ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Research paper Acta Neurobiol Exp 2014, 74: 15–25

Perirhinal cortex lesions attenuate stimulus generalization in a tactual discrimination task in rats

Juan M.J. Ramos

Department of Psychobiology and Mind, Brain and Behavior Research Center (CIMCYC), University of Granada, Campus de Cartuja, Granada, Spain, Email: jmjramos@ugr.es

Response generalization to a novel stimulus occurs when the new stimulus shares common features with the stimulus used in the original learning. Given the many recent studies suggesting that the perirhinal cortex is critical for disambiguating stimuli that share representational/perceptual elements, we hypothesize that lesions sustained to this region would attenuate response generalization. In the first part of this experiment lesioned and control rats learned a feature-ambiguous tactual discrimination task until they had all reached the same level of performance. In this task animals were asked to discriminate among 3 tactual stimuli simultaneously exposed in 3 arms of a 4-arm plus-shaped maze. In the second part of this experiment, the same rats were given a generalization test 24 h after acquisition of the tactual discrimination. In the generalization test the original tactual stimulus associated with reward during the learning of the discrimination was replaced by a novel tactual stimulus while the other two remained the same. Of the 3 stimuli used in the generalization test, the novel stimulus had the highest degree of feature overlap with respect to the original target stimulus used during the learning of the discrimination. The generalization test took place over two consecutive days, with 8 trials each day. On the first day of generalization, the results indicated that the lesioned rats generalized significantly worse than the control rats during the first 4 trials, but not during the last 4 trials. On the second day of generalization, however, both groups performed the test perfectly. These findings suggest that, in addition to the well-known mnesic function in object processing, the perirhinal cortex may also be involved in perceptual functions.

Key words: learning, tactual discrimination, medial temporal lobe, maze, rat

INTRODUCTION

Since publication in 1957 of the seminal case of patient H.M., numerous studies, performed on both neuropsychological patients and experimental animals, have suggested that the medial temporal lobe (MTL) is specialized in declarative/relational learning and memory (Squire and Zola-Morgan 1991, Eichenbaum et al. 2007, Brown et al. 2010, Yonelinas et al. 2010). According to this view, known as the "mnemonic hypothesis" of the MTL, all deficits appearing after MTL lesions can be explained exclusively by a failure in the learning and memory process, but not in the perceptual/representational process (Shrager et al. 2006, Suzuki 2009, 2010, Suzuki and Baxter 2009, Clark et al. 2011, Kim et al. 2011).

Recent reports, however, have put forward an alternative position that challenges the above conception. According to this perspective, the "perceptual-mnemonic hypothesis", the MTL performs a critical role in high-level perception, in addition to its well-known role in relational memory (Eacott et al. 1994, Buckley and Gaffan 1998, Buckley et al. 2001, Bussey and Saksida 2002, Bussey et al. 2002, Buckley and Gaffan 2006, Murray et al. 2007, Baxter 2009, Barense et al. 2012, Kivisaari et al. 2012, Watson and Lee 2013). Proponents of this perspective, also known as the representational-hierarchical view, suggest that the object's low-level features are represented in the lower levels of processing in a given sensorial system. However, it further proposes that intra-object conjunction of individual features, for the purpose of repre-

Correspondence should be addressed to J.M.J. Ramos
Email: jmjramos@ugr.es

Received 27 June 2013, accepted 27 November 2013

senting the whole object, may depend on higher levels of processing, mainly in the perirhinal cortex (Prh) (Bussey and Saksida 2002, Cowell et al. 2006, Barense et al. 2012). Supporting this representational-hierarchical view, damage to the high-level representations in the Prh is followed by a profound deterioration in object discrimination tasks when there is feature ambiguity among the stimuli to be discriminated. In contrast, no impairment after Prh lesions has been observed when the discrimination involved simple/individual features, even when the task was difficult (Buckley et al. 1997, 2001, Bussey et al. 2002, 2003, Gilbert and Kesner 2003, Bussey and Saksida 2005).

In rats the perceptual-mnemonic hypothesis has been supported using different sensory systems, including the visual (Eacott et al. 2001, Norman and Eacott 2004, Bartko et al. 2007; but see Aggleton et al. 2010, Clark et al. 2011), auditory (Lindquist et al. 2004, Campolattaro and Freeman 2006, Kholodar-Smith et al. 2008), olfactory (Feinberg et al. 2012) and somatosensory modalities (Ramos 2013a). These functional data agree with connectivity studies showing that all of these sensory systems projects to the Prh (Suzuki and Amaral 1994, Burwell and Amaral 1998, Agster and Burwell 2009). Thus, both the anatomical and functional data suggest that the Prh may represent a common mechanism for intra-object feature conjunction, binding stimulus elements together into unitary representations in different sensorial modalities (Kholodar-Smith et al. 2008, Winters and Reid 2010; see also Murray et al. 2000, Goulet and Murray 2001, Taylor et al. 2006, Holdstoch et al. 2009).

