Research report

Modelling recovery of cognitive function after traumatic brain injury: spatial navigation in the Morris water maze after complete or partial transections of the perforant path in rats

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Abstract

The Morris water maze (MWM) has been used to assess cognitive function in rats after a variety of lesions designed to model brain damage and to assess the effects of drugs, growth factors, and neural transplants on post-operative deficits. The present study examined recovery of spatial navigation in the MWM over time in order to model the spontaneous recovery of cognitive function seen in humans. Diffuse axonal injury, a neuropathology commonly associated with traumatic brain injury (TBI), was modelled by transecting the perforant path (PP) bilaterally, either caudal to the hippocampus or dorsal to it at the decussation of the dorsal hippocampal commissure. Both groups with PP cuts showed substantial deficits initially, but spatial performance recovered with time and training. Recovery of platform finding was nearly complete within 14 days of testing, but recovery of platform searching did not occur for 2 or 3 more weeks. When the platform was moved to a new location, a continuing deficit in learning rate was revealed. When the platform was moved to a new position every day, this deficit was even more evident. These results illustrate the multi-faceted nature of recovery after brain injury and provide a new model for assessing the effects of manipulations designed to modulate recovery. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

Animal models of recovery of function after human traumatic brain injury (TBI) should provide a means for studying mechanisms and possible treatments, but only if they accurately model both the neuropathology of TBI and the cognitive-behavioural deficits commonly observed.

In humans, TBI (also called closed-head injury) occurs when the head strikes or is struck by another object at speed, and usually results from a motor vehicle accident [67]. The resulting brain damage varies greatly in severity and location depending on the circumstances, but there are a few common patterns (see [77] for a recent review). First, there tends to be damage to the cortex at the point of impact (the ‘coup’) and at the diametrically opposite pole (the ‘contra-coup’) [38]. Second, there is often damage at the tips of the frontal poles (particularly in the orbital frontal region), the tips of the temporal poles, and around the tentorium, due to the shape of the interior surface of the skull [1,73,118]. Third, there tends to be diffuse axonal injury from axonal shearing within the cortical and subcortical white matter, due to rotational forces [53,84]. Finally, there is often damage to the hippocampus due to...
its vulnerability to ischemia [127], and its position in the temporal lobe at the end of long fibre tracts [65,66]. These neuropathologies, including excitotoxic neuronal damage, occur even in mild head injury [44]. Animal models purporting to study the cognitive effects of some or all of these pathologies should be clear about which pathology is being simulated [35].

TBI also causes a wide range of behavioural and cognitive deficits. The period immediately following emergence from unconsciousness (a hallmark of TBI), is often characterised by severe disorientation and dense anterograde amnesia (called post-traumatic amnesia; PTA) which can last from hours to weeks depending on the severity of the injury [9,27,34,156]. This is followed by a period of fatigue, difficulties with concentration, impairments of attention, slowed learning, and poor memory [126,150]. Other problems, such as impassivity, excess emotionality, and social inappropriateness vary in severity depending upon the particular site of injury [52,119,140]. These deficits tend to improve considerably over the first 3–6 months [109,107] but also tend to persist for long periods (if not indefinitely) thereafter [49,122,137,151]. Once again, animal models should be clear about which cognitive deficits are being modelled and whether the model is concerned only with the initial deficit or also with ‘spontaneous’ recovery (i.e. in the absence of specific recovery-targeted treatments).

The term ‘recovery’ also requires careful defining. In different animal models, definitions have ranged from generous (i.e. any post-injury performance improvement [74]), to rigorous (i.e. complete restoration of the originally lost cognitive ability [3,57]). Presumably, the term ‘recovery’ should be applied to circumstances in which there is a demonstrable post-injury deficit which lessens or disappears with either time (i.e. spontaneously), training (cf. rehabilitation), or treatment (e.g. a drug or a graft). Perhaps a reasonable definition of recovery is: a lessening of post-injury performance deficits occurring with time, training or treatment, to a criterion used for uninjured individuals. By this definition, performance need not return to the same level as that achieved by control animals given comparable training, but only to levels that would satisfy standard criteria for demonstration of a particular cognitive or behavioural ability in uninjured animals. After all, it is unreasonable to ask more of brain-injured rats than is asked of controls. Inherent in this definition is the principle that partial recovery may be observed under some circumstances. However, this definition does not remove the need to distinguish the recovery of performance from the recovery of the underlying cognitive process. It is also important to remember that when recovery of learning and memory are being considered, recovery of learning rate and across-time retention needs to be evaluated as well.

In sum, there are at least seven questions which animal models of TBI should address. Two relate to external validity: is the neuropathology analogous to some component of human TBI, and is the behavioural deficit analogous to a cognitive impairment common in humans with TBI? Consideration should be given to the relative merit of simulating the cause of the TBI (e.g. impact), versus the effect of the impact (e.g. axonal shearing, contusion of frontal and temporal lobes). Five questions relate to the nature of the recovery being studied: (i) how severe is the deficit?; (ii) does it resolve spontaneously with time or training?; (iii) does performance return to control, pre-injury, or criterion levels?; (iv) does the recovered behaviour require the same cognitive processing as the lost behaviour or is it ‘behavioural compensation’ that represents a different solution to the behavioural task?; and finally (v) do the treatments given alleviate the deficit, and facilitate (spontaneous) recovery, or do they produce recovery that would not otherwise occur? Finger et al. [26] provide several excellent discussions of these issues. The primary purpose of the present study is to describe a new model for investigating recovery of cognitive function after TBI which addresses each of these concerns.

Quite a few animal models of TBI and recovery have already been proposed. One quite successful approach has been to model sensory, motor, or sensorimotor deficits, examine the effects of drugs on recovery, and investigate both neural mechanisms of recovery and potential clinical interventions. Early examples of this approach include: (i) recovery of beam walking after motor cortex damage (e.g. [24]); (ii) recovery from sensory neglect after sensorimotor cortex damage (e.g. [123]); (iii) recovery of eating and drinking after bilateral or unilateral damage to hypothalamic-dopaminergic systems (e.g. [74]); (iv) recovery of visual discrimination after damage to the visual system [15,83]; (v) recovery of conditioned avoidance after occipital ablation [32]; and (vi) recovery of posture and paw placement after hemispherectomy [152]. Considerable progress has been made in understanding the neurochemical basis of recovery in these tasks, and there have been very promising confirmations that findings in these animal models apply to humans (e.g. recovery of motor abilities after stroke; [36]). However, at least one laboratory has shown that the effect of a given drug (in this case, diazepam) in one paradigm (recovery from sensory neglect) does not generalise to another (recovery of working memory [123]).

A different approach taken in the past has been to investigate the recovery of spatial cognition (viz. navigation, learning and memory), often in the context of investigating recovery of hippocampal function. This approach has the basic premises that spatial cognition is a complex and advanced form of information processing (especially for a rat), which requires either a
cognitive map [96] or the processing of stimulus configurations [141], and which needs both a functioning cholinergic system and a functioning hippocampal system. The cholinergic system is of interest due to its putative role in the memory deficits associated with Alzheimer’s disease (see [10] for a review), while the hippocampal formation is of particular interest because of speculations that damage here is causal to the memory deficits of age (e.g. [7,160]). Alzheimer’s (e.g. [42,50,149]) and TBI (e.g. [9,14,120,121,136]). Early and recent examples of three of these paradigms are the T-maze [98,102,108,124], radial-arm maze (RAM; [51,99]) and the MWM [69,154]. Dunnett [22] provides an excellent comparison of behavioural tasks in their ability to reveal deficits after brain injury and ameliorative effects of neural transplants.

