Recovery of Spatial Performance in the Morris Water Maze Following Bilateral Transection of the Fimbria/Fornix in Rats

by

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We accept this thesis as conforming to the required standard

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Abstract

A considerable body of research implicates the hippocampus in spatial cognition. In particular, lesion studies have shown that damage to the various components of the hippocampal system (including the hippocampus proper, dentate gyrus, entorhinal cortex, subiculum, and fimbria/fornix [FF]) produces deficits on a wide variety of spatial tasks. However, an increasing number of studies have also shown that, in some instances, spatial performance recovers after subtotal lesions to the hippocampal system. This suggests that considerable capacity for spatial cognition may recover or persist following such lesions. The present study sought to determine whether spatial performance in the Morris water maze (MWM) recovers after bilateral transection of the FF in rats, whether such recovery results from restored or residual spatial cognitive capacity, and what contribution, if any, pre-operative training makes to such recovery. Rats were administered extensive training to a constant submerged platform location with probe tests utilized frequently to assess performance strategies. Following the attainment of asymptotic performance levels, rats were tested for acquisition of a subsequent platform location. FF lesions were found to produce a severe impairment both in pre-operatively trained rats (a retention or retrieval deficit) and in naive rats (an acquisition deficit) as shown by the use of indirect routes to the platform on submerged platform trials and an absence of localized searching in the platform's area on probe trials. However, with extensive training, performance recovered in both groups, such that they eventually used direct escape routes to the submerged

platform and showed highly localized searching in its area on probe trials. When tested for acquisition of a second platform location, a substantial deficit reappeared which was again followed by recovery with extensive training. Pre-operative training was found to attenuate the initial post-operative deficit and speed recovery but did not affect asymptotic performance levels nor acquisition of a subsequent platform location. These data show that, though spatial cognition is impaired, spatial performance in the MWM eventually recovers after FF lesions and pre-operative training, though perhaps initially beneficial, is not essential for this recovery. The deficit shown in acquisition of the second platform location argues against the occurrence of recovery of spatial cognition and suggests that the basis of recovered performance is residual spatial cognitive capacity which has the following limitations: i) rate of acquisition of spatial information is reduced, ii) utilization of spatial information stored pre-operatively is restricted, and ii) translation of spatial information into navigational behaviour is less efficient. The neural bases of this residual system are speculated to include spared intra-hippocampal storage mechanisms and/or mechanisms involved in extra-hippocampal long-term memory consolidation while the neural bases of the FF's contribution to spatial information storage in the intact brain are speculated to involve theta synchronization of hippocampal activity and the induction and expression of hippocampal long-term potentiation.

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Introduction

The hippocampus has been associated with mnemonic functions for almost forty years, since Scoville and Milner (1957) first reported the case of H.M. H.M. was a man in his late twenties who had undergone bilateral temporal lobe resection, which included both hippocampi, to treat intractable epilepsy. He subsequently exhibited a profound amnesic syndrome which Scoville and Milner attributed to hippocampal damage since other patients who had undergone similar procedures, with the exception that their hippocampi were substantially spared, failed to show any notable memory disturbance. Though infrequent, subsequent reports of patients with hippocampal pathology have supported a role for the hippocampus in learning and memory processes (Grabowska, Luczywek, Fersten, Hermsaan, & Szatkowska, 1994; Sass, Spencer, Kim, Westerveld, Novelly, & Lencz, 1990; Zola-Morgan, Squire, & Amaral, 1986). More important, however, are the animal data which now overwhelmingly suggest that the hippocampus plays a role in at least a subset of mnemonic functions (see Eichenbaum, Otto, & Cohen, 1992; Squire, 1992 for reviews).

Spatial Cognition

A landmark in the attempt to define the type of memory supported by hippocampal function was the cognitive mapping hypothesis of O'Keefe and Nadel (1978). In their treatise entitled The Hippocampus as a Cognitive Map, they synthesized a diverse set of findings into a coherent, plausible, and readily testable hypothesis which stated that the hippocampus plays an essential role in spatial cognition. Spatial cognition was defined as a variety of mental operations necessary for the processing, storage, retention, retrieval,

and utilization of information pertaining to space as defined by allocentric (viewer-independent) relationships among elements within an environment. An important distinction is made between space defined in this manner and space defined by egocentric relationships to the environment, such as position relative to a single cue or body orientation, since the latter do not require the hippocampus for cognitive processing.

The basis for much of O'Keefe and Nadel's hypothesis (1978) was derived primarily from two observations, both obtained with rats. The first was that certain hippocampal neurons, coined "place cells", fired preferentially in response to different locations within a particular environment (O'Keefe, 1976; O'Keefe & Dostrovsky, 1971). These "place cells" were immediately recognized as a potential mechanism for the encoding of spatial information in the hippocampus. The second important observation was that hippocampal lesions impaired performance on tasks requiring the use of allocentric spatial information (*e.g.*, Hsiao & Isaacson, 1971; O'Keefe, Nadel, Keightley, & Kill, 1975). Both of these lines of evidence continue to play an important role in characterizing the hippocampus' role in spatial cognition (see O'Mara, 1995 for a review of place cell studies and Barnes, 1988 for a review of lesion studies).

Though it now appears that the hippocampus may have a more general role in mnemonic functions than originally hypothesized by O'Keefe and Nadel (Eichenbaum et al., 1992; Squire, 1992; Sutherland & Rudy, 1989), considerable evidence has accumulated suggesting that, especially in rodents, the hippocampus does indeed play a crucial role in spatial cognition (see Barnes, 1988 for a review). Furthermore, it has been suggested that even if spatial cognition does not represent the hippocampus' sole function,

it is at least a particularly good example of what function the hippocampus does perform (Eichenbaum et al., 1992).

The goal of the experiment underlying my thesis is to further our understanding of the hippocampus' role in spatial cognition by studying the effects of lesions to an important hippocampal input and output pathway, the fimbria/fornix, on spatial cognition. However, in contrast to the more usual rationale behind lesion experiments, which is to demonstrate a deficit and make inferences about functions of the lesioned structure (see Olton, 1986), the rationale behind the present experiment was to investigate behavioural recovery in order to make inferences about recovered or residual functions of the remaining brain. The difference between these approaches is captured in the distinction between asking "what can the brain *not* do after damage to X" and "what can the brain *still* do after damage to X".

The remainder of this introduction will concentrate mostly on a discussion of deficits and recovery on tasks which have been used to assess spatial cognition following hippocampal lesions. However, before briefly reviewing this literature, it is worthwhile to examine some basics of hippocampal anatomy. Lesions which are called "hippocampal" vary considerably both in their location and extent and may produce behavioural effects which are dependent upon this variation (see Jarrard, 1991).

Anatomy of the Hippocampal System

The hippocampus[1] forms part of a closely associated group of cortical structures commonly referred to as the hippocampal formation (HF) (Amaral & Witter, 1989; Swanson, Köhler, & Björklund, 1987). These include the hippocampus proper (which can be divided into three regions - CA1, CA2, and CA3), the dentate gyrus, the entorhinal cortex, and the subiculum. Within these structures is contained the classic hippocampal tri-synaptic circuit which consists of connections from: 1) the entorhinal cortex to the dentate granule cells via the perforant path, 2) the dentate granule cells to the CA3 pyramidal cells via the mossy fibres and, 3) the CA3 pyramidal cells to the CA1 pyramidal cells via the Schaffer collaterals. In addition to this circuit, the HF contains a substantial projection from the CA1 pyramidal cells and the subiculum back to the entorhinal cortex via the perforant path.

The HF also has widespread extrinsic connections to a variety of cortical and subcortical structures (Amaral & Witter, 1989; Sakanaka, Shiosaka, Takagi, Senba, Takatsuki, Inagaki, Yabuuchi, Matsuzaki, & Tohyama, 1980; Swanson et al., 1987). The cortical connections represent a diffuse set of largely reciprocal projections between diverse areas of association cortex[2] and both the entorhinal cortex and subiculum. These projections are thought to have particular significance in the HF's mnemonic functions

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[1] The term "hippocampus" is often used to refer to the dentate gyrus and hippocampus proper collectively. I will also employ this usage in my thesis.

[2] The major exception is that of direct input from the olfactory system. At one time, this lead to the belief that the HF functioned primarily as olfactory association cortex.

since they provide hippocampal access to complex multimodal perceptual information (Squire, 1992). The HF's subcortical connections are contained primarily in a large, discrete bundle of fibres called the fimbria/fornix (FF). Hippocampal afferents originate in the diagonal band/medial septum, hypothalamic nuclei, substantia inominata, anterior thalamic nuclei, and monoaminergic brainstem nuclei including the raphe nuclei and the locus coeruleus, and project to the dentate gyrus, all CA cell fields, and the subicular complex. Hippocampal efferents originate largely from CA3 and subicular neurons and project to the lateral septum, mammillary nuclei, nucleus accumbens, hypothalamic nuclei, and both the anterior and midline thalamic nuclei. The FF is generally considered to be important in providing the hippocampus with information regarding the emotional or motivational significance of stimuli or events (Swanson, 1983).

The individual components of the HF as well as their subcortical connections via the FF, which collectively I will refer to as the hippocampal system (see Becker, Walker, & Olton, 1980 or Olton, Walker, & Wolf, 1982 for similar usage of this term), have all been implicated in spatial cognition by lesion studies[3] (see Barnes, 1988 for a review).

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[3] The cortical connections of the HF have not been directly linked to spatial cognition by lesion studies primarily because such a diffuse set of fibres is very difficult to selectively lesion. Indirect evidence for their importance, however, comes from observations that lesions to the perirhinal cortex, one of the HF's major cortical connections, disrupt spatial cognition (Wiig & Bilkey, 1994a; 1994b).

Performance of Spatial Tasks after Hippocampal System Lesions

Deficits

Two of the most commonly used tasks to assess spatial cognition after hippocampal system lesions are the Morris water maze (MWM) and the radial-arm maze (RAM). Therefore, much of my discussion will focus on these two tasks.

Morris Water Maze. In the MWM[4], the subject (usually a rat or mouse) is required to escape onto a submerged platform located in a constant position within a pool filled with cool, opaque water (Morris, 1984; 1981). Because no local cues mark its presence, the platform is most efficiently located by its position relative to extra-maze cues, a process which requires spatial cognition (Nadel, 1991). Performance in the MWM is impaired by lesions to the dentate gyrus (Sutherland, 1985; Whishaw, 1987), CA1 (Obata, 1994; Olsen, Scheel-Kruger, Moller, & Jensen, 1994), CA3 (Whishaw, 1987), hippocampus (Bolhuis, Stewart, & Forrest, 1994; Morris, Garrud, Rawlins, & O'Keefe, 1982; Morris, Schenk, Tweedie, & Jarrard, 1990), entorhinal cortex (Nagahar, Otto, & Gallagher, 1995; Schenk & Morris, 1985), subicular complex (Bolhuis et al., 1994; Morris et al., 1990), PP (Skelton & McNamara, 1992a), or FF (Sutherland & Rodriguez, 1989; see also Brandeis, Brandys, & Yehuda, 1989 for a review of lesion effects on MWM performance).

Radial-Arm Maze. In the standard version of the RAM, the subject is required to choose among arms which radiate from the centre of a choice area to obtain appetitive

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[4] The procedure described constitutes the standard spatial version of the MWM (often called place learning). Note that alternative configurations of the pool can be used to assess both non-spatial performance and different types of spatial performance.

rewards located at the end of each arm (Olton & Samuelson, 1976). On each trial, the rat is allowed to explore until all the rewards present have been obtained or until a specified duration has elapsed. Accurate performance demands that the subject choose correctly between arms that have already been visited and those that have not. Since no local cues differentiate the arms, their location relative to extra-maze cues provides the basis for correct discriminations. Similar to findings obtained in the MWM, RAM performance is impaired by lesions to the dentate gyrus (Jarrard, Okaichi, Steward, & Goldschmidt, 1984b), CA1 (Jarrard, 1978), CA3 (Handelmann & Olton, 1981), hippocampus proper (Jarrard, 1993), entorhinal cortex (Hölscher & Schmidt, 1994; Olton et al., 1982), or FF (Jeltsch, Cassel, Neufang, Kelche, Hertting, Jackisch, & Will, 1994; Olton, Walker, & Gage, 1978).

Other Tasks. Other tasks used to assess spatial cognition include delayed-match-to-place, spatial discrimination, and T-maze tasks. Research using these tasks corroborates the above observations that lesions to the various components of the hippocampal system all impair spatial cognition (*e.g.*, Cho & Jaffard, 1994; Fowler & Olton, 1984; Hunt, Kesner, & Evans, 1994; O'Keefe et al., 1975).

Thus, lesion data continue to support O'Keefe and Nadel's hypothesis (1978) that the hippocampus, and indeed the whole hippocampal system, functions in spatial cognition. However, these data do not address whether the hippocampal system or each of its components makes an *essential* contribution to spatial cognition. This question is addressed in studies of recovery on spatial tasks after hippocampal system lesions.

Recovery

If the components of the hippocampal system each make an essential contribution to spatial cognition, then animals with hippocampal lesions should not be able to successfully perform tasks requiring spatial cognition. This prediction can be difficult to assess, however, since most spatial tasks can be performed quite accurately utilizing either spatial or non-spatial strategies, thus making recovery difficult to interpret. Therefore, recovery of performance which is based upon the use of spatial information must be carefully differentiated from that which is based upon non-spatial compensation strategies. To this end, probe tests are employed (where possible) in addition to standard testing procedures to obtain a broader behavioural profile from which inferences about strategies underlying performance can be made with greater confidence (see Olton, 1979 for a discussion of the nature and importance of probe tests).

Increasing evidence suggests that, on some spatial tasks, performance does indeed recover after hippocampal system lesions. Importantly, in many cases, probe trials have been used to confirm that recovered performance is indeed based upon the use of spatial information.

One dimension which may affect whether recovery is observed on a particular spatial task or not may be the sub-type of memory which is required. Some spatial tasks require reference memory, which refers to long-term memory for information which is constant from trial to trial, while others require working memory, which refers to short-term memory for information which is trial-specific (see Honig, 1978 for an eloquent discussion of this classification of memory functions). Recovery following hippocampal

system lesions is observed more often and more consistently on tasks which demand reference memory.

MWM. The MWM is classified as a reference memory task since the goal, escape to a single platform in a fixed position, remains constant within a trial and between trials. Recovery on this task has been observed following lesions to the hippocampus (Morris et al., 1990), entorhinal cortex (Schenk & Morris, 1985), subiculum (Bolhuis et al., 1994; Morris et al., 1990), perforant path (Skelton & McNamara, 1992b), or CA1 (Obata, 1994), though in most cases only after extensive training. One of the advantages of the MWM is that it can be readily configured for probe trials by simply removing the platform (or lowering it to the bottom of the pool). The extent to which the subject shows localized searching in the platform' location, then, provides a sensitive assay for determining whether a spatial strategy is indeed guiding performance. In the case of each of the above studies, probe trial data provided important evidence that recovery depended upon the use of a spatial strategy to locate the platform. Interestingly, recovery has not been observed in the MWM following more extensive lesions to the hippocampal system, such as those including both the entorhinal cortex or hippocampus and subicular complex (Morris et al., 1990; Schenk & Morris, 1985), or after lesions to the FF (Nilsson, Shapiro, Gage, Olton, & Björklund, 1987; Sutherland & Rodriguez, 1989). Recovery, or the absence of recovery, in the MWM after FF lesions is of special interest and will be dealt with in more detail below.

RAM. The standard version of the RAM assesses spatial working memory since, within each trial, different responses (either approach or avoidance) are required to each

arm depending upon whether or not the bait contained in that arm has already been obtained. On this version, recovery has been observed following lesions of the hippocampus (Gage, 1985), CA1 (Jarrard, 1978), or CA3 (Handelmann & Olton, 1981). The RAM can also be configured to assess both working and reference memory simultaneously by leaving half of the arms unbaited. Unbaited arms, then, test reference memory, since they require the same response throughout every trial (avoidance), while baited arms, as in the standard version, test working memory. On this version, recovery on both components has been observed following lesions to the dentate gyrus (Jarrard et al., 1984b), or hippocampus (Jarrard, 1986), while recovery, primarily restricted to the reference memory component, has been observed following lesions of the FF (Jarrard, Kant, Meyerhoff, & Levy, 1984a; Olton & Pappas, 1979).

Other Tasks. Recovery on a number of other spatial tasks has been observed following lesions to the hippocampal system. Hunt and colleagues (1994) utilized a modified RAM task in which only a single arm was baited. In the reference memory version, this arm remained constant from trial to trial while in the working memory version, this arm changed after every pair of trials[5]. Following lesions to the hippocampus, recovery was observed on the reference memory version but not on the working memory version. Olton and colleagues (Becker & Olton, 1981; Becker et al., 1981; Walker & Olton, 1984) utilized a set of spatial discriminations which assessed

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[5] This two-trial procedure is an example of a delayed-match-to-place task. On the first trial the rat is forced to choose a particular arm. On the second trial the rat must return to the previously chosen arm to obtain a reward.

spatial reference memory. These problems consisted of appetitively motivated discriminations between otherwise like objects based upon their location in an open field. With extensive training, rats with FF lesions showed recovery to criterion performance levels. Importantly, performance on probe trials, which consisted of releasing the rat from a novel start location, suggested that similar spatial strategies underlay accurate discriminations by both lesioned and intact rats.

Recovery of Spatial Performance in the MWM after FF Lesions

Unlike the results obtained after lesions to other components of the hippocampal system, results in the MWM following FF lesions have been either negative or equivocal with respect to recovery. For example, in a number of studies (Pitsikas, Spruijt, Josephy, Algeri, & Gispen, 1991; Segal, Greenberger, & Pearl, 1989; Tarricone, Keim, Simon, & Low, 1991), FF lesioned rats have shown little improvement in finding the submerged platform and no localized searching in the platform's location on probe trials. In some cases, similar results have been obtained even after extensive training (Li, Simon, & Low, 1992; Nilsson et al., 1987). More equivocal results were obtained by Sutherland and Rodriguez (1989) who found that FF lesioned rats showed considerable improvements in latency to locate the submerged platform, but did not show disrupted performance when the platform's location was reversed (*i.e.*, moved to the diagonally opposite location in the pool). Therefore, the authors concluded that improvements in performance were based upon the utilization of an effective non-spatial search strategy which entailed circling the pool at a specific distance from the pool wall. This strategy would allow the platform to be located equally well in any location of the pool so long as it remained a constant

distance from the wall (which, in their study, it did). Unfortunately, probe trials, which could have provided more detailed evidence for dissociating solution strategies, were not utilized.