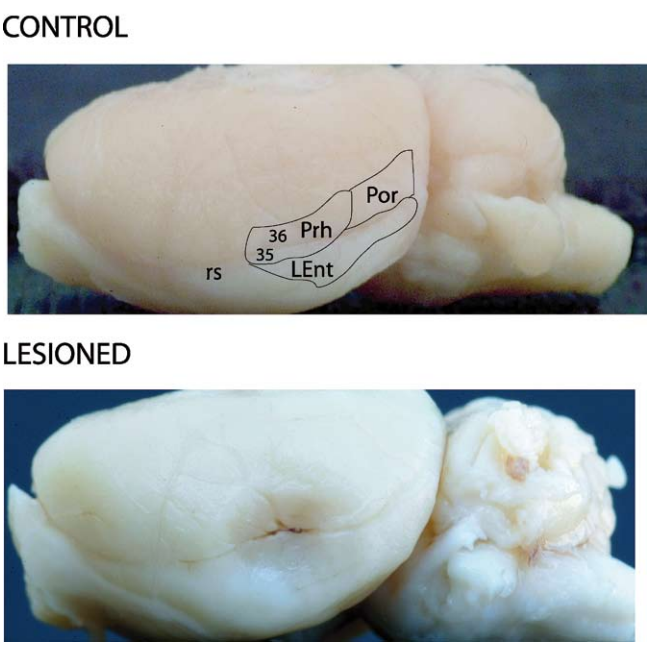

Fig. 1. Lateral view of a representative control and perirhinal cortex lesioned rat. (rs) rhinal sulcus; (35 36 Prh) areas 35 36 of the perirhinal cortex; (Lent) lateral entorhinal cortex; (Por) postrhinal cortex.

In a previous study we showed that the Prh is essential for discriminating among tactual stimuli with a high degree of feature ambiguity. Importantly, our data suggested that the deficit observed in the execution of this type of discriminative task after perirhinal damage could be explained in perceptual and not mnemonic terms (Ramos 2013a). The aim of the present study was therefore to further investigate the disambiguating functions attributed to the Prh in complex tactual discrimination tasks, but in this case using a generalization test. The generalization of responses to similar stimuli is thought to occur when the new stimulus shares common features with the old stimulus used in the original discrimination (Mackintosh 1974, Wagner 2003, Harris 2006). So, in both generalization and complex discrimination learning, there must be a mechanism that precisely differentiates between stimuli that share representational elements (Hampton and Murray 2002, Harris 2006, Robinson et al. 2010). Based on these ideas, in the first phase of the study, rats with Prh lesions acquired a complex tactual discrimination learning task until they reached criterion. Animals had to discriminate among 3 textures with different degrees of roughness that were simultaneously exposed in 3 arms of a 4-arm plus-shaped maze. When the animals chose the right texture (the target stimulus) they received reinforcement. In the second experimental phase, the animals performed a generalization test that involved a new target stimulus, one that shared many features with the original target stimulus. We hypothesize that since the new and the original target stimuli presented feature overlap, to be able to correctly generalize the response to the new target the animals would need a mechanism to disambiguate the stimuli with feature ambiguity. Such a mechanism would allow the animals to select – from among the stimuli presented – the stimulus most similar to the original target stimulus, a process in which it seems that the Prh plays an essential role.

METHODS

Subjects

The subjects were 15 naïve male Wistar rats from Harlan Laboratories (Barcelona, Spain). The rats, ini-

tially weighing between 280–310 g, were individually housed in single cages and maintained on a 12:12 h light:dark cycle at a constant temperature of 22±1°C. Behavioral testing was carried out in the morning, during the light phase of the cycle, but during this period all the lights of the experimental room were turned off and the only light source was a red-tinted light bulb of 25 W. The bulb was hanging from the ceiling 1.6 m above the center of the testing apparatus. All experimental procedures were performed in conformity with European (86/609/EEC) and Spanish (BOE 252, 2005) legislation and were approved by the Ethics Committee for Animal Research of the University of Granada.

