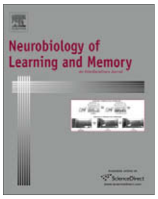
Neurobiology of Learning and Memory 91 (2009) 408–414

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

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



Damage to the retrosplenial cortex produces specific impairments in spatial working memory

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ARTICLE INFO

Article history:
Received 24 September 2008
Revised 17 October 2008
Accepted 21 October 2008
Available online 10 December 2008

Keywords:
Cingulate
Hippocampus
Radial arm maze
Amnesia
Allocentric
Egocentric
Prospective
Retrospective

ABSTRACT

Mounting evidence indicates that the retrosplenial cortex (RSP) has a critical role in spatial navigation. The goal of the present study was to characterize the specific nature of spatial memory deficits that are observed following damage to RSP. Rats with RSP lesions or sham lesions were first trained in a working memory task using an 8-arm radial arm maze. Rats were allowed 5 min to visit each arm and retrieve food pellets and a 5-s delay was imposed between arm choices. Consistent with previous research, rats with RSP damage committed more errors than controls. In particular, RSP-lesioned rats committed more errors of omission (failing to visit an arm of the maze), but there were no lesion effects on errors of commission (revisiting an arm). Neither group of rats exhibited a turn bias (i.e., always turning a certain direction when choosing an arm). At the end of the training phase of the experiment, both groups had reached asymptote and committed very few errors. In the subsequent test phase, a longer delay (30-s) was imposed during some sessions. Both control and RSP-lesioned rats continued to make few errors during sessions with the standard 5-s delay, but RSP-lesioned rats were impaired at the 30-s delay and committed more errors of commission, consistent with an increase in taxing spatial working memory.

1. Introduction

Recent research in humans and laboratory animals has consistently implicated retrosplenial cortex (RSP), a posterior region of cingulate cortex, in the processing of spatial information. For example, RSP lesions impair allothetic navigation in which subjects must use landmarks for successful task completion (Cain, Humpartzoomian, & Boon, 2006; Harker & Whishaw, 2002, 2004; Lukoyanov, Lukoyanova, Andrade, & Paula-Barbosa, 2005; Vann & Aggleton, 2002, 2004; Vann, Kristina Wilton, Muir, & Aggleton, 2003). Furthermore, previous reports have described head direction and place cells in RSP (Chen, Lin, Green, Barnes, & McNaughton, 1994; Cho & Sharp, 2001), and damage to RSP results in deficits in ideothetic navigation in which self-motion cues are used for successful task completion (reviewed in Aggleton & Vann, 2004; Harker & Whishaw, 2004). Other studies have demonstrated that RSP damage disrupts the ability to detect spatial changes in the configurations of objects (place recognition), while recognition of the objects themselves is unaffected (Ennaceur, Neave, & Aggleton, 1997; Parron & Save, 2004; Vann & Aggleton, 2002). These studies suggest that RSP plays an integral role in processing spatial information and contributing to both allothetic and ideothetic navigation.

In addition to these findings, there is growing evidence that RSP has a close functional relationship with the hippocampus. RSP has significant connections with the hippocampus and related medial temporal lobe structures (Burwell & Amaral, 1998a, 1998b; van Groen & Wyss, 1990, 1992, 2003; Wyss & van Groen, 1992). Also, Cooper and Mizumori (2001b) found that the normal location of hippocampal place fields was altered following temporary inactivation of RSP, providing a behavioral substantiation of this relationship. Other recent behavioral studies in non-human species also suggest that interactions between hippocampus and RSP are critical for processing contextual information (Smith, Wakeman, Patel, & Gabriel, 2004; Talk, Stoll, & Gabriel, 2005). Furthermore, damage to the hippocampus results in considerable reductions in *c-fos* and *zif*-268 expression in RSP when rats are exposed to behavioral tasks that are typically associated with high levels of immediate-early gene (IEG) expression in RSP (Albasser, Poirier, Warburton, & Aggleton, 2007). Together, these studies suggest a bidirectional functional relationship between RSP and hippocampus, indicating that RSP can influence hippocampal function and vice versa. Indeed, one prominent theory about the role of RSP in spatial navigation is that it acts as an integrator between the hippocampus and other cortical and subcortical structures (van Groen & Wyss, 2003). Finally, RSP may be important for long-term storage of hippocampally-consolidated memories as there is now evidence for a prolonged role of RSP in long-term spatial and contextual memory (Campbell, Keene, Chowdhury, & Bucci, 2008; Haijima & Ichitani, 2008; Maviel, Durkin, Menzaghi, & Bontempi, 2004).

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doi:10.1016/j.nlm.2008.10.009

In spite of these findings, there has been little insight into the specific nature of the contributions of RSP to spatial learning and memory. To further examine this, sham-lesioned and RSP-lesioned rats were trained in a standard radial arm maze working memory task. A thorough analysis of behavioral responding was conducted to characterize the nature of deficits in this task following damage to RSP. In addition, following training, longer delays were introduced to further tax short-term mnemonic processing and determine the contributions of RSP to working memory.

2. Materials and methods

2.1. Subjects

A total of 36 male Long Evans rats (~300 g) were obtained from Harlan Sprague–Dawley (Indianapolis, IN). Rats were housed individually and allowed 7 days to acclimate to the vivarium with food available ad libitum (Purina standard rat chow; Nestle Purina, St. Louis, MO). Throughout the study, rats were maintained on a 14:10 light–dark cycle and monitored and cared for in compliance with Association for Assessment and Accreditation of Laboratory Animal Care Guidelines and the Institutional Animal Care and Use Committee at Dartmouth College. After recovering from surgery, rats were placed on a restricted feeding regimen for 7–10 days to gradually reduce body weight to 85% of their initial free-feeding body weights. Rats were maintained at 85% body weight for the duration of the behavioral procedures.

2.2. Surgery

Anesthesia was induced with 3% isoflurane gas in oxygen and maintained with 1.5–2% isoflurane. The skin was retracted and holes were drilled through the skull above each of the intended lesion sites using the rat brain atlas of Paxinos and Watson (1998). The RSP lesion target included the granular and agranular regions of retrosplenial cortex defined by the Paxinos and Watson (1998) atlas (i.e., areas RSG and RSA, respectively). Twenty-two rats received bilateral electrolytic lesions (2 mA, 15 s) of RSP prior to behavioral training using the stereotaxic coordinates outlined in Table 1. The 14 rats in the control group received sham lesions consisting of a craniotomy and shallow, non-puncturing burr holes to minimize damage to underlying cortex. All rats were allowed to recover for 2 weeks prior to food restriction and behavioral training.

2.3. Apparatus

Spatial learning was assessed using a standard 8-arm rat radial arm maze (Med Associates, St. Albans, VT). The maze consisted of an octagonal-shaped central hub (35 cm diameter) and 8 arms radiating from the central platform and spaced at equal angles around the hub. Each arm was 61 cm in length, 9 cm in width, and 16.8 cm in height and recessed food cups were located 2 cm from the end of each arm. Doors could be raised and lowered to separate each arm from the central hub and were used to impose delays between arm choices. The maze was located in a small soundproof room with visually distinct cues mounted on 3 walls and on a curtain that separated the behavioral apparatus from the computer (used to control arm doors) and experimenter. Data from our laboratory indicate that rats use a hippocampal-dependent allothetic strategy in navigating this maze (Chess, Simoni, Alling, & Bucci, 2007).

Table 1
Stereotaxic coordinates for RSP lesions.

Retrosplenial cortex lesion coordinates		
AP	ML	DV
−2.0	±0.3	−1.2 and −2.5
−3.5	±0.4	−1.5 and −2.5
−5.0	±0.4 and ±1.0	−1.6 and −2.2 (medial site), −2.2 (lateral site)
−6.5	±0.8 and ±1.4	−1.6 and −2.0 (medial site), −2.7 (lateral site)
−8.0	±1.0 and ±2.0	−2.0 (medial site), −2.4 (lateral site)

All AP, ML, and DV measurements are derived from bregma, midline, and surface of the skull, respectively (measurements are in mm).

2.4. Behavioral procedures

2.4.1. Habituation

Rats were first trained to retrieve 45 mg food pellets (Bio-Serv, Frenchtown, NJ) from the food wells at the end of each arm over the course of 4 daily habituation sessions. During each session, the rat was placed in the center hub with all 8 doors open and allowed to explore the entire maze for 5 min. On the first two habituation sessions, food pellets were scattered along each arm and in the recessed food cups. During the last 2 sessions food was only available in the food cups. Rats were monitored to ensure that they were eating food pellets out of all the food cups by the end of habituation training.

2.4.2. Working memory training

Following habituation, rats received 18 daily training sessions. For each session, the rat was placed in the central hub of the maze and always oriented in the same direction. The doors of all arms were raised simultaneously and rats could enter any of the 8 arms to obtain food reward. Arm entry was defined as placing all 4 paws inside the arm. Following an arm entry, the doors to the remaining arms were simultaneously closed. The door to the entered arm remained open. After consuming the food, the rat left the arm and returned to the central hub and the door to that arm was then closed. After a 5-s delay, all doors opened again and the rat was allowed to choose any of the 8 arms. This process was repeated until all 8 arms were entered and all food was consumed or until 5 min elapsed.

2.4.3. Working memory testing

After the training phase, daily sessions continued as above for an additional 6 days, except that for some sessions, a 30-s delay between arm choices was used instead of the 5-s delay. Rats in each group received a random sequence of 5-s or 30-s delays that were counterbalanced over six days such that each rat had 3 daily sessions at each delay. Rats were allotted 300 or 575 s to complete the sessions using the 5-s and 30-s delays, respectively.

2.5. Behavioral observation and analysis

The experimenter was blind to lesion condition and monitored the rats' behavior via a video monitor located behind an opaque curtain in the testing room. A videotape was made of each session and was used to assess two types of errors: an error of commission was defined as re-entry into an arm after food reward had previously been obtained from that arm; an error of omission was defined as failure to enter a baited arm during the session. The sequence of arm entries was also recorded during each session. For this latter measure, a score of +1 was assigned when a rat chose an arm to the right of the one it had most recently visited. A score of −1 was assigned for left hand turns. Adding these scores together resulted in a high absolute value if a rat adopted a consistent strategy of turning either left or right. A score of zero indicated the absence of a turn bias.

Data from the training phase of the experiment were analyzed in 3-session blocks using a repeated measures analysis of variance