The MWM is a paradigm of particular interest because it offers a number of advantages for investigating mechanisms of recovery of cognitive function and treatments for TBI. It is very sensitive to loss of hippocampal function [88,142] and the cognition which it requires may represent the rodent analogue of the mnemonic cognition the hippocampus is thought to subserve in humans [92,96,139]. Hippocampal damage may also underlie the severe disorientation and anterograde amnesia (i.e. PTA) observed immediately after TBI [9] and some of the memory problems which persist for years [136]. The MWM also has the ability to characterise the severity of the deficit in either spatial learning or in spatial recall (navigation plus memory). The MWM permits regular and repeated assessments of spatial cognition which can track the recovery over time and reveal whether performance returns to control, pre-injury, or at least, criterion levels. Finally, the MWM allows for probe trials which can dissociate spatial search strategies from those based on cues or responses (see [80] for a more extensive discussion).

The MWM has already been used to investigate deficits after brain injury and neurochemical interventions (anatomical and pharmacological) in the context of investigating brain-behaviour relations (see [11,80] for reviews), as well as in the context of models of brain damage resulting from age (e.g. [16,30,148]), lesion models (e.g. [5,12,13,115,145]), ischemia (e.g. [46,70,97]), and TBI (e.g. [40,45,135]). These last three references are particularly interesting because they promote the MWM as a tool for assessing factors contributing to deficit severity after injuries, and speculate that recovery of function could be investigated, but focus almost exclusively on the deficits. However, the more recent work by these authors has made progress in studying recovery (see below) and Hicks et al. [45] is particularly interesting because it identifies hippocampal damage as being important for deficits in spatial memory after experimental brain injury (fluid percussion) and documents the sensitivity of the MWM.

Two different approaches have commonly been taken in studies of recovery of function. The first could be termed ‘deficit alleviation’, and involves the documentation of an injury-produced behavioural deficit and the capacity for a treatment to alleviate it, usually in a three-group design (uninjured control, injured-un-treated, injured-treated) with behavioural measurement taken only once, after the treatment has had a chance to work. While this approach has considerable efficiency and clinical utility, it does not examine spontaneous recovery and so cannot distinguish recovery modulation from recovery generation.

The second approach could be termed ‘recovery facilitation’; it evaluates any treatment effects against a baseline of spontaneous recovery, with the assumption that the treatment may facilitate a recovery process which is occurring naturally. The advantages of this approach include: (i) better modelling of human recovery patterns; (ii) the ability to distinguish ‘state’ versus ‘trait’ effects, i.e. those dependent on the continued presence of the treatment versus those that produce lasting effects; and (iii) a greater likelihood of distinguishing recovery of original function from behavioural compensation.

To date, most of the studies using the MWM to investigate the effects of pharmacological, neurochemical, and neuroanatomical (transplant) treatments on spatial performance after impairments due to age or brain injury have taken the deficit alleviation approach. For example, there have been studies to see if the deleterious effects of age can be ameliorated with transplants of foetal tissue [23,28,29], and studies to see if the effects of ischemia can be reduced or reversed with drugs [113] or foetal transplants [93]. Some studies have sought to reverse the deficits due to experimental lesions (often in models of brain damage, e.g. fimbria-fornix transections or neurotoxic lesions of the nucleus basalis magnocellularis to simulate cholinergic loss from Alzheimer’s) using pre-operative drugs [159] or postoperative drugs [4,71,106,112], growth factors [21,31,72], or foetal transplants [94,110,138,157], with one study looking at both transplants and growth factors [8]. Recently, several studies have examined the effects on recovery from experimental TBI of pre- or post-injury MK-801 [41], pre-operative administration of a hydroxyl radical scavenger [69], post-injury muscarinic antagonists [18,19,104], and post-operative progesterone [114] or environmental enrichment [116,117]. However, of all of these studies, only two have examined the effect of the manipulations relative to spontaneous recovery levels [19,117].

Two studies have serendipitously observed (spontaneous) recovery of function in the MWM after retro-hippocampal lesions [89,125] and a few others have speculated that recovery of function could account for the absence of expected lesion-induced deficits.
There have been a few studies which have used the MWM to investigate the recovery process itself. Several (reviewed in [59]) have tested the Kennard principle and the effects of environmental enrichment or noradrenaline on recovery after cortical lesions in infancy by examining spatial abilities in adulthood [55,56,58,64,154] or after adulthood lesions [115,117]. Although many studies have examined the effects of grafts, the study by Kolb et al. [62], is notable for comparing graft effects at two different points in time, and assessing graft effects against a background of spontaneous recovery. Similarly, a study of the effects of diazepam on recovery of MWM working memory performance after sensorimotor cortex lesions is notable for its examination of a drug effect on the recovery process, and not just the deficit [123]. One very good recent study examined the change in sensitivity to anticholinergic drugs before and after recovery from experimental TBI [19].

In sum, the MWM is widely considered to be a valuable tool for assessing deficits after cortical and hippocampal injury and for investigating the recovery process, but very few studies have actually examined spontaneous recovery in order to determine whether the effects of treatment create or modulate recovery. Furthermore, many (though not all) of these previous studies have tested only acquisition (which cannot reveal spontaneous recovery), or have not used visible platform trials to assess non-spatial deficits or probe trials to distinguish recovery of spatial abilities from refinement of non-spatial behaviour. The present study was undertaken to determine whether the MWM can be used to (i) assess the severity of initial deficits, (ii) track spontaneous recovery, and (iii) investigate the nature of that recovery using a new model of TBI.

To model axonal shearing seen in TBI [100] and hippocampal damage [65,66], bilateral knife cuts were made to the perforant path (PP), the prime cortical input/output pathway from the entorhinal cortex to the hippocampus [144]. Although several models have been developed to simulate an impact on the skull (see [35] for a review), the nature of the pathology resulting from these manipulations is unclear, but seems to be primarily focal, at the point of impact and radiating conically in line with the direction of the force [17,20,78]. With a knife cut to the PP, the locus of the injury is more circumscribed and identifiable. Bilateral knife cuts were placed at two different locations where the PP is known to be dense: one in the angular bundle where stimulation is often delivered to evoke potentials in the dentate gyrus for electrophysiological studies (e.g. [134]) and one further anterior which previous research had shown to be along the same projection of the PP to the dorsal dentate gyrus [133]. This latter position was intended to produce partial PP lesions with correspondingly smaller deficits and/or a faster recovery. At the outset of this study it was not known whether any recovery would be observed after either transection.

Damage to the PP has already been proposed as a model for investigating mechanisms of neuronal trauma and regeneration following CNS trauma [103]. However, in that study, the lesion was unilateral and aspirative, and though it damaged much of the dorsal subiculum, it produced very little impairment in MWM acquisition. The present study used bilateral knife cuts to lesion the PP more completely, discretely, and with greater behavioural effect.

The rats were pretrained prior to surgery to increase the visibility of post-operative deficits and testing was begun shortly after surgery in order to model recovery from PTA. Testing continued daily for 14 days, to track recovery, and then weekly for 6 weeks to test retention and longer-term recovery. The rats were then tested with the platform in a new position, to test spatial learning, and then with the platform in a different position each day for 5 days to test for deficits in working memory [86] or learning set acquisition [153], or most simply, learning rate. A preliminary report of these findings was made previously [129].

2. Materials and methods

2.1. Subjects

Twenty-four male Long-Evans rats (Charles River, Canada) weighing 410–520 g were housed individually in shoebox cages with food and water ad libitum. All tests were conducted during the light portion of the 12:12-h light-dark cycle.