Surgery

Under the effects of sodium pentobarbital anesthesia (50 mg/kg, i.p., Sigma Chemical, St. Louis, MO, USA), the rats were placed in a David Kopf stereotaxic apparatus (mod. 900, David Kopf Instruments, Tujunga, California) with the incisor bar adjusted so that lambda and bregma were level. Rats were randomly assigned to either an experimental or a control group. The lesioned subjects (n=7) received bilateral injections of N-methyl-D-aspartic acid (NMDA, Sigma Chemical, PBS, pH 7.4, 0.07 M) through the insertion of a 30-gauge stainless steel cannula in eight sites of the perirhinal cortex. The cannula was oriented laterally at 26° from the vertical. The coordinates were derived from the atlas of Paxinos and Watson (1998) and based on the anatomical location of the perirhinal cortex, as delineated by Burwell and colleagues (Burwell et al. 1995, Burwell and Amaral 1998, Burwell 2001). The anteroposterior (AP) stereotaxic coordinates were calculated relative to bregma, the lateral (L) relative to the midline and the dorsoventral (V) relative to the top of the skull: AP=−2.5, L=±2.4, V=9.8; AP=−3.6, L=±2.9, V=9.8; AP=−4.8, L=±3.3, V=9.8; AP=−5.8, L=±2.8, V=9.8. NMDA was administered in a 0.4 µl volume at each site through the cannula that was attached to a 5 µl Hamilton microsyringe (Teknokroma, Barcelona, Spain). The solution was delivered by a Harvard Apparatus pump set (model 22, Panlab-Harvard Apparatus, Barcelona, Spain) at an infusion rate of 0.1 µl/min. The cannula was left in situ for an additional 5 min before being withdrawn. The control group (n=8) received identical surgical procedures, except equivalent volumes of phosphate-buffered saline (PBS) were infused into the Prh.

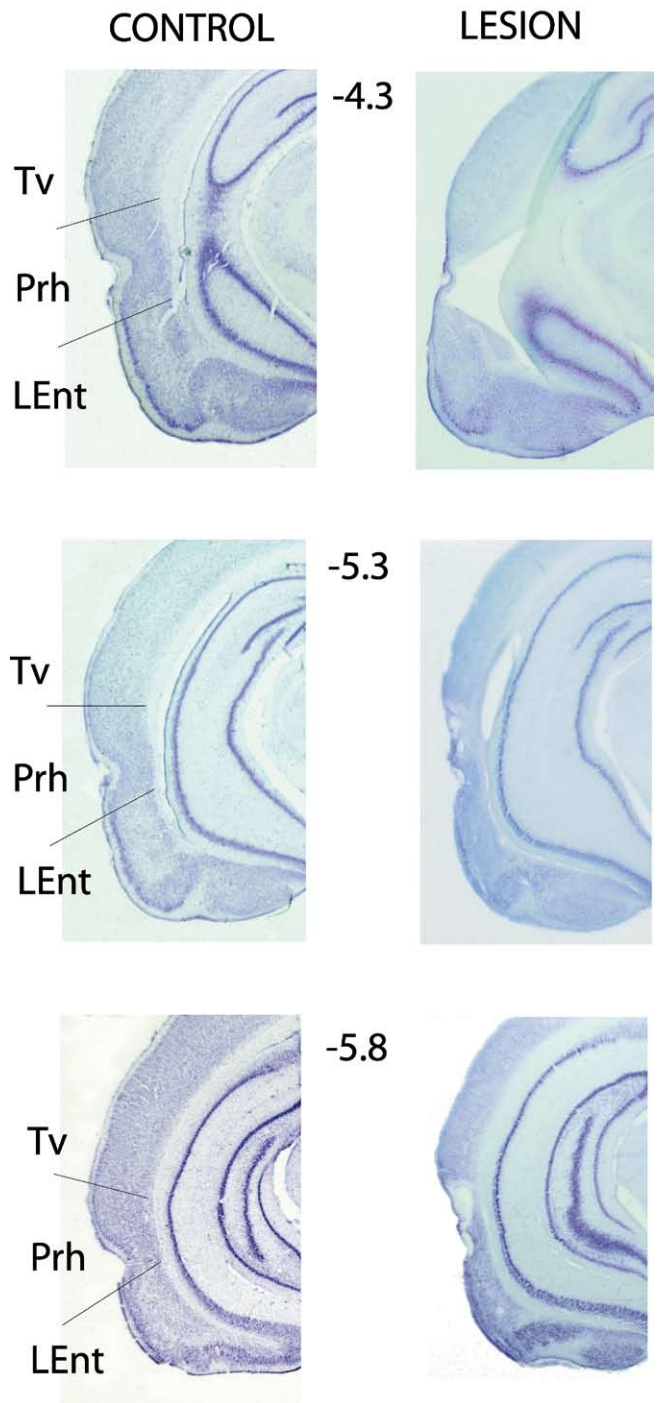

Fig. 2. Photomicrographs of coronal sections stained with cresyl violet from a representative control and lesioned rat. Numbers (center) represent the distance (mm) posterior to bregma. (Tv) ventral area TE; (Prh) perirhinal cortex; (Lent) lateral entorhinal cortex.