Some positive evidence for recovery of spatial performance in the MWM after FF lesions was obtained by Eichenbaum, Stewart, and Morris (1990). They found that lesioned rats learned to escape rapidly to the submerged platform and showed spatially biased searching in its location on a probe trial. However, these researchers utilized a number of deviations from standard MWM procedures (*e.g.*, they released the rat from a constant start location and utilized a platform visible above the water's surface on alternating trials). This training protocol may have encouraged rats to use an egocentric *guidance* (O'Keefe & Nadel, 1978) strategy dependent upon an approach or avoidance response to a single cue, rather than an allocentric spatial strategy, since the platform could always be approached using the same trajectory. Therefore, it cannot be said with any confidence that their FF lesioned rats showed true recovery of spatial performance.

Thus, a still unresolved question is - does spatial performance in the MWM recover after FF lesions? This is a particularly important question for a number of reasons. Firstly, as discussed above, recovery of spatial performance in the MWM after FF lesions has not been convincingly demonstrated. If such a finding could not be obtained it would stand in marked contrast to results following lesions to other components of the hippocampal system and could indicate an especially important role for the FF in hippocampal function. This would be surprising given that greater importance is usually attributed to the hippocampus' cortical connections (*e.g.*, Squire, 1992) since these provide

the hippocampus with direct access to multimodal perceptual information with which memories are presumably constructed. Secondly, the MWM is currently the prevailing test of choice for spatial reference memory (Brandeis & Brandys, 1989; McNamara & Skelton, 1993) and any discrepancy between results obtained in the MWM and other tests of spatial reference memory (in which recovery after FF lesions has been observed) would be sufficiently disconcerting to warrant further investigation. Thirdly, the investigation of recovery after FF lesions may be of particular clinical relevance since FF lesions are frequently used as a model to assess interventions with therapeutic potential in the treatment of Alzheimer's disease (Dunnet, 1990). Understanding under what circumstances spontaneous recovery is observed and elucidating its underlying mechanisms may provide insights into the effects of interventions currently studied and may facilitate the development of novel treatment strategies.

My experiment was devised, therefore, to test whether spatial performance in the MWM recovers after FF lesions. I employed a protocol which was designed to enhance the likelihood of both the occurrence and accurate detection of recovery of spatial performance as follows: Prior to any spatial testing[6], I administered visible platform training so rats could acquire some of the procedural components of the task (e.g., successfully mounting the platform) and habituate to the testing apparatus and procedure in general before being confronted with spatial testing. During spatial testing, I

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[6] Spatial testing and hidden platform testing will be used synonymously to refer to the combined use of submerged platform trials and probe trials in the assessment of spatial performance.

administered extensive submerged platform training (four trials per day for 13 days with the platform in a constant location) and frequent "non-extinction" probe trials (see Methods) in order to further assess platform-locating strategies. Importantly, the protocol for submerged platform trials conformed to usual standards (Morris, 1984; 1981) in that varying start positions were used and local cues marking the platform's location were not present on any trial (unlike Eichenbaum et al., 1990). This protocol was most likely to require a truly spatial (*i.e.*, allocentric) strategy for optimal performance. The criteria I utilized to determine spatial performance were those normally employed - 1) direct routes to the platform on submerged platform trials as shown by escape distance and escape latency and, 2) extensive searching in the platform's location on probe trials as shown by percentage of time spent in the platform's quadrant and number of crossings of the platform's exact location (Morris, 1984; 1981).

Two additional questions relating to recovery of spatial performance, if observed, were also addressed. The first concerned the contribution of pre-operative training to recovery. Some evidence indicates that recovery of spatial performance after hippocampal system lesions is restricted to rats receiving training prior to surgery (Gage, 1985; Handelmann & Olton, 1981; Jarrard, 1978; 1993). This suggests that components of the hippocampal system may have an essential role in the storage but not the retention or retrieval of spatial information. Other findings, however, indicate that while pre-operative training may attenuate the initial post-operative deficit and speed recovery, it is not essential for recovery, since rats without pre-operative training also recover (Gage et al., 1983; Morris et al., 1990; Schenk & Morris, 1985). These data suggest that the

components of the hippocampal system do not play an essential role in the storage of spatial information either. Thus, to assess whether the FF has an essential role selective to the storage of spatial information, and to assess the contribution of pre-operative training to post-operative recovery in general, I trained half of my rats until they had acquired the platform's location and left the other half untrained before subjecting all rats to surgery. Recovery restricted to pre-operatively trained rats would suggest that the FF plays an essential role in the storage but not the retention or retrieval of spatial information.

The second question I addressed concerned the basis of recovered spatial performance. One possible basis of recovered spatial performance is that spatial cognitive function becomes restored, a phenomenon commonly referred to as recovery of function. An alternative possibility is that recovery results from the persistence of some residual capacity for spatial cognition (*i.e.*, partial sparing of function). To differentiate these possibilities, I tested FF lesioned rats for acquisition of a second platform location after their performance had reached asymptote at a first location. Control-level performance would indicate that spatial cognitive function had been restored (*i.e.*, recovery of function had occurred), while an impairment would suggest that any recovery observed at the previous platform location had resulted from residual, but reduced, capacity for spatial cognition.

Methods

Subjects

Thirty-four male Long Evans hooded rats (Charles River) weighing 380-440 g at the beginning of the study were used as subjects. Food and water were available *ad lib* throughout the experiment. Rats were maintained in pairs in shoe box cages with the exception of a six-day post-surgery recovery period in which they were individually housed. All experimental procedures were carried out during the light portion of the 12:12 hour light/dark cycle.

A two by two design was employed for group assignment with training (pre-operatively trained [prtr] or naive [nve]) and surgery (sham [SH] or fimbria/fornix [FF] lesioned) as factors. Thus, four groups were created: prtr-FF (n=9), nve-FF (n=9), prtr-SH (n=8), and nve-SH (n=8). One prtr-SH animal died due to surgical complications thus reducing n to seven in that group.

Surgery

In preparation for surgery, all animals were anaesthetized with sodium pentobarbital (65mg/kg) and given methyl scopolamine (1mg/kg) to reduce respiratory congestion. Rats were placed in a Kopf stereotaxic apparatus, incisions were made, and the skin was retracted to expose the skull landmarks *lambda* and *bregma*, whose coordinates were then used to level the skull. Slots were drilled in the skull 1.4 mm posterior to bregma and 0.5 to 5.2 mm laterally on either side of the sagittal suture. In the FF groups, a disposable microscalpel (Fisher, 15° blade) was lowered to dura with the

blade facing laterally and angled a further 15° towards the skull at the following coordinates relative to *bregma*: 1.4 mm (posterior), and 0.8 mm (lateral). The knife was inserted 4.8 mm (as measured by the vertical scale of the manipulator), moved laterally 3.0 mm (as measured on the horizontal scale of the manipulator in the coronal plane), and then retracted at the same angle as insertion. This procedure was completed bilaterally (see Fig.1). In the SH groups the knife was not inserted. The drill slots were sealed with sterile bone wax and tetracycline and a topical antifungal-antibacterial agent were applied. The wound was sutured and animals were returned to a recovery cage with a heat lamp for several hours. Surgery was followed by a seven-day recuperation period.

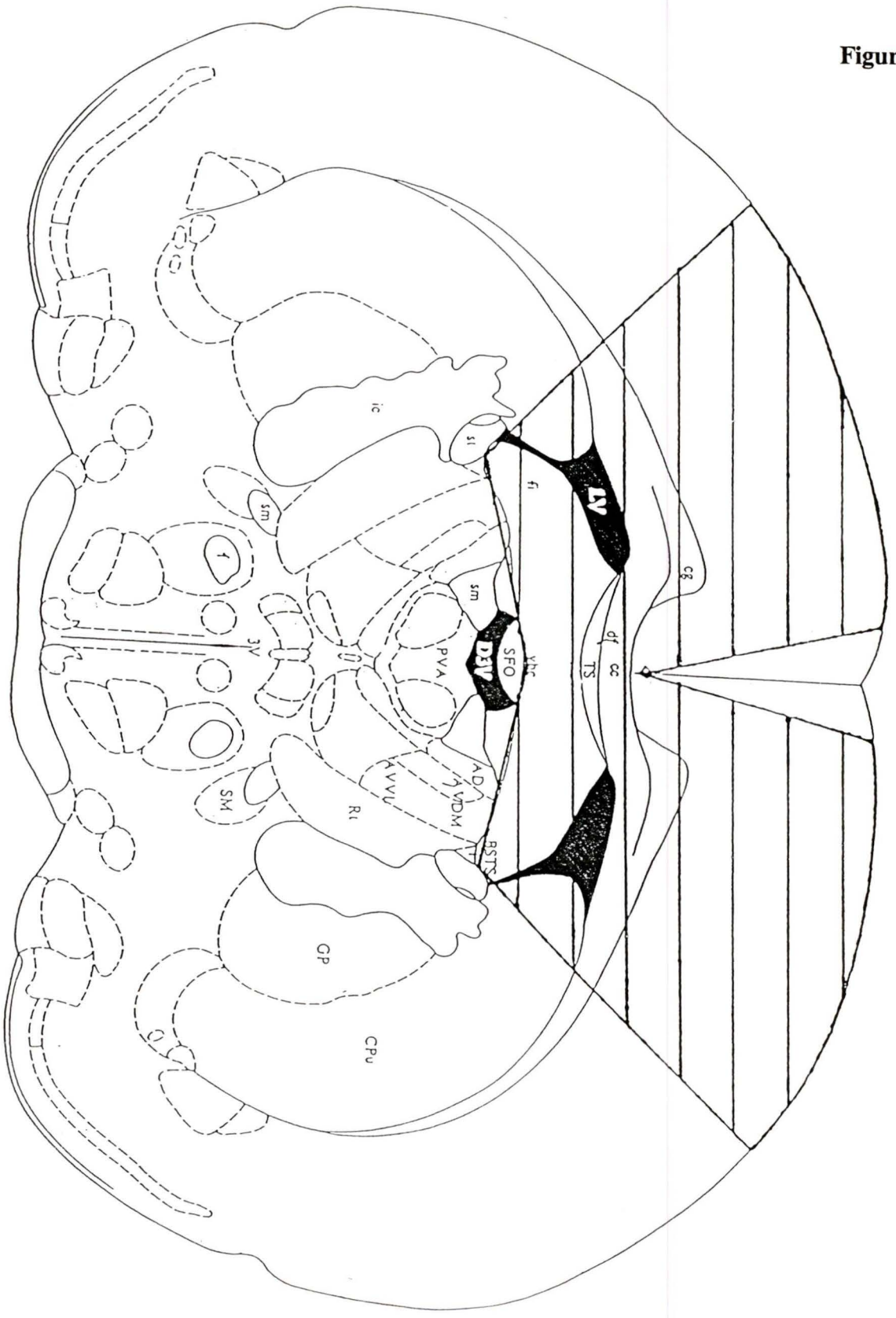
Apparatus

Behavioural assessment was conducted in a Morris water maze (Morris 1984; 1981). The maze consisted of a circular pool 45 cm high and 150 cm in diameter with featureless white walls. The pool was filled to a height of 26 cm with 22 ± 1°C water rendered opaque with 1500-2000 ml of skim milk powder. Two different platforms were used in the pool: 1) The Atlantis platform: a movable aluminum platform with a 12 x 13 cm upper face mounted with a hydraulic mechanism which could be operated remotely to adjust the height of the platform from 10 to 28 cm, and 2) a movable plexiglass platform 30 cm in height including a top-mounted 5 cm high black-sided wooden cube with a 11 x 11 cm upper face. The maze was located in a windowless room with white walls and two doors. Various items placed on the walls provided visual cues while background noise was produced by a radio. The movement of rats in the pool was recorded and analysed with

Fig. 1. The intended path of the bilateral knife cuts, depicted on a coronal section 1.4 mm posterior to *bregma* (adapted from Paxinos & Watson, 1978). Horizontal lines depict the area of the transection. The coordinates were chosen to produce a near complete transection of the fimbria/fornix while minimizing damage to underlying structures such as the subfornical organ, the stria medularis, the stria terminalis, and the dorsal thalamic nuclei.

3V 3rd ventricle, AD anterodorsal thalamic nucleus, AVDM anteroventral thalamic nucleus dorsomedial aspect, AVVL anterodorsal thalamic nucleus, ventrolateral aspect, BSTS bed nucleus of the stria terminalis, supracapsular aspect, cc corpus callosum, cg cingulum, CPu caudate putamen, D3V dorsal 3rd ventricle, df dorsal fornix, f fornix, fi fimbria, GP globus pallidus, ic internal capsule, LV lateral ventricle, PVA paraventricular thalamic nucleus, anterior aspect, Rt reticular thalamic nuclei, SFO subfornical organ, sm stria medullaris, SM nucleus of the stria medullaris, st stria terminalis, TS triangular septal nucleus, vhc ventral hippocampal commissure

Figure 1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a video camera coupled to a microcomputer by an image analyser. A remote switch was used to start and stop recording.

Procedure

The following procedures were common to all three types of trials run in the water maze: i) the rat was placed in the pool with its head facing the wall of the pool, ii) trials were terminated after the rat found the platform or a specified duration transpired, iii) if the rat did not find the platform after a duration specific to each trial type, it was gently guided to the platform, iv) the rat was left on the platform for approximately ten seconds at the end of each trial after which it was removed to a holding pen 2.5 m from the pool with a 250 W heat lamp located 45 cm above, and v) an inter-trial interval of three to five minutes was given.

Visible Platform Task

Simple cue learning and memory was tested with a visible platform variant of the water maze task. On visible platform trials (VIS), the plexiglass platform with its attachment was placed in one of eight positions in the pool (none of which matched any position used on submerged platform trials) and curtains were put up to hide extra-maze visual cues. The rat was placed in the pool at one of two randomly alternated positions lying 45^{0} in either direction from the most distal point from the platform and allowed to swim for a maximum of 60 seconds. Latency and distance to escape onto the platform were recorded. This task requires similar motivation and sensorimotor abilities as the hidden platform task but demands only a relatively simple association of a visual cue (the

platform) with escape. Hence, performance of this task can be used to assess gross sensorimotor, motivational, or nonspecific mnemonic impairments (Morris, 1984; 1981).

Hidden Platform Task (Spatial testing)

Spatial cognition was tested using the standard hidden platform variant of the water maze task, which consisted of submerged platform trials (SUB) and probe trials (P).

SUB Trials. On SUB trials, the Atlantis platform was adjusted to a height three cm below the milk's surface and was placed in the centre of one of four quadrants defined by the N-S and E-W axes. The rat was placed gently into the pool at one of the four start positions (N,W,S,E) and allowed to swim for a maximum of 60 seconds. SUB trials were given in blocks of four with each start position utilized once in pseudorandom order. Latency and distance to escape onto the platform and dwell times in each of the pool's four quadrants were recorded.

P Trials. Since both spatial and nonspatial platform finding strategies are available to the rat on SUB trials, P trials were utilized to differentiate performance based on different strategies. On P trials, the Atlantis platform, located in the same position as on SUB trials, was lowered to its completely collapsed position (16 cm below the water's surface) such that it could not be detected by a swimming rat. To start a trial, the rat was placed into the pool at one of two positions located 45° in either direction from the point most distal from the platform and allowed to swim for 30 seconds. At this point, the platform was raised with a remote plunger to the submerged platform level (3 cm below the water's surface) and the rat was permitted to swim for a maximum of another 30 seconds. This procedure reduces the extinction effect associated with standard probe trials

(in which the platform remains unavailable to the rat throughout the trial), since escape to the platform in its usual position becomes possible at the end the trial. Dwell times in each of the pool's four quadrants and crossings over the platform and its corresponding locations in the other three quadrants were recorded. From these data, correct quadrant dwell percentage (dwell time in the correct quadrant / 30 seconds $\times$ 100%) and crossing preference (crossings of the correct platform location - [crossings of the corresponding location in the other three quadrants / 3]) were calculated.

Training Protocol

Pre-operatively Trained Groups

The groups prtr-FF and prtr-SH were divided into three squads of five or six animals and given the following schedule of treatments:

Visible Platform Training (Day -7) - One VIS trial was given at each of eight locations.

Phase A: Pre-operative Training (Days -6 to -1) - Four SUB trials were given with the platform located in the NW quadrant which, on Day -2 only, were followed by one P trial.

Surgery and Recuperation (Days 0 to 7) - On Day 0, animals underwent surgery which was followed by five days of recovery. On Day 5, animals were first handled to assess reactivity and on Day 6 they were rehoused in pairs. On Day 7 they were again handled to assess reactivity.

Phase B: Retention/Reacquisition (Days 8 to 20) - On Day 8, water maze training resumed with one P, four SUB, and two VIS trials in that order. The next day, the rats

were given four SUB, one P, and two VIS trials. On Days 10 to 20, rats were given four SUB trials and one P trial. The platform was in the NW quadrant on SUB and P trials and in arbitrarily chosen positions on VIS trials.

Phase C: Reversal (Days 21 to 33) - The platform was moved to the SE quadrant. On Day 21, one P, and four SUB trials were given. On Days 22 to 33, four SUB trials were given which on Days 26 and 28 to 33 were followed by one P trial.

Naive Groups

The groups nve-FF and nve-SH were divided into three squads of five or six animals and underwent the following schedule of treatments:

Surgery and Recuperation (Days 0 to 6) - On Day 0, animals underwent surgery which was followed by five days of recovery. On Day 5, animals were first handled to assess reactivity and on Day 6 they were rehoused in pairs.

Visible Platform Training (Day 7) - Eight VIS trials were given as above for the pre-operatively trained groups.

Phase B: Acquisition (Days 8 to 20) - On Days 8 to 13, training was identical to that given to the pre-operatively trained groups during Days -6 to -1 (Phase A). On Days 14 to 20, training was identical to that given pre-operatively trained groups on the same days (see Phase B).

Phase C: Reversal (Days 21-33) - Training was given as above for pre-operatively trained groups in Phase C.

Note that the training protocols were nearly identical for pre-operatively trained and naive groups. Specifically, both groups began training with one day of visible platform

trials and then commenced submerged platform training. The basic training segment at both platform locations (NW in Phases A and B; SE in Phase C) consisted of thirteen days of submerged platform trials with probe trials being given on the fifth and seventh to thirteenth days of training. For pre-operatively trained groups, visible platform training and the first six days of the segment for the NW platform location were administered prior to surgery (Phase A). The remaining seven days of the basic training segment were administered after surgery followed by an additional six days of submerged platform trials and probes. The only other additions to the training protocol for pre-operatively trained groups were two visible platform trials at the end of the training session on each of the first two days of testing following surgery (Phase B).