2.2. Surgery

The rats were anaesthetised with sodium pentobarbita-
tal (Nembutal 60 mg/kg) and placed in a Kopf stereotaxic with skull level. Bilateral knife cuts were placed in either the posterior portion of the PP, to sever the entire pathway (n = 8), or at a midpoint on the pathway to sever the innervation of the dorsal hippocampus while sparing the innervation of the temporal portion (n = 8). Knife cuts were made using a disposable arteriotomy knife (Moira; Fine Science Tools) which had a triangular blade 7 mm long, 2 mm wide at the base and 0.2 mm thick, with an edge angled 15° to the handle. In the ‘posterior PP cut group’, a 2.5 mm-wide slot was drilled in the skull centred 1.7 mm
anterior to the intraaural line and extending bilaterally from 0.5 mm to 5.0 mm lateral to the midline, with most of the bone over the sagittal sinus removed as well. The knife was mounted on a manipulator angled 20° from vertical in the coronal plane, so that the knife edge was angled a total of 35° from vertical. It was positioned 1.7 mm anterior to the intraaural line, 4.0 mm lateral to the midline on the left side, and then inserted 5.0 mm (as measured by the vertical scale of the manipulator), penetrating at a 20° angle. It was then moved 2.5 mm medially (as measured by the ‘horizontal’ scale of the manipulator), then withdrawn using the ‘vertical’ adjustment of the manipulator. The procedure was repeated on the right side. Fig. 1A shows the intended paths of the posterior PP knife cuts.

In the ‘anterior PP cut group’, a 2.5 mm-wide slot was drilled bilaterally, centred 3.7 mm anterior to the intraaural line and extending from 0.3 mm to 5.3 mm lateral to the midline. The knife was held vertically, with the point medial and the 15° knife edge facing lateral, positioned 3.7 mm anterior to the intraaural line and 0.5 mm lateral to the midline. The knife was inserted 3.0 mm below the surface of the cortex, then moved laterally 3.5 mm. After making the cut on the left side, the knife was rotated to face to the right and the procedure was repeated. The path of these knife cuts (Fig. 1B) was intended to transect the PP at a point where previous electrophysiological studies had shown the PP projection to the septal dentate gyrus to be most dense [133], in the CA1 region just dorsal to the hippocampal fissure. In the Sham-operated group, slots were drilled in the skull at either the posterior or the anterior position, but the knife was not inserted. After the cuts were complete, the slots in the skull were sealed with sterile bone wax, the wound was treated with antiseptic ointment (Hibitane) and then sutured. All rats were returned to a recovery cage with a heat lamp overnight. Testing began the day immediately following a single recovery day, approximately 48 h after surgery.

2.3. Apparatus

The Morris water maze consisted of a circular pool (150 cm diameter, 45 cm high), with a featureless white inner surface, filled to a depth of 25 cm with 26°C (+1°C) water, rendered opaque by the addition of 1500 ml skim milk powder. The submerged platform was a clear Plexiglas stand with a 13 × 13-cm top submerged 2.5 cm below the surface of the water so as to be invisible at water level. The visible escape platform was black and its top (13 × 13 cm) protruded 5 cm above the surface. The maze was housed in a windowless room with some lights directly over the pool and others illuminating the walls, a variety of visual cues on the surrounding walls, and a radio providing background noise.
2.4. Procedures

Before surgery, all rats were trained to locate the submerged platform over 6 days, with four trials per day. On the last 3 days of this pretraining, two trials were added: a probe trial without any platform and a visible platform trial.

All four submerged platform trials were begun by placing the rat gently into the water, facing the wall at one of four randomly determined starting positions (arbitrarily called north, east, south or west; N, E, S or W). The platform was submerged in the centre of the NW quadrant (position 'A', Fig. 2). Rats that failed to locate the platform within 60 s were gently guided to it and allowed to climb on. Rats were left on the platform for 15 s, and were then returned to a holding cage under a warming lamp for the intertrial interval (approximately 5 min). On the fifth trial (probe — no platform), the rats were started from the south pole and allowed to swim freely in the pool for 30 s. On the sixth trial, the visible platform was located in a quadrant adjacent to the ‘correct’ quadrant on submerged trials (i.e. NE or SW) and the rats were started from one of the two poles farthest away (i.e. S or W for NE, and N or E for SW). Swim paths and latencies for submerged and visible platform trials, and quadrant dwell times for probe trials were recorded and analysed using a Chromotrack videotracker (San Diego Instruments) attached to a microcomputer.

Rats were operated on the day following the sixth pretraining day, and postoperative testing began after a single recovery day (approximately 48 h after surgery). Postoperative testing consisted of four submerged platform trials, a probe trial and a visible platform trial daily for 14 days, then weekly for 5 weeks. After that, to assess place learning (as opposed to retention or relearning), the location of the submerged platform was ‘reversed’ to the opposite (SE) quadrant (position ‘B’, Fig. 2), and the rats were tested daily with four submerged platform trials and a probe trial for 7 days.

One week after completion of reversal training, all three groups were tested for 5 days with a ‘vary-maze’ procedure in which the platform was placed in a different position each day (cf. [86,153]) (Fig. 2). Each session consisted of eight trials, begun from one of the polar starting positions in pseudorandom order, and lasting 60 s or until the rat reached the platform. Rats failing to find the platform were guided to it. All rats were left on the platform for 15 s and then removed to a heated area for the intertrial interval (approximately 5 min). As before, distance and latency to find the platform were recorded by the video-tracking system. On the last (fifth) day, an additional 30-s probe trial without a platform was given, and the time spent in all four quadrants was recorded.

2.5. Histology

After all testing, the rats were sacrificed with an overdose of sodium pentobarbital and perfused with saline and formalin. The brains were frozen and sectioned horizontally through the entire hippocampus. Knife-cut damage to cell and fibre areas of each rat was documented by matching thionine-stained serial sections to one of 12 horizontal plates from Paxinos and Watson [101] and drawing the direct damage on a reproduction of the plate. Cellular degeneration in pyramidal cell layers II and III of the entorhinal cortex and the granule and pyramidal cell fields of the hippocampus was evaluated. Equivalent sections from control and lesioned rats were visually compared for number and density of cells at 0.5-mm intervals through the entorhinal cortex (as defined by [103]), and cell loss at each level was rated as complete, substantial, minimal, or absent (when all cell density appeared to be normal).

2.6. Data analysis

Distance, latency, swim speed, and quadrant preference (percent dwell time) were all analysed using a repeated measures multivariate analysis of variance (MANOVA) with group (Sham, anterior PP and posterior PP) as the independent variables and days postoperative as the repeated measure, testing for trends on all
factors involving ‘days’. Significant effects of days were explored for simple effects by testing each group on its own, while simple interactions were tested by conducting pairwise comparisons of the groups using additional MANOVAs. To compensate for these (in effect) five planned comparisons, alpha was adjusted from the $P < 0.05$ used for the original MANOVA, to $P < 0.01$. Where appropriate, post-hoc comparisons between groups were analysed using Tukey $B$ tests with one-tailed hypotheses and alpha of $P < 0.05$. All analyses were conducted using SPSS® for Windows.

3. Results

3.1. Histology

Anterior PP cuts produced very little damage to either the overlying cortex or the underlying hippocampal cell fields in all but one rat. This exception sustained substantial damage to the left dorsal hippocampus and subiculum, and was excluded from further analysis. In the other seven rats, tissue loss was evident only upon careful comparisons between anterior cut rats and controls, at a dorso-ventral level dorsal to the most dorsal plate in the atlas [101]. Loss of commissural fibres at this level was 40–90%, and six of the seven rats had 25–100% loss of fibres extending rostromedially from the angular bundle (Fig. 3A). Sham-operated (control) rats sustained only minor damage to the cortex under the trephine holes.