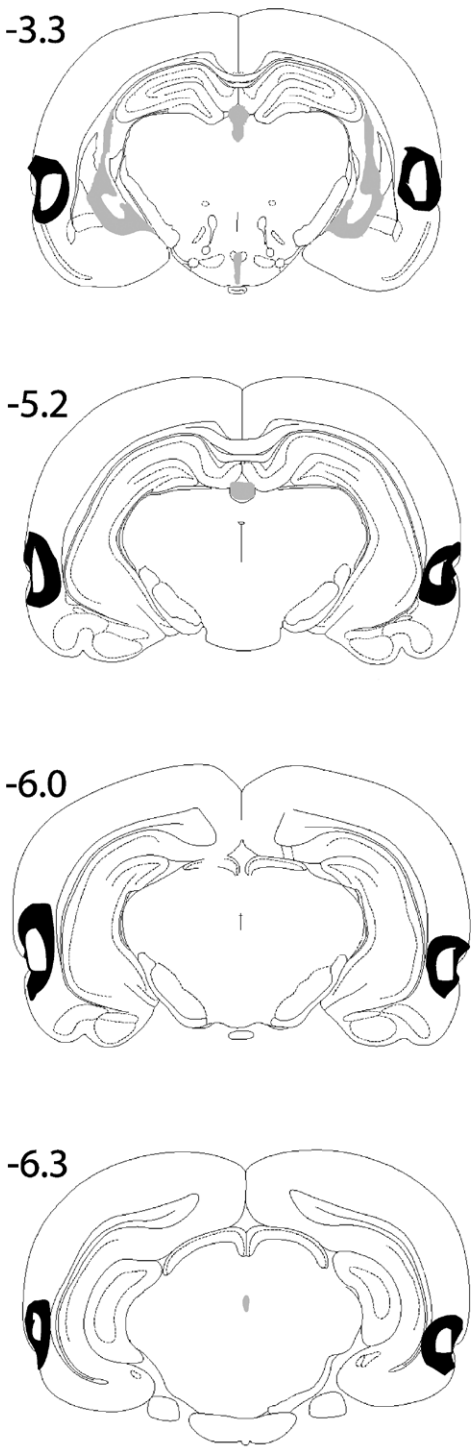

Fig. 3. Coronal sections showing the largest (black area) and smallest (central white area) perirhinal lesions. Numbers (left) represent the distance (mm) posterior to bregma. Sections are taken (modified) from the atlas of Paxinos and Watson [Paxinos G, Watson C (1998) The Rat Brain in Stereotaxic Coordinates (4th ed.). Academic Press, New York, NY.© Elsevier] with permission from Elsevier.

Apparatus

A four-arm plus-shaped maze, built by the University of Granada Technical Services Department, was used. Each arm of the maze measured 60 cm in length and 10 cm in width and was connected to an octagonal central platform 35 cm in diameter. The walls of the central platform were made of transparent Plexiglas and were 15 cm in height. The walls of each arm were made of wood and measured 5 cm in height. The maze was 60 cm from the floor.

Phase 1: acquisition of a complex tactual discrimination task

The main goal of the present study was to demonstrate, in the same rats, that Prh lesions can cause impairment in the acquisition of complex/ambiguous discrimination tasks and in a generalization test. To perform both of these tasks, the animals must use a mechanism for perceptual disambiguation between stimuli that share representational features. Therefore, in the first experimental phase, lesioned and control rats learned a complex tactual discrimination task developed in our lab. In the discrimination learning task rats had to discriminate among three pieces of aluminum oxide sandpaper that differed in roughness. In a four-arm radial maze, one of the arms was used as an exit arm and in the other three arms sandpaper of different textures was placed all along the floor. The sandpaper placed in the arms of the maze extended 5 cm into the central platform of the maze, which allowed for simultaneous exposure to the three stimuli. Each piece of sandpaper thus measured 10×65 cm. The degree of feature overlap among the discriminanda was determined by the grain density and by the average particle diameter of the sandpaper. The mean grain density was calculated by counting, under the microscope (Olympus SZ40, Técnicas Médicas MAB, Barcelona, Spain), the number of grains per 0.5 cm^2. This operation was carried out 4 times on each grade of sandpaper, in different randomly selected areas. To facilitate the counting, we used a microslide upon which we had marked columns of 0.5×0.1 cm^2. The microslide was placed over the different areas in which the counting was done. The results indicated the following average grain densities for the three grades of sandpaper used: 147.2±5.6, 222.2±4.1 and 294.0±9.1 per 0.5 cm^2. The average particle diameter of each

grade of sandpaper, according to information provided by the manufacturer (www.sgabrasivos.es), was 156.0 µm, 97.0 µm and 78.0 µm, respectively. The sandpaper was Debray or Norton brand and was supplied by Saint-Gobain Abrasivos S.A. (Navarra, Spain). Textures defined by these two variables share a number of features, making them complex tactual stimuli that are difficult to discriminate (Johnson 2001, Maricich et al. 2012, Wu et al. 2013). Previous studies in our lab have made it possible to classify these three stimuli as having an apparently high degree of feature ambiguity (Ramos 2013a).