Histology

Following behavioural testing, animals were sacrificed with an overdose of sodium pentobarbital and perfused with saline. Brains were fixed in formalin and then frozen before 80 μm sagittal sections were taken through 4 mm on both sides of the sagittal fissure. Every third section was mounted and then thionine stained. The area of fibre damage and cell loss was documented by matching sections with one of eight plates from Paxinos and Watson (1988).

Data Analysis

Data analysis was completed using the statistical software package SPSS® for Windows™. Distance, latency, correct quadrant dwell percentage, and crossing preference measures were subjected to analyses with repeated measures ANOVA, and *t* tests.

Results

Histology

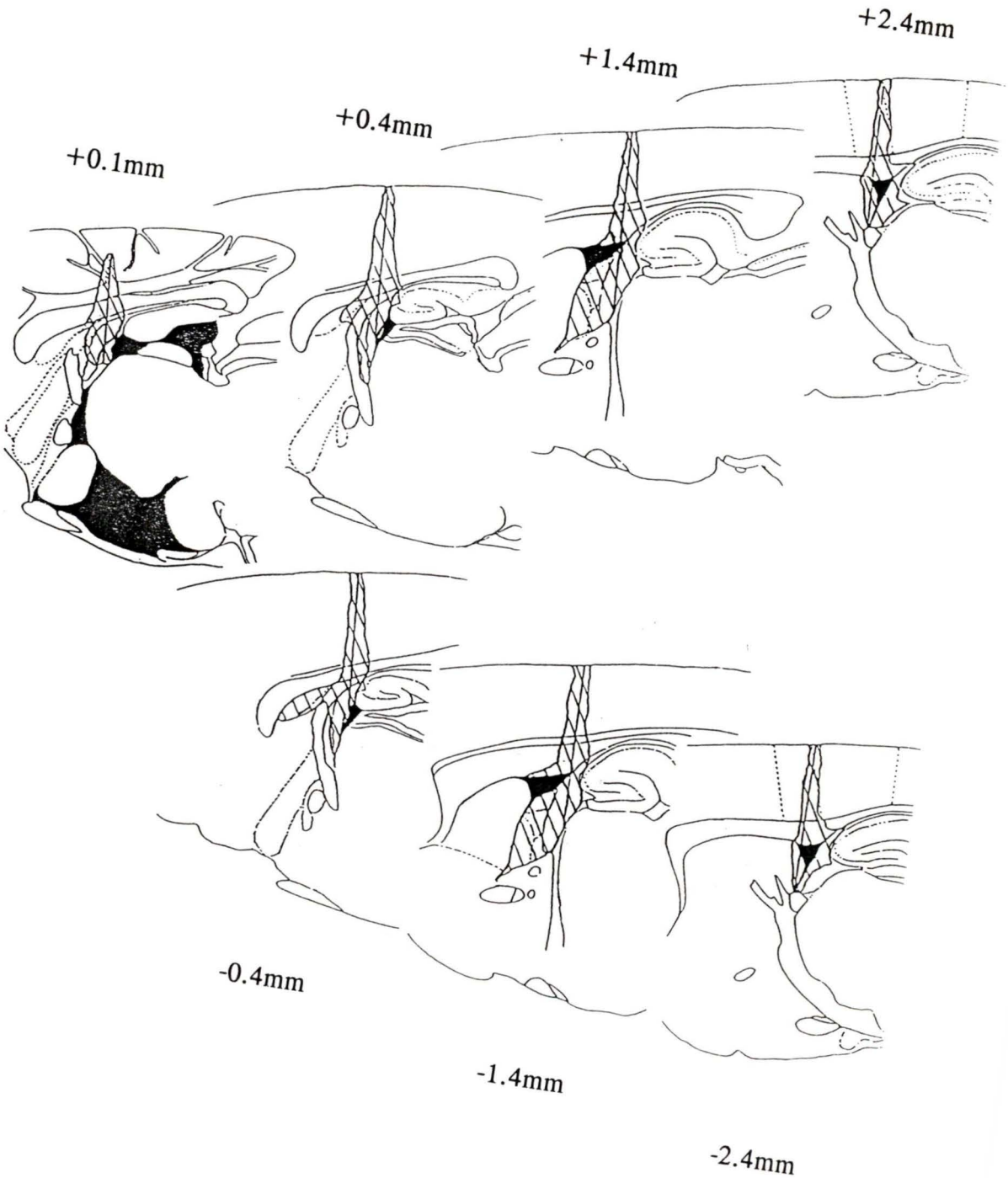
The knife cuts transected the dorsal fornix, the fimbria, and the ventral hippocampal commissure at a position posterior to the septum and anterior to the dorsal hippocampus (see Fig.2). The fimbria/fornix (FF) was transected completely or near completely bilaterally in all lesioned animals. In some cases, the lateral tips of the fimbria were spared. Cell loss was detectable in the CA3 pyramidal cell layer and in the septal region. Other studies suggest that the septal degeneration likely involved both cholinergic and non-cholinergic neurons of the medial septum (Armstrong, Terry, Detersa, Bruce, Hersch, & Gage, 1987; O'Brien, Svendsen, Isacson, & Sofroniew, 1990). Additionally, damage extended to the overlying portions of the corpus callosum, the supracallosal striae, and the cortex. The overall range of damage was comparable in pre-operatively trained and naive lesioned groups.

General Behaviour

As observed elsewhere (*e.g.*, Pitsikas, Spruijt, Algeri, & Gispen, 1990), FF lesioned animals exhibited hyper-reactivity similar to that observed following septal lesions (see Albert & Chew, 1980 for a review). It appeared gradually over several days following surgery and dissipated within a week to ten days. During this period, lesioned rats responded to loud noises with vocalizations and frenetic movement, and exhibited defensive behaviours such as tail flicking, bearing of teeth, vocalizing, and squirming in

Fig. 2. Area affected by the knife cuts in a representative animal depicted in sagittal sections ± 2.4 mm, ± 1.4 mm, ± 0.4 mm, and 0.1 mm from midline (adapted from Paxinos & Watson, 1978). Dark line indicates estimated path of knife while the back slashed area represents region of tissue damage.

Figure 2



response to being approached. Other than hyper-reactivity no discernable general behavioural differences were noted between lesioned and unlesioned rats.

Morris Water Maze Testing

Visible Platform Task

Lesioned groups showed intact simple cue learning and memory on the visible platform variant of the water maze task. Lesioned rats with pre-operative training (group prtr-FF) swam quickly and directly to the platform on even their first post-surgery visible platform trial and were almost identical to controls (prtr-SH) in distance required to escape (see Fig.3, trials 9 to 12; $F(1,14)=0.19$, $p>.66$; latency data will not be reported but showed a similar pattern of results). Lesioned rats without pre-operative training (group nve-FF) acquired the task very rapidly and utilized optimal escape routes within 4 or 5 trials. Again, distance required to escape was almost identical for lesioned rats and controls[7] (see Fig.3, trials 1 to 8; $F(1,31)=0.13$, $p>.72$). These data indicate that FF lesions did not produce gross sensorimotor or motivational deficits, or a global mnemonic deficit, since both retention and acquisition of this task were not impaired by the lesion.

Hidden Platform Task

Phase B: Deficit. Lesioned rats showed severely impaired performance on the hidden platform variant of the water maze task. Prior to surgery (Phase A), rats in groups prtr-SH and prtr-FF learned to swim directly to the hidden platform and showed accurate knowledge of its location by searching extensively in its area during a probe trial.

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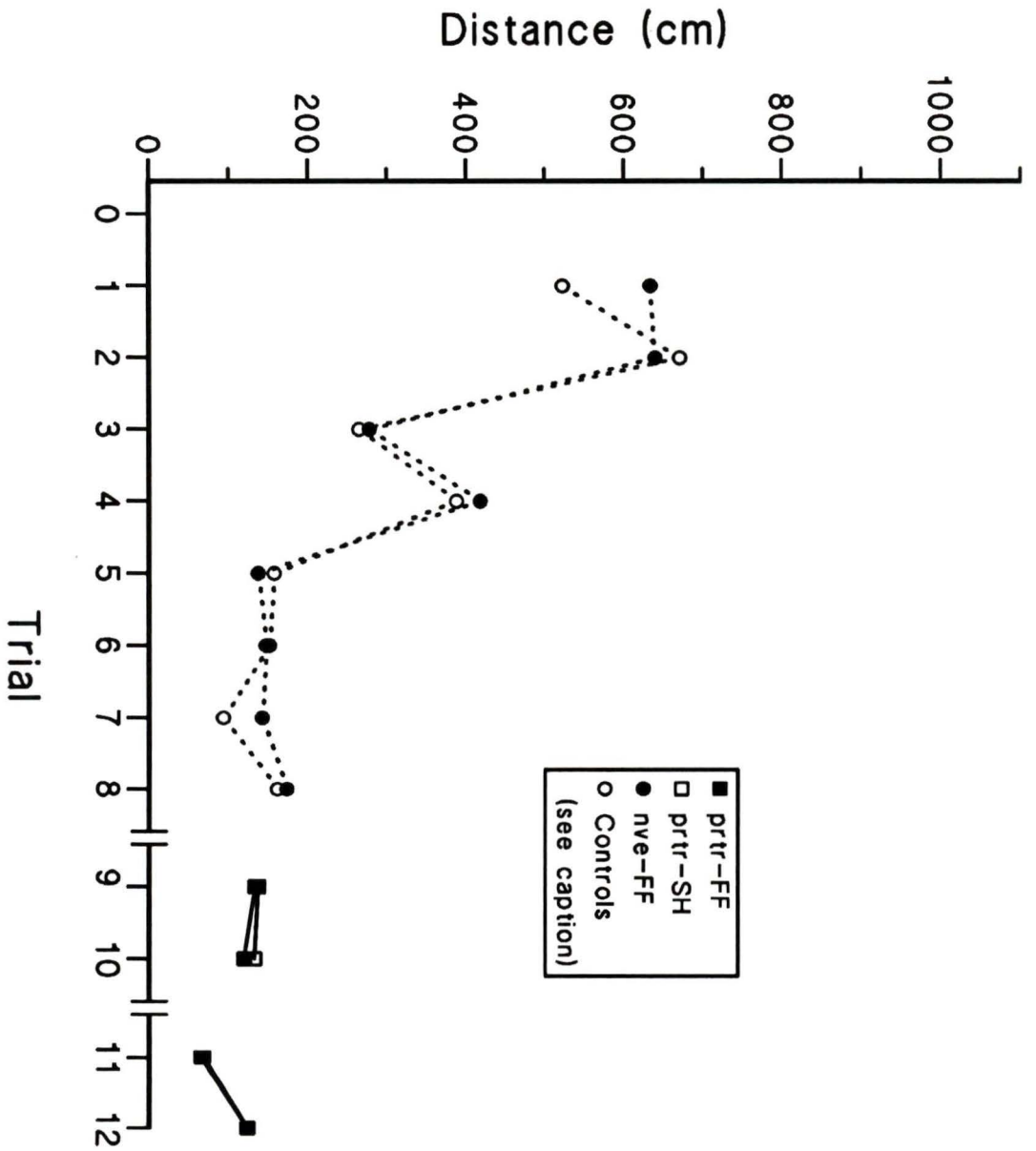
[7] Controls consisted of prtr-FF and prtr-SH during Phase A (pre-operative training) and nve-SH during Phase B.

Fig. 3. Mean distances to escape on visible platform trials. Trials 1-8 took place on the first day of training for all groups (pre-surgery for prtr- groups, and post-surgery for nve- groups), and trials 9-10 and 11-12 took place on the first and second day of post-operative water maze training respectively for prtr- groups only. Note the almost identical performance of: i) nve-FF and controls (nve-SH; prtr-FF and prtr-SH pre-operatively) over trials 1-8 and, ii) prtr-FF and prtr-SH over trials 9-12.

Figure 3


Distance (cm)
0
200
400
600
800
1000
Trial
0
1
2
3
4
5
6
7
8
9
10
11
12
prtr-FF
prtr-SH
nve-FF
Controls
(see caption)

Comparisons between the groups revealed no differences in distances to escape on submerged platform trials (see days -6 to -1 on Fig. 4a; $F(1,14)=0.63$, $p>.51$; latency data will not be reported but revealed a similar pattern of results), or either correct quadrant dwell percentages ($t(14)=0.09$, $p>.90$) or crossing preferences ($t(14)=0.26$, $p>.79$) on a single probe trial (see day -2 on Figs. 4b & c). However, when tested following surgery (Phase B), prtr-FF's performance was significantly impaired. On their first trial of Phase B (a probe trial), lesioned rats failed to demonstrate retention of the platform's location as they exhibited no bias in searching in the platform's area. This was shown by both correct quadrant dwell percentages ($t(8)=0.47$, $p>.37$) and crossing preferences ($t(8)=1.7$, $p>.06$) which were not above chance[8] levels (see day 8 on Figs.4b & c). In contrast, sham-operated rats showed a significant bias in searching near the platform's location as shown by both correct quadrant dwell percentages ($t(6)=2.23$, $p<.035$) and crossing preferences ($t(6)=6.97$, $p<.001$) which were significantly greater than chance. However, it should be noted that prtr-SH's performance, though above chance, was notably worse than pre-surgery levels (correct quadrant dwell percentage - $t(6)=1.91$, $p<.053$; crossing preference - $t(6)=1.81$, $p<.061$) suggesting that some 'normal' forgetting occurred in controls and may have contributed to lesioned rats' drop in performance also. On submerged platform trials, prtr-FF also showed disrupted retention (see days 8 to 20 on Fig.4a). Compared to their last day of pre-surgery

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[8] Chance probe trial performance should lead to no systematic bias for any of the four quadrants or possible annulus locations in the pool and, thus, a correct quadrant dwell percentage of 25% and a crossing preference of 0.

Figs. 4a-c). Performance of prtr- groups in Phase A (pre-operative training; days -6 to -1) and all groups in Phase B (days 8 to 20). **a).** Mean distances to escape on submerged platform trials. **b).** Mean correct quadrant dwell percentages on probe trials. **c).** Mean crossing preferences on probe trials. Things to note include: 1) no difference between prtr-FF and prtr-SH prior to surgery (Phase A), 2) the substantially greater escape distances, lower correct quadrant dwell percentages, and lower crossing preferences shown by lesioned groups (prtr-FF, nve-FF) relative to their respective sham-operated groups (prtr-SH, nve-SH) in Phase B, especially over the early trial blocks, 3) the marked improvement exhibited by lesioned groups over days, and, 4) the shorter distances, higher correct quadrant dwell percentages, and higher crossing preferences shown by pre-operatively trained lesioned rats (prtr-FF) relative to naive lesioned rats (nve-FF) for most of Phase B.

Figure 4a

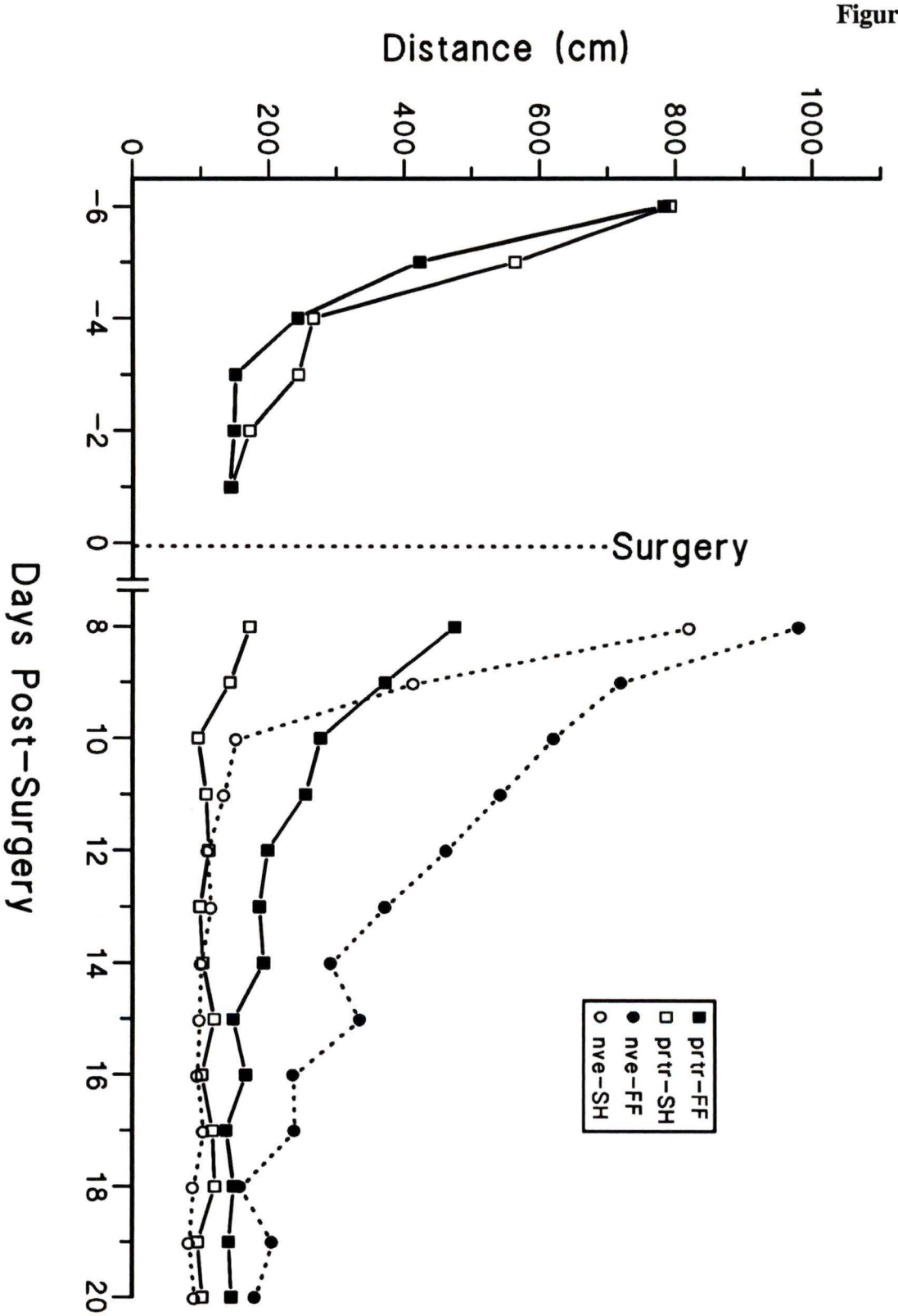

Distance (cm)
0
200
400
600
800
1000
-6
-4
-2
0
Surgery
8
10
12
14
16
18
20
Days Post-Surgery
prtr-FF
prtr-SH
nve-FF
nve-SH