Posterior PP knife cuts transected the posterior neocortex at the antero-posterior level of the subiculum, separating the entorhinal cortex and posterior perirhinal cortex from the more rostral parts of the brain (Fig. 3B). They directly damaged most of the PP, part of the subicular complex and a small amount of the overlying cortices (occipital, perirhinal, and retrosplenial). In seven of the eight rats, knife cuts passed through the angular bundle and transected the corpus callosum anterior to the forceps major in both hemispheres. At the time of histology, 6 months after surgery, most of the angular bundle was simply not there (Fig. 3B). In the eighth rat, the angular bundle was damaged only unilaterally, and this rat was excluded from further analysis. The other seven rats had substantial transections of the dorsal hippocampal commissure bilaterally. Little chromatolysis surrounded the lesion site and tissue damage consisted primarily of white matter loss in the angular bundle and forceps of the corpus callosum, with occasional loss of tissue in the neighbouring subicular regions. Four of the seven rats had complete or near complete loss of pyramidal cells in layers II and III of the entorhinal cortex bilaterally, as defined for measurement by [103]. Of the remaining three rats, one had moderate cell loss bilaterally while the other two showed moderate loss of cells in the entorhinal cortex on one side and partial loss on the other. In contrast, no damage or cell loss in the dentate gyrus or pyramidal cell fields of the hippocampus was evident.

3.2. Behaviour

3.2.1. Overview

After the preoperative training, all groups took short paths to the platform on submerged platform trials (Fig. 4) and preferred the correct quadrant on probe trials (Fig. 5). The early days of postoperative testing revealed substantial deficits in both cut groups, indicated by longer distances (Fig. 4), longer latencies (not shown) and loss of quadrant preferences (Fig. 5). Continued daily testing/retraining revealed rapid recovery
of distance and latency, with slower recovery of quadrant preferences over 2 weeks. Subsequent weekly testing revealed further recovery of quadrant preferences, to control levels or better. Repositioning the platform to the opposite quadrant and daily testing uncovered a residual deficit in new learning. This impairment was even more apparent when the rats were tested with a new platform position every day. All deficits appeared to be specific and spatial, since no group showed any impairments on visible platform trials or swim speeds on submerged platform trials (Figs. 6 and 7).

Analyses of all five dependent variables (distance, latency, quadrant preference, swim speed and visible platform latency) from the five phases of the experiment were conducted separately. The five phases (and their component test days) were: (i) initial deficit (pre-versus postoperative day), (ii) immediate recovery (14 daily post-operative tests), (iii) longer-term recovery (five weekly tests), (iv) new learning (seven daily tests in reversal), and (v) rapid learning (five daily ‘vary-maze’ tests).

3.2.2. Initial deficit

Both cut groups showed clear initial deficits. Comparison of immediately pre- and postoperative performance showed significant changes on all three measures, with both cut groups changing in distance ($F(1,6)$’s $> 19.8$, $P < 0.004$), latency ($F(1,6)$’s $> 23.7$, $P < 0.003$), and quadrant preference ($F(1,6)$’s $> 6.5$, $P < 0.05$). There was no significant change in the control group on any of the three measures, and no change in any group in swim speed or visible platform latency. The transection-induced deficit was also evident as a significant difference between the control group and each of the two cut groups on all three dependent variables over the first 14 postoperative test days (pairwise MANOVAs, all $F(1,13)$’s $> 9.7$, $P < 0.01$).

3.2.3. Immediate recovery

Both cut groups improved their performance over the first 14 postoperative test days. The Sham group showed a slight (non-significant) deficit in distance scores and almost no change in quadrant preference on the first few test days (Fig. 6). In contrast, the two cut groups showed clear deficits on distance, latency and quadrant preference, but there was considerable recovery beginning almost immediately: there were significant linear trends in all three variables ($F(1,19) > 19.4$, $P < 0.005$) (Figs. 5 and 6). In fact, by the end of the 14 daily tests, performance had returned almost to control levels. The difference between the stable quadrant preferences of the Sham group and the recovery in the cut groups was confirmed by a significant group-by-day interaction of the linear trend in the posterior PP group ($F(1,13) = 5.8$, $P < 0.03$), though not in the anterior PP group ($F(1,13) = 2.5$, $P = 0.13$). This difference was also evident in the length of time required for quadrant preferences to rise above chance levels. The Sham group was significantly above chance from Day 4 onwards ($P < 0.05$, one-tailed $t$-test against 25%; Fig. 5) whereas neither cut group rose above chance on any of the initial 14 postoperative test days. Comparison of days to criterion (i.e. number of test days required to achieve two successive days significantly above chance) showed that rats in the Sham group required an average of only 4.0 days ($\pm 0.9$), the posterior PP group 13.7 ($\pm 2.2$) days and the anterior PP group 12.9 ($\pm 2.0$) days, and that both cut groups were different from the Shams (Tukey $B$, $P < 0.05$).
Fig. 5. Mean percentage dwell times in the correct quadrant on probe trials. Filled symbols (● ■ ▲) indicate which mean dwell times were significantly greater than chance (25%). Preference for the previously correct quadrant (NW) at the end of the first day of reversal training (Day 56, SE quadrant) is shown as Day 56’. Abbreviations as per Fig. 1. Note the failure of both cut groups to acquire a significant quadrant preference during the retention/recuperation phase and their achievement of it during maintenance testing. Also note the extinction of quadrant preference on the first day of reversal and the ultimate acquisition of a strong quadrant preference.

The surgery produced few, if any, non-specific deficits. Swim speed remained reasonably constant throughout (Fig. 6), with no systematic or significant differences between the groups. Visible platform latencies were not significantly different between the groups and though the posterior PP group had slightly longer latencies initially and showed improvement over the first 7 days (linear trend, $F(1,6) = 11.7, P < 0.014$), this was the only change in any dependent variable of any group.

Although the cut groups showed rapid recovery, it was demonstrably incomplete for distance and latency. On the last two of the 14 daily test, both cut groups were still significantly different from the Sham group on distance and latency (Tukey $B$, $P < 0.05$) and still did not show significant quadrant preference.

3.2.4. Longer-term recovery

Both cut groups sustained their performance levels when tested at weekly intervals, and actually improved their quadrant preferences over the five weekly tests, relative to the 5 preceding test days ($F(2,19) = 13.33, P < 0.002$), achieving control-level performance in quadrant preference (Fig. 5). The anterior PP group showed a significant linear trend ($F(2,19) = 38.9, P < 0.001$), the posterior PP group showed nearly significant quadratic and quartic trends ($P < 0.05$ but $> 0.01$), and the Sham group had no significant trends ($P < 0.01$). The anterior PP group was significantly better than the posterior PP group ($F(2,19) = 12.8, P < 0.004$) and was almost significantly better than the Sham group ($F(2,19) = 8.6, P = 0.012$). Distances on submerged platform trials remained stable from the end of the daily tests through to the end of the weekly tests, and both cut groups remained significantly worse than the Sham group (distance and latency, $F(2,19) > 10.8, P < 0.01$). There were no significant differences between the groups or changes over weeks in either swim speed or visible platform latency. Thus the two cut groups recovered their ability to search correctly for the platform, but did not regain the ability to swim to it as directly as controls.

3.2.5. New learning

Reversal of the platform to the opposite quadrant revealed two aspects of the recovery in the cut groups. First, the recovered performance reflected the recovery of spatial cognition and second, the learning rate had not completely recovered. Recovery of spatial cognition was indicated by the increased distance and latencies and decreased preference for the previously correct quadrant (dependent $t$-tests, $P < 0.05$) on the first reversal day, showing that the rats had been attuned to its previous location. Impairment of new learning was indicated by the first probe trial, on which the Sham group showed significant preference for the new location ($t$-test vs. 25%, $P < 0.05$; Fig. 5), while the two cut groups remained at chance and were significantly worse (Tukey $B$, $P < 0.05$).

