Behavioural Brain Research 278 (2015) 360–374

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

# The impact of fornix lesions in rats on spatial learning tasks sensitive to anterior thalamic and hippocampal damage

Julie R. Dumont*, Eman Amin, Nicholas F. Wright, Christopher M. Dillingham, John P. Aggleton

*School of Psychology, Cardiff University, 70 Park Place, Cardiff CF10 3AT, Wales, UK*

## HIGHLIGHTS

- Fornix damage mildly impair spatial biconditional and passive place learning tasks.
- Fornix lesions impair spatial go/no-go and alternation problems.
- Fornix lesions impair tests making flexible demands on spatial memory.
- Fornix connections are not always required for learning fixed spatial responses.

## ARTICLE INFO

*Article history:*
Received 9 September 2014
Received in revised form 7 October 2014
Accepted 12 October 2014
Available online 18 October 2014

*Keywords:*
Biconditional learning
Cognitive map
Configural learning
Hippocampus
Incidental learning
Thalamus

## ABSTRACT

The present study sought to understand how the hippocampus and anterior thalamic nuclei are conjointly required for spatial learning by examining the impact of cutting a major tract (the fornix) that interconnects these two sites. The initial experiments examined the consequences of fornix lesions in rats on spatial biconditional discrimination learning. The rationale arose from previous findings showing that fornix lesions spare the learning of spatial biconditional tasks, despite the same task being highly sensitive to both hippocampal and anterior thalamic nuclei lesions. In the present study, fornix lesions only delayed acquisition of the spatial biconditional task, pointing to additional contributions from non-fornical routes linking the hippocampus with the anterior thalamic nuclei. The same fornix lesions spared the learning of an analogous nonspatial biconditional task that used local contextual cues. Subsequent tests, including T-maze place alternation, place learning in a cross-maze, and a go/no-go place discrimination, highlighted the impact of fornix lesions when distal spatial information is used flexibly to guide behaviour. The final experiment examined the ability to learn incidentally the spatial features of a square water-maze that had differently patterned walls. Fornix lesions disrupted performance but did not stop the rats from distinguishing the various corners of the maze. Overall, the results indicate that interconnections between the hippocampus and anterior thalamus, via the fornix, help to resolve problems with flexible spatial and temporal cues, but the results also signal the importance of additional, non-fornical contributions to hippocampal-anterior thalamic spatial processing, particularly for problems with more stable spatial solutions.



## 1. Introduction

Lesions of the hippocampus and the anterior thalamic nuclei produce a similar array of spatial learning deficits in rats. Both structures are, for example, vital for location learning in a Morris water maze, radial-arm maze foraging, and T-maze alternation [4,5,9,16,40,44,47,58,90]. The inference is that these interconnected structures function jointly to enable spatial learning, a view supported by crossed-lesion disconnection studies [32,87,88]. It has, therefore, often been supposed that the hippocampus primarily drives anterior thalamic nuclei activity, principally via its fornical projections (e.g., [1,2,19]). These hippocampal influences essentially comprise the direct fornical projections to the anterior thalamic nuclei, along with the indirect fornical projections via the mammillary bodies [59,70].

* Corresponding author at: Dartmouth College Psychological Brain Sciences, 6207 Moore Hall Building, Hanover, NH 03755, USA. Tel.: +1 603 646 3181; fax: +1 603 646 1419.
*E-mail address:* Julie.Dumont@dartmouth.edu (J.R. Dumont).

http://dx.doi.org/10.1016/j.bbr.2014.10.016

The notion that the direct and indirect fornical projections from the hippocampus to the anterior thalamic nuclei are sufficient to explain the importance of their joint interactions for learning and memory can be questioned on several fronts. The first is anatomical. In the rat brain there are some direct projections from the presubiculum and postsubiculum to the anterodorsal and dorsal anteroventral thalamic nuclei that do not involve the fornix [73,74], while the retrosplenial cortex provides an indirect route to and from the anterior thalamic nuclei that again is non-fornical [75–77,82]. The second point relates to the fact that crossed-lesion disconnection studies cannot determine a direction of effect when the two target sites are reciprocally linked. Thus, it is possible that projections from the anterior thalamic nuclei to the hippocampus, which join the cingulum rather than the fornix [21], are critical in regulating their combined role in learning and memory. This notion receives support from recent behavioural studies examining the importance of nonhippocampal inputs to the mammillary bodies for spatial learning [79,80].

Perhaps of more direct concern are the findings from those behavioural studies in which fornix lesions are less disruptive than either hippocampal or anterior thalamic lesions on tests of spatial learning and memory. An influential set of such findings comes from configural learning tasks, which can appear sensitive to hippocampal, but not fornix damage (e.g., [42]). Of particular note are the results from tests of spatial biconditional learning. Although some spatial biconditional problems appear sensitive to hippocampal lesions but not anterior thalamic lesions [61–63], other spatial biconditional tasks are highly sensitive to both anterior thalamic and hippocampal lesions [13,23,66]. Furthermore, the functional link between these two structures for such spatial biconditional tasks has been confirmed by a cross-lesion disconnection study [32]. It is, therefore, striking that fornix lesions can spare those same spatial biconditional tasks that are impaired by both anterior thalamic and hippocampal damage ([24,60,62]; see also [41]). This null result is all the more surprising as fornix lesions will disconnect the hippocampal formation from multiple sites, i.e., not just the anterior thalamic nuclei and mammillary bodies [59].

The start point for the present study was to re-examine the impact of fornix lesions on spatial biconditional learning. The first criterion was to adopt a biconditional task (if in location A choose digging pot X not pot Y, if in location B choose digging pot Y not X) known to be sensitive to both hippocampal and anterior thalamic lesions ([13,23]; see also [32]). The second criterion was to use a task that can be acquired in relatively few trials. A shortcoming with spatial biconditional tasks previously used to address this issue is that they typically require a great many trials before normal rats reach their learning criterion (~400 trials in [24,41,60]; ~800 trials in [62]). This feature not only means that task acquisition is incremental and varied, so potentially reducing the ability to detect group differences, but the lengthy training period may increase the likelihood of unintended task solutions by the rats. The present study, therefore, used a location-digging task as in previous studies it had been acquired more rapidly. Furthermore, this task readily lends itself to control comparisons, e.g., learning a matching, non-spatial (contextual) biconditional problem that is spared by both hippocampal and anterior thalamic lesions [13,23], as well as learning location and digging media discriminations. Such tasks were, therefore, used to both cast light on any biconditional learning deficit and to characterise better those spatial tasks that appear to be spared by fornix lesions. The latter goal relates to the issue of how nonfornical pathways may support spatial interactions between the hippocampus and anterior thalamus.

The final experiment extended the study of fornix lesions to another category of spatial task that is sensitive to both anterior thalamic and hippocampal damage [26,37]. This experiment assessed incidental location learning in a water-maze [26,29,35].

**Table 1**
Summary table depicting testing arrangements and outcomes of fornix lesions on the various biconditional and spatial tasks in the present study (Experiments 1–8). Performance is indicated as being markedly impaired ('yes'), mildly impaired ('mild'), or unimpaired ('no').

| Experiment | Description | Room | Impaired? |
|---|---|---|---|
| Exp 1 | Contextual biconditional discrimination | Pre-train A Test B | No |
| Exp 2 | Spatial biconditional discrimination | B | Mild |
| Exp 3 | Digging media discrimination | B | No |
| Exp 4 | Spatial go/no-go discrimination | B | Yes |
| Exp 5 | Place/Direction cross-maze | C | No |
| Exp 6 | Place alternation T-maze | D | Yes |
| Exp 7 | Place alternation two T-mazes | D | Yes |
| Exp 8 | Passive place learning. One wall probe | Pre-train E Test F | Mild |
| | Passive place learning. Two wall probe | F | Mild |

The procedure is of particular interest as it forces the rat to navigate according to the spatial disposition of specific maze cues [29,35]. In this task, rats are repeatedly placed on a submerged platform in a square water-maze in which the escape location is signalled by the unique spatial arrangement of cues on the adjoining walls of the pool. Both hippocampal and anterior thalamic lesions disrupt the rat's spatial behaviour on the critical test trial, when the rat is first allowed to swim to find the escape location [26,37]. These findings raise the question of whether fornix lesions would have similar effects. This task appears particularly relevant as previous studies with monkeys indicate that fornix lesions only impair spatial biconditional learning when the subject has to discriminate between scenes that contain common elements [28], an integral feature of this passive learning task in the water-maze [29,35].

## 2. Materials and methods

A total of eight experiments are described in the order in which testing occurred (see Table 1).

### 2.1. Subjects

The study used 27 male Lister Hooded rats (Charles River, Kent, U.K.). At the time of their surgery the rats weighed 277–307 g and were three months old. All rats were housed in pairs under a 12-hour light/dark cycle. The animals were given free access to water, but were maintained at 85% of their free-feeding weight for the duration of the experiments with the exception of the water-maze tasks, where the rats were given food *ad libitum*. All animals were habituated to handling before the start of the first experiment. The experiments were performed in accordance with the UK Animals (Scientific Procedures) Act (1986) and associated guidelines. These procedures were also approved by the appropriate ethics committee at Cardiff University.

### 2.2. Surgical procedures

Rats either received bilateral fornix lesions (Fornix = 15) or sham surgeries (Sham = 12). For the fornix lesions, the rats were first anaesthetised using an isoflurane–oxygen mix. The rat was then placed in a stereotaxic frame (Kopf Instruments, Tujunga, CA), with the incisor bar set at +5.0 mm, and the rat administered with 0.1 mg/kg of the analgesic Metacam (Boehringer Ingelheim Vetmedica, Germany) subcutaneously. A sagittal incision was made