Figure 4b

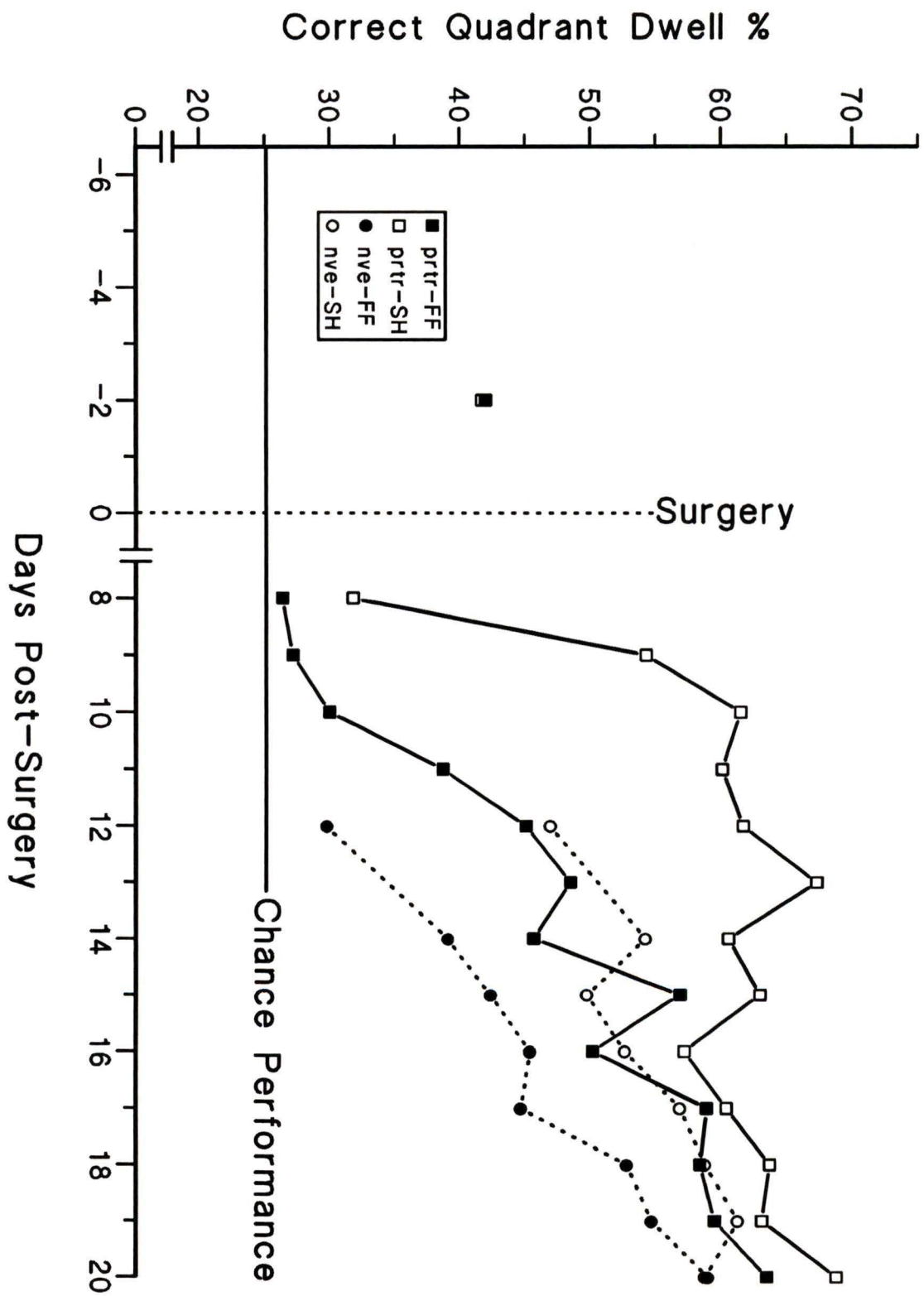
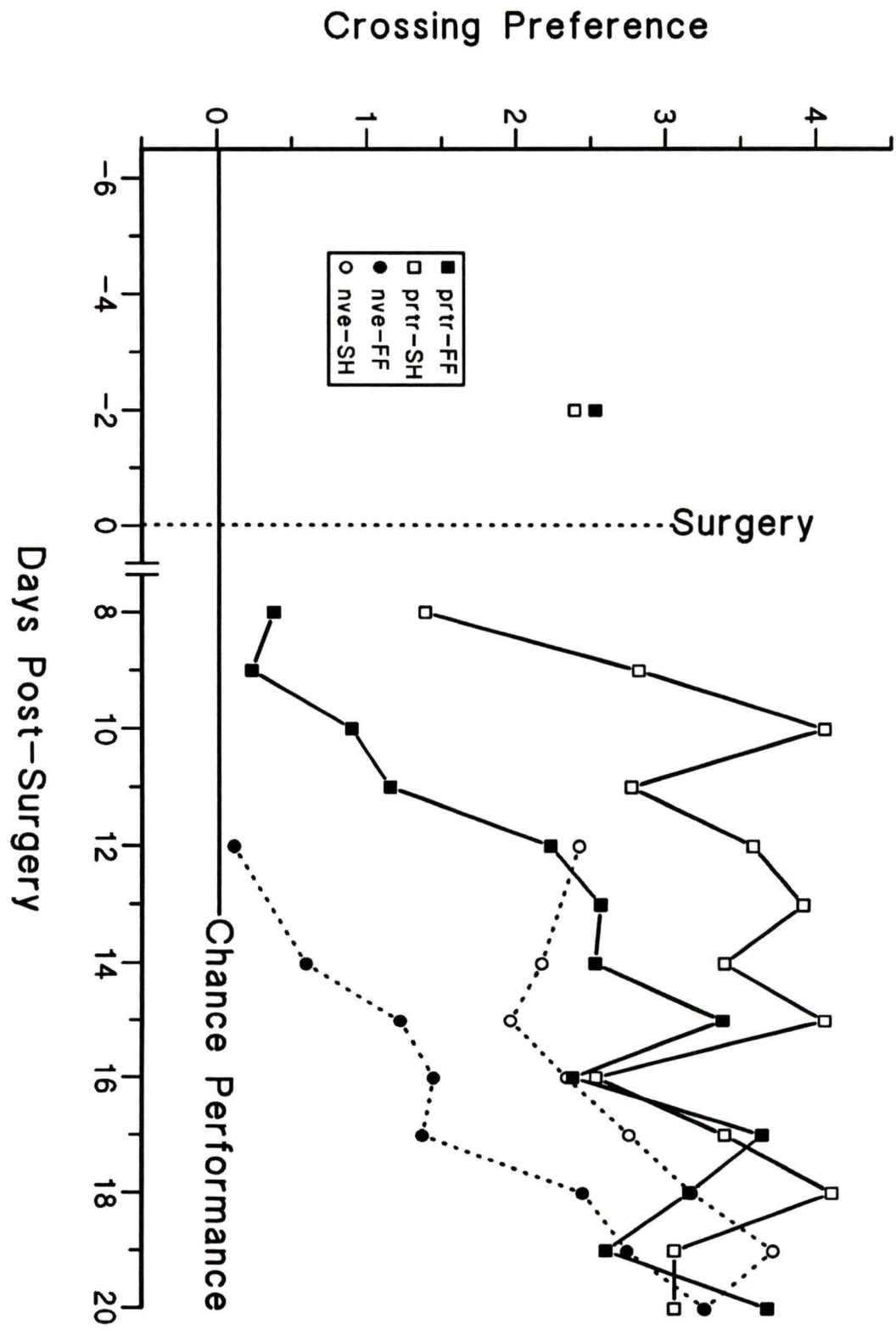

Correct Quadrant Dwell %
70
60
50
40
30
20
0
prtr-FF
prtr-SH
nve-FF
nve-SH
Surgery
Chance Performance
-6
-4
-2
0
8
10
12
14
16
18
20
Days Post-Surgery

Figure 4c


Crossing Preference
0
1
2
3
4
prtr-FF
prtr-SH
nve-FF
nve-SH
Surgery
Chance Performance
-6
-4
-2
0
8
10
12
14
16
18
20
Days Post-Surgery

submerged platform training, lesioned rats required greater distances to escape on each of the first six days of testing in Phase B (all $t(8)$'s$\geq$1.99, $p<.05$). Moreover, prtr-FF exhibited an overall impairment relative to prtr-SH in Phase B in terms of escape distances on submerged platform trials ($F(1,14)=30.22$, $p<.001$) and both correct quadrant dwell percentages ($F(1,14)=18.14$, $p<.001$) and crossing preferences ($F(1,14)=11.71$, $p<.005$) on probe trials.

A significant hidden platform deficit was also exhibited by lesioned rats without pre-operative training (group nve-FF). On submerged platform trials, nve-FF acquired direct routes to the hidden platform more slowly than their respective controls (group nve-SH) as shown by longer escape distances overall in Phase B ($F(1,15)=32.05$, $p<.001$). On probe trials, nve-FF searched less in the platform's location than nve-SH as shown by lower correct quadrant dwell percentages ($F(1,15)=8.11$, $p<.02$) and crossing preferences ($F(1,15)=20.79$, $p<.001$) overall in Phase B. Furthermore, on their first probe trial of Phase B, nve-FF exhibited no bias in searching near the platform's location as shown by both correct quadrant dwell percentages ($t(8)=1.18$, $p>.13$) and crossing preferences ($t(8)=0.28$, $p>.39$) which were not significantly greater than chance. Performance on this probe trial reflects a complete failure to acquire the platform's location up to this point in training.

Phase B: Recovery. The impairment produced by FF lesions, however, did not appear to be absolute, since performance by both lesioned groups (prtr-FF and nve-FF) showed substantial recovery over the course of training in Phase B (see days 8 to 20 on Figs.4a, b, & c). Both prtr-FF and nve-FF utilized increasingly efficient escape routes

on submerged platform trials as shown by significantly shorter distances required to escape across days ($F(5,70)=25.62$, $p<.001$; $F(5,75)=30.59$, $p<.001$). By the seventh day of training in Phase B, prtr-FF's escape distances dropped to a level equivalent to those shown on their last day of pre-operative training (all $t(8)$'s≤ 1.46, $p>.09$, one-tailed), while nve-FF's performance reached similar levels by the eleventh day of Phase B (all $t(16)$'s≤ 1.64, $p>.06$, one-tailed). Additionally, prtr-FF achieved escape distances which were equivalent to their respective controls (prtr-SH) on the eighth, tenth, and eleventh day of training in Phase B (all $t(14)$'s≤ 1.22, $p>.12$, one-tailed), though, with the exception of the first day of training, nve-FF's performance was significantly worse than their respective controls (nve-SH) on all days of Phase B (all $t(15)$'s≥ 2.21, $p<.03$, one-tailed).

The achievement of relatively short escape distances, however, does not ensure that lesioned rats were utilizing a truly spatial (*i.e.*, allocentric) strategy to locate the platform. An analysis of probe trial data provides the critical evidence in this respect. Similar to performance on submerged platform trials, both lesioned groups showed substantial improvement over days in terms of both correct quadrant dwell percentages (prtr-FF - $F(5,70)=15.93$, $p<.001$; nve-FF - $F(4,60)=11.92$, $p<.001$) and crossing preferences (prtr-FF - $F(5,70)=9.01$, $p<.001$; nve-FF - $F(4,60)=15.31$, $p<.001$). More importantly, however, both prtr-FF and nve-FF searched persistently in the platform's general area, as shown by correct quadrant dwell percentages which were significantly greater than chance by the fourth and seventh days of training in Phase B respectively (prtr-FF - $t(8)=2.76$, $p<.02$; nve-FF - $t(8)=2.98$, $p<.01$), and repeatedly crossed over

the platform's exact location as shown by crossing preferences which were significantly greater than chance by the third and eighth days of training in Phase B respectively (prtr-FF - $t(8)=2.02$, $p<.04$; nve-FF - $t(8)=2.79$, $p<.02$ respectively). In comparison to pre-surgery performance levels, prtr-FF showed equivalent or superior correct quadrant dwell percentages ($t(8)=0.54$, $p>.31$) and crossing preferences ($t(8)=0.37$, $p>.36$) by the fourth and fifth days of training in Phase B, respectively. In comparison to these same performance levels, nve-FF showed equivalent or superior correct quadrant dwell percentages ($t(16)=0.48$, $p>.31$) and crossing preferences ($t(16)=1.14$, $p>.13$) by the seventh and eleventh days of training in Phase B respectively. Finally, both prtr-FF and nve-FF achieved probe trial performance levels equivalent to their respective controls (prtr-SH, nve-SH) by the eighth day of Phase B on correct quadrant dwell percentages (prtr-FF - $t(14)=0.97$, $p>.17$; nve-FF - $t(15)=1.31$, $p>.10$) and by the fifth and eighth day of Phase B respectively on crossing preferences (prtr-FF - $t(14)=1.28$, $p>.11$; nve-FF - $t(15)=1.36$, $p>.09$). The demonstration of highly localized search behaviour on probe trials provides strong evidence that, by the latter part of training, lesioned rats utilized allocentric spatial information to navigate to the platform.

Phase C: Deficit. Following Phase B, rats were tested for acquisition of a new hidden platform location in the pool (reversal - Phase C). Lesioned groups again exhibited a significant impairment. In comparison to their respective controls (prtr-SH, nve-SH), both prtr-FF and nve-FF acquired direct routes to the hidden platform more slowly, as shown by longer distances to escape on submerged platform trials overall in Phase C (see Fig.5a; prtr-FF - $F(1,14)=43.32$, $p<.001$, nve-FF - $F(1,15)=49.49$, $p<.001$). On

Figs. 5a-c). Performance by all groups in Phase C (reversal). **a).** Mean distances to escape on submerged platform trials. **b).** Mean correct quadrant dwell percentages on probe trials. **c).** Mean crossing preferences on probe trials. Things to note include: 1) the substantially greater escape distances, lower correct quadrant dwell percentages, and lower crossing preferences shown by lesioned groups (prtr-FF, nve-FF) relative to their respective sham-operated groups (prtr-SH, nve-SH), especially over the early trial blocks, 2) the marked improvement exhibited by lesioned groups over days and, 3) the comparable escape distances, correct quadrant dwell percentages, and crossing preferences shown by pre-operatively trained lesioned rats (prtr-FF) and naive lesioned rats (nve-FF).

Figure 5a

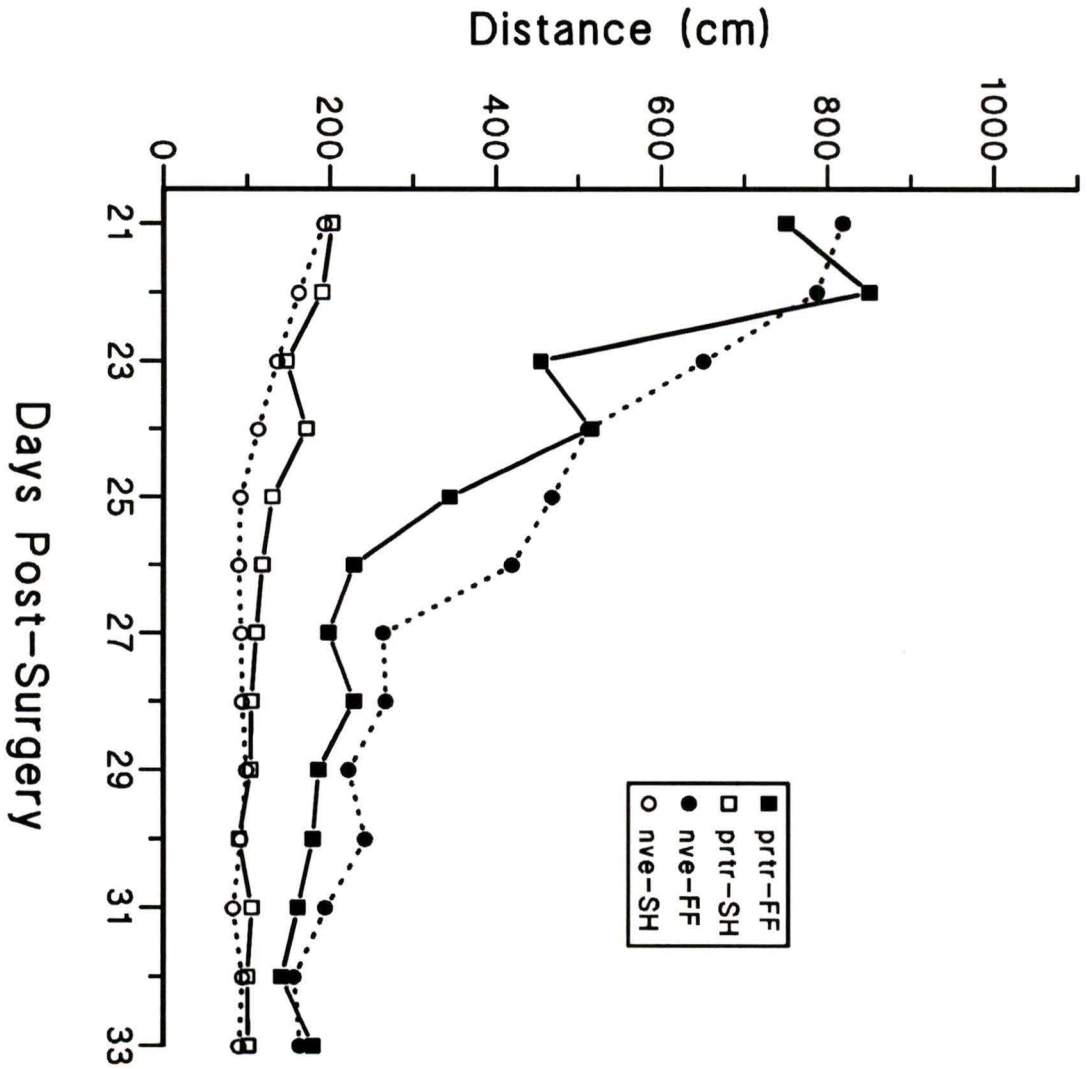

Distance (cm)
0
200
400
600
800
1000
21
23
25
27
29
31
33
Days Post-Surgery
prtr-FF
prtr-SH
nve-FF
nve-SH