The partial recovery of spatial learning was evident in the performance of the cut groups over the 7 days of testing with the reversed platform location. All three groups acquired the new platform location, taking increasingly direct paths to the platform, with significant linear trends in distance and latency ($P < 0.01$; Fig. 4). On submerged platform trials, the posterior PP group was virtually indistinguishable from the Sham group, and the anterior PP group was not significantly differ-
On probe trials, the Sham group showed high, stable preferences, whereas the two cut groups improved over time, showing significant linear trends ($P < 0.01$). Impaired acquisition in the two cut groups was evident in the slower acquisition of preference for the newly correct quadrant. The Sham group showed a significant preference from the first day onwards, while the cut groups did not acquire a significant preference until day 3 or 4 (Fig. 5). Pairwise comparisons of linear trends revealed significant difference from the Sham group by the anterior group ($P < 0.01$) and (almost) by the posterior group ($P = 0.02$). Once again, there were no significant differences or no changes in swim speeds ($P < 0.05$; Fig. 6).

### 3.2.6. Rapid learning

When challenged with the task of learning a new platform position each day, rats that had apparently recovered their ability to locate the platform spatially now displayed a severe continuing deficit. Fig. 8 illustrates the performance of each group over trials and over days in the ‘vary maze’ and shows that the cut groups generally took longer paths to the platform, showed less learning each day (i.e. decreasing distances over trials), and were more erratic from trial to trial.

The data from the vary maze were analysed in several different ways to assess different performance characteristics. The data were analysed for group effects and trends across both days and trials for all three groups, then within each group (simple effects), and then pairwise between cut and control groups. Alpha was $P < 0.05$ for the initial analysis, and adjusted to $P < 0.01$ for the six simple-effects analyses. Overall, there was a significant effect of group ($F(2,19) = 9.8$, $P < 0.001$), though pairwise comparisons showed only the anterior PP group to be significantly different from the Sham group ($F(1,13) = 16.3$, $P < 0.001$), while the posterior PP group was not quite different from either the Sham group ($F(1,13) = 7.7$, $P < 0.016$) or the anterior PP group ($F(1,12) = 4.6$, $P = 0.052$).

Examination of trends over days indicated that the three groups showed different long-term learning in this task (Fig. 9, left panel). The Sham group showed a significant quadratic trend over days ($P < 0.01$), indicating rapid learning to asymptote, the posterior PP group showed only a significant linear trend ($P < 0.0001$), indicating slow and steady learning, and the anterior PP group had no significant trend over days ($P > 0.15$), indicating an absence of learning over days.
Fig. 8. Distances travelled by each group on each trial (Tr1–Tr8) of each day of 'vary-maze' training, in which the platform was put in a new position each day. Note the relatively smooth learning curves of the Sham-operated group on each day, contrasted with the relatively erratic performances of both anterior and posterior PP cut groups.
Examination of changes over trials (collapsed across days) showed that both cut groups were impaired at finding the platform and learning its position (Fig. 9, right panel). The Sham group appeared to take only a few trials to learn the platform position whereas the two cut groups improved more slowly over trials and did not reach asymptote within eight trials. This difference in learning rates was confirmed by significantly different linear and quadratic trends to the group by trial interactions (linear $P < 0.02$, quadratic $P < 0.002$).

The Sham group had significant linear and quadratic trends ($P < 0.0001$), indicating rapid learning to asymptote; the posterior PP group had only a significant linear trend ($P < 0.001$), indicating slow steady learning; and the anterior PP group had no significant trend ($P = 0.018$, n.s. with adjusted alpha). The trends of the cut groups were both different from the Sham group, but not from each other, indicating differing learning rates over trials. Thus the pattern of learning over trials was similar to that of learning over days.

Several novel analyses of the data were undertaken, due the potential uses of the vary maze for evaluating drug effects or recovery over time. To assess the knowledge of the platform location after the first trial, the distances of trials two to four were averaged (cf. [147]) and collapsed over days. By this measure, the Sham and anterior PP groups were different (Tukey $B$, $P < 0.05$). To assess learning rates, the slopes of distance over the first four trials of each rat were calculated and averaged over days. By this measure, both of the cut groups were worse than the Sham group (Tukey $B$, $P < 0.05$). However, this measure might be overly sensitive to distance on the first trial, and being a linear transformation, might not be truly suitable for data that may well be exponential rather than linear. If distances change as a proportion of their value rather than by a fixed amount per trial, like the exponential decay of an error-correction function (Sham group Fig. 9, right for example), then it would be better to transform the distances to their log10 values before calculating the slope. These slopes would then reflect the proportional change per trial. When the data were transformed in this manner and slopes were calculated for each rat each day and then averaged over days, both cut groups were significantly different from the Sham group (Tukey $B$, $P < 0.05$).

All of the preceding analyses were based on averages of distance data across animals within a group. However, such summary data may mask a key feature of the performance, namely, the variability across trials shown by individuals. For example, on Day 3 most rats in the Sham group (six or seven of eight) took long paths to the platform only for the first trial or two, and took consistently short paths thereafter (Fig. 10). In contrast, most of the rats in the posterior PP group (five of seven) tended to take longer swim paths with less consistency over trials, while most rats in the anterior PP group (six of seven) took an exceptionally long path averaged over days. By this measure, both of the cut groups were worse than the Sham group (Tukey $B$, $P < 0.05$). However, this measure might be overly sensitive to distance on the first trial, and being a linear transformation, might not be truly suitable for data that may well be exponential rather than linear. If distances change as a proportion of their value rather than by a fixed amount per trial, like the exponential decay of an error-correction function (Sham group Fig. 9, right for example), then it would be better to transform the distances to their log10 values before calculating the slope. These slopes would then reflect the proportional change per trial. When the data were transformed in this manner and slopes were calculated for each rat each day and then averaged over days, both cut groups were significantly different from the Sham group (Tukey $B$, $P < 0.05$).

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Fig. 10

Sham Operated

Distance (cm)

Trial

Posterior PP Cut

Distance (cm)

Trial

Anterior PP Cut

Distance (cm)

Trial

Fig. 10
to find the target at least once on the last six trials. To quantify and analyse this variability in swim path lengths over trials and over days, the standard deviation of distance was calculated for each rat for each day on trials 3–8 (Fig. 11, top panel). By this measure both cut groups were different from the Sham group (Tukey B, $P < 0.05$).

The inconsistency of the swim paths was also quantified and analysed by counting the number of ‘outlier’ trials, defined as those that were significantly longer than those of the Sham group (i.e. the expected value) using a criterion value of mean plus $t(7)$, $P < 0.005$, one-tailed (alpha adjusted for the eight trials assessed each day). Fig. 11 (bottom) shows that the Sham group had few outlier trials throughout, the posterior PP group varied over days, and the anterior PP group had the most outlier trials but improved steadily over days. Pairwise comparisons of the groups showed that both cut groups had more outlier trials than the Sham group ($F(1,12) > 41.1, P < 0.0001$) and that the linear trend of the anterior PP was nearly different from that of the Sham group ($F(1,13) = 8.25, P = 0.013$). Thus, both cut groups took inconsistently long paths with the anterior PP group showing worse performance but some improvement over days.

The final measure of spatial cognition was taken from a probe trial at the end of the last day of vary-maze testing (Day 5). The Sham group had a significant quadrant preference ($P < 0.05$) but neither cut group did (Fig. 12) and there was a significant difference between the Sham and anterior PP groups ($P < 0.05$). These data again confirm that even 10 weeks after the lesion, the cut rats were impaired at spatial acquisition.

4. Discussion

In the present study, bilateral transections of the PP at two different levels produced deficits in navigation to a previously learned platform position, increasing swim distances and decreasing preferences for the correct quadrant. These deficits did not appear to be due to non-specific impairments in motivation, sensori-motor integration or cue-learning because latencies on visible
platform trials and swim speeds were largely unaffected. Although the surgical procedures and anaesthesia did produce a temporary spatial deficit, this resolved within 3 or 4 days of testing. Lesion-specific spatial deficits persisted for 2 weeks or more, though considerable recovery was evident during this period. Switching from daily to weekly tests revealed no retention deficits and rats with PP cuts improved under this regime, regaining control-level performance over 3–5 weeks. ‘Reversing’ the platform position to the opposite quadrant led to a loss of quadrant preference and increase in swim path distances, confirming that the ‘recovered’ rats had been using a spatial strategy to find the original platform position. This test of new learning also revealed a continuing deficit in learning rate but not ultimate performance level. Within 7 days of testing with the new platform, the preference for the new position was even greater in the lesioned rats than in the controls. However, the continuing learning rate deficit in the lesioned ‘recovered’ rats was again evident when they were challenged with a new platform position every day.

These results speak to three issues, to be addressed in turn: (i) the relation between the PP and spatial cognition, (ii) the presence and nature of recovery after hippocampal damage, and (iii) the suitability of the present paradigm as a model of cognitive recovery after experimental TBI.

4.1. The PP and spatial cognition

The first major finding of this study was that transection of the PP impairs retention of previously learned location, in addition to acquisition [128]. This finding reaffirms the importance of the PP to spatial learning and to spatial navigation. At this point, there are no behavioural tests to distinguish the computational demands of spatial navigation from the mnemonic demands of spatial learning and recall. The present finding is also consistent with impairments in retention following retrohippocampal lesions [125], and confirms that retrohippocampal damage produces deficits by disrupting hippocampal function. Surprisingly, rats with sham operations (craniotomy under pentobarbital anaesthesia) showed deficits in distance and quadrant preference for the first 4–5 days of testing. This deficit appeared to be specific to spatial cognition, since there was no effect on swim speed or latency to escape to the visible platform. This deficit presumably manifested because of the short interval between surgery and retention testing (i.e. only 48 h), since subsequent studies have shown that it can be avoided by waiting as little as 5 days before resuming testing [128,131]. However, it might have been due to a residual GABA agonist effect of the pentobarbital used, similar to the deficit seen during acute diazepam administration (e.g. [79]) or following withdrawal from chronic diazepam treatment [81]. Although the non-specific effects of surgery might have exacerbated the specific deficit due to the PP cuts and though recovery from the non-specific effects might have accounted for some of the recovery seen, most of the recovery by the PP cut groups occurred well after the non-specific effects of the sham surgery had resolved.

Neither short-term non-specific nor longer-term lesion-induced deficits appeared to be due to changes in motivation, sensorimotor integration, or cue use since there was little or no impairment evident on visible platform trials, and no systematic decrements in swim speed. Therefore, these results indicate that the PP is as important for retention and recall (and processing) of spatial information as it is for spatial learning.

The deficits observed after the posterior PP cuts were likely to have been due to the separation of the entorhinal cortex from the hippocampus, since there was only minor damage to the subiculum, retrosplenial cortex and splenial corpus callosum, and because extensive lesions of the occipital cortex produce only small deficits in MWM acquisition [115]. Peterson et al. [103] proposed that unilateral aspiration of the subiculum (to remove the PP) could provide a useful model for studying recovery of function. However, their unilateral lesions produced no deficits when the rats were tested at 8 weeks, and though the lesions might have produced a deficit that disappeared before the 8-week test, preliminary studies for the present experiment revealed no deficits following unilateral lesions of the PP at either the anterior or posterior site (or from bilateral lesions, one anterior, one posterior).

An interesting finding of the present study was that transection of anterior portions of the PP was as debilitating as damage to posterior portions, despite the expectation that the latter damage would transect greater numbers of PP fibres and denervate much larger sections of the hippocampus [47,68,82]. It is difficult to be sure which damage was responsible for the deficits, and surprising that the deficits in retention and relearning were as severe as those produced by the posterior PP cuts. One possibility is that the deficits were due entirely to the PP damage produced, and that the deficits were severe because the cuts removed the cortical input to the dorsal hippocampus, and because only the dorsal hippocampus is critically involved in spatial learning. This speculation is supported by the recent observation that lesions of the dorsal but not the ventral hippocampus disrupt learning in the MWM [90]. A second possibility is that the anterior lesions produced their behavioural effect by damaging commissural fibres, which indeed were partially absent on histological examination. This interpretation is supported by the finding that corpus callosotomy disrupts acquisition in the MWM [13]. A third alternative is that
the cuts damaged the cingulate gyrus and/or rostro-caudal associational fibres, though the contributions of these two areas to spatial cognition remain unclear (but see [2]). Of course, these three possibilities are not mutually exclusive, and the deficits could have resulted from the combination of damage to anterior PP, commissural, and associational cortical fibres. Although this lesion might prove valuable for investigating the neural basis of spatial cognition, it does not appear suitable for comparing recovery from complete versus partial lesions.

4.2. Recovery of spatial cognition after hippocampal damage

Perhaps the most important observation in the present study was that spatial cognition recovered after PP damage, even without restorative physiological manipulations. Swim path distances returned to preoperative levels within 2 weeks, and quadrant preferences became significantly greater than chance within 3–5 weeks. Four issues regarding this observation will be discussed: (i) whether it was ‘true’ recovery of spatial cognition; (ii) how it compared to recovery previously observed after hippocampal damage; (iii) how complete the recovery was; and (iv) what mechanism might have been responsible for the recovery.

The first issue is whether the recovery of performance observed was recovery of spatial cognition (i.e. a restitution of function), or compensation through adaptation to loss (e.g. by using non-spatial strategies to find the platform). Kolb [59] points out the dangers of inferring that function has recovered when the animal appears to be able to do again what it did prior to the lesion, because on closer examination the behaviours can be quite different, and he emphasises the difficulty in doing so for cognitive functions. He also distinguishes the outcomes of (i) compensation by adaptation to loss (functional substitution), (ii) partial restoration of original function, and (iii) complete restoration (restitution) of original function. Earlier, Kolb and Whishaw [57] proposed three criteria for claiming that recovery or sparing of behaviour had occurred: (i) the spared/recovered behaviour is the same as the behaviour lost, (ii) its reappearance is not at the expense of other behaviours, and (iii) the spared behaviour is spared immediately after the brain damage and later too. Clearly, it is very difficult to be sure that ‘true’ recovery has occurred and it would be easiest just to claim that it can never occur because one could never be sure that the behaviour is exactly the same as before. However, it might be useful to consider a behaviour or cognitive process to have ‘recovered’ if it can be shown that after a deficit, the animal can satisfy the behavioural criteria normally applied to that behaviour or cognitive process. For example, the presence of spatial cognition is usually granted when rats achieve efficient swim paths to a submerged platform in the water maze, and show greater than chance dwell times in the correct quadrant on probe trials [85,130], and possibly when translocation of the platform produces a significant increase in path distance [143]. It seems reasonable to apply these same criteria to the demonstration of recovery. By these criteria, the rats in the present study recovered their spatial cognition: efficient swim paths and significant quadrant preferences, initially lost, returned to preoperative criterion levels with time and retraining. Further, even though these distances and preferences did not reach the level shown by control rats given equivalent training, both distance and preference were good enough to satisfy reasonable criteria for spatial performance, both were significantly disrupted by platform relocation, and both provided evidence for new learning over the next few days of reversal testing. This demonstration of recovery of spatial learning in this reversal phase was an important demonstration of spatial learning, since the recovery shown in the ‘retention’ phase of the experiment was presumably a mixture of recovery of spatial navigation, spatial recall, and possibly spatial learning.

The recovery observed here exceeds that observed previously in the MWM after damage to the retrohippocampal formation, quite possibly due to the extended post-operative retraining. Schenk and Morris [125] observed improvements in distance after lesions limited to the entorhinal cortex, but felt it reflected sparing of ‘procedural spatial memory’ (a form of behavioural compensation) rather than restitution of ‘declarative spatial memory’. In many ways, the recovery observed in the present paper resembles the pattern of behaviour observed by Morris et al. [89], after ibotenate lesions of the hippocampus or subiculum, in which rats with lesions of either (but not both) structures were able to acquire or relearn efficient swim paths and quadrant preferences but were still impaired on a delayed match-to-place task. The authors concluded that the ultimate performance was not due to a recovery of function, but rather represented the (unmasked) operation of the rest of the brain. The deficits observed were attributed to first, slowed learning due to the loss of memory-formation processes mediated or facilitated by the hippocampal formation, and second, inefficient spatial navigation due to the loss of hippocampally mediated spatial recall processes which integrate current sensory information about location in space with spatial memory information to guide movement-control systems. The present data are consistent with these interpretations, and extend the original findings by showing recovery of quadrant preference to control levels. This superior performance may have been due to the greater post-operative training, the longer post-operative recovery/retraining period (8 weeks), or the location of the damage (PP rather than hippocampus proper).
It is difficult to compare the recovery observed here to that reported in studies investigating the ‘Kennard principle’. Whishaw et al. [154], showed that neonatal rats given hemidecortication did better than rats given such lesions in adulthood, when all were tested in adulthood, confirming the Kennard principle in this instance. Although in this example it is not clear whether recovery from neonatal damage represents the same kind of recovery as that shown after adulthood lesions, the same lab also showed that rats learned the MWM faster if tested 90 days after hemidecorticitation rather than 1 day after, and that this recovery could be prevented by prior (neonatal) depletion of norepinephrine or facilitated by environmental enrichment [154]. In studies by Kolb and colleagues, young rats given cortical lesions at different ages and tested in adulthood [59] showed smaller deficits as adults than did adults given lesion, and in the last study, a deficit present 10 days after the lesion was not as severe 5 weeks later, indicating that truly spontaneous recovery of spatial learning had occurred in the absence of training or physiological intervention. Considerable spontaneous recovery is also evident in unpublished data (described in [59]) showing that adult rats with prefrontal lesions who fail to learn the MWM 1 month after the lesion succeed 5 months later. Comparison of the these findings to the present ones is problematic. In addition to the problems of comparing recoveries when tested in different ways over different time-courses, the other studies did not test for quadrant preferences.

Other examples of ‘spontaneous’ recovery of function can be found by looking at the performance of select control groups in certain studies of the effects of drugs or neural grafts on recovery after brain damage. For recovery to be observable in such studies, there needs to be a post-lesion assessment of deficit (from which to recover), plus a later test of spatial performance. Studies which test post-operative acquisition provide no opportunity to assess recovery of spatial learning, unless acquisition is tested a second time. Similarly, studies which test post-operative retention provide only minimal opportunity to observe recovery if the testing lasts only a few days. Further, studies without probe trials are interesting but unconvincing, since swim paths can improve without commensurate changes in quadrant preference [89,125]. Nevertheless, there are six suggestive examples. Pitsikas et al. [105], examining the effect of the ACTH analogue Org 2766 on recovery of spatial learning acquired prior to unilateral fimbria-fornix (FF) transection, retrained for 5 days and found improvements in latencies but no significant quadrant preferences. Similarly, Bannon et al. [6], found a surprisingly mild deficit in quadrant preference after radio-frequency lesions of the medial septum which was not affected by four post-operative training trials. Garofalo and Cuello [31], and Kolb et al. [62] found improvements in latencies in untreated rats after unilateral cortical devascularisation or frontal cortex aspiration (respectively), but gave no probe trials to assess spatial localisation. Nilsson et al. [94,95] showed that swim path distances improved but quadrant preferences did not develop with extensive retraining trials after either FF aspirations or cholinergic-serotonergic neurotoxic lesions. However, there have been at least four studies of grafting in which ungrafted control rats demonstrated improvements on both distance and quadrant preference, though in three of these studies the recovery was quite modest [8,54,158]. In the fourth [93], extensive examination of spatial behaviour after ischemia revealed good recovery of distance and quadrant preference 4 weeks post-operatively, though with a continuing deficit in a match-to-place/learning set task (cf. [153]).

Some other serendipitous examples of spontaneous recovery are questionable because they are largely speculations of spontaneous recovery offered as explanation for unexpectedly small or transient deficits. Mundy et al. [91] found a small deficit in MWM acquisition (latency only) after colchicine lesions of the nucleus basalis magno cell ularis (NBM) with no deficit on a probe trial after 40 training trials. The deficit was absent by the second reversal (after 16 days of training) suggesting the presence of spontaneous or training-induced recovery. However, the same laboratory found no evidence of spontaneous recovery even 12 months after colchicine lesions of the dentate gyrus [145]. Similarly, Taube et al. [146] found that after n-methyl-D-aspartate (NMDA) lesions of the presubiculum, deficits were worse on the first behavioral test (RAM) than on the second (MWM) and suggested that spontaneous recovery might account for the difference. However, since there was only one probe trial (at the end) and the testing was in acquisition, it is difficult to know how severe the initial deficit was and therefore, how much recovery had occurred. Hagan et al. [39] found that 7 weeks after ibotenate entorhinal-subicular lesions, there was a surprisingly small deficit in MWM acquisition and reversal, which appeared to be largely due to impairment of between-day retention. In the absence of an initial assessment of the deficit, it is difficult to be sure that its small size was due to spontaneous recovery. Gayoso et al. [33] found that rats were able to achieve control-level latencies within 80 trials after systemic kainate lesions, and considered this to be recovery, though no probe trials were given and the ‘recovered’ rats were equally impaired at finding the platform after a 10-day rest as were a group of pretrained newly lesioned rats. Thus, it is unclear whether any recovery had occurred, or whether the rats had simply learned more slowly and less well.

Although the rats in the present study recovered well enough to sustain performance over week-long inter-session intervals, and eventually achieved quadrant preferences as high as controls, it is clear that recovery was not complete. Specifically, rats in both lesion groups had a
continuing deficit in spatial learning rate, which manifested in reversal and may have also been responsible for the deficits observed in the ‘vary-maze’ task. Although the vary-maze deficits could be seen as a failure of ‘spatial working memory’ [86], in that rats were unable to revisit a platform they had just visited despite being able to learn the position of a constant platform, or alternatively, as a failure of ‘learning set’ formation [153], because there was little or no improvement over days, the inability of the rats to learn the first reversal in eight trials over 2 days suggests that their subsequent failure to learn the platform position within the eight daily trials of the vary-maze task was due not to the failure of some special memory process (working memory or set-learning) but rather to a slowing of spatial learning rate. This reduction in learning rate could well have led the rats to adopt a non-spatial strategy, which would be reasonably efficient on most trials but which would fail spectacularly on others, thereby producing ‘outlier’ trials, possibly due to the specific combination of start and target locations plus the particular strategy adopted. In other words, the rats were not using a different strategy on outlier trials, rather, the strategy they were using was successful on most trials, but failed on these ones. This residual deficit in spatial cognition (and the ability of a task requiring rapid learning to reveal it) is consistent with previous reports of deficits on delayed match-to-place tasks in the absence of substantial deficits in MWM acquisition [5,37,89,93,111,112].

Because it is difficult to specify the nature of the recovery, it is difficult to specify its cause. Some of the initial recovery (seen in both Shams and PP cut groups), was presumably due to recuperation from surgery, including the residual effects of the barbiturate anaesthesia. Presumably, recovery in the first week or two might also have resulted from recovery from diaschisis due, for example, to a re-equilibration of intrinsic hippocampal processing following loss of the cortical input via the PP. This mechanism is thought to mediate recovery of sensorimotor deficits after motor cortex lesions (see [25] for a review).

At the moment, it is not clear whether the recovery depended more on time or retraining. It is possible that later recovery was due to a reaccessing of previously learned information, similar to the recovery of visual discrimination after cortical lesions [15] though such an account would not be consistent with the observation that reversal learning by the lesioned rats, though slower than controls, was faster than reacquisition. Alternatively, recovery might have been mediated by experience-dependent modification of residual neural circuits [123], which perhaps could be called ‘learning’. Such learning (or re-learning) could be mediated either by undamaged projections from the PP to the hippocampus, by alternate projections to the hippocampus, or by circuits which do not involve the hippocampus at all. Given that histological examination revealed nearly complete transections of the PP (at least in the posterior cut group) and substantial degeneration (not regeneration) of PP fibres, it seems unlikely that homotypic reinnervation could have been much of a factor. Rather, it seems more reasonable to propose that retraining led to the recovery or unmasking of extra-hippocampally mediated spatial navigational abilities, that the ability to form new spatial memories rapidly depended upon the cortico-hippocampal and hippocampo-cortical connections of the PP [144], and that this ability did not recover (see [43] for a more extensive treatment of this issue).

It is not clear what areas mediated the residual function. It has been suggested that “the hippocampus encodes new spatial information within a working memory system, whereas the entorhinal cortex represents spatial information within a reference memory system” [48]. Alternatively, there is much evidence for the critical role of the parietal and frontal lobes in MWM learning and performance (e.g. [60,61,63,75,76]) and a close examination of recovery from frontal lobe or entorhinal lesions with extensive retraining might reveal a complementary deficit to that observed here (i.e. rapid learning within a session with little retention between sessions). Perhaps an understanding of the relative contributions of time and retraining will provide valuable clues to and markers of potential mechanisms.

4.3. This paradigm as a model of recovery from TBI

The introduction described seven attributes by which animal models of post-TBI recovery should be judged: their ability to model (i) the neuropathology of TBI, and (ii) the cognitive/behavioural deficits; combined with an ability to reveal (i) an initial deficit, (ii) recovery with time or training, (iii) a return to criterion levels, (iv) functional recovery rather than behavioural compensation, and (v) whether treatments facilitate or produce recovery. The merits of the present paradigm will be discussed with respect to each of these attributes.

4.3.1. Modelling of human TBI

As described in Section 1, the transections of the PP are a model of axonal shearing in the temporal lobe, simulating hippocampal damage from TBI. In this regard it resembles not only diffuse axonal injury but also hippocampal damage from ischemia. The present model shares the benefits of the one proposed by Peterson et al. [103] in that both look for recovery of spatial cognition after hippocampal or parahippocampal damage, but has several advantages deriving from the use of
bilateral pathway transection rather than unilateral subicular aspiration. First, there is an initial deficit from which to recover. Second, by being bilateral and relatively restricted, PP cuts more accurately model one component of damage often seen in TBI. Third, the present model provides recovery of spatial function, unlike the other, in which performance was worse at 14 months post-lesion, rather than better. Although the present data indicate the value of using bilateral transection of the PP as a model manipulation, the commendation applies primarily to the posterior location, and not the anterior one. In the present experiment, transection of the PP projecting to the dorsal hippocampus did not have the expected effect of producing a smaller deficit or a faster and more complete recovery. Thus as a means of modelling partial axonal shearing, or allowing greater opportunity for homotypic reinnervation, this manipulation was not successful. The reason why such a limited and superficial lesion should produce such a large and lasting deficit might provide new clues as to hippocampal (or cortical) mediation of spatial cognition and warrants further investigation.

Spatial behaviour and cognition, especially as measured in the MWM, is analogous to behavioural cognitive deficits after TBI in two ways. First, as mentioned earlier, spatial cognition in a rat is a ‘higher’ function, requiring complex calculations and dynamic interactions between multi-sensory information, previous experience (i.e. memory) and complex, goal-directed motor output [96]. Presumably, analysis of recovery of spatial function in rats will tell us more about recovery of cognitive function in humans than would analysis of simpler tasks like classical conditioning or beam-walk. Second, the importance of the hippocampal formation to spatial cognition in rats seems much like the importance of the hippocampus to episodic memory formation in humans [139], suggesting that recovery of often damaged memory function in humans may parallel recovery of spatial function in rats. The MWM is well known for its sensitivity to hippocampal dysfunction.

4.3.2. Assessment of recovery

The present paradigm satisfies the other five criteria very well. Measuring in retention or even acquisition clearly demonstrates the initial deficit after transection of the PP, or the fimbria-fornix [43]. Spatial performance returns with time and training, and though at this point the relative contributions of the two are not known, the present paradigm makes it very feasible to test. In this paradigm, spatial performance recovers to criterion level and satisfies the usual criteria for being based on a spatial strategy rather than on cue- or response-based strategies. It therefore can be considered to be functional recovery, rather than behavioural compensation. Finally, the recovery occurs in the absence of physiological manipulations, similar to the spontaneous recovery characterising human recovery [67,137]. Therefore, future physiological manipulations should be testable for their ability to augment already-occurring processes, and should therefore be much more applicable to human recovery.

An additional advantage of the present paradigm is that spatial performance can be tracked over time using daily (or semi-daily) probe trials (cf. [30]) making it possible for future studies to dissociate treatment effects on timecourse and endpoints. Testing after discontinuation of treatment makes it possible to distinguish treatments that produce temporary changes (a state) from those which produce lasting changes (a trait), and to distinguish deficit reduction from recovery facilitation [57,59]. The time course of recovery in the present paradigm is short enough to be practical and long enough to permit facilitation to be observed. The ability of this paradigm to assess learning repeatedly means that recovery of learning rate can be measured independently after recovery of spatial performance. Finally, the vary-maze procedure (cf. [87,153]) is very sensitive to residual deficits due to deficits in set learning, working memory, or learning rate [155].

In summary, the present experiment showed that bilateral PP transections interrupting cortico-hippocampal connections to all or just the dorsal hippocampus produce a severe deficit in both spatial recall and spatial learning which abates with time and training. Although the rats eventually show criterion levels of spatial cognition, the recovery is not complete, since the lesioned rats remain slower at acquiring new platform positions and employ non-spatial strategies when tested with a new platform position every day. This paradigm should provide a valuable model for studying recovery of function after TBI in humans since it combines hippocampal damage with spontaneous recovery and distinguishes restitution of function from behavioural compensation.

5. Note

Hardiman et al. (1997), found that mice showed partial recovery of spatial learning (distance and probes) by 70 days after unilateral, but not bilateral lesions of the entorhinal cortex. Thus, in comparison to the present study, less recovery was seen even after unilateral lesions of the cortex (as opposed to bilateral lesions of the perforant path), possibly because post-operative training was less extensive. Hardiman, R, Evans, DJ, Fellows, L, Hayes, B, Rupniak, HT, Barnes, JT, Higgins, GA. Evidence for recovery of spatial learning following entorhinal cortex lesions in mice. Brain Res, 1997;758:187–200.
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