General training procedure

The rats were given 10–12 days to recovery from the surgery. Following this period all subjects were placed on a food-deprivation schedule to maintain them at 90% of their free-feeding body weight. Beginning on the same day as the deprivation program, all rats were handled on 7 successive days for 10 minutes each. On the following day training began for the discrimination learning task. Rats received eight trials per session, one session per day, until they reached learning criterion. An animal was considered to have reached the learning criterion when its performance on two consecutive days was 87%. At the beginning of a trial, the four guillotine-doors separating the arms from the central platform were raised and the rat was placed at the end of the starting arm, with its back to the central platform. The reward, two 45-mg food pellets (P.J. Noyes Company Inc., Lancaster, New Hampshire), was placed in the food cup located at the end of the goal arm. Identification of the goal arm by smell was prevented by placing five inaccessible 45-mg food pellets under each of the four arms. The pellets were placed at the end of each arm, under the food cup, using adhesive tape. The pellets were replaced by fresh ones every 2 days. The order in which each of the four arms was used as starting or goal arm was randomized from trial to trial. The rat was considered to have made a choice when, having entered an arm, it crossed the halfway point with all four limbs. After a choice was made the guillotine-doors were lowered and the animal was left in the chosen arm for 10–12 s. The rat was then picked up and confined in a box for an intertrial interval of 30 s. When the animals showed signs of a certain amount of learning, specifically when in the previous day's training session they had reached a performance of 62% (5 correct trials out of 8), the intra-maze stimuli on the floor of the arms were replaced, halfway through each animal's daily session, by new ones or by ones that had been used by other animals in order to control the use of olfactory cues by the rats.

Phase 2: the generalization test

The generalization test took place on the two days following the day on which the animals reached the learning criterion. On these two days, the original target stimulus associated with reward during acquisition of the task was replaced by a new target stimulus. The new target was a 10×65 cm piece of aluminum oxide sandpaper that had a high degree of feature overlap with respect to the original target. More specifically, of the three stimuli used during the training, the target stimulus that had been associated with the reward was the one with an average grain density of 147.2±5.6 per 0.5 cm^2 (average particle diameter of 156.0 µm).

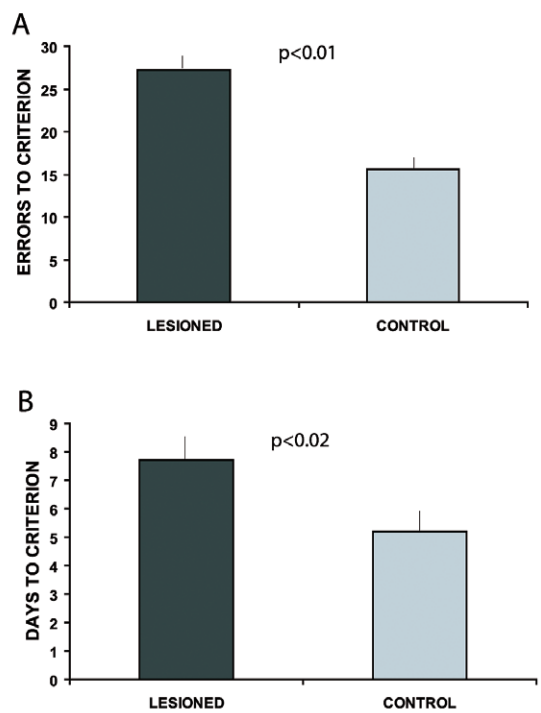

Fig. 4. Experimental phase 1 (acquisition): (A) Mean (±SEM) number of errors to criterion for the perirhinal and control groups during the acquisition of a feature-ambiguous tactual discrimination task. (B) Mean (±SEM) number of days to criterion for the perirhinal and control groups during the acquisition of a feature-ambiguous tactual discrimination task.

During the generalization test this stimulus was replaced by a different one, with an average grain density of 106.5±5.3 per 0.5 cm^2 and an average particle diameter of 326.0 μm. Thus, the difference between the new target and the original target in terms of average grain density was 40.7 per 0.5 cm^2.