Figure 5b

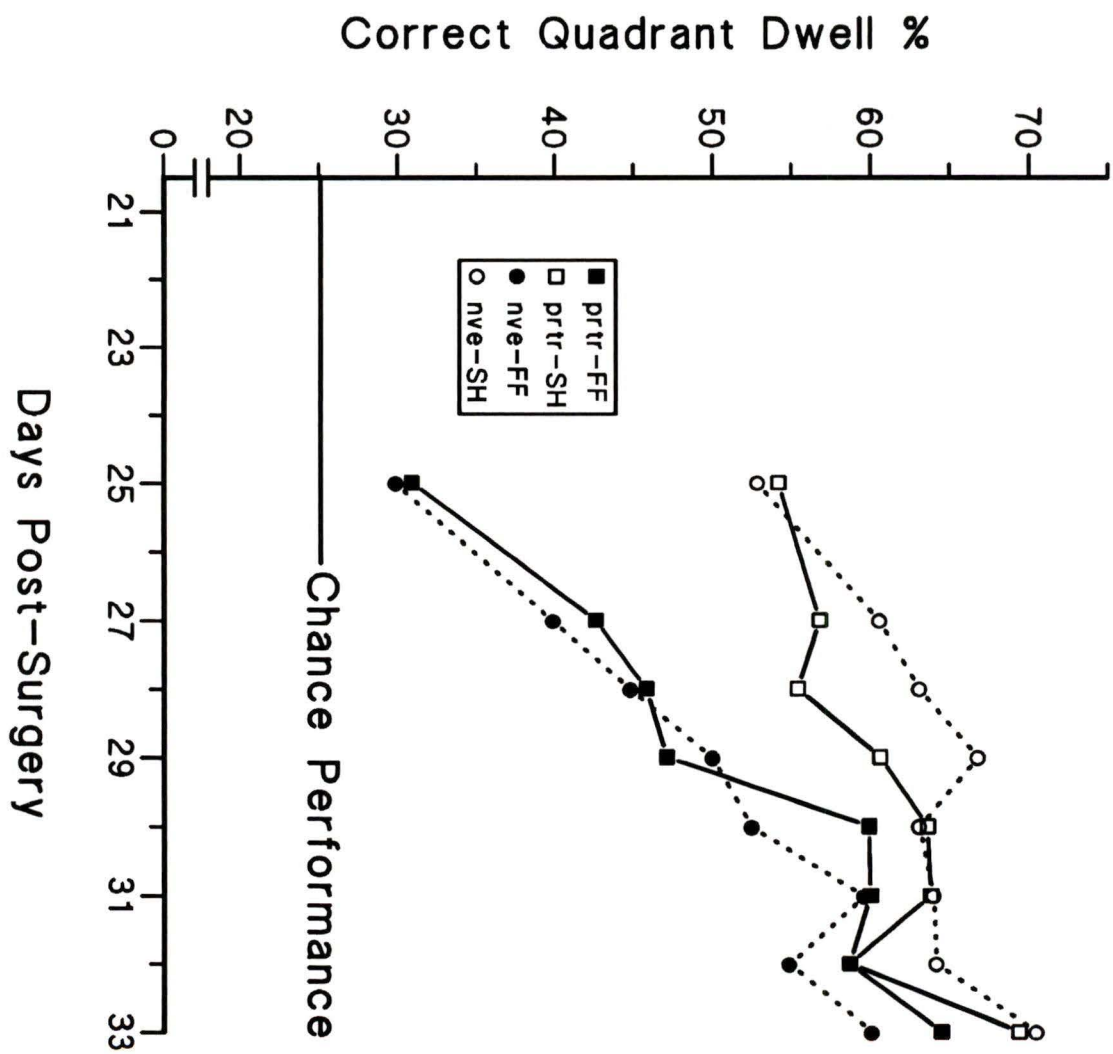
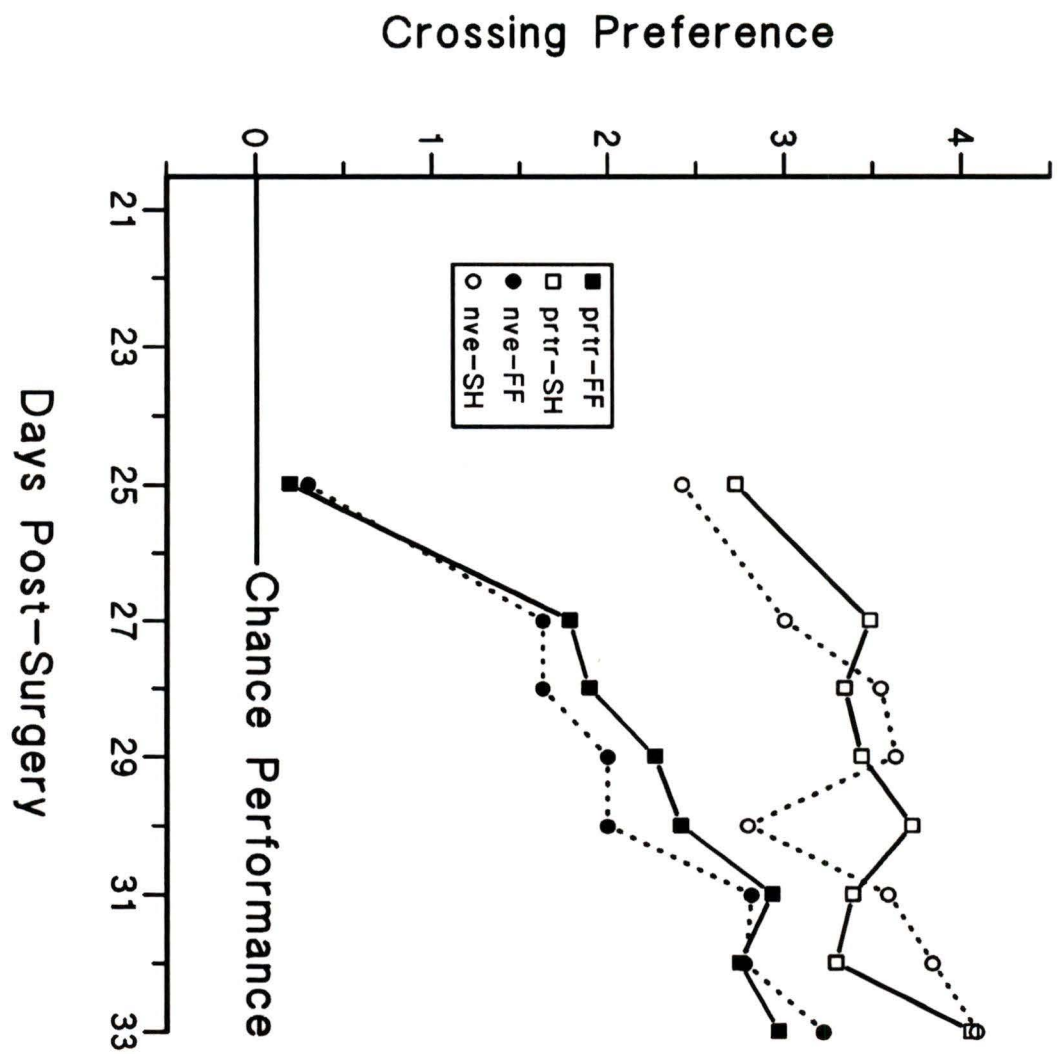

Correct Quadrant Dwell %
70
60
50
40
30
20
0
prtr-FF
prtr-SH
nve-FF
nve-SH
Chance Performance
21
23
25
27
29
31
33
Days Post-Surgery

Figure 5c


Crossing Preference
0
1
2
3
4
prtr-FF
prtr-SH
nve-FF
nve-SH
Chance Performance
21
23
25
27
29
31
33
Days Post-Surgery

probe trials, lesioned rats searched less in the platform's location in comparison to shams, as shown by both lower correct quadrant dwell percentages (see Fig.5b; prtr-FF - $F(1,14)=6.58$, $p<.023$, nve-FF - $F(1,15)=7.58$, $p<.015$) and crossing preferences (see Fig.5c; prtr-FF - $F(1,14)=14.88$, $p<.003$, nve-FF - $F(1,15)=10.30$, $p<.007$) overall in Phase C. Furthermore, on their first probe trial of Phase C, both lesioned groups exhibited chance levels of performance in terms of both correct quadrant dwell percentages (prtr-FF - $t(8)=1.73$, $p>.06$, nve-FF - $t(8)=0.8$, $p>.22$) and crossing preferences (prtr-FF - $t(8)=0.38$, $p>.35$, nve-FF - $t(8)=0.62$, $p>.27$) indicating that FF lesions completely disrupted acquisition of the platform's new location up to that point in training. To determine whether the severity of the lesion-related deficit was reduced from Phase B to Phase C, performance by lesioned groups in Phase C was compared to that of nve-FF in Phase B[9]. It was found that both lesioned groups' deficits in Phase C were equally severe as that of nve-FF in Phase B in terms of distance to escape on submerged platform trials, and both correct quadrant dwell percentages and crossing preferences on probe trials (see Figs.6a, b, & c; all $F(1,16)$'s<2.32, $p>.14$).

However, a comparison between the deficits in Phase B and Phase C must be viewed cautiously since a perseverative deficit specific to spatial reversal may have contributed to the magnitude of the deficit only in Phase C. To assess this possibility, quadrant dwell percentages on the first five days of submerged platform trials in Phase C

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[9] Nve-FF's performance in Phase B, rather than prtr-FF's performance in Phase B, was chosen as the appropriate comparison because the training protocol that was followed in Phase C was identical to that given to nve- groups, but not prtr- groups, in Phase B.

Figs. 6a-c). Comparison of performance by lesioned groups in Phase C (SE platform location) and performance by nve-FF in Phase B (NW platform location). **a).** Mean distances to escape on submerged platform trials. **b).** Mean correct quadrant dwell percentages on probe trials. **c).** Mean crossing preferences on probe trials. Note that performance by either lesioned group in Phase C was comparable to that of nve-FF in Phase B.

Figure 6a

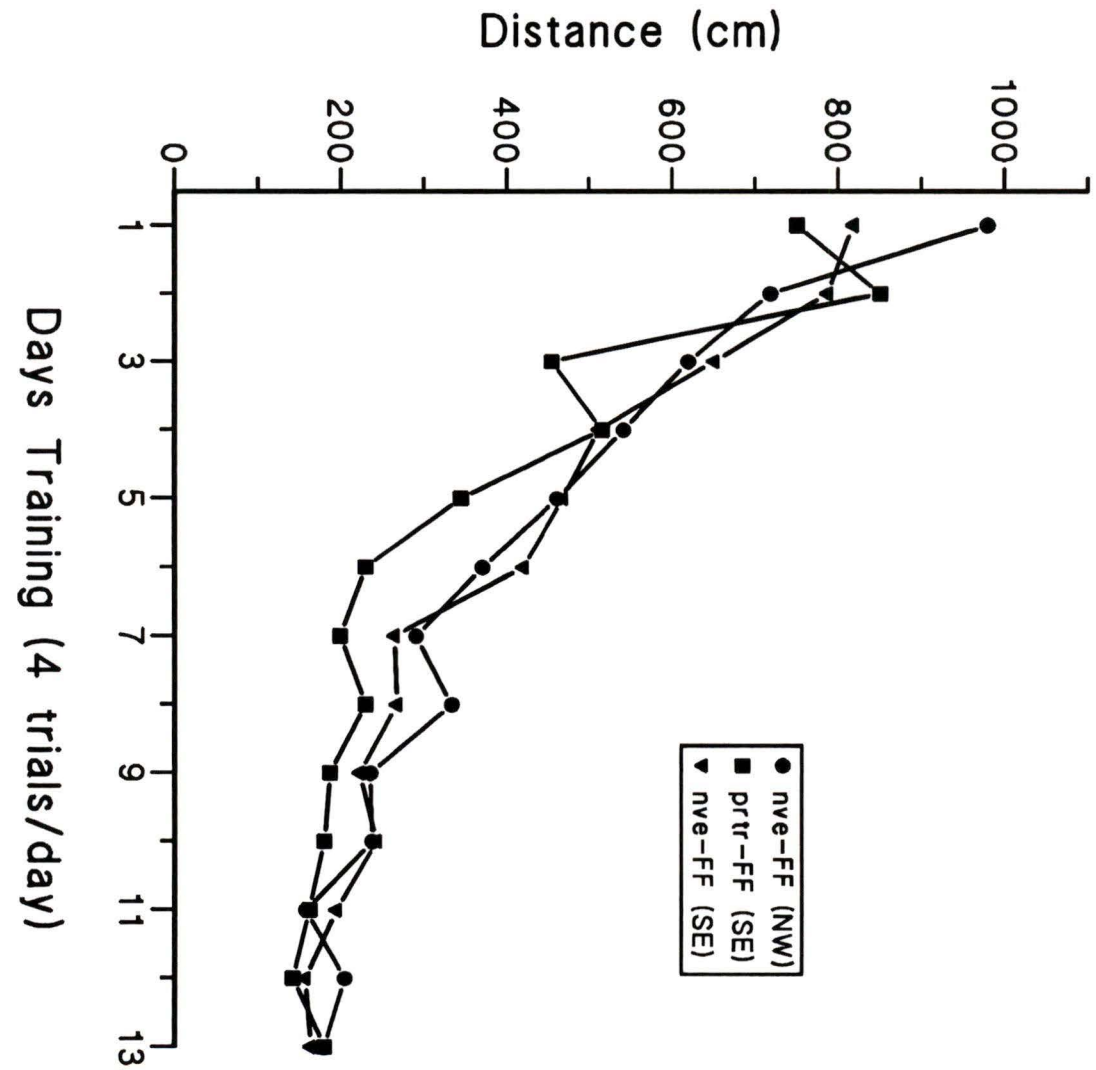

Distance (cm)
0
200
400
600
800
1000
1
3
5
7
9
11
13
Days Training (4 trials/day)
nve-FF (NW)
prtr-FF (SE)
nve-FF (SE)

Figure 6b

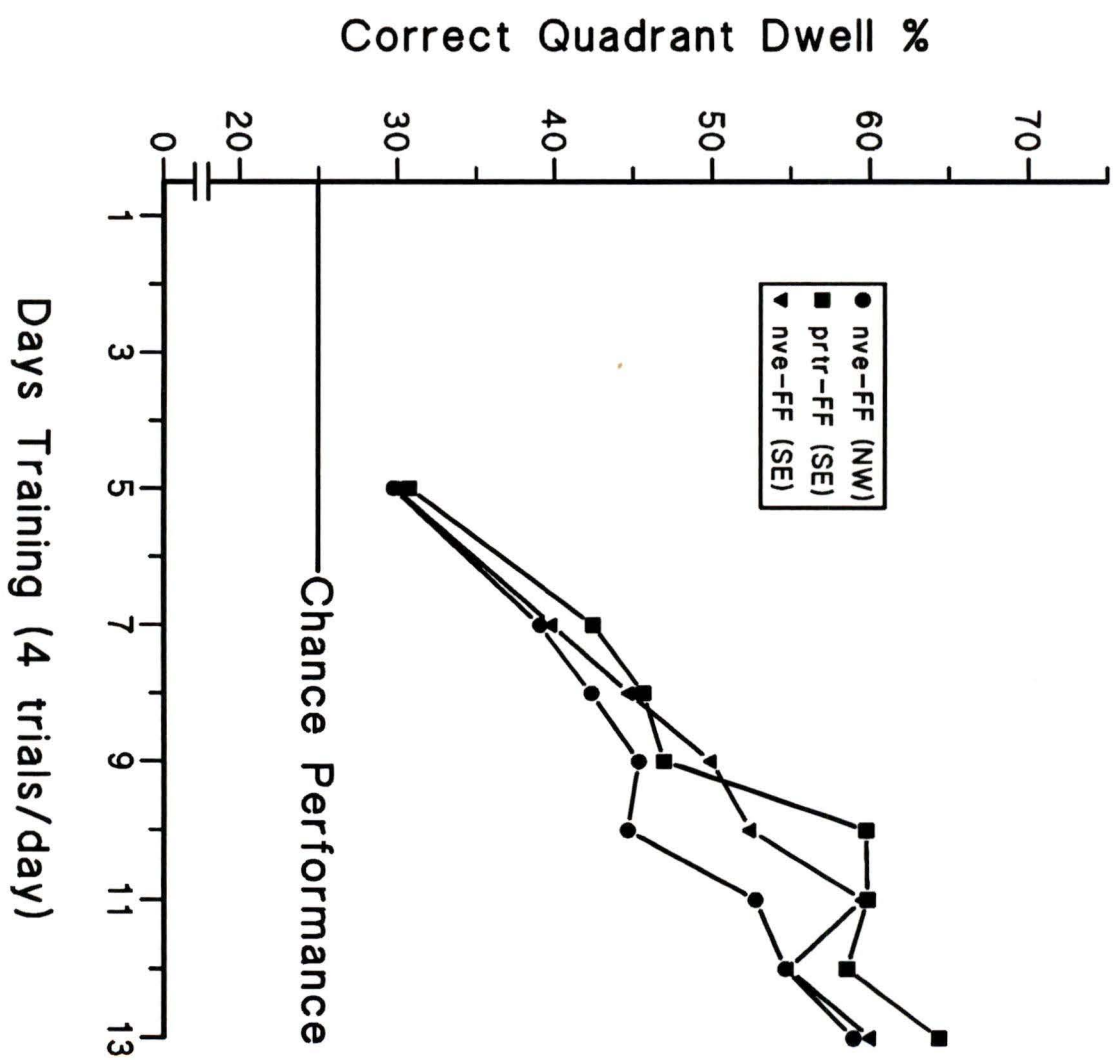
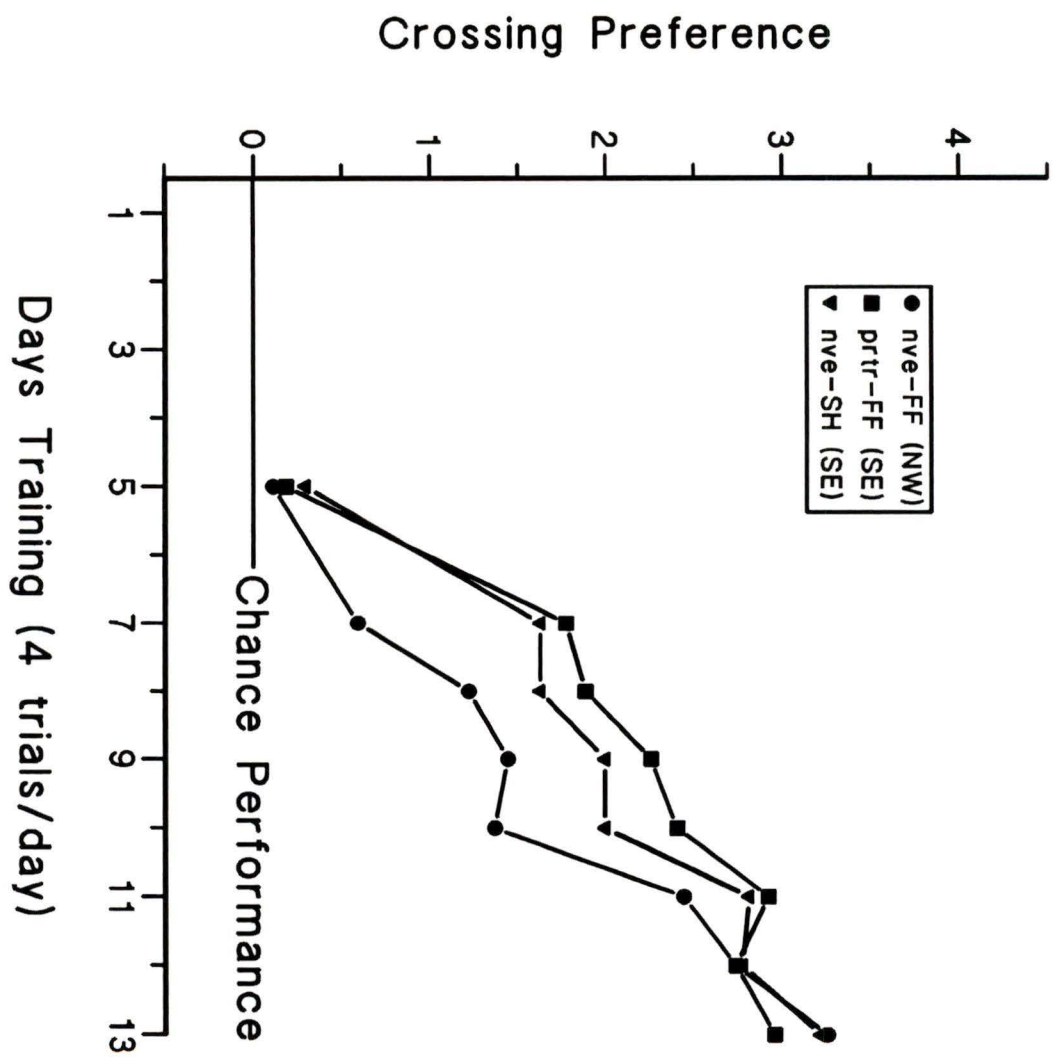

Correct Quadrant Dwell %
70
60
50
40
30
20
0
nve-FF (NW)
prtr-FF (SE)
nve-FF (SE)
Chance Performance
1
3
5
7
9
11
13
Days Training (4 trials/day)

Figure 6c


Crossing Preference
4
3
2
1
0
nve-FF (NW)
prtr-FF (SE)
nve-SH (SE)
Chance Performance
1
3
5
7
9
11
13
Days Training (4 trials/day)

and on the probe trial which succeeded this training were examined. Analyses revealed that lesioned groups did spend a greater share of their time searching in the old correct quadrant than sham groups on both submerged platform trials (see Fig.7a; $F(1,29)=13.43$, $p<.001$) and the probe trial ($F(1,29)=6.24$, $p<.02$). However, one possible explanation of this difference could be that sham groups acquired the new platform location more rapidly and thus reduced their search time in the old location proportionately. To assess whether lesioned groups showed a bias for the old quadrant independent of their deficit in acquiring the new platform location, I derived a new measure termed error bias. Error bias was calculated as: (dwell time in the previously correct quadrant - the average dwell time in the other two incorrect quadrants) ÷ trial duration$*100\%$. Lesioned groups did, in fact, show an above chance[10] error bias for the old correct quadrant on the first three days of Phase C (see Fig.7b; both $t(8)$'s>1.95, $p<.05$, one-tailed). However, by the fourth day of reversal training, lesioned rats' error bias for the old correct quadrant disappeared. This finding was corroborated by data from the probe test on the following day, which showed that lesioned groups exhibited neither an above chance dwell percentage (*i.e.*, $>25\%$; all $t(8)$'s$<.5$, $p>.74$, one-tailed) nor error bias (*i.e.*, >0; all $t(8)$'s<1, $p>.60$, one-tailed) associated with the previously correct quadrant. Moreover, it is worth noting that sham groups also showed an error bias for the old correct quadrant that was significantly above chance (0) for the first two days of Phase C (prtr-SH - all $t(6)$'s>4.53, $p<.005$; nve-SH - all $t(7)$'s>2.49, $p<.05$, one-tailed) and did not differ

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[10] Chance performance should lead to no bias for any quadrant in the pool and therefore an error bias score of 0.

Figs. 7a-b). Assessment of perseveration in the previously correct quadrant (NW; Phase B) on the first five days of submerged platform training and subsequent probe trial in Phase C. **a).** Mean old correct quadrant dwell percentages. Things to note include: 1) the higher old correct quadrant dwell percentages shown by lesioned groups relative to sham-operated groups 2) the decrease in old correct quadrant dwell percentages over days shown by all groups and, 3) the chance old correct quadrant dwell percentages shown by lesioned groups on the probe trial. **b).** Old correct quadrant error bias calculated as: old correct quadrant dwell percentage - dwell percentage in the other two incorrect quadrants / 2. Things to note include: 1) the significant error bias for the old correct quadrant shown by lesioned and sham-operated groups on the first three and first two days of training in Phase C respectively, 2) no old correct quadrant error bias shown by any group on the fourth or fifth day of submerged platform training or the probe trial and, 3) no overall difference between lesioned and sham-operated groups on submerged platform trials or the probe trial.

Figure 7a

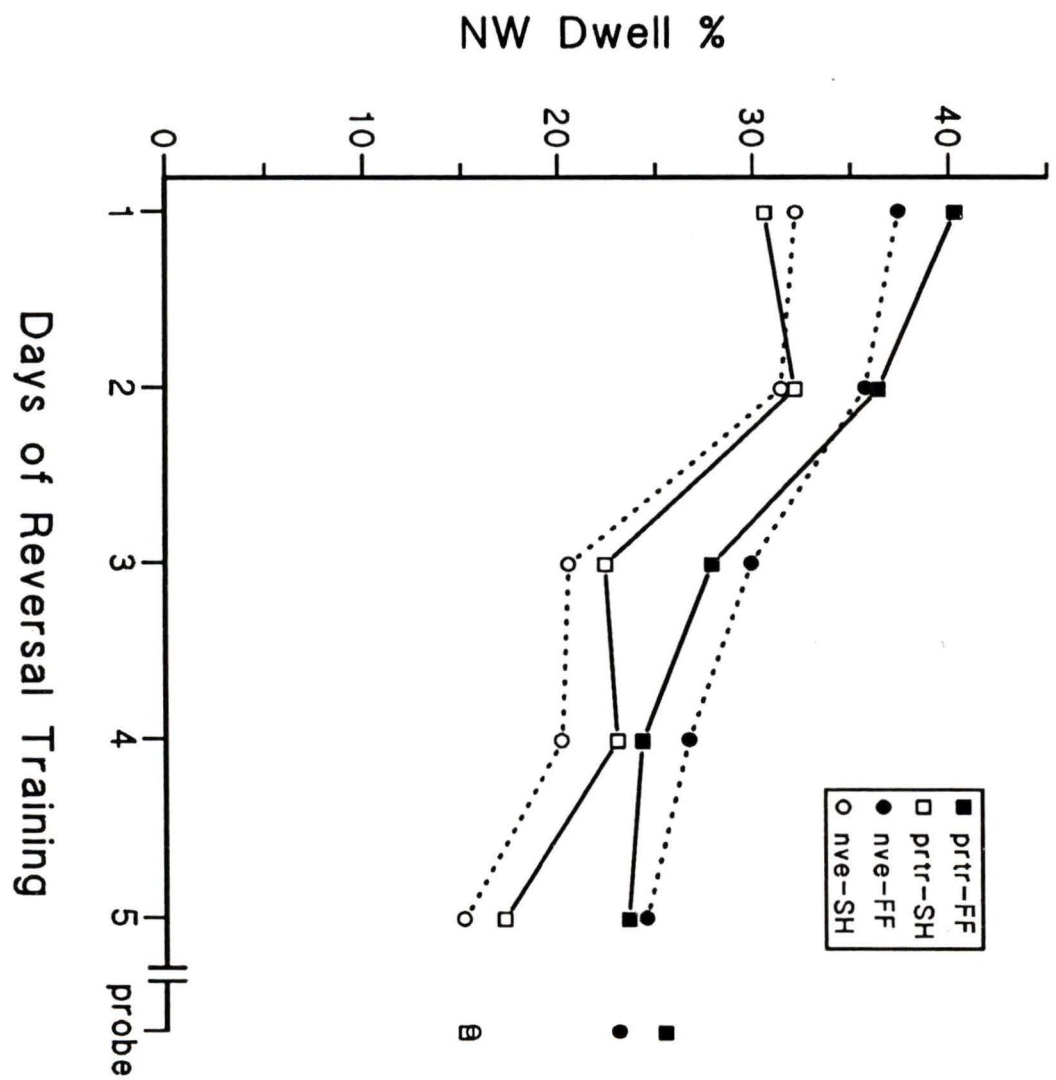
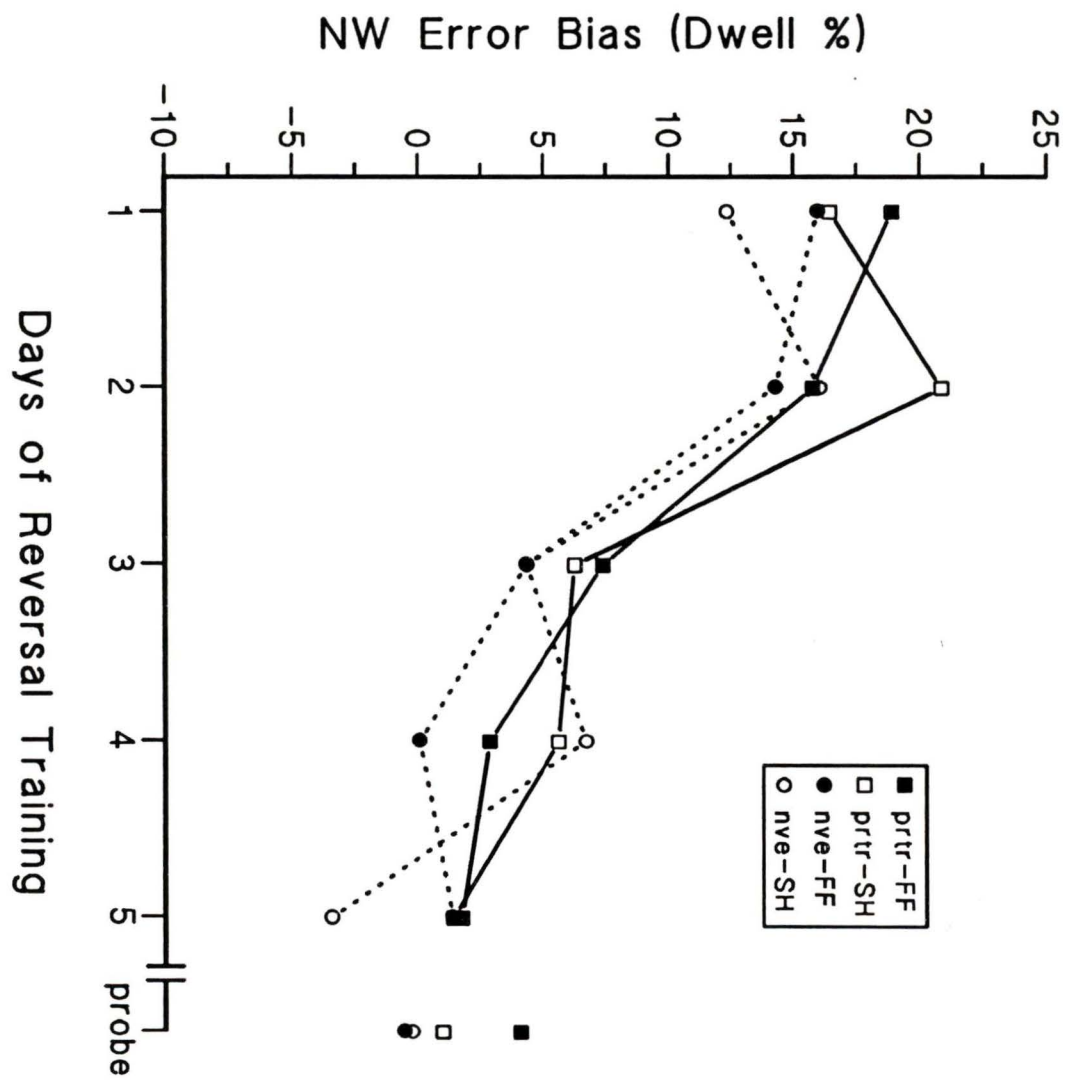

NW Dwell %
0
10
20
30
40
1
2
3
4
5
probe
Days of Reversal Training
prtr-FF
prtr-SH
nve-FF
nve-SH

Figure 7b


NW Error Bias (Dwell %)
-10
-5
0
5
10
15
20
25
1
2
3
4
5
probe
Days of Reversal Training
prtr-FF
prtr-SH
nve-FF
nve-SH

from that shown by the lesioned groups across the first five days of submerged platform trials ($F(1,29)<1$, $p>.85$) or on the probe trial ($F(1,29)<1$, $p>.68$). In spite of their error bias, sham animals showed very rapid acquisition of the new platform location. Overall, these data suggest that the unique contribution of perseveration to lesioned rats' deficit, if present at all, was restricted to the first three days of reversal training.

Phase C: Recovery. Similar to in Phase B, performance by lesioned groups showed substantial recovery over the course of training in Phase C. Both prtr-FF and nve-SH utilized increasingly efficient escape routes on submerged platform trials as shown by significantly shorter distances to escape across days (see Fig.5a, prtr-FF - $F(2,22)=61.5$, $p<.0005$; nve-FF - $F(3,43)=54.9$, $p<.0005$). Though neither lesioned group achieved escape distances equivalent to their respective sham-operated groups (prtr-FF vs prtr-SH - all $t(14)$'s≥ 1.76, $p<.05$; nve-FF vs nve-SH - all $t(15)$'s≥ 2.52, $p<.02$), both groups showed low escape distances which were equivalent to those shown by prtr-FF on the last day of pre-operative training by the ninth and eleventh days of training in Phase C respectively (prtr-FF - $t(8)=1.27$, $p>.12$; nve-FF - $t(16)=1.57$, $p>.07$). On probe trials, lesioned groups also showed significant improvement across days on both correct quadrant dwell percentages (see Fig.5b, prtr-FF - $F(3,24)=14.1$, $p<.005$; nve-FF - $F(3,24)=15.7$, $p<.001$), and crossing preferences (see Fig.5c, prtr-FF - $F(3,24)=3.5$, $p<.03$; nve-FF - $F(1,14)=1.51$, $p>.23$). More importantly, by the seventh day of training in Phase C, both prtr-FF and nve-FF searched persistently in the platform's general area, as shown by correct quadrant dwell percentages which were significantly greater than chance (prtr-FF - $t(8)=2.71$, $p<.014$; nve-FF - $t(8)=2.66$, $p<.02$), and

crossed over the platform's exact location repeatedly, as shown by crossing preferences which were also significantly greater than chance (prtr-FF - $t(8)=3.65$, $p<.005$; nve-FF - $t(8)=2.79$, $p<.02$ respectively). Furthermore, both lesioned groups achieved correct quadrant dwell percentages which were equivalent to their respective controls by the tenth day of training in Phase C (prtr-FF - $t(14)=0.5$, $p>.31$; nve-FF $t(15)=1.51$, $p>.07$), and crossing preferences which were equivalent to their respective controls by the eleventh and tenth days of training in Phase C respectively (prtr-FF - $t(14)=0.64$, $p>.26$; nve-FF - $t(15)=0.90$, $p>.19$). As in Phase B, the demonstration of highly localized search behaviour on probe trials provides strong evidence that, by the latter part of training, lesioned rats utilized spatial information to navigate to the platform.

Pre-operative Training. Pre-operative training had a relatively selective effect on performance by FF lesioned rats. It reduced the lesion-related deficit during the first phase of post-surgery testing (phase B) in that, relative to nve-FF, prtr-FF required less distance than nve-FF to locate the platform on submerged platform trials ($F(1,16)=29.5$, $p<.0005$), and showed higher correct quadrant dwell percentages ($F(1,16)=4.63$, $p<.05$) and crossing preferences ($F(1,16)=8.37$, $p<.011$) on probe trials overall in Phase B (see days 8 to 20 of Figs.4a, b, & c). However, both lesioned groups performed at comparable levels by the end of training in Phase B in terms of escape distances on the tenth and twelfth days of training (both $t(16)$'s≤ 1.65, $p>.06$) and in terms of correct quadrant dwell percentages and crossing preferences from the eleventh day of training onwards (all $t(16)$'s≤ 1.29, $p>.10$). Interestingly, when prtr-FF's and nve-FF's performance in Phase B is compared by days of overall training rather than by days post-surgery, no differences

are detected on either escape distances on submerged platform trials (see Fig.8a, $F(1,16)=1.83$, $p>.19$) or crossing preferences on probe trials (see Fig.8c, $F(1,16)=1.62$, $p>.22$). This suggests that the benefits derived from pre-operative training may be simply due to providing additional training and that this training could be provided post-surgery with equal effectiveness. Moreover, the same comparison on correct quadrant dwell percentage revealed that prtr-FF's performance was significantly worse than that of nve-FF (see Fig.8b; $F(1,16)=7.12$, $p<.02$), which suggests that post-surgery training may be even more effective. When tested for acquisition of a new platform location (Phase C), prtr-FF and nve-FF showed comparable escape distances on submerged platform trials and correct quadrant dwell percentages and crossing preferences on probe trials (see Figs.5a, b, & c, all $F(1,16)$'s<2.19, $p>.19$).

Figs. 8a-c). Comparison of post-surgery performance by lesioned groups in Phase B by days of training at the same platform location. Training days 1-6 were prior to surgery for prtr-FF. **a)** Mean distances on submerged platform trials. **b).** Mean correct quadrant dwell percentages on probe trials. **c).** Mean crossing preferences on probe trials. Note that nve-FF showed equivalent escape distances, equivalent crossing preferences, and higher correct quadrant dwell percentages in comparison to prtr-FF.

Figure 8a

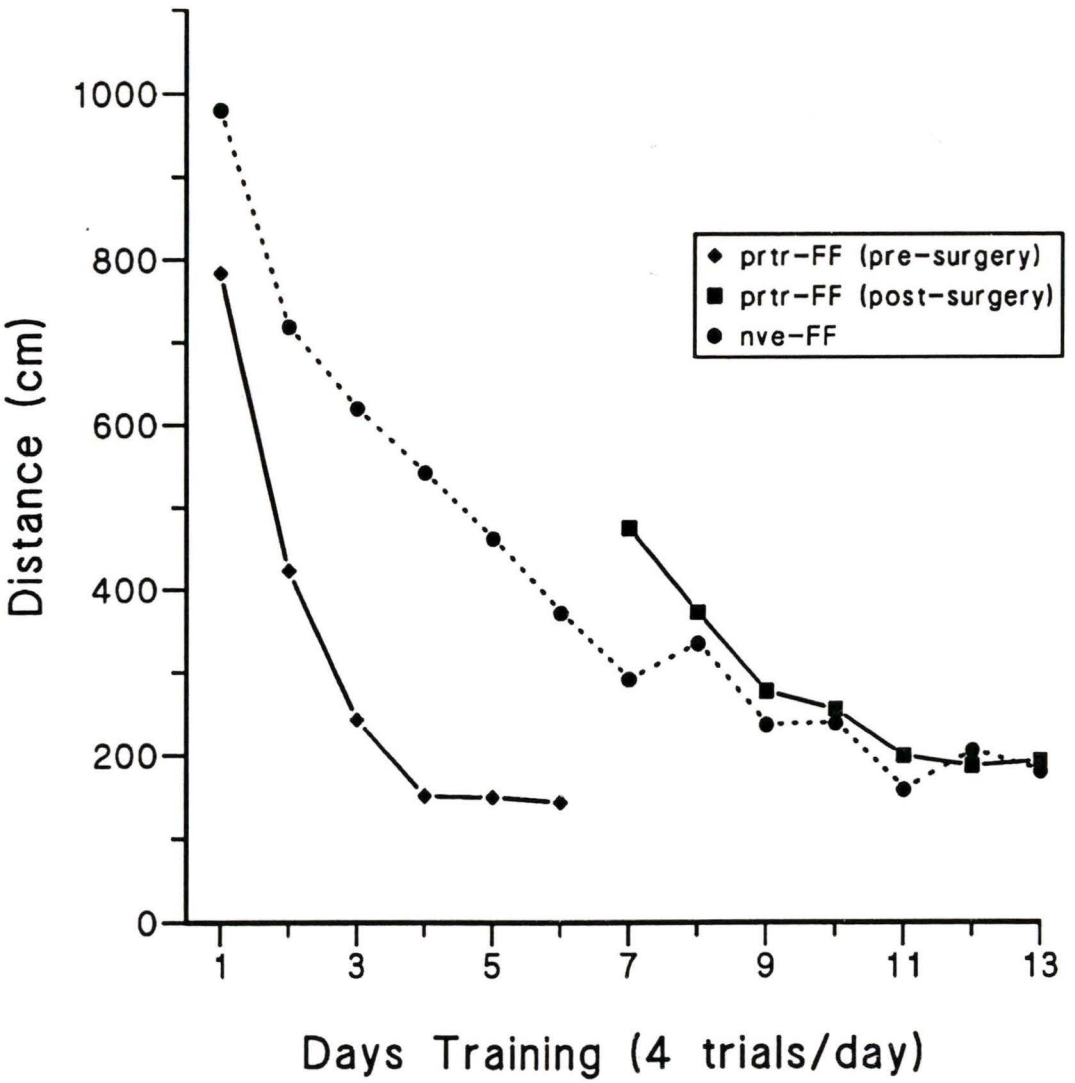

1000
800
600
400
200
0
Distance (cm)
1
3
5
7
9
11
13
Days Training (4 trials/day)
prtr-FF (pre-surgery)
prtr-FF (post-surgery)
nve-FF

Figure 8b

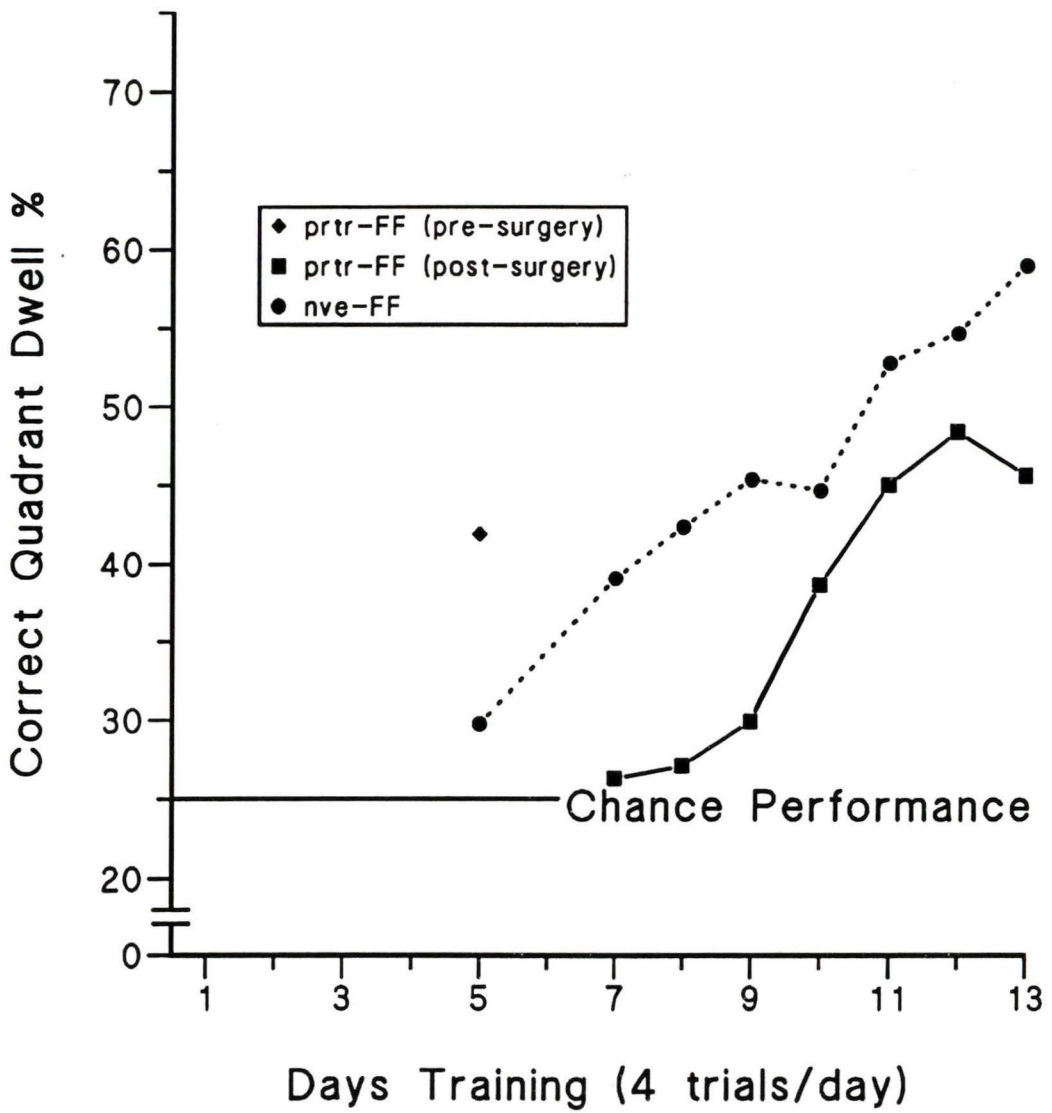
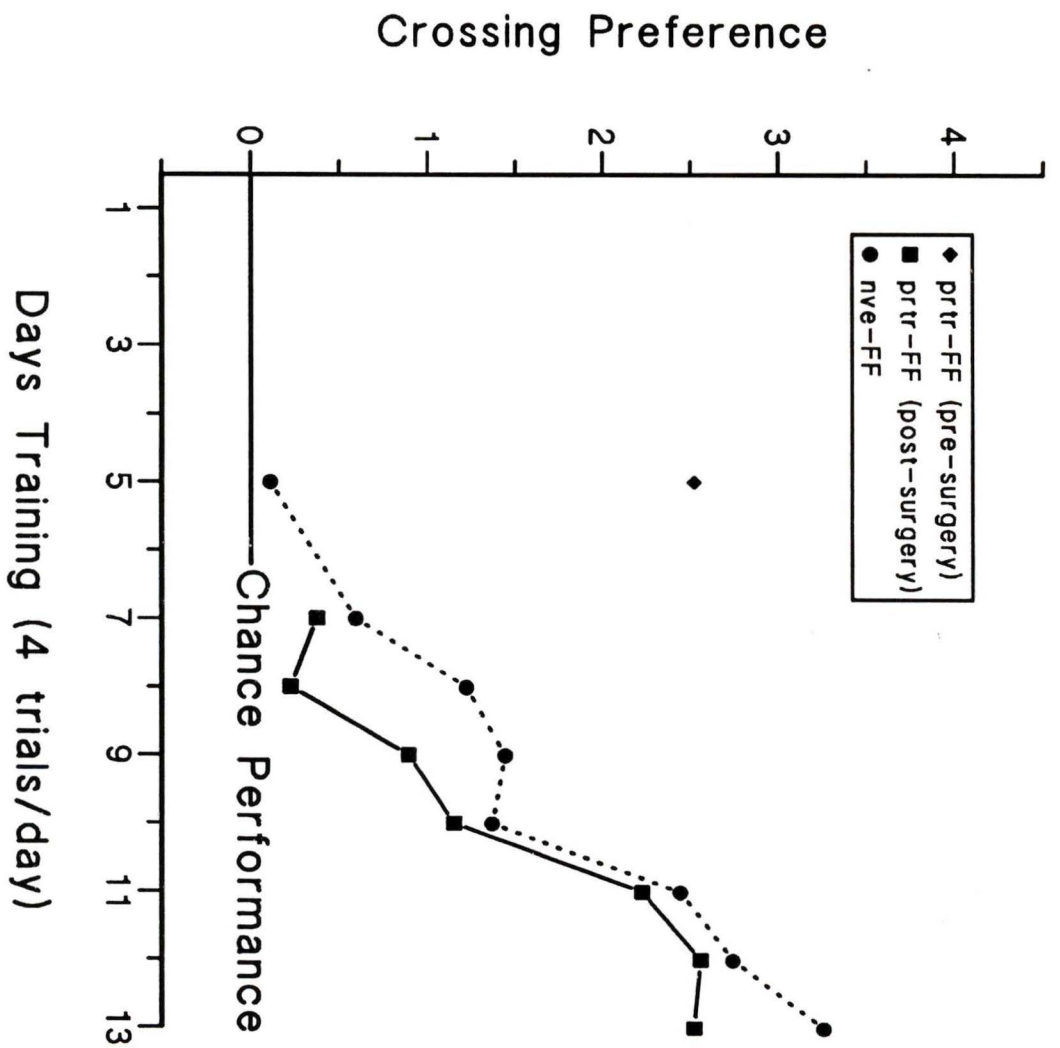

prtr-FF (pre-surgery)
prtr-FF (post-surgery)
nve-FF
Correct Quadrant Dwell %
70
60
50
40
30
20
0
Chance Performance
1
3
5
7
9
11
13
Days Training (4 trials/day)

Figure 8c


Crossing Preference
4
3
2
1
0
prtr-FF (pre-surgery)
prtr-FF (post-surgery)
nve-FF
Chance Performance
1
3
5
7
9
11
13
Days Training (4 trials/day)

Discussion

The effects of bilateral transection of the fimbria/fornix (FF) in the present study can be summarized as follows: 1) neither acquisition nor retention of a visible platform (VP) task in the Morris water maze (MWM) was impaired, 2) both acquisition and retention of the standard hidden platform (HP) task in the MWM were impaired, 3) recovery to near control levels of performance was achieved with extensive training and, 4) acquisition of a subsequent hidden platform location (reversal learning) was impaired, though performance again recovered. In addition, pre-operative training was found to speed post-operative attainment of asymptotic performance levels, but did not affect their magnitude or any aspect of performance in reversal learning.

Nature of the Deficit

The selective HP deficit in the MWM shown by lesioned rats suggests that cognitive processes necessary for spatial learning and memory were disrupted by transection of the FF. Optimal HP performance, and that shown by normal rats, relies heavily upon the use of allocentric spatial information (*i.e.*, the relationship of the platform to distal cue configurations). A disruption in spatial cognition, therefore, could easily account for the large impairments shown by lesioned rats in locating the platform. Moreover, the observation that FF lesions did not disrupt VP performance excludes a number of other possible impairments. For example, FF transection did not produce a global mnemonic impairment since the simple cue-reward associations required for VP task performance were acquired and retained by lesioned rats equally well as by controls. In

addition, since both the VP and HP tasks relied upon the same motivation (escape from 22^{0}C water) and some of the same sensorimotor abilities (*e.g*, coordinated, goal-directed swimming, climbing onto a platform out of water), a general performance impairment resulting from disruption of these shared components of water maze behaviour was also not produced. However, the contribution of more subtle sensory impairments and any interaction these may have had with learning, memory, motivation, and/or motor processes cannot be excluded since, relative to the VP task, the HP task required the use of more distal cues. Nonetheless, it seems unlikely that such a subtle sensory impairment could wholly account for the large HP impairments shown by lesioned rats. Moreover, any such deficits, if present, did not prevent accurate performance of the task after extensive training. The interpretation that FF lesions disrupted spatial cognition is also consistent with one of the most prevalent hypotheses of hippocampal function, the cognitive mapping hypothesis of O'Keefe and Nadel (1978; Nadel, 1991), as well as numerous accounts of FF lesions disrupting performance on a variety of tasks designed to test spatial cognition (*e.g.*, the MWM - Morris, Garrud, & Woodhouse, 1980; Nilsson et al., 1987; Pitsikas et al., 1991; Segal et al., 1989; Sutherland & Rodriguez, 1989; Tarricone et al., 1991; the radial arm maze - Becker & Olton, 1981; Becker et al., 1980; Cassel & Kelche, 1989; Dalrymple-Alford, Kelche, Cassel, Toniolo, Pallage, & Will, 1988; Jarrard et al., 1984b; Kelche, Dalrymple-Alford, & Will, 1987; Olton & Pappas, 1979; Packard, Hirsch, & White, 1989; spatial alternation - Daniloff, Bodony, Low, & Wells, 1985; Dunnet, Low, Iversen, Stenevi, & Björklund, 1982; Gage, Björklund, Stenevi, & Dunnet, 1983; Rawlins & Olton, 1982; Rothblat & Kromer, 1991; Shaw & Aggleton, 1993; Thomas, 1978;

Wible, Shiber, & Olton, 1992; and several other tasks - Aggleton, Keith, Rawlins, Hunt, & Saghal, 1992; Becker & Olton, 1981; Becker, Olton, Anderson, & Breitinger, 1981; Bresnahan, Wiser, Muth, & Ingram, 1992; Dalrymple-Alford et al., 1988; Dunnet, 1985; Fagan & Olton, 1986; Kametani, Bresnahan, Chachich, Spangler, & Ingram, 1989; Kelche, Dalrymple-Alford, & Will, 1988; Markowska, Olton, Murray, & Gaffan, 1989; M'Harzi, Palacios, Monmaur, Willig, Houcine, & Delacour, 1987; O'Keefe et al., 1975; Walker & Olton, 1984).

Recovery of Spatial Performance

The most important finding of the present study, however, is not that FF lesions impaired spatial cognition but rather that, with extensive training, spatial performance (*i.e.*, performance dependent upon the use of allocentric spatial information) eventually recovered. During the course of training, lesioned rats located the submerged platform with increasing efficiency such that, by the end of testing at both platform locations (Phase B and Phase C), they were able to navigate directly to the platform using a variety of swim trajectories from four different starting points. Although they were not as efficient in navigating to the platform as sham-lesioned rats with equal training, their escape distances were in the range normally exhibited by intact rats who have just reached asymptotic performance levels (*e.g.*, pre-operatively trained rats at the end of pre-operative training). However, since both spatial and non-spatial strategies can sustain proficient submerged platform trial performance, probe trial data provide critical evidence for determining whether the improvements shown by lesioned rats involved the use of an allocentric spatial strategy, and hence represented true recovery of spatial performance, or whether they

reflected the operation of an effective non-spatial strategy. On the first several probe trials in each post-surgery phase, lesioned rats searched randomly over the four cardinal quadrants of the pool, suggesting that any improvement they had shown on submerged platform trials derived from an increase in non-spatial search efficiency such as could be achieved by consistently swimming away from the walls of the pool. By the end of testing in each phase, however, lesioned rats spent more than half of their time searching in the platform's quadrant and crossed over the platform's exact location more than three times as often as the corresponding location in any of the other three quadrants, suggesting that performance eventually depended upon knowledge of the platform's precise location. This behaviour was comparable to that of controls in terms of both probe trial measures utilized (correct quadrant dwell percentage and crossing preference) and satisfies the usual criteria for verifying the use of a spatial strategy to locate the platform in the MWM (Morris, 1984). The localized searching shown by lesioned rats ensures that performance was dependent upon the use of extra-maze cues, since they provide the only basis for differentiating regions within the featureless white walls of the pool. Moreover, though a non-spatial *guidance* (O'Keefe & Nadel, 1978) strategy dependent upon an approach or avoidance response to a single extra-maze cue could produce some localized search behaviour, the observations that lesioned rats used multiple trajectories to the platform from different starting points on submerged platform trials and repeatedly crossed over the platform's precise location on probe trials indicate a navigational sophistication which only an allocentric spatial strategy could provide. Thus, the present observations provide strong

evidence that, with extensive training, spatial performance in the MWM recovers following FF lesions.

Comparison to Other Findings

The results of the present study contrast with those of several other studies of FF lesion effects in the MWM in which no evidence for recovery of spatial performance was obtained (Li et al., 1992; Nilsson et al., 1987; Pitsikas et al., 1991; Segal et al., 1989; Tarricone et al., 1991). However, several explanations can account for this discrepancy. Firstly, in three of the studies (Pitsikas et al., 1991; Segal et al., 1989; Tarricone et al., 1991) fewer hidden platform trials were given (< 30) than in the present study (60). In these cases, recovery may simply have required further training. In two cases where more trials were given (Li et al., 1992; Nilsson et al., 1987), large aspirative lesions were utilized which produced considerable damage extraneous to the FF and may have resulted in additional non-spatial impairments. Indeed, in Nilsson et al.'s (1987) study, FF lesioned rats showed a significant deficit on VP trials, in contrast to other findings with FF lesioned rats (the present study; Sutherland & Rodriguez, 1989), indicating that gross sensorimotor or motivational impairments, possibly unrelated to FF damage, were present and may have antagonized recovery of spatial performance. Unfortunately, no assessment of gross sensorimotor abilities or motivation was undertaken in Li and colleagues' study (1992), though the observation that their lesioned rats even failed to develop an effective non-spatial search strategy provides some indication that processes in addition to spatial cognition were impaired.

