loops® pieces and an additional Froot Loop® piece in the center to encourage the rat to move from the start arm. Once the rats moved from the start arm only the three food cups were baited. When all rats were eating the Froot Loops® from the food cups, the rats proceeded to training.

On each training day, the rats were moved to the training room. Each rat was removed from its home cage and carried in a clockwise direction to the maze. The rat was then placed on the appropriate start arm facing the experimenter. For all training trials, rats were only allowed to travel on the single plus maze that contained the food reward. To accomplish this, for the first sixteen training trials all rats were restricted to the part of the maze that contained the food reward by placing two Plexiglas (13.5 x 20 cm) barriers at the end of either side arm. The rats were allowed to explore the maze for 1 minute, or until they found and ate the food reward. For the remaining trials, both Plexiglas barriers were removed. At this point rats did not travel beyond the goal wells located at the end of the side arms before they were removed from the maze and thus did not traverse more than a single plus maze on any given trial. Following trial 16, the rat was removed from the maze if it had not moved from the start arm within 30 s or had made an incorrect choice. An incorrect choice was indicated by the presence of the rat's body, excluding the tail, on an un-baited arm. If the rat did not move from the start arm during the time limit for a trial then that trial was removed from the analysis. Each of the rats received 4 trials per day (inter-trial interval was 1-5 min), until a criterion of 18 correct trials out of 20 was reached. After each trial, the rat was carried back to its home cage in a counter-clockwise direction and the maze was re-baited for the next rat. Local maze cues were controlled by frequent 90° maze rotations. The maze was wiped free of debris (e.g., stray shavings) during training and at the end of each day the maze was cleaned with soap and water. Training was stopped at 275 trials for those rats that did not meet criterion.

### 2.2.2. Results

Rats in the Two Maze and the Three Maze-Unreliable Start Location groups, which were trained on the double-plus maze, reached criterion in fewer trials than those in the One Maze group, which were trained on the single plus maze. Three of the six rats in the One Maze group failed to reach criterion. A one-way ANOVA comparing trials to criterion across groups revealed significant differences between the groups [$F$ (2, 16) = 13.57, $p < .05$] (Figure 2.2). Post-hoc Newman-Keuls tests revealed that the One Maze group on average took more trials to reach criterion than the Two Maze and Three Maze-Unreliable Start Location groups ($ps < .05$), which did not differ ($p > .05$).

### 2.2.3. Discussion

The One Maze group replicated the earlier findings of Blodgett, McCutchan, and Mathews (1949) and Skinner *et al.* (2003) that rats started from a single location on a surface had difficulty solving a place problem when the surface was moved a short distance. In fact, three of the six rats in the One Maze group failed to reach criterion. The Two Maze group showed that rats could solve the same place problem over the same short displacement distance if there were two start locations relative to the surface boundary. The Three Maze-Unreliable Start Location group also solved the place problem over the same short displacement distance. The only strategy available to solve this problem was the use of distal cues. In this group when the rat started from a location between two mazes, neither a response nor a direction strategy, nor a response based on surface boundaries such as ‘go toward the center’, permitted a solution (see Figure 2.1C).

The success of rats in the Three Maze-Unreliable Start Location group in going to the correct place using distal cues demonstrates that this solution was available to rats in the One Maze group. The question thus becomes why one group is able to shift from a surface boundary-dominated strategy to a distal cue-dominated strategy. Rats appear to benefit by the extended surface in the Three Maze-Unreliable Start Location group even though they have never traversed that surface in its entirety. They remain on a single plus maze for any given trial.

The critical difference between the single plus maze and the double plus maze configurations of this problem is either the extended surface or the possibility of multiple start locations, relative to the surface of the apparatus. One of these two variables must be contributing to the use of distal cues. In the next experiment we assessed the role of the extended surface *per se* in place problem solution dependent on the use of distal cues.

### 2.3. Experiment 2

In Experiment 2, a Three Maze-One Start Location group was added. This group was used to determine whether the Three Maze-Unreliable Start Location group successfully used distal cues because of the extended surface or because of multiple start locations. For the Three Maze- One Start Location group an extended surface was employed, but the rat’s start location relative to surface boundaries was invariant. The three mazes were displaced by the same distance from trial to trial such that the rat started from the two distal cue-defined locations used for previous groups.

If the rats benefited from the extended surface in solving the place problem in the earlier Two Maze and Three Maze groups, then the Three Maze-One Start Location rats should successfully solve the place problem. If the Three Maze-One Start Location rats are unsuccessful, as were the One Maze rats, this would suggest that the perception of multiple start locations relative to the surface was the feature that enabled rats in the previous experiment to use a distal cue strategy.

### 2.3.1. Methods

*Subjects.* Thirty-one naïve, male, Long Evans rats, weighing between 173 g – 223 g at the start of the experiment, were used. Rats were maintained as in Experiment 1.

*Apparatus.* The apparatus was the same as that used in Experiment 1. The training room (850 x 680) had foil covered windows taking up much of the south and west walls. The east wall contained a chalkboard (275 x 180 cm); the north wall contained a door and was lined with cabinets and counters. The northeast corner of the room contained a sink and the south and west walls contained stacks of wooden tables and chairs. In addition, the room contained several wooden stools, a large garbage can, the double plus maze, and the rat racks, which were brought to the room at the start of the first trial of the day. These racks were positioned in front of the tables and chairs that lined the west wall. One of the tables along the south wall held the cages of the group currently being tested while all other rats were left on the racks.

*Training Groups.* Rats were assigned to one of four groups on the basis of body weight and included a One Maze group (n = 8), a Two Maze group (n = 8), a Three Maze-Unreliable Start Location group (n = 8), and a Three Maze-One Start Location group (n =

7). The first three groups were trained as in Experiment 1. For the Three Maze-One Start Location group, the rats always started on the center arm and the three mazes were moved such that the arm varied between the two distal cue-defined start locations as for the other groups (see Figure 2.1D).

*Procedure.* Pre-training procedures, training procedures and criterion levels were identical to Experiment 1. Training was stopped at 300 trials for those rats that did not meet criterion.

### 2.3.2. Results

Rats in the Three Maze-One Start Location and the One Maze groups were impaired relative to the other groups. None of the rats in the One Maze group reached criterion on the place problem. Only one rat in the Three Maze-One Start Location group reached criterion. A one-way ANOVA comparing trials to criterion across groups revealed significant differences among the groups [$F(3,27) = 21.81$, $p < .05$] (Figure 2.3). Follow up Newman-Keuls tests showed that the rats in the Two Maze group reached criterion in fewer trials than the Three Maze-Unreliable Start Location group ($p < .05$), which reached criterion in fewer trials than the Three Maze-One Start Location and One Maze groups ($p < .05$), which did not differ ($p > .05$).

### 2.3.3. Discussion

The comparable performance of the One Maze group and the Three Maze-One Start Location group suggests rats do not use distal cues simply because they have an extended surface. Multiple start locations, as in Experiment 1, did enable the rats to use distal cues. Within the multiple start locations groups, the Two Maze group required fewer trials than the Three Maze-Unreliable Start Location group. The Three Maze-Unreliable Start Location group may have used surface boundaries initially, and then shifted to distal cues, while the Two Maze group could succeed with either strategy. In Experiment 1, these two groups were not significantly different, but trials to criterion showed a similar trend to that seen here.

The data from the Three Maze-Unreliable Start Location condition suggest that rats will shift from a surface location strategy to a distal cue strategy to solve the place problem when surface location is variable and uninformative. Rats do not use a distal cue strategy when an apparently stable start location is available, even though the positional shift of the rat with respect to distal cues is the same (One Maze group or Three Maze-One Start Location group). In the next experiment, we evaluated whether another source of unreliable surface information can induce a strategy shift to distal cues. We gave rats a change in surface texture and assessed whether variable surface texture would induce a strategy shift to distal cues.

### 2.4. Experiment 3

In Experiment 3, all rats were tested on the one maze problem. An Unreliable Surface Texture group was used to assess the hypothesis that an uninformative change in surface texture would induce a shift to distal cues. For this group, when the single plus maze was moved between the two start locations, surface texture changed from rough to smooth in a variable pattern. Two control groups were included. For one control group, the Reliable Surface Texture group, surface texture changed from rough to smooth, if and only if, the start location changed. The second control group was a Constant Surface

Texture group, which was the equivalent of the One Maze group from the previous experiments.

If any surface change is sufficient to promote distal cue use, then rats in the Unreliable Surface Texture group should perform better than rats in the Constant Surface Texture group. On the other hand, if rats in the Unreliable Surface Texture group and rats in the Constant Surface Texture group do not differ, this result, together with the results of the earlier experiments, would suggest location changes with respect to surface boundaries lead to distal cue use, while qualitative changes in surface properties do not promote the use of distal cues.

### 2.4.1. Methods

*Subjects.* Twenty-five naïve, male, Long Evans rats, weighing between 189 g–215 g at the start of the experiment, were used. Rats were maintained as in Experiment 1.

*Apparatus.* The same maze and training room were used as in Experiment 1. All groups were trained on a single plus maze. A wire mesh was placed over the plus maze to create the rough surface texture condition.

*Training Groups.* Rats were assigned to one of three groups on the basis of body weight and included an Unreliable Surface Texture group (n = 9), a Reliable Surface Texture group (n = 8), and a Constant Surface Texture group (n = 8). All groups were trained to locate the food reward in a consistent place with respect to the distal cues (as in Figure 2.1A). For the Reliable Surface Texture group, the surface cues were consistent with respect to maze position (e.g., when the maze was on left, the surface was always rough, and when the maze was on the right, the surface was always smooth or vice versa). For the Constant Surface Texture group, the surface cues were the same regardless of maze position, (e.g., always rough or always smooth) making this group equivalent to the One Maze groups in Experiments 1 and 2. For the Unreliable Surface Texture group, when the maze was on the left, the surface was rough for half the trials and smooth for the other half of the trials. Similarly, when the maze was on the right, the surface was rough for half the trials and smooth for the other half of the trials, making the surface cues uninformative with respect to goal location.

*Procedure.* Pre-training procedures, training procedures and criterion levels were identical to Experiment 1. Training was stopped at 298 trials for those rats that did not meet criterion.

### 2.4.2. Results

A one-way ANOVA comparing trials to criterion across groups revealed significant differences among the groups [$F(2,22) = 11.85$, $p < .05$] (Figure 2.4). The Reliable Surface Texture group reached criterion in fewer trials than the Unreliable Surface Texture and the Constant Surface Texture groups (Newman-Keuls test, $p < .05$), which did not differ ($p > .05$). Five out of nine rats and three out of eight rats failed to reach criterion in the Unreliable Surface Texture and Constant Surface Texture groups respectively.

### 2.4.3. Discussion

An unreliable qualitative change in the surface properties of the plus maze did not promote distal cue use. Rats were sensitive to the qualitative change in surface since the Reliable Surface Texture group readily solved the problem. The Reliable Surface

Texture group readily solved the problem because this task is essentially a conditional discrimination task which is easily solved by rats (Guillamon, Valencia, Cales, & Segovia, 1986; Modo, Sowinski, & Hodges, 2000). The Unreliable Surface Texture group was comparable to the Constant Surface Texture group. Thus, animals do not readily use distal cues to solve a place problem when they start at a single point on surfaces that have either constant or unreliable textures. The failure of random variations in surface texture to promote place learning based on distal cues occurs despite evidence that this type of surface information can modulate hippocampal place fields (Knierim 2002). In conjunction with the results of Experiments 1 and 2, these results suggest variable surface location with respect to surface boundaries has a unique role, relative to other qualitative surface properties, in promoting the use of distal cues.

### 2.5. Summary and Conclusions

The present experiments demonstrate both success and failure to solve a place problem with an identical translational position change. The only difference between failure and success is the existence of multiple start positions when rats are successful. The present experiments replicated the impairment in place learning when a rat's location on the maze apparatus is unaltered, even though its location in the larger environment with respect to distal cues is changed by a 93 cm translation (Experiments 1, 2, and 3). Place learning can occur with the same 93 cm displacement in start locations if both locations are part of a larger apparatus surface consistent with place fields being controlled by apparatus boundaries (Wills, Lever, Cacucci, Burgess, & O'Keefe, 2005) (Experiments 1 and 2). The new finding in the present studies is the demonstration that discriminable, but uninformative, start locations on a larger apparatus also promote place learning (Experiments 1 and 2). Control experiments demonstrated that discriminable, but uninformative surface texture changes do not lead to place learning (Experiment 3), nor do large surfaces in the absence of multiple start locations (Experiments 2).

These experiments replicated the earlier reports of Blodgett, McCutchan, and Mathews (1949) and Skinner *et al.* (2003), which showed impairments in place learning with apparatus translations of 85-122 cm. Similarly, Weisend *et al.* (1995) reported that when a Morris water maze was shifted to a new location in a familiar larger environment, rats navigated relative to apparatus boundaries, not distal cues. It appears that the apparatus surface dominates mapping with small translational distances. If this is the case then the rats in the Blodgett, McCutchan, and Mathews (1949), Skinner *et al.* (2003), Weisend *et al.* (1995), and the present study would be predictably insensitive to the translational change of apparatus location in the room environment.

How does the identification of multiple start points promote distal cue use over the 93 cm translation? It has been suggested that since rotations of distal cues cause most place fields on an apparatus to rotate, distal cues confer direction (Yoganarasimha & Knierim, 2005). I suggest that the identification of multiple start points necessitates different directional information in an egocentric framework, meaning that multiple start points may aid the rats in distinguishing two different path directions to the food relative to its start location. This type of direction information differs significantly from the type of direction information encoded by head direction cells. Head direction cells encode allocentric direction in some global framework. Providing two start locations, as in the present experiments, leads rats to appreciate that there are different directions to the fixed goal. Distal cues are then used to discriminate direction as in the better studied rotational experiments. Larger translations also impose larger directional changes relative to a goal and may modulate distal cue mapping in the same way. This hypothesis predicts that distal cue control will be demonstrable whenever the rat notices a directional change (i.e., a new travel possibility).

This hypothesis also explains why rats in the One Maze group performed so poorly. It is possible that rats in the One Maze group could not appreciate that the goal location was in a different direction from the two start points because the rats may not have realized the maze had moved positions. If rats identify their start points, or at the least obtain their initial orientation from distal cues, rats in the One Maze group would have had great difficulty in noticing that there were two different directions to the goal because there was great overlap in the array of distal cues the rat would have used in discriminating between the two start locations.

# Chapter 3 – Role of the Hippocampal Formation During Place Learning On a Translational Problem

***Author's Note:*** *The logic of this experiment has been questioned as the results seem to be predictable and redundant given the results of the behavioural work presented in chapter two of this thesis. It must be made clear that this experiment was conducted at the same time as Experiment 1. I used behavioural and lesion techniques to answer the same question.*

## 3.1. Introduction

Traditionally, the hippocampus has been known as the neural substrate of the cognitive map (O'Keefe & Nadel, 1978). Evidence for this arises from lesion studies (Compton, 2004; Fremouw, Jackson-Smith, & Kesner, 1997; McDonald & White, 1994), temporary inactivation studies (Chang & Gold, 2003; Packard & McGaugh, 1996), and studies using immunohistochemical techniques looking at cfos and pCREB (Colombo, Brightwell, & Countryman, 2003; Teather, Packard, Smith, Ellis-Behnke, Bazan, 2005). Compelling evidence for cognitive mapping in the hippocampus also comes from cell recording studies that have shown that place cells (cells that fire only when the rat is in a specific place) are located in the hippocampus (O'Keefe, 1976; O'Keefe & Dostrovskey, 1971). It was also shown that place cell firing was controlled by distal cues (O'Keefe & Conway, 1978). In contrast, Knierim and colleagues have shown that the firing of the majority of place cells is determined by the rat's location on an apparatus rather than by the rat's location in the room (Knierim & Rao, 2003; Siegel, Rao, Lee, & Knierim, 2005; Yoganarasimha & Knierim, 2004).

If the suggestion in Chapter 2 is correct, that the existence of multiple start locations with respect to a fixed goal necessitates different direction information, and therefore promotes distal cue use (for orientation), hippocampal lesions should impair place learning on the Two Maze problem (see Figure 2.1B). Hippocampal impairment would provide neurobiological evidence that rats have shifted from a surface boundary to a distal cue dominated strategy. If rats are using a surface boundary dominated strategy (i.e., moving towards the centre of the maze) then lesioned rats might not be impaired.

## 3.2. Methods

*Subjects.* The subjects were 27 naïve, male, Long Evans rats, weighing between 274 g – 316 g at the start of the experiment. Rats were maintained as in Chapter 2, Experiment 1.

*Surgery.* Fifteen rats were given neurotoxic lesions of the hippocampus. Each rat was anaesthetized with an initial dose of Avertin (2 mL/100 g, i.p.), and then placed in a standard stereotaxic instrument in the skull-flat position. Supplements of approximately ¼ of the initial dose of Avertin were given when necessary throughout surgery. An injection of Marcaine (0.2 mL) was given below the surface of the scalp to reduce bleeding during surgery. After the scalp incision was made, six holes were drilled, three over the right hemisphere, and three over the left hemisphere (AP -2.8 and ML +/-2.0; AP -4.2 and ML +/-3.0; AP -5.6 and ML +/-5.0). Bregma was used as the reference point for all drilling and injection sites. N-methyl-D-Aspartate (NMDA) was dissolved in phosphate buffered saline (pH 7.4) at 20 mg/mL. Injection sites, and volumes of NMDA injected are shown in Table 3.1. A 33-gauge cannula was used for the injection, as well as a microinjector instrument. The NMDA solution was injected at a rate of 0.1 μL/min.

The cannula was set in position, and left in place for 30 seconds prior to an injection to allow brain tissue to settle around the cannula. At the end of the injection, the cannula remained in place for an additional 120 seconds before removal to prevent back-flow. This process was repeated for the remaining injection sites. After the injections were completed, the rats were sutured, and placed under a heat lamp until the rats could eat and drink. Eleven rats were sham controls. Five of these rats were given the anaesthetic and nothing else (un-operated controls), and six rats had holes drilled, but no cannula placement, or injections (operated controls) were conducted. All rats were allowed to recover for a one-week period before pre-training began, while remaining on ad libitum food and water.

*Apparatus.* The same maze and training room were used as in Chapter 2, Experiment 1. All groups were trained on the two maze configuration (See Figure 3.1)

*Training Groups.* Rats were assigned to one of two groups on the basis of body weight: a Direction group (n = 13), and a Place group (n = 14). The Direction group contained 5 shams (2 operated; 3 un-operated) and 8 lesions. The Place group contained 6 shams (4 operated; 2 un-operated) and 8 lesions. The Direction group was trained to go in a constant direction (east or west) to find the food reward (See Figure 3.1B), and the Place group was trained to locate the food reward located in a constant place with respect to distal cues (See Figure 3.1A). Both groups were trained using two mazes. The Direction group was included in the present study as a behavioural verification of the effectiveness of hippocampal lesions. It has been shown that hippocampal lesions impair direction learning on a similar task (Stringer, Martin, & Skinner, 2005).

*Procedure.* Pre-training procedures, training procedures and criterion levels were identical to Chapter 2, Experiment 1. Training was stopped at 240 trials for those rats that did not meet criterion.

*Histology.* After behavioural training was completed, each rat was anaesthetized with Avertin (3 mL/100 g, i.p.), and decapitated. The brains were removed, and submerged in 2-methyl butane that had been cooled in a -70°C freezer. The brains were allowed to freeze completely. To verify the extent of the lesions, each brain was cut into 40 μm cryostat sections, and mounted on slides, and stained with cresyl violet. A hippocampal lesion was considered acceptable if more than 50% of the hippocampus was damaged in each hemisphere. A trained observer who was blind to the experimental setup was used to determine the extent of the lesions to reduce experimenter bias.

## 3.3. Results

*Histology Results.* Upon completion of behavioural testing, a blind histological analysis was carried out. Six rats were excluded from the behavioural analysis because the hippocampal damage was restricted to one hemisphere, or because damage was not sufficient. The exclusion of these rats resulted in the following group sizes: Direction group (4 lesions, 5 shams), and Place group (6 lesions, 6 shams).

In the remaining rats, 3 out of 4 and 4 out of 6 rats in the Direction and Place groups respectively had more extensive damage in the dorsal hippocampus than in the ventral hippocampus. All rats had shrinkage of fibers in the fimbria-fornix as well as some or total damage to all subfields of the hippocampus (i.e., CA1 - CA3, DG). There was little damage to adjacent structures, and little or no evidence of damage to overlying cortex. Figure 3.2 is a photograph showing a representative hippocampal lesion.

*Behavioural Results.* Rats with hippocampal lesions were impaired on both the direction and place problems. A two-way ANOVA [Group (sham or lesion) x Problem (Direction, or Place)] comparing trials to criterion revealed significant main effects of Group [$F(1,17) = 42.26, p < .05$], Problem [$F(1,17) = 47.02, p < .05$], and a significant Group x Problem interaction [$F(1,17) = 7.82, p < .05$]. A Newman-Keuls test on the Group x Problem interaction revealed that sham rats reached criterion in fewer trials than lesioned rats on both the Direction and Place problems ($p$'s $< .05$) (Figure 3.3). Lesioned rats trained on the place problem required more trials to criterion than both Direction shams and lesions ($p$'s $< .05$). In fact two of the six lesioned Place rats failed to reach criterion. The Place shams and Direction lesions did not differ on trials to criterion ($p > .05$).

### 3.4. Summary and Conclusions

In the present experiment, the majority of hippocampal lesions were restricted to the dorsal hippocampus. Few studies have shown both ventral and dorsal hippocampal contributions to spatial learning, unless the task was highly sensitive to hippocampal function (Ferbinteanu, Ray, & McDonald, 2003). The majority of the literature has shown the dorsal hippocampus involved in spatial navigation, while lesions to the ventral hippocampus produce no clear spatial deficits (Bannerman, Good, Yee, Heupel, Iversen, & Rawlins, 1999; Long & Kesner, 1996; Moser, Moser, & Anderson, 1993). In view of these studies, behavioural data from rats that had lesions restricted to the dorsal hippocampus (bilateral) were included. Rats with hippocampal lesions were impaired, relative to controls, on both the direction and place problems.

In Chapter 2 it was suggested that the existence of multiple start points promotes distal cue use for orientation. These results provide evidence that rats are not using a surface boundary dominated strategy such as learning to approach the centre of the maze. It is more likely that in the presence of multiple start locations, the rats shift to a distal cue dominated strategy. The impairment in the Place group is consistent with the hypothesis that hippocampal lesions disrupted place learning based on distal cues (Jarrard, 1995; Morris, Garrud, Rawlins, & O'Keefe, 1982; McDonald & White, 1995; Packard & McGaugh, 1996). It is also consistent with the electrophysiological data. The presence of place cells (O'Keefe, 1976; O'Keefe & Dostrovskey, 1971), and the fact that head direction cells provide orientation based on distal cues (O'Keefe & Nadel, 1978; Yoganarasimha & Knierim, 2004), suggested the involvement of hippocampus in this task was predicted. Also, head direction cells are suspected to guide movement on arms of mazes (Dudchenko & Taube, 1997) and possibly modulate place field activity (Yoganarasimha & Knierim, 2004).

Direction learning was also impaired in lesioned rats. DeCoteau, Hoang, Huff, Stone and Kesner (2004) showed an involvement of the hippocampus in working memory for direction information. The present study replicated Stringer, Martin, and Skinner (2005) showing direction and place learning share a common neural substrate. It is possible that direction can be perceived as a crude place problem (always approaching a certain array of cues, such as a specific wall). It is also possible that rats could be using conditional discrimination strategy to solve the direction task (e.g., if starting at A, turn right; if starting at C, turn left), which previous studies (Murray & Ridley, 1999; Sutherland, McDonald, Hill, & Rudy, 1989) have shown to be hippocampal dependent. Rats could also be using a sense of direction that guides path integration (Whishaw, 1998). Recent electrophysiological studies show head direction cells (Leutgeb, Ragozzino, & Mizumori, 2000), and place cells (O'Keefe, 1976; O'Keefe & Dostrovskey, 1971), as well as place-by-direction cells (Cacucci, Lever, Wills, Burgess, & O'Keefe, 2004) are located in the hippocampus. Disrupting these cells may impair place and direction learning. It is possible that these head direction cells, as observed by Leutgeb, Ragozzino, and Mizumori (2000) might be responsible for orientation during initial cognitive map formation, therefore disrupting these cells would explain the impairment observed in the present study.

It is also possible that other brain regions may be responsible for encoding direction information independent of the hippocampus. Head direction cells are found in multiple brain areas including the postsubiculum (Taube, Kesslak & Cotman, 1992; Taube, Muller & Ranck, 1990a; Taube, Muller & Ranck, 1990b), the striatum (Wiener, 1993), the lateral dorsal nucleus of the thalamus (Mizumori & Williams, 1993), the posterior cortex (Chen, Lin, Barnes & McNaughton, 1994), and the anterior thalamic nuclei (Taube, 1995). Also, evidence suggests that the hippocampus is not the only site capable of path integration (Alyan & McNaughton, 1999). These studies suggest that other areas may compensate for the hippocampus when needed. This may explain why, in the present study, all direction rats eventually reached criterion. Further investigation on the convergence of place and direction information in the hippocampus is warranted.

## Chapter 4 – General Discussion

The behavioural and neurobiological evidence in the present thesis are consistent with recent place field data (Knierim & Rao, 2003; Siegel, Rao, Lee, & Knierim, 2005; Yoganarasimha & Knierim, 2005). In those studies, place fields were insensitive to maze translations of 33-120 cm, and were predominantly anchored to the apparatus rather than to the distal cues of the room. In the present experiments, when the maze was translated 93 cm, rats failed to use distal cues to solve the place problem. This failure to solve the place problem was not due to the rats' inability to use distal cues, but rather rats' inability to discriminate between multiple start points. The same 93 cm difference was associated with place learning success when rats had multiple discriminable, even though uninformative, start positions on the apparatus. It was also determined that only local cues that provide positional information aid rats' ability to incorporate distal cues into a cohesive cognitive map. Although apparatus texture changes supported learning, discriminable uninformative textures did not promote distal cue use when the apparatus was translated.

These results replicate earlier behavioural studies that show a local surface boundary dominated strategy with small translational distances (Blodgett, McCutchan, & Mathews, 1949; Skinner *et al.,* 2003; Weisend *et al.,* 1995). If the apparatus surface dominates spatial mapping with small translational distances, then the rats in the studies by Blodgett, McCutchan, and Mathews (1949), Weisend *et al.* (1995), Skinner *et al.* (2003), and the present study would be insensitive to the translational change of apparatus location in the larger room. It is suggested that the overlap of the distal cue array is too great to elicit a change in orientation from the two start locations. Since there is much similarity between the arrays of distal cues, the rat does not realize the maze has changed positions, therefore, the rats fail to receive correct orientation information from the distal cues at the two start positions and the shift to a distal cue strategy is prevented. In contrast, an apparatus rotation causes an immediate change in orientation due to the difference in distal cues, and rats are able to solve the place tasks. This same shift to distal cue use would be predicted with larger translational distances because the larger separation would provide a large noticeable difference in distal cues. With successful orientation, rats appreciate that there are different paths to the goal and are able to solve the place problem.

McDonald and White (1993) developed a task in which two arms on a radial arm maze were available to the rat. One arm was paired with food, while the other arm contained no food. Paired and unpaired arms were separated by at least one other arm. This task was called the Conditioned Cue Preference task. For half of the trials, rats were placed on the paired arm and remained there for 30 minutes. For the other half of the trials, the rats were left on the unpaired arm for 30 minutes. On test day, no food was placed on the maze and rats had free access to both arms for 20 minutes. Time spent in each arm was recorded. The Conditioned Cue Preference paradigm was originally developed to examine the function of the amygdala with respect to stimulus-affect memory, but it could also be used as a behavioural measure of place learning. McDonald and White (1995) used a different variation of the Conditioned Cue Preference task that emulates that of a small translational problem on the radial arm maze. Rats placed at the ends of adjacent radial arms, 50 cm apart, with food on only one of the two arms, did not show a place preference for that arm. Simple placement on the closely spaced arms from the home cage is treated as a single position, and as in the translational experiments in the present studies, is associated with insensitivity to distal cue differences at the two positions. The present experiments demonstrate, however, that when procedures are used that enable rats to identify two positions on the apparatus (multiple discriminable start locations), rats successfully solve the place problem. In the McDonald and White (1995) paradigm two procedures enable the rats to show place preference learning with adjacent arms. These include travelling between food-paired and food-unpaired arms during training (McDonald & White, 1995), or multiple successive arm relocations within a training session (i.e., passive movement) (White & Ouellet, 1997). I suggest, as in the present study, these procedures provide positional information that enables the rat to successfully discriminate between two positions on the apparatus, therefore showing evidence of distal cue use. Similarly, McDonald and White (1995), and White and Ouellet (1997) observed that rats failed to show a place preference when the fimbria fornix was lesioned. The present results, showing that hippocampal lesions disrupt place learning on an apparatus that has multiple discriminable start points, are consistent with these findings. The findings of McDonald and White (1995), White and Ouellet (1997), and the present study, suggest that positional information aids rats' use of distal cues, and further promotes the formation of a cognitive map based on those cues. The use of distal cues is hippocampal dependant, consistent with the view that the hippocampus is the neural substrate for the cognitive map (O'Keefe & Nadel, 1978).

Why do uninformative texture changes not promote distal cue use? It is unlikely that changes in surface textures were not perceptible to the rats because surface texture promoted learning when and only when the surface texture was reliable. The Reliable Surface Texture problem is comparable to a conditional discrimination task. During these tasks, discrimination between surfaces followed by a context specific response is required (e.g., when the surface is rough, turn right; when the surface is smooth, turn left). Conditional discrimination tasks are easily acquired by rats (Guillamon, Valencia, Cales, & Segovia, 1986; Modo, Sowinski, & Hodges, 2000) and insects (Zhang, Bartsch, & Srinivasan, 1996). Rats are successful at most conditional discrimination tasks including ones that involve black/white discriminations (Murray & Ridley, 1999; Sutherland, McDonald, Hill, & Rudy, 1989), brightness of light (Sutherland, McDonald, Hill, Rudy, 1989) and surface textures (sandpaper versus rubber) (Trobaon, Chamizo, & Mackintosh, 1992). In other behavioural paradigms, failure to take notice of surface cues or qualitative changes in the apparatus to solve spatial tasks is not uncommon. Rats fail to take notice of featural information (colour and texture) in experiments of apparatus/room geometry (Cheng, 1986), odour trails on maze surfaces fail to direct choice behaviour in the rat (Olton & Collision, 1979), and in general olfactory cues fail to interfere with the rats spatial navigational abilities (Zoladek, & Roberts, 1978; Maki, Brokofsky, & Berg, 1979). Unlike positional cues (e.g., multiple start points), unreliable surface textures failed to support place learning based on distal cues.

Phylogenetic mechanisms may account for why rats failed to use qualitative changes in surface cues. It has been shown that caching birds rely on global cues to relocate their food, because local cues are unstable, and are susceptible to change (Brodbeck, 1994; Clayton & Krebs, 1994). This same line of reasoning may be applied to rats. In the natural environment, surface textures may not be reliable cues to successfully find food, or return home after an outward journey. It is possible that surface textures are constantly changing, therefore over time, evolutionary mechanisms may have suppressed rats' disposition to use these cues. This is consistent with the view that the environment to which an organism is exposed governs which cues will be used by the organism, and suggests that previous experience may have a fundamental influence over whether local or distal cues are used. Odling-Smee and Braithwaite (2003) took three-spined sticklebacks from unstable river and stable pond habitats. They proposed that since in rivers, the flow of water would render the use of local visual landmarks unreliable, these fish would rely on visual cues less than fish inhabiting visually stable habitats (i.e., ponds). When these fish were trained in a water T-maze, the fish learned at similar rates, but their dependency upon what they used to navigate their environment was different. The fish from the unstable river habitats relied on a turning response and were less affected when the local landmarks were repositioned (having fewer pauses than the pond fish).

How does the identification of two or more start positions on an apparatus trigger the use of distal cues over a 93 cm translational distance? To reiterate, the existence of multiple start locations with respect to a fixed goal necessitates different directional information, and by providing two start locations and a fixed goal, leads the animals to appreciate that there are different directions to the goal. Another view emphasizes the rat's sensitivity to surface or room boundaries. Initially this model was constructed by Wills, Lever, Cacucci, Burgess and O'Keefe (2005) and later extended by Yoganarasimha and Knierim (2005). Wills, Lever, Cacucci, Burgess and O'Keefe (2005) recorded place cells when rats were trained in a square apparatus and then later tested in morphed shapes ranging from a square apparatus to a circle apparatus, with four intermediate shapes that were either more square-like or circle-like. They observed remapping of place fields of 17 out of 20 place cells when the rat was moved from a square or square-like apparatus to a circle or circle-like apparatus. This study provided evidence that rats are sensitive to apparatus or room boundaries. Yoganarasimha and Knierim (2005) extended this model and suggested that this sensitivity to boundaries in combination with the rat's direction sense, which is controlled by distal cues, may drive the firing of place cells. In the One Maze problem with small translations, the rat's position with respect to apparatus boundaries remains unchanged, as does his sense of direction, and the rat fails to solve the place problem. In the Three Maze-Unreliable Start Location problem, the rat's position with respect to apparatus boundaries changes, although its sense of direction remains unchanged. The data suggest that the change in place field firing driven by changes in apparatus boundaries may increase the rat's sensitivity to room boundaries and/or distal cues.

The data from cell recording studies (e.g., Knierim and Rao, 2003), and much of the behavioural data with small translations, suggest that the dominance of the apparatus bound place field map in the hippocampus prevents place solutions, based on a global room framework, to these problems. However, Chai and White (2003) have shown that when the adjacent arm place preference problem is successfully solved it requires an intact hippocampus, consistent with the present lesion results. The hippocampus is also required for solution of a place problem similar to that used in the present task in which distinct start points were provided (Stringer, Martin, & Skinner, 2005). When rats were given distinct start points by a 90° rotation, normal rats were successful, but hippocampal lesioned rats were impaired (Stringer, Martin, & Skinner, 2005). Thus, a change in the hippocampal representation would be predicted to accompany instances of successful place learning with small translational movements of an apparatus, possibly observed in the remapping of place fields when the rats alternated between the two discriminable start positions. However, Knierim (2002) suggested two independent hippocampal representational systems. Knierim (2002) observed that when local cues were rotated in opposition to distal landmarks (mismatched trials), a subset of place fields followed local cues, and another subset of place fields (simultaneously recorded) followed distal cues. Given these findings I would predict that when rats are successful at the small translational place problem a larger proportion of place fields are being controlled by distal cues than by local cues. Further exploration of translational behavioural tasks should illuminate the relationship between hippocampal representations and behavioural solutions of hippocampal-dependent place problems.

## 4.1. Future Directions

The traditional view of cognitive maps (O'Keefe & Nadel, 1978) has been given a simplistic characterization by many investigators over the years. It states that an animal can enter a room and encode the relationships between cues in the environment and form a cohesive cognitive map of every point in space in a single experience. This is unlikely given the present results. The present research clearly supports the existence of cognitive maps, but how a rat reaches that point at which it has a complete map, in terms of a global map, was the main focus of this thesis. A rat may over time develop a global map of its environment, but it is unlikely that the rat encodes information in terms of a global framework from the beginning. It is suggested that with very little experience and little information, such as what is provided with small translations, rats do not have a detailed cognitive representation of their environment. It is likely rats have a surface boundary dominated strategy, and use an apparatus map (e.g., a local map) to navigate (see Skinner *et al.*, 2003). Rats form a more global map if and only if there are elements in the environment, more specifically positional cues, which necessitate the use of distal cues. The present research shows that the presence of multiple discriminable start points on a surface is one of the elements of the environment that encourages the use of distal cues and the formation of a cognitive map. A change in orientation is suspected to be another element that may encourage the use of distal cues. The interaction between multiple start points and orientation needs to be further examined. Although multiple start points aid rats' use of distal cues, is it the only thing that can promote distal cue use? Previous literature would suggest not. McDonald and White (1993) showed that normal rats acquired a place preference when the arms were separated greater than or equal to a 90° change in orientation. Later, using the same paradigm, McDonald and White (1995) showed that normal rats do not show a place preference when using adjacent arms and a 45° change in orientation. These studies suggest that if a change in orientation is large enough, perhaps even without multiple start locations, rats will shift from a surface boundary to a distal cue dominated strategy.

Other questions that arise from this work concern the view of the room. Is it simply just orientation, or does the view of the distal cues matter? Typically a rat on a maze has a view of one array of distal cues (e.g., east wall) and when the maze is rotated 90° the rats gets another view of a completely different array of distal cues (e.g., north wall). What would happen if the 90° rotation occurred where the two start positions were facing the same array of distal cues (e.g., facing the same wall)?

It appears that much work is needed to completely understand the interaction between location on an apparatus and location in the room. Many things need to be considered (e.g., multiple start points, orientation, and view of the room) before a more complete theory of cognitive map formation is formulated.

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Table 3.1:

*Stereotaxic coordinates (in mm) with Bregma as a reference point and injection volume of NMDA*

| A-P | M-L | D-V | Volume |
|---|---|---|---|
| -2.8 | 2.0 | -3.4 | 0.4 µL in 4 min. |
| -2.8 | -2.0 | -3.5 | 0.4 µL in 4 min. |
| -4.2 | 3.0 | -3.4 | 0.4 µL in 4 min. |
| -4.2 | -3.0 | -3.5 | 0.4 µL in 4 min. |
| -5.6 | +/- 5.0 | -7.5 | 0.25 µL in 2.5 min. |
| -5.6 | +/- 5.0 | -6.2 | 0.20 µL in 2 min. |
| -5.6 | +/- 5.0 | -5.1 | 0.15 µL in 1.5 min. |
| -5.6 | +/- 5.0 | -4.3 | 0.10 µL in 1 min. |

Figure Captions

*Figure 2.1. A* shows the location of the plus maze for the two different trial types in the One Maze group. The rats in this group had one start location relative to the surface of the apparatus but two start locations relative to distal cues in the room. X indicates the location of the goal and A, B, C, D indicate start arms. The arrows show the correct response to locate the goal and the circles indicate the presence of food cups. Half the rats started at A and B, while the other half started at C and D. *B* shows the location of the double plus maze for the two trial types for rats in the Two Maze group. Rats in this group had two start locations relative to the surface of the apparatus and relative to distal cues. *C* shows the location of the apparatus for two of the four possible trial types for rats in the Three Maze-Unreliable Start Location group. When rats were started at position A, the extension was on the left for half the trials and on the right for half the trials. In both cases, the correct response was a right turn. Similarly, when the rats were started at position B (not shown), the extension was on the left for half the trials and on the right for half the trials. In both cases, the correct response was a left turn. *D* shows the location of the apparatus for the two trial types for rats in the Three Maze-One Start Location group. The rats in this group had one start location relative to the surface of the apparatus but two start locations relative to distal cues in the room.

*Figure 2.2.* Mean (+SEM) trials to criterion (18/20) for rats trained on the One Maze, Two Maze and Three Maze-Unreliable Start Location problems in Chapter 2, Experiment 1.

*Figure 2.3.* Mean (+SEM) trials to criterion (18/20) for rats trained on the One Maze, Two Maze, Three Maze-Unreliable Start Location and Three Maze-One Start Location problems in Chapter 2, Experiment 2.

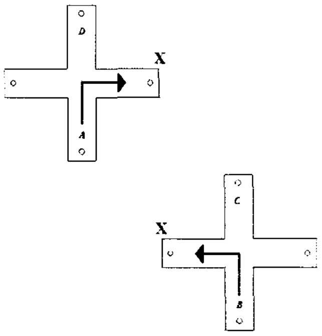
*Figure 2.4.* Mean (+SEM) trials to criterion (18/20) for rats trained on the Constant Surface Texture, Reliable Surface Texture, and Unreliable Surface Texture problems in Chapter 2, Experiment 3. All groups were trained on the One Maze place problem.

*Figure 3.1. A* shows the location of the plus maze for the two different trial types in the Place group. Rats in this group had two start locations relative to the surface of the apparatus and relative to distal cues. X indicates the location of the goal and A, B, C, D indicate start arms. The arrows show the correct response to locate the goal and the circles indicate the presence of food cups. Half the rats started at A and B, while the other half started at C and D. *B* shows the location of the apparatus for two trial types for rats in the Direction group. In both cases, the correct response was to go east. Half the rats started at A and C (go east), while the other half started at B and D (go west; not shown)

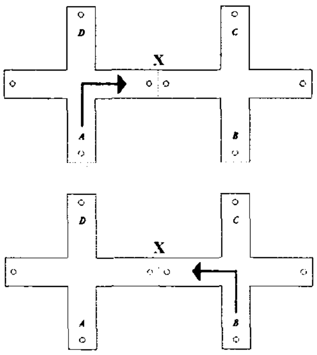
*Figure 3.2.* Representative Hippocampal lesion from Chapter 3.

*Figure 3.3.* Mean (+SEM) trials to criterion (18/20) for rats trained on the Two Maze and Direction problems in Chapter 3. Shams and Hippocampal Lesions are indicated as black and white respectively.

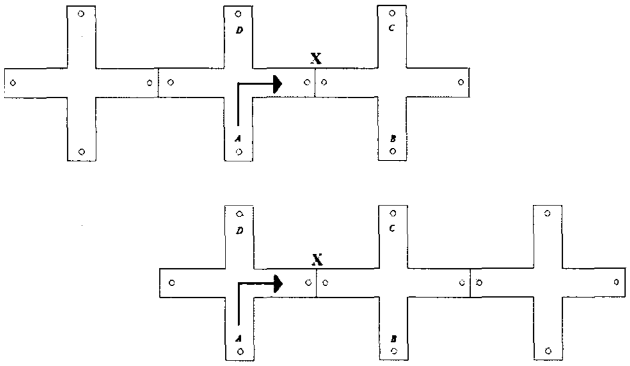
A. One Maze Group



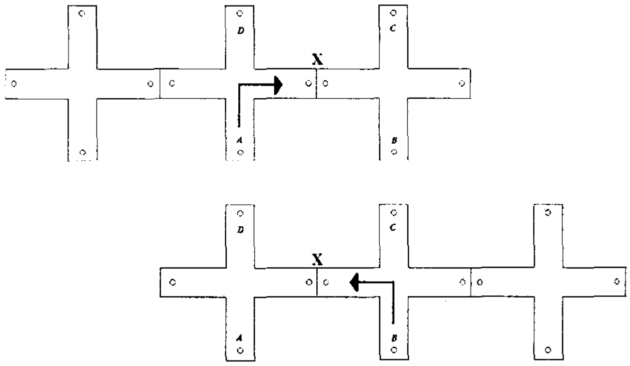
B. Two Maze Group

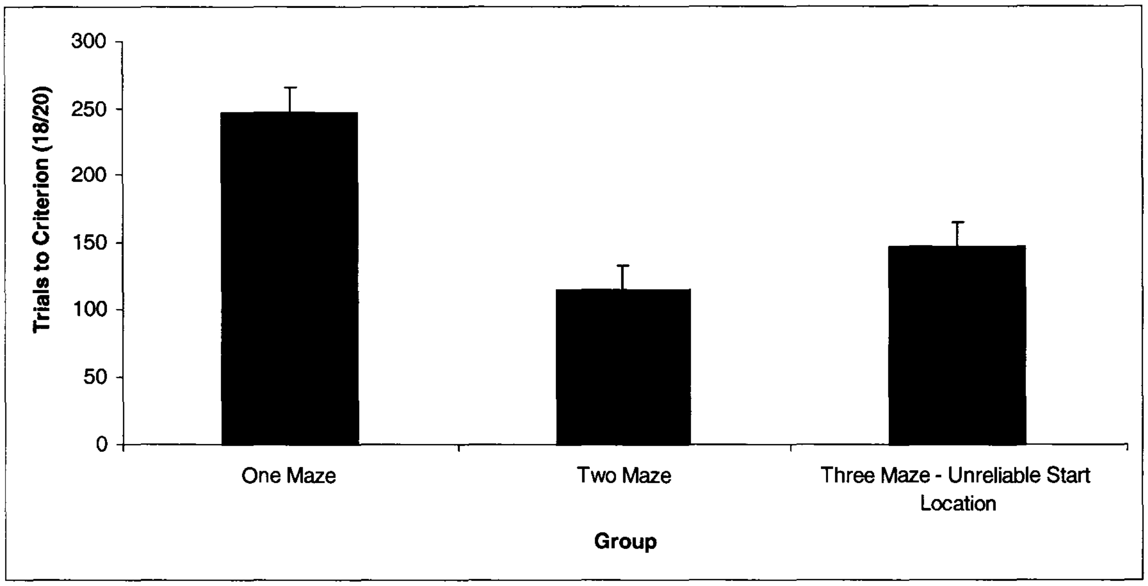


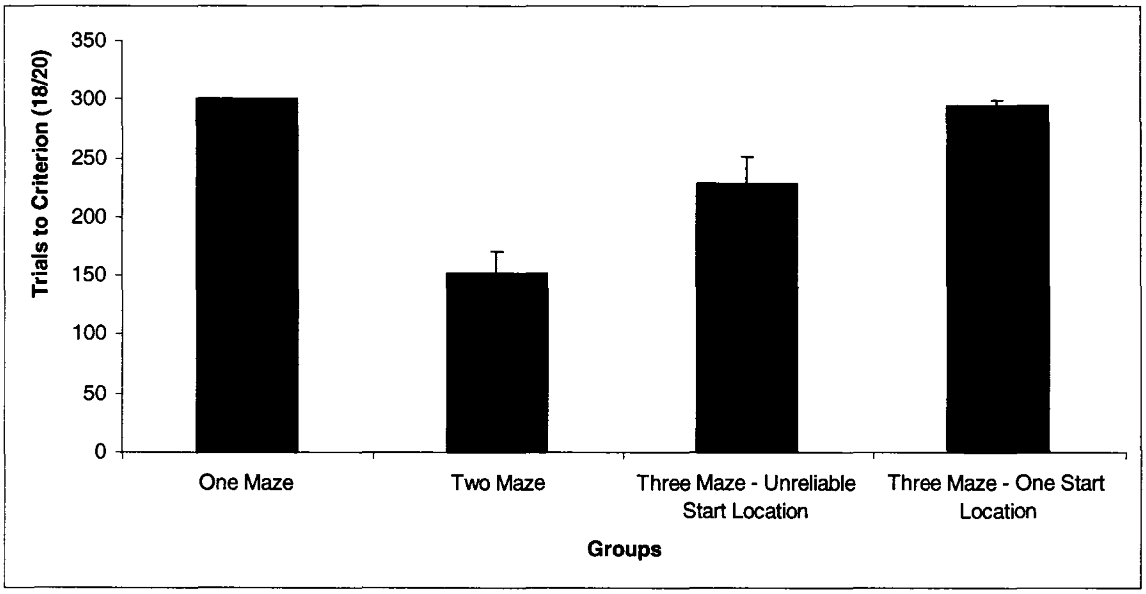
C. Three Maze - Unreliable Start Location Group

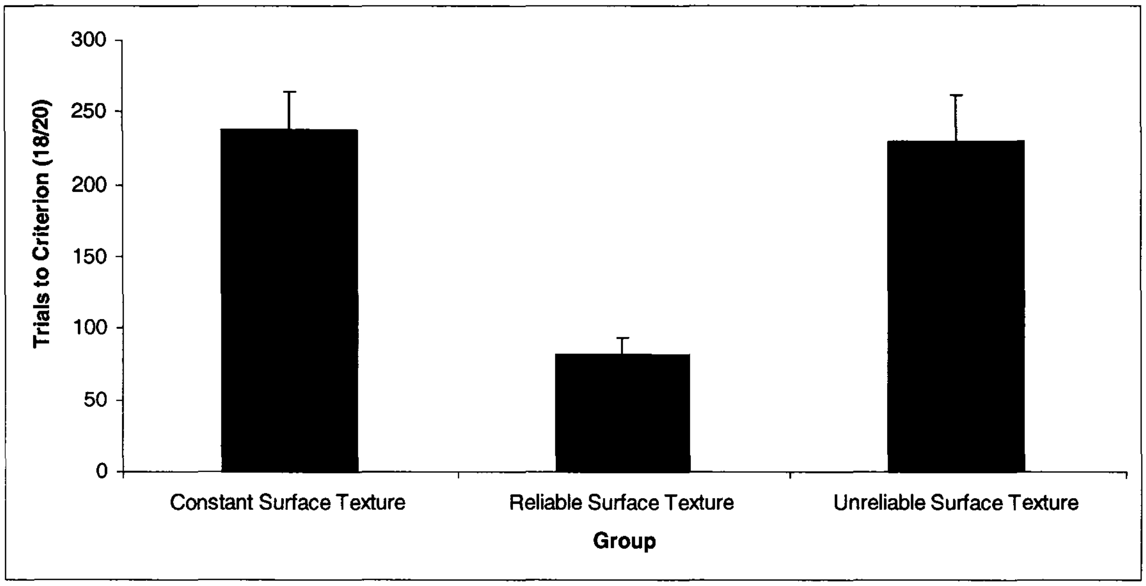


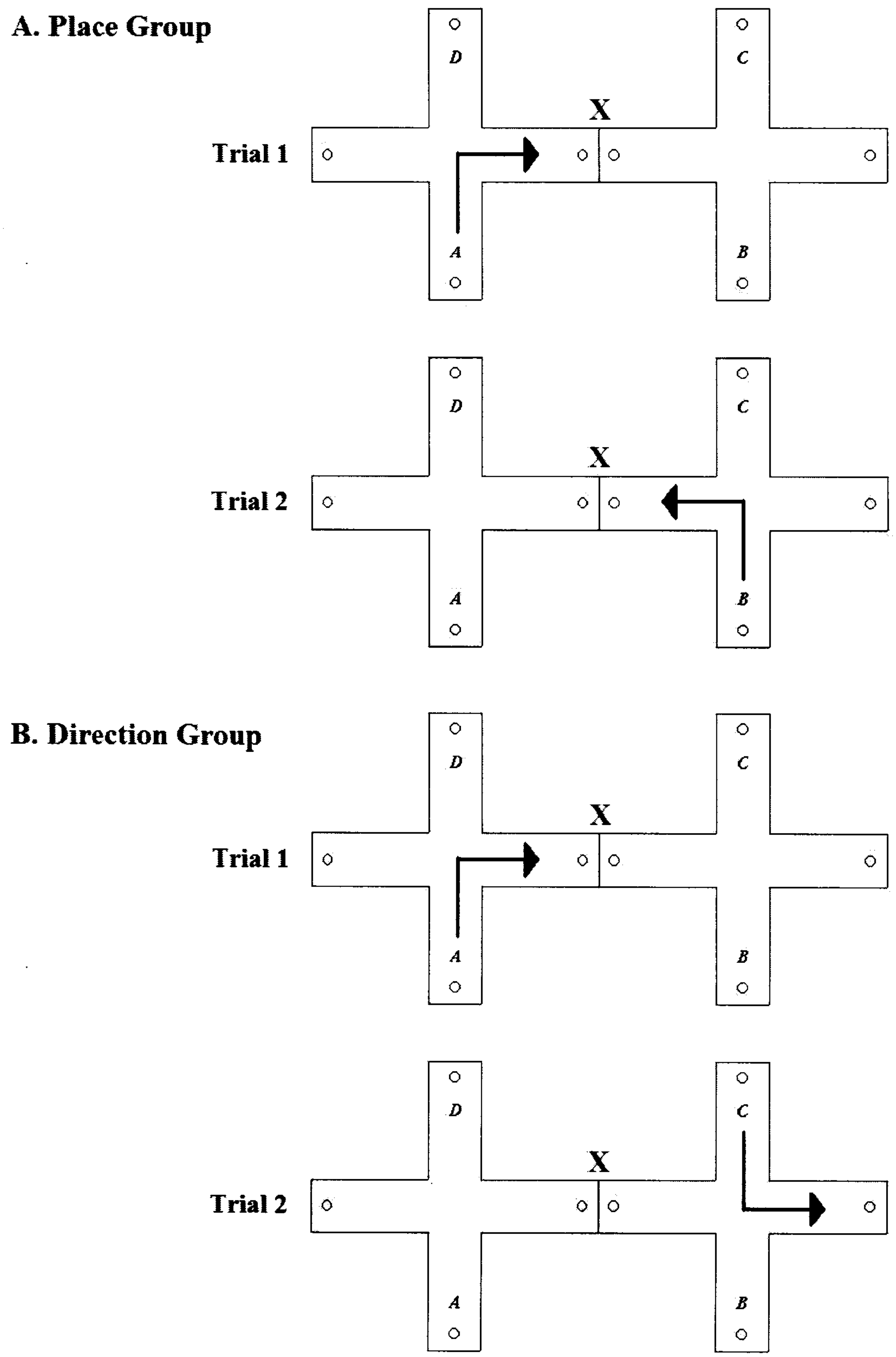
D. Three Maze - One Start Location Group

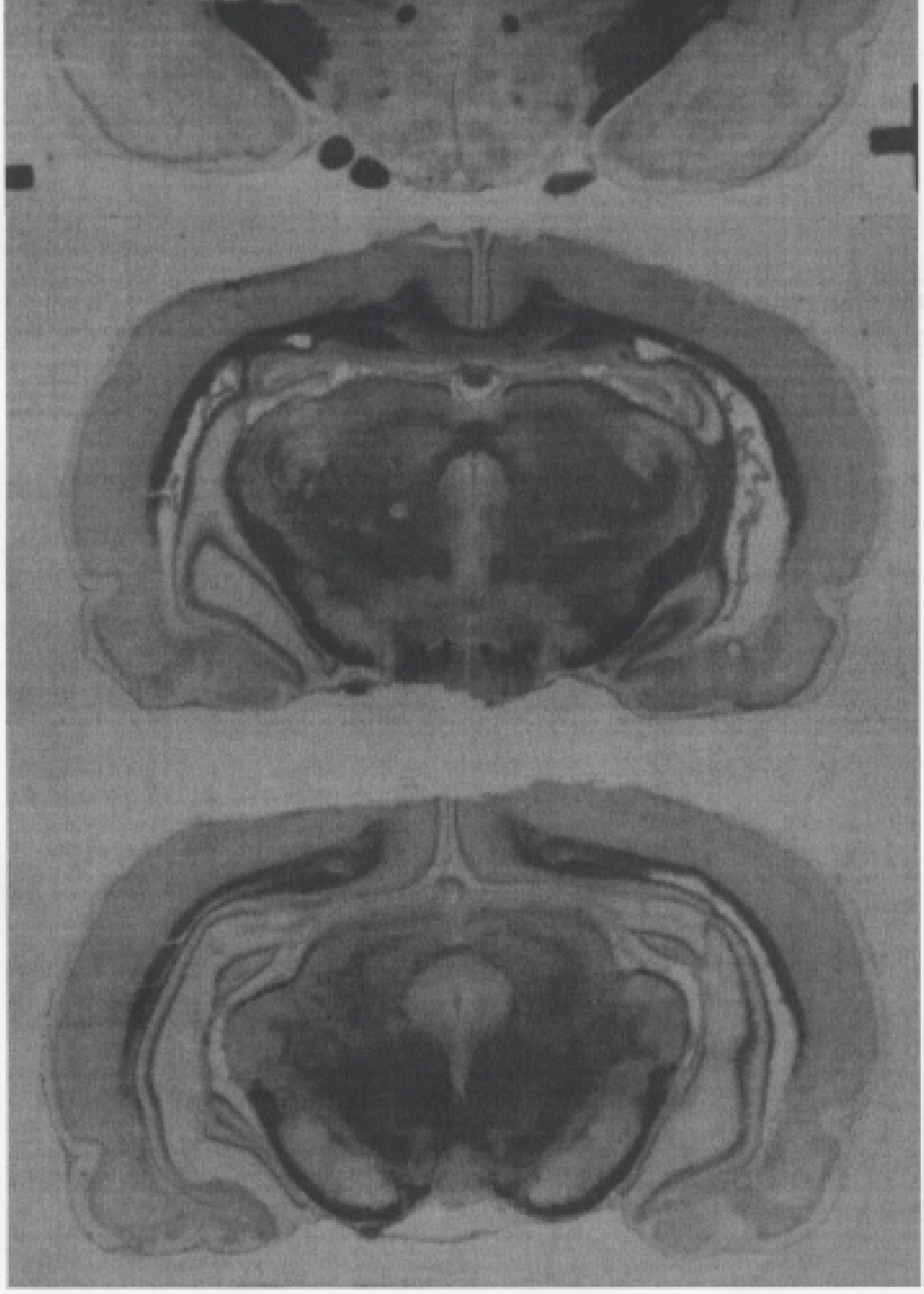


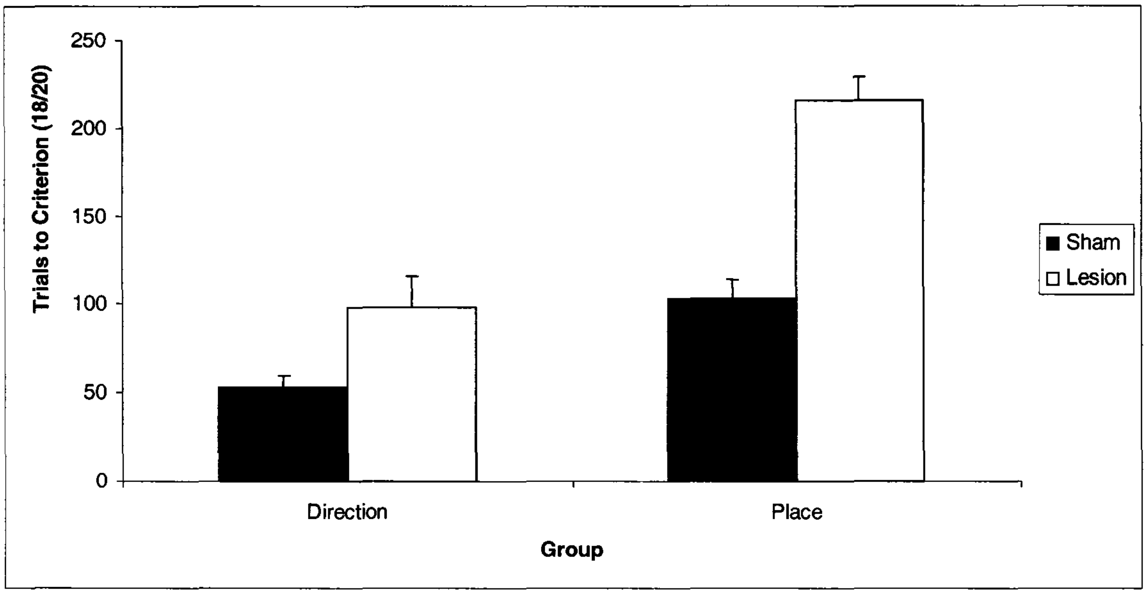

Trials to Criterion (18/20)
300
250
200
150
100
50
0
One Maze
Two Maze
Three Maze - Unreliable Start Location
Group


Trials to Criterion (18/20)
350
300
250
200
150
100
50
0
One Maze
Two Maze
Three Maze - Unreliable Start Location
Three Maze - One Start Location
Groups


300
250
200
150
100
50
0
Trials to Criterion (18/20)
Constant Surface Texture
Reliable Surface Texture
Unreliable Surface Texture
Group


A. Place Group
Trial 1
D
C
X
A
B
Trial 2
D
C
X
A
B
B. Direction Group
Trial 1
D
C
X
A
B
Trial 2
D
C
X
A
B




Trials to Criterion (18/20)
250
200
150
100
50
0
Direction
Place
Group
■ Sham
□ Lesion