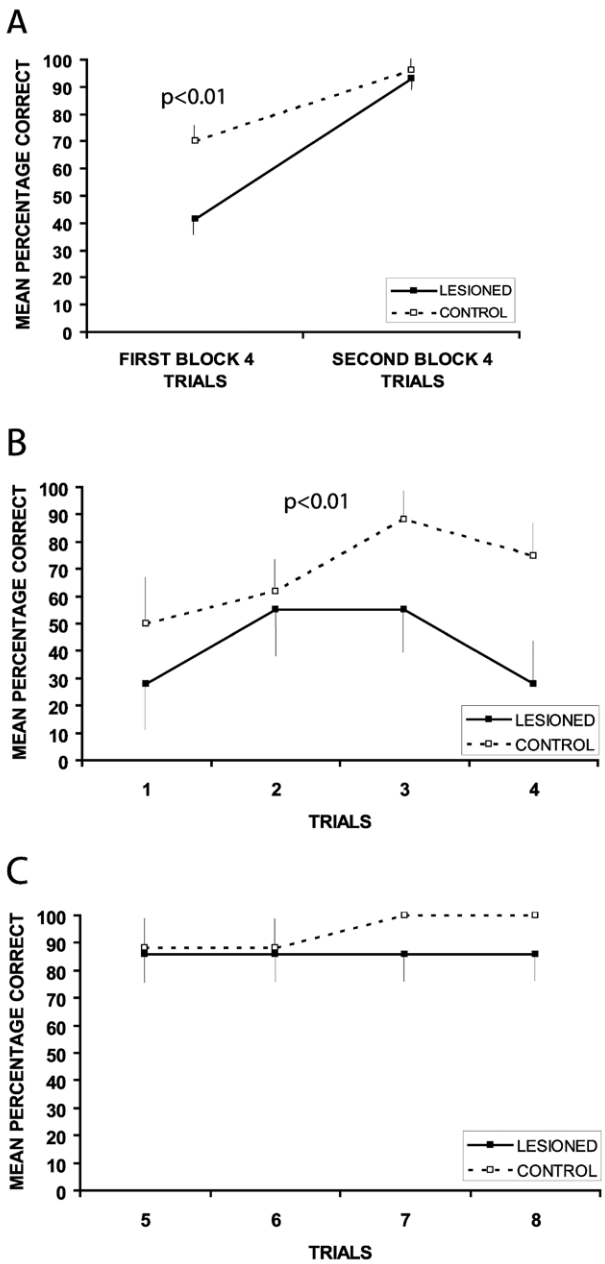

Fig. 5. Experimental phase 2 (first day of generalization): (A) Mean (±SEM) percentage of correct responses observed in lesioned and control rats during the 8 trials taking place on the first day of generalization. (B) Mean (±SEM) percentage of correct responses observed in lesioned and control rats during the first 4 trials individually on the first day of generalization. (C) Mean (±SEM) percentage of correct responses observed in lesioned and control rats during the last 4 trials individually on the first day of generalization.

During each day of generalization, the rats received 8 trials, following the same procedure as used during the first, or acquisition, phase. In order to analyse the evolution of the animals' conduct during the two days of generalization, the data was grouped into 4 blocks of 4 trials.

Histology

When the behavioral testing was completed, the rats were deeply anesthetized with sodium pentobarbital (90 mg/kg, i.p.) and perfused intercardially with 0.9% saline, followed by 10% formalin. After extraction from the skull, the brains were post-fixed in 10% formalin for several days and subsequently in 10% formalin-30% sucrose until sectioning. Coronal sections (40 μm) were cut on a cryostat (Leica CM 1850, Leica Microsystems, Germany) and stained with cresyl violet, a Nissl stain.

In order to quantify the extension of the damage in each lesioned rat, regions of cell loss and gliosis identified microscopically were plotted on drawings of coronal sections from the atlas of Paxinos and Watson (1998). For each perirhinal-lesioned rat, the reconstruction of the lesion was made based on eight coronal sections (anteroposterior levels from bregma: −3.3, −3.8, −4.3, −4.8, −5.2, −5.6, −6.0 and −6.3). Each coronal section was digitized and the lesioned area was measured by a computer program (ImageJ, www.imagej.nih.gov/ij). The anatomical limits of the perirhinal, entorhinal and postrhinal cortices were defined using works by Burwell and associates (Burwell 2001, Burwell et al. 1995, Burwell and Amaral 1998). The volume of damage was expressed as a percentage of normal volume.

Analysis of the data

ANOVA and *t*-test were performed where necessary.

RESULTS

Histological results

Tissue damage was microscopically identified by pronounced thinning of the cortex, necrosis, or missing tis-

sue. The lesions, aimed at areas 35 and 36, were generally limited to the target area, creating a longitudinal groove on both sides of the rhinal fissure (Figs 1, 2 and 3). The volumetric analysis performed with the software ImageJ indicated that the percentage of damage to the Prh was 67.1±4.2% (mean ± SEM). Two Prh-lesioned rats showed partial unilateral damage in the CA1 field of the ventral hippocampus. Minor damage to the lateral entorhinal cortex (8.9±2.1%) and to the associative temporal cortex dorsal to the Prh region (11.9±2.5%) was also observed in 4 and 6 experimental rats, respectively. The postrhinal cortex appeared intact in all 7 lesioned rats.

Behavioral results

Phase 1: acquisition

During acquisition of the discrimination learning task, both groups of animals learned the task perfectly, attaining the same degree of learning at the end of training. Specifically, the mean percentage of correct responses on the last day of training for the Prh-lesioned group was 98.1±1.85 (mean ± SEM), compared to the 95.1±0.75 observed in the control group ($F_{1,13}$=0.95, P=0.34). However, although both the lesioned and the control rats learned the task perfectly, perirhinal rats made more mistakes before reaching criterion ($F_{1,13}$=7.11, P<0.01. Fig. 4A) and they needed more days of training to reach criterion ($F_{1,13}$=6.23, P<0.02. Fig. 4B) compared to the control animals. These results replicate previous data indicating that Prh-lesioned rats show a profound impairment in a texture discrimination learning task when the stimuli have a high degree of feature ambiguity (Ramos 2013a).

Phase 2: generalization test

On the day after reaching criterion the target stimulus originally associated with the reward abruptly changed to a new target stimulus with shared characteristics and the experimental group's performance worsened significantly compared to that of the controls (Fig. 5A). A two-way repeated measures ANOVA (group × block) indicated a significant effect of group ($F_{1,13}$=9.14, P<0.01) and block ($F_{1,13}$=43.58, P<0.0001) but only a marginal effect of interaction ($F_{1,13}$=3.42, P=0.08). Given the marginal effect of interaction, in an effort to analyse the results more in depth, two t-tests for independent samples were performed. These tests showed that the performance of both groups differed significantly during the initial block of four trials (t_{13}=2.74, P<0.01) but not during the second block of four trials (t_{13}=0.73, P=0.47). In order to further investigate the aforementioned effect, we analysed the first four trials individually during the generalization test. A two-way repeated measures ANOVA (group × trial) revealed a significant effect of group ($F_{1,13}$=7.51, P<0.01; see Fig. 5B) but an absence of significant differences both in the trial factor ($F_{3,39}$=1.04, P=0.38) and in interaction ($F_{3,39}$=0.39, P=0.75). A similar repeated measures ANOVA, individually analysing the last four trials of the generalization test, did not detect signifi-

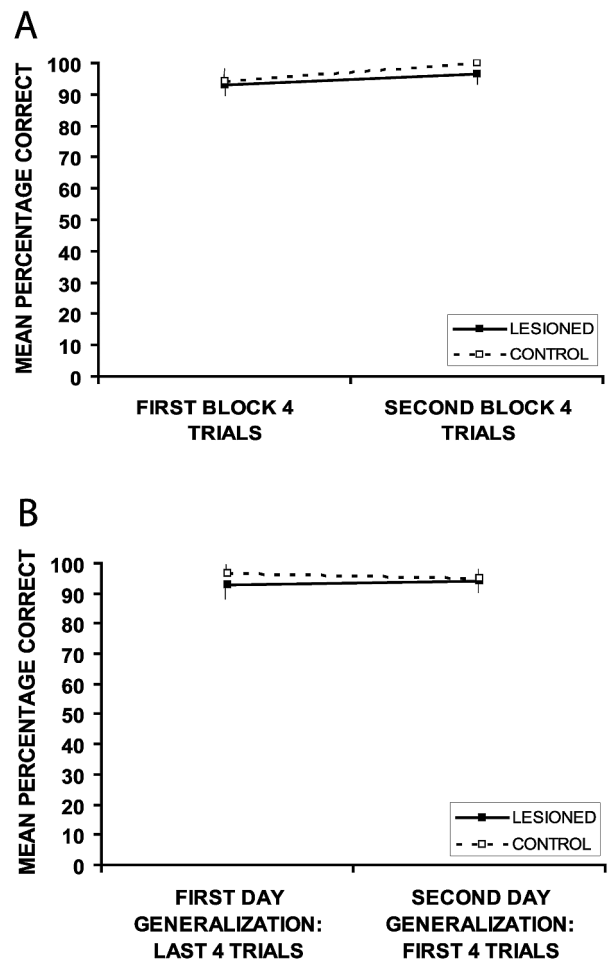

Fig. 6. Experimental phase 2 (second day of generalization): (A) Mean (±SEM) percentage of correct responses observed in lesioned and control rats during the 8 trials taking place on the second day of generalization. (B) Mean (±SEM) percentage of correct responses observed in lesioned and control rats during the last 4 trials of the first day of generalization and during the first 4 trials of the second day of generalization.

cant differences ($F_{1,13}$ group =0.48, P=0.50; F trial $_{3,39}$ =0.18, P=0.90; $F_{3,39}$ interaction =0.67, P=0.57; see Fig. 5C).

On the second day of generalization, a two-way repeated measures ANOVA (group × block) detected no significant differences between lesioned and control rats ($F_{1,13}$ group =0.48, P=0.49; $F_{1,13}$ block =0.48, P=0.21; $F_{1,13}$ interaction =0.13, P=0.72; see Fig. 6A). Finally, in order to evaluate a possible retention deficit in lesioned animals, a two-way repeated measures ANOVA detected no significant differences between lesioned and control rats when comparing the performance during the four final trials of the first day of generalization with the performance during the first four trials of the second day of generalization ($F_{1,13}$ group =0.24, P=0.62; $F_{1,13}$ block =0.26, P=0.61; $F_{1,13}$ interaction =0.25, P=0.62; see Fig. 6B).

DISCUSSION

The present study investigated the effect of perirhinal cortex lesions on response generalization. Generalization was evaluated by presenting a new target stimulus having a certain degree of feature overlap with the original target stimulus that had been associated with reward during the discrimination learning task. The main findings can be summed up in three points. First, in experimental phase 1, using a tactual discrimination learning task with a high degree of feature ambiguity, Prh lesions delayed but did not prevent the acquisition of the discrimination. According to previous findings in our lab (Ramos 2013a) the task used was sensitive to perceptual demands. Second, in experimental phase 2, the abrupt introduction of a new target stimulus having considerable feature overlap with the original target stimulus significantly worsened the performance of the Prh-lesioned animals compared to the control group. Third, the deficit observed in experimental phase 2 was restricted to the initial block of 4 trials. No significant differences were found between lesioned and control rats during the second block of 4 trials on the first day of generalization, nor at any time on the second day of generalization. Finally, no significant differences were detected upon comparing the performance of both groups in the last 4 trials of the first day of generalization with the first 4 trials of the second day of generalization. This last piece of data suggests that Prh-lesioned rats can retain the tactual discrimination task perfectly for at least 24 h.

Results of experimental phase 1 replicate previous data obtained in our lab (Ramos 2013a). In the earlier study, rats with Prh lesions showed a profound impairment in a texture discrimination learning task when the degree of feature ambiguity among the stimuli was high but not when it was low (Ramos 2013a, experiments 1a and 1c). Importantly, it is unlikely that the delay in the acquisition of the feature-ambiguous task observed in Prh-lesioned rats in the present study can be explained by a mnemonic deficit. In support of this, our previous study, using a reversal learning paradigm, revealed a profound deficit in the initial learning phase with feature-ambiguous tactual stimuli, but unimpaired acquisition during a reversal learning phase with identical stimuli (Ramos 2013a, experiment 5). Thus, results from experimental phase 1 of the present series agree with our previous data, suggesting that the Prh may play a role in somatosensory representational functions.

The data obtained in the present study's generalization test can also be interpreted from a representational point of view. In order for generalization to occur, a mechanism capable of precisely representing stimuli that share features is necessary (Hampton and Murray 2002). Such a mechanism should reduce interference among stimuli that have a certain degree of feature ambiguity, allowing the subject to respond to the stimulus that is most similar to the original target (Harris 2006, Robinson et al. 2010, Hunsaker and Kesner 2013). Therefore, the fact that in the generalization test – in which the new and the original target stimuli have a great deal of feature overlap – Prh-lesioned rats perform worse than the controls suggests a possible representational deficit. However, the present study has a limitation and it would be necessary to replicate these data in a study using different degrees of similarity between the training and generalization test tactile stimuli. Future research should try to determine using different groups of rats, with different degrees of similarity between training and generalization test stimuli, whether the nature of the impairment observed in the Prh-damaged rats is graded. Based on previous findings (Ramos 2013a) and the present data, it can be hypothesised that during the generalization test Prh-lesioned rats will probably show progressively worse performance in comparison with control rats, the higher the degree of similarity between the shared features of training and test stimuli.

Another possibility is that the impairment observed in the generalization test is not only due to a representational deficit regarding complex stimuli that share representational elements, but to a mnemonic deficit (Suzuki 2009, Clark et al. 2011). This interpretation, however, is difficult to accept. Firstly, in the generalization test, Prh-lesioned rats reveal a significant deficit only at the beginning of the test, during the first block of 4 trials. Both groups of animals reach the same degree of performance during the second block of 4 trials of the first day of generalization. Secondly, on the second day of generalization no differences between Prh-lesioned and control rats were observed. Thirdly, Prh-lesioned animals are perfectly able to retain, for at least 24 h, the new target stimulus presented during the generalization test. In support of the foregoing, no significant differences were observed upon comparing the performance of the two groups during the first day (last 4 trials) and the second day (first 4 trials) of generalization. Consequently, it is unlikely that the deficits observed in the Prh-lesioned animals during the generalization test can be explained in mnemonic terms.

The two sets of data of the present study, discrimination and generalization deficits among stimuli with feature overlap, could be interpreted using the representational-hierarchical view (Bussey and Saksida 2002, Cowell et al. 2006, Saksida and Bussey 2010). According to this perspective, the Prh may function as a disambiguating mechanism among stimuli with a high degree of feature overlap (Bussey et al. 2002, Buckley and Gaffan 2006, Murray et al. 2007). Without a mechanism of this type, the above hypothesis predicts that the animals would fail in a feature-ambiguous discrimination task and in a generalization test involving the choice of one stimulus among various, based on representational similarity with the original target stimulus (Hampton and Murray 2002, Murray et al. 2007, Saksida and Bussey 2010). The present report confirms these two predictions in the same rats.

In addition, the above interpretation is coherent with numerous studies demonstrating that the Prh is involved in object processing (Eacott and Gaffan 2005, Abe et al. 2009), in within-object association of features (Kholodar-Smith et al. 2008) and in binding crossmodal object features (Goulet and Murray 2001, Taylor et al. 2006, Holdstock et al. 2009, Winters and Reid 2010) but not in context or visuo-spatial processing. In contrast with these functional characteristics, other related areas of the medial temporal lobe, such as the hippocampus and the postrