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Research report

The rat retrosplenial cortex is required when visual cues are used flexibly to determine location

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HIGHLIGHTS

- Combined loss of areas 29 and 30 impairs place discriminations.
- Area 30 is needed for the control of place learning by visual cues.
- Novel discrimination tasks described for place and perspective learning.
- Areas 29 and 30 assist the integration of different classes of spatial information.

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ABSTRACT

The present study examined the consequences of retrosplenial cortex lesions in rats on two novel spatial tasks. In the first experiment, rats discriminated opposing room views from the same general location, along with their opposing directions of travel ('Perspective' task). Rats were trained with food rewards using a go/no-go design. Extensive retrosplenial cortex lesions involving both the granular and dysgranular areas impaired acquisition of this discrimination, which relied on distal visual cues. The same rats were then trained on a non-spatial go/no-go discrimination between different digging media. No lesion effect was apparent. In the final experiment, rats discriminated between two locations within a room ('Location' task) such that direction of travel at each location would be of less help in solving the problem. Both extensive retrosplenial lesions and selective dysgranular retrosplenial lesions impaired this Location task. These results highlight the importance of the retrosplenial cortex (areas 29 and 30), including the dysgranular cortex (area 30), for the effective use of distal visual cues to solve spatial problems. The findings, which help to explain the bias away from visual allocentric solutions that is shown by rats with retrosplenial cortex lesions when performing spatial tasks, also support the notion that the region assists the integration of different categories of visuospatial information.

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1. Introduction

Multiple areas in the rodent brain appear to support spatial learning and navigation [1]. The assumption is that these multiple areas function in different but complementary ways. The retrosplenial cortex (areas 29 and 30) is one such site. Both its connectivity and the outcome of lesion studies strongly suggest that the spatial functions of the retrosplenial cortex region are closely linked to those of the hippocampus and the anterior thalamic nuclei [2–9]. Consistent with this notion is the finding of head direction cells in the rat retrosplenial cortex [10,11]. These neurons signal the direction an animal is heading, independent of location. Additional support comes from studies of patients with pathologies involving the retrosplenial cortex, particularly in the right hemisphere [12,13]. Many of these patients report an inability to use familiar visual landmarks to navigate, despite retaining knowledge of the landmarks themselves, while some appear unable to orient themselves either in a novel or familiar environment [12,13]. A barrier to determining the particular importance of the human retrosplenial cortex is the lack of patients with pathologies confined to this region [14].

To address this issue, selective retrosplenial cortex lesions have been examined in rats. Previous studies have found spatial deficits in a variety of behavioural protocols, including water-maze, T-maze and radial-arm maze tasks [7,15–19]. These same lesion studies often reveal a reluctance by the rats to use allocentric visual cues when other spatial strategies are available. In addition, spatial tests in the dark have implicated the retrosplenial cortex in some forms of idiothetic learning [19–21], leading to the notion that this region

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may assist in the integration of visual with idiothetic spatial information [22]. A related, broader notion is that the retrosplenial cortex has a 'translational' function in the integration and transformation between multiple spatial codes, including allocentric representations into egocentric ones and *vice versa* [14,23,24]. Support comes from fMRI studies showing that the retrosplenial cortex is activated during a task requiring people to imagine looking at the same scene from different viewpoints [25,26].

The present study sought to examine the effects of retrosplenial cortex lesions on two related spatial tasks where the use of distal visual cues could be assessed. The first task concerned the ability to distinguish the features of a room from a set viewpoint ('Perspective' task, Experiment 1). The second task concerned the ability to discriminate between two locations within a room, irrespective of the direction faced ('Location' task, Experiment 3). These closely related tasks were selected as the demands of the second task build onto those of the first task, including the ability to unite different perspectives from the same place.

Two cohorts of rats were examined, the first with lesions in both areas 29 and 30, the second with lesions targeted at just area 30 (dysgranular retrosplenial cortex). The goal was to test whether the dysgranular cortex is a critical access point for visual processing within the retrosplenial region. However, only the findings from the first cohort (combined area 29 and 30 lesions) are described for the 'Perspective' task (Experiment 1). This omission reflects procedural differences that restrict comparisons across the two cohorts (see below). Both Experiments 1 and 3 used go/no-go discriminations where rats were only reinforced for digging when in the correct viewpoint or location. Experiment 2, therefore, tested whether such go/no-go procedures, with their emphasis on withholding responses, are appropriate for rats with retrosplenial damage. In this control study, rats were trained on a non-spatial go/no-go task involving the discrimination of different cups containing distinct digging media.

2. Methods

2.1. Experimental methods

Two cohorts of animals were trained and tested. Both cohorts completed all three experiments in the same rooms. For Experiment 1 there were, however, procedural differences in the number and type of probe tests, the use of background white noise, and the immediately prior behavioural task. The control rats in Cohort 1 acquired the Perspective task at about twice the rate of their counterparts in Cohort 2, further weakening any cohort comparisons. For these reasons, the methods and results from Cohort 2 are not described for Experiment 1. Thereafter, the training of the two Cohorts was matched.

2.1.1. Animals

Subjects were 52 male Lister Hooded rats (Harlan, Bicester, UK). The rats were housed in pairs in a temperature-controlled room. Lighting was kept on a 12-hour light/dark cycle, from 08:00 to 20:00. Water was available *ad libitum* throughout the experiments. For all behavioural experiments, the animals were placed on a food-restricted diet where they were able to gain weight. Their weights did not fall below 85% of their free-feeding weights. All experiments were carried out in accordance with UK Animals (Scientific Procedures) Act, 1986 and associated guidelines, and were approved by local ethical committees (Cardiff University). Rats were provided with cardboard tubes and wooden chew sticks in their home cages. Animals in Cohort 1 received either a bilateral combined excitotoxic lesion of areas 29 and 30 (RScomb, $n = 16$) or a sham lesion (Sham1, $n = 12$). Their weight at the time of surgery was between 278 and 387 g. Subjects for the dysgranular cortex study (Cohort 2, 294–314 g) received either a bilateral excitotoxic lesion within area 30 of the retrosplenial cortex (RSdysg, $n = 14$) or a sham lesion (Sham2, $n = 10$).

2.1.2. Surgical procedures

Rats were deeply anaesthetized with an intraperitoneal (i.p.) injection of sodium pentobarbital (60 mg/kg pentobarbital sodium salt; Sigma-Aldrich, U.K.). All animals were given a subcutaneous injection of 0.06 ml Metacam (Boehringer Ingelheim, Alkmaar, NL, USA) to reduce post-operative pain, as well as 0.1 ml Millophylline (i.p.; Arnolds Veterinary Products Ltd, Shrewsbury, UK) to regulate breathing. The scalp was shaved and the animal then placed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA) with the nose bar set at +0.5. The skull was exposed and a bilateral craniotomy extending from bregma to lambda was made in the skull using a dental drill. Consequently, two strips of skull above the retrosplenial cortex were removed, leaving a bridge of bone approximately 2 mm wide along the length of the central sinus.

Lesions were made by injecting 0.09 M N-methyl-D-aspartate (NMDA; Sigma, Poole, UK) dissolved in phosphate buffer (pH 7.2), into 14 injection sites at a rate of 0.05 μl per minute using a 1 μl Hamilton syringe (gauge 25s; Bonaduz, Switzerland). The stereotaxic coordinates of the lesion placements are stated relative to bregma in the anterior-posterior (AP) axis, and relative to the central sinus in the lateral-medial (LM) axis. Dorsal-ventral (DV) coordinates are taken relative to the surface of the cortex, using the eye of the needle.

The coordinates for the combined lesion cohort (RScomb) were AP-1.6, LM ± 0.4, DV-1.3; AP-2.8, LM ± 0.5, DV-1.4; AP-4.0, LM ± 0.5, DV-1.4; AP-5.3, LM ± 0.5, DV-2.6; AP-5.3, LM ± 0.9, DV-1.6; AP-6.6, LM ± 1.0, DV-2.0; AP-7.5, LM ± 1.1, DV-1.3. Injections of 0.25 μl NMDA were made in the three most rostral pairs of sites, with 0.26 μl injected in the next three pairs of sites. In the most caudal site 0.1 μl was injected. Coordinates for the dysgranular lesion group (RSdysg) were: AP -1.6, LM ± 0.4, DV-1.0; AP-2.8, LM ± 0.5, DV-1.1; AP-4.0, LM ± 0.5, DV-1.1; AP-5.3, LM ± 0.5, DV-2.4; AP-5.3, LM ± 0.9, DV-1.4; AP-6.6, LM ± 0.9, DV-1.8; AP-7.5, LM ± 1.0, DV-1.1. At each site 0.25 μl of NMDA was injected, apart from for the most caudal pair of injections, where the injections were 0.1 μl NMDA.

After each infusion the needle was left in place for 5 min before being slowly withdrawn. On occasion, animals received an additional dose of 0.05 ml sodium pentobarbital to maintain anaesthesia. If further anaesthesia was still required <2% inhaled isoflurane was given. Oxygen was provided throughout the surgery. Following surgery, the scalp was sutured and a subcutaneous injection of 5 ml glucose-saline was given to replace lost fluids. Lidocaine (Xylocaine, AstraZeneca, UK) and antibiotic powder (Dalacin C, Pharmacia, UK) were applied topically to the wound and animals were left to recover in a warm, quiet area before being returned to their home cage. Sham animals underwent the same procedure, except that the needle was not lowered and injections of neurotoxin were not made. Post-operative care was identical for all groups. All animals recovered well following surgery.

2.2. Experiment 1 - viewpoint discrimination ('perspective' task)

Only the procedure for Cohort 1 is described.

2.2.1. Pre-training

Pre-training for the combined retrosplenial lesion rats (Cohort 1) started two months after surgery and followed testing on an object-in-place task. All rooms used in the study were novel to the rats. During pre-training, two round digging cups (6.5 cm tall and 7 cm in diameter) made of black plastic were used to train rats to dig

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