A number of methodological variables may also have played an important role in the recovery of spatial performance observed in the present study. Prior to any spatial testing, all rats received VP testing, which led to the positive transfer of at least some shared procedural components of the two tasks. For example, thigmotaxia, which is often displayed by FF lesioned rats (*e.g.*, Nilsson et al., 1987), was rapidly abandoned by both lesioned and sham-operated rats during VP trials and subsequently was shown infrequently by either group during spatial testing. Additionally, a well-distributed training schedule (4 trials per day for 13 days), repeated "non-extinction" probing, a cooler water temperature than often used (22^0C *vs.* 26^0C), and a relatively large platform area to pool area ratio (approximately 1:113; see Mactutus & Booze, 1994) may all have played roles of varying importance in promoting recovery.

Other studies, both in the MWM and in other tasks which assess spatial reference memory, have obtained results which are more consistent with the present findings. Using an unusual MWM testing protocol (releasing the rat from a constant start location and alternating visible and submerged platform trials with the platform in a constant location), Eichenbaum and colleagues (1990) observed that FF lesions produced an initial deficit followed by recovery of spatial performance as shown by a considerable reduction in escape latency and persistent searching in the platform's quadrant on both a novel start probe trial and the first trial of reversal. Also with FF lesions, Sutherland & Rodriguez (1989) found that, after extensive submerged platform training in the MWM (as many as 92 trials), lesioned rats showed a considerable decrease in latency to find the submerged platform, though the authors concluded that this improvement was based on the use of an

effective search strategy, rather than a spatial strategy, since lesioned rats' performance was not significantly disrupted when the platform's location was reversed (*i.e.*, moved to the opposite quadrant of the pool but held at a constant radius from the pool's centre). However, following reversal and visible platform testing, the platform was moved back to its original location and lesioned rats' latencies dropped from approximately 17 seconds (last trial block of reversal) to 6 seconds. This marked improvement in performance suggests that lesioned rats had indeed acquired spatial knowledge specific to the first platform location. Finally, a number of studies have shown recovery after FF lesions on other tasks that, like the MWM, demand spatial reference memory. For example, in two studies using the radial-arm maze configured to test both spatial working and spatial reference memory simultaneously, FF lesions have been observed to produce an enduring deficit of spatial working memory but only a more transient deficit followed by recovery on the spatial reference memory component (Jarrard et al., 1984; Olton & Pappas, 1979). Also, in several studies using a variety of discrimination tasks requiring spatial reference memory, FF lesions have been observed to produce a deficit in discrimination performance followed by recovery to criterion levels (Becker & Olton, 1981; Becker et al., 1981; Walker & Olton, 1984). In these cases, probe tests confirmed that accurate performance by both lesioned and control rats relied upon the use of spatial information.

Also of interest are several other studies using the MWM, which have shown recovery of spatial performance following substantial lesions to other components of the hippocampal system (*e.g.*, hippocampus - Morris et al., 1990; entorhinal cortex - Schenk & Morris, 1985; subiculum - Bolhuis et al., 1994; Morris et al., 1990). These data, along

with the present findings, suggest that recovery of spatial performance in the MWM may occur following a variety of subtotal lesions to the hippocampal system.

The observation of recovery of spatial performance after FF lesions, and perhaps subtotal hippocampal system lesions in general, suggests that, following such lesions, spatial cognitive capacity must either recover or not be completely eliminated. The present study provides some basis for differentiating these possibilities, at least with respect to FF lesions.

The Basis of Recovered Spatial Performance

Recovery of Function

One interpretation of recovered spatial performance is that those spatial cognitive abilities which are impaired by the lesion become restored with time and/or training (*i.e.*, 'recovery of function' occurs). Thus, as the capacity for spatial cognition returns, lesioned animals become capable of accurate spatial performance and should show normal acquisition of subsequent spatial problems. In the present study, however, after their spatial performance had recovered during testing at the first platform location, FF lesioned rats exhibited a severe impairment in acquiring a second platform location. This observation indicates a continued impairment of spatial cognition and argues against the occurrence of recovery of function.

One point to consider, however, is that recovery of function, in this instance, may have been masked by a deficit specific to reversal learning since the second platform location utilized was diagonally opposite to the previous platform location in the same pool and room and, therefore, presented a problem of spatial reversal. Rats with damage to the

hippocampus, or the FF, are well known to show deficits on tasks demanding reversal learning, particularly if the reversal involves spatial information (hippocampus - Douglas, 1967; O'Keefe & Nadel, 1978; FF - Becker et al., 1981; Fagan & Olton, 1984; Jarrard et al., 1984b; M'Harzi et al, 1987). One proposed basis for these reversal deficits is perseveration, or a failure of response inhibition (Douglas, 1967). According to this hypothesis, the inability to extinguish previously rewarded responses plays a unique etiological role in the emergence of deficits such as that observed in spatial reversal. However, an alternative interpretation is that perseverative tendencies are a response to an impairment in spatial cognition rather than a unique factor contributing to deficits (Ammassari-Teule et al., 1985; Ellen & Weston, 1983; Gaffan, 1972; O'Keefe et al, 1975; Olton & Werz, 1978). In the present study, lesioned rats did show some initial perseveration in searching at the previously correct platform location. However, sham-operated rats also showed some perseveration, yet they acquired the new platform location *more quickly* than the previous one. Furthermore, though lesioned rats exhibited perseveration over only the first three days of reversal testing, their deficit was present until the last few days of testing. Notably, lesioned rats showed no bias for either the previous correct quadrant or the new correct quadrant on their first probe trial of reversal (after five days of submerged platform testing), suggesting simultaneously that they no longer perseverated at the old location yet still had not learned the new location. Thus, perseveration, at most, may have contributed to the initial deficit shown by lesioned rats, and the severe deficit they showed in acquiring the new platform location primarily reflected a continued impairment in spatial cognition.

Partial Sparing of Function

If FF lesioned rats' recovery of spatial performance did not reflect recovery of spatial cognition then it must have reflected the operation of some residual capacity for spatial cognition which persisted after the lesion. Therefore, I hypothesize that FF lesions disable only a restricted component of the circuitry which normally participates in the processing, use, storage, and retrieval of spatial information and thus permit the eventual attainment of spatial performance based on the operation of spared components of this circuitry. However, in comparison to the capabilities of the intact system those of this residual spatial system appear to be limited in the following manner: i) *rate* of learning about places is severely reduced, ii) spatial information stored pre-operatively by the intact system is either destroyed (*i.e.*, retention is disrupted) or cannot be accessed (*i.e.*, retrieval is disrupted), and iii) efficiency of spatial navigation is compromised.

Reduced Learning Rate. The reduced learning rate is the most conspicuous feature of the residual spatial system left by FF lesions. In particular, it is apparent in the large acquisition deficits which are consistently observed on spatial tasks after FF lesions (e.g., Bresnahan, Kametani, Spangler, Chachich, Wiser, & Ingram, 1988; O'Keefe et al., 1975; Sutherland & Rodriguez, 1989). Since normal rats acquire spatial tasks very rapidly (see O'Keefe & Nadel, 1978 or Olton, 1979 for a discussion), and lesioned rats, dependent upon the slow residual system, can only acquire them very slowly, large differences in performance will be particularly apparent early into training on new spatial problems. The reduced learning rate of the residual spatial system also accounts for the observation that recovery after FF lesions is restricted to instances where extensive training is given (*e.g.*,

the present study; Becker et al., 1981; Walker & Olton, 1984), since spatial performance can emerge only at the slow rate (*i.e.*, over many trials) at which spatial information can be acquired. Finally, the reduced learning rate of the residual system may also help explain why recovery after FF lesions is observed on spatial reference memory tasks (*e.g.*, MWM - the present study; other reference memory tasks - Becker & Olton, 1981; Olton & Pappas, 1979; Walker & Olton, 1984) but not on spatial working memory tasks (*e.g.*, the standard version of the RAM - Becker & Olton, 1981; Jeltsch et al., 1994; other working memory tasks - Aggleton & Saghal, 1993; Rawlins & Olton, 1982; Wible et al., 1992). Reference memory tasks require that the same solution be applied on every trial and thus permit very gradual development of appropriate responses as information necessary for this response is slowly acquired. Thus, if sufficient training is given, such tasks can be acquired by animals that are only capable of slow information storage. In contrast, working memory tasks require different solutions to be applied from trial to trial (or within trials). Accurate performance demands that information which is necessary for making the appropriate response within a particular trial be stored immediately during that trial. Thus, performance is difficult, or impossible, for animals that are unable to store information rapidly (*i.e.*, within a single trial).

Partial Disruption of Retention or Retrieval. Were a reduction in learning rate the only limitation of the residual spatial system, then animals trained pre-operatively to criterion levels should not exhibit a deficit after FF lesions. Yet, in the present study, as well as others using the MWM (*e.g.*, Nilsson et al., 1987; Sutherland & Rodriguez, 1989) or other tests of spatial reference memory (*e.g.*, Becker et al., 1981; Kametani et al.,

1989), FF lesions produce impairments in pre-operatively trained animals. These observations suggest that an additional consequence of FF lesions must be either to destroy pre-operatively stored spatial memories or leave them inaccessible to the residual spatial system.

However, performance by pre-operatively trained rats after FF lesions does not typically drop to the levels of naive rats (Kametani et al., 1989; Sutherland & Rodriguez, 1989). For example, in the present study, though pre-operatively trained animals demonstrated no post-operative retention of the platform's location, as shown by chance performance on probe trials on each of the first two days of post-operative testing, they did perform significantly better and recover more quickly than animals with only post-operative training. This suggests that some information is retained after FF lesions which facilitates non-spatial search behaviour and participates in promoting recovery of spatial performance. One likely possibility is that procedural aspects of water maze performance, such as knowing to swim away from the walls of the pool and knowing to escape onto any object encountered, are retained. An alternative, or additional, possibility is that a storage site and/or format for spatial information which is not disrupted by FF lesions operates in parallel to the one which is disrupted by FF lesions. After pre-operative training, this parallel site or format would already support a partially developed engram which, though unable to sustain accurate spatial performance at the time, could, with further development through post-operative training, eventually support recovery. Indeed, pre-operatively trained and naive lesioned rats' post-operative performance was very similar when compared according to total days of training rather than days of post-operative training as

would be predicted if a storage mechanism which operated after FF lesions also operated in parallel to a FF-dependent mechanism in the intact brain.

Navigational Impairment. Finally, in addition to the above two mnemonic limitations of the residual spatial system, it appears that the spatial navigational capabilities of the residual system are also reduced in comparison to those of the intact system. Though lesioned rats eventually exhibited comparable knowledge of the platform's location as controls on probe trials, they still exhibited a slight deficit in navigating directly to the platform on submerged platform trials, as shown by slightly longer escape distances than controls. This suggests that lesioned rats exhibited a residual navigational impairment even after having accurately learned the platform's location. The basis of this impairment could be the tendency of lesioned animals to use abnormal swimming patterns, such as swimming in wide arcs or in loops. During the early segments of testing in each post-operative phase, FF lesioned rats developed a search strategy which involved circling the pool at a specific distant from the wall. As training progressed, this circling became increasingly localized in the area of the platform and on some trials was not shown at all. However, this pattern of swimming was seldom completely abandoned and added considerably to escape distances both on trials where a gradual arc was taken to the platform rather than a straight line and trials where near misses were followed by a gradual loop back rather than a sharper turn. These swimming patterns are similar to those seen after hippocampal lesions (Morris et al., 1990), or muscarinic receptor blockade (Whishaw & Petrie, 1988), and may reflect a disruption in the integration of spatially relevant sensory information with motor output (Bland, 1986) and/or a shift in the mobility gradient

(Whishaw, Cassel, Majchrzak, Cassel, & Will, 1994).

Neural Substrates of FF-Dependent and FF-Independent Storage

Thus, my hypothesis purports that, in the intact brain, spatial information may be stored in at least two forms. One is dependant upon the integrity of the FF and underlies the rapid acquisition and very efficient use of spatial information shown by normal animals. The other is independent of the FF, both for the storage and maintenance of spatial information, and is only capable of slower acquisition of spatial information and its less efficient translation into navigational behaviour. Though the present study provides no evidence as to the neural substrates underlying these two forms of spatial information storage, some basis for speculation exists.

FF-Dependent Storage Mechanisms. One candidate for the mechanism underlying the rapid storage of spatial information which is disrupted by FF lesions is hippocampal LTP. LTP is one of the leading physiological models of information storage in the mammalian nervous system (Barnes, 1988; Brown, Chapman, Kairiss, & Keenan, 1988; Eichenbaum et al., 1992; Morris 1990) and in the hippocampus, in particular, has been linked to spatial cognition (*e.g.*, Davis, Butcher, & Morris, 1992). FF lesions have been shown to prevent the induction of LTP in the dentate gyrus (Abe, Ishyma, & Saito , 1992; Buszáki & Gage, 1989; Valjakka, Lukkarinen, Koivisto, Lammintausta, Airaksien, & Riekkinen, 1991), and to disrupt the hippocampal theta rhythm (Buzsáki, Gage, Czopf, & Björklund, 1987; M'Harzi & Monmaur, 1985; Turnbull, Jiang, & Racine, 1994), which, itself, is thought to play an important role in naturally-occurring LTP generation (Larson & Lynch, 1986; Pavlides, Greenstein, Grudman, & Winson, 1988; Rose &

Dunwiddie, 1986) and has been implicated in spatial cognition (Turnbull et al., 1994; Winson, 1978). The significance of the loss of theta activity to the resultant mnemonic disruption following FF lesions was dramatically illustrated in a study by Turnbull and colleagues (1994). They showed that by imposing theta patterns of activity in the hippocampus via stimulation of an electrode in the perforant path, spatial working memory performance could be restored in previously impaired FF lesioned rats. On the basis of the above considerations, then, I suggest that the impairment produced by FF lesions results from a disruption of theta synchronization of hippocampal activity which, in turn, prevents the induction, and possibly expression, of hippocampal LTP.

FF-Independent Storage Mechanisms. Since both intrahippocampal and cortico-hippocampal circuitry remains largely intact after FF lesions, it is reasonable that considerable processing and storage capacity may still be retained within these residual components of the hippocampal system. For example, LTP at sites in the CA3 region is not affected by lesions to the medial septum, the source of much of the cholinergic and GABAergic innervation of the hippocampus via the FF (Feasey-Truger, Li, & ten Bruggencate, 1992), and may provide a basis for residual intrahippocampal storage capacity. Alternatively or additionally, cortical sites, several of which have been shown to play an important role in spatial cognition (*e.g.*, Sutherland & Rodriguez, 1989; Wiig & Bilkey, 1994a; 1994b), and whose connections with the hippocampus remain intact after FF lesions, may provide a basis for residual extrahippocampal storage capacity.

There are at least two sources of evidence for the existence of a slower storage mechanism for information which is "normally" hippocampal-dependent that could persist

after FF lesions. The first comes from studies on retrograde amnesia. After hippocampal system lesions, it is observed that memories more temporally distant from the time of lesioning show an increased probability of being retained (see Squire, 1992 for a review). This phenomenon, known as temporally graded retrograde amnesia, suggests that hippocampal dependent memories consolidate extrahippocampally over time, presumably at cortical sites (Squire, 1992; Swanson, 1983), and eventually no longer require the hippocampus for retention or retrieval. The fact that this process occurs much more slowly than normal hippocampal-dependent learning parallels nicely the slow learning shown by FF lesioned animals. The second source of evidence comes from studies on the effects of NMDA receptor blockade. The NMDA receptor plays a critical role in the induction of LTP in a number of sites including the dentate gyrus and CA1 region of the hippocampus (Errington, Lynch, & Bliss, 1987; Harris, Ganong, & Cotman, 1984). NMDA receptor blockade prevents induction of LTP at these sites and has been shown to produce profound learning impairments on a number of spatial tasks (e.g., Kant, Wright, Robinson, & D'Angelo, 1991; Kesner & Dakis, 1993; Lalonde & Joyal, 1993; Morris, Andersen, Lynch, & Baudry, 1986; Shapiro & Caramanos, 1992; Spangler, Bresnahan, Garofola, Muth, Heller, & Ingram, 1991; Walker & Gold, 1992; Ward, Mason, & Abraham, 1990). However, in some instances, slow learning has been observed after NMDA receptor blockade (Davis et al., 1992; Staubli, Thibault, DiLorenzo, & Lynch, 1989), even at doses which were shown to completely block LTP induction in the dentate gyrus (Davis et al., 1992). This suggests that similar information may be encoded in more than one format, one rapid and LTP-like which is dependent on the NMDA receptor and another

slower which is not dependent upon the NMDA receptor (see Staubli, 1989). Again, a nice parallel exists between slow NMDA-independent learning and slow FF-independent learning, particularly as both may reflect the operation of LTP-independent storage mechanisms.

Conclusions and Implications

In summary, the present study has shown that, following FF lesions, spatial performance in the MWM, though severely disrupted, eventually recovers with extensive training. The extension of recovery to the MWM is important since the probe procedures this task affords provide strong evidence that recovered performance after FF lesions indeed involves the use of allocentric spatial information. The present finding also corroborates a growing body of evidence which suggests that spatial performance recovers after subtotal lesions to the hippocampal system and indicates that, at least after FF lesions, this recovery is dependent upon residual capacity for spatial cognition rather than recovery of spatial cognition. The persistence of spatial cognitive capacity after subtotal hippocampal system lesions indicates that significant redundancy exists within this system and that each subunit makes additive, but individually non-essential, contributions to spatial cognition. The present results also suggest that residual spatial cognitive capacity which persists after FF lesions may represent a suitable target for therapeutic interventions with potential in the treatment of Alzheimer's Disease. Finally, the present results suggest that further evaluation of the nature and underlying mechanims of spatial learning and memory in FF-lesioned rats may be a useful model to study parallel storage mechanisms for qualitatively similar information in the brain and may provide insights into important

but little understood phenomena such as extrahippocampal memory consolidation and both LTP-dependent and LTP-independent storage mechanisms.

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DARREN KEITH HANNESSON

Sept. 29 / 1995

HEMISPHERIC DIFFERENCES IN PROCESSING PICTORIAL MATERIAL

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF ART

In the Department
of
Psychology

We accept this thesis as conforming
to the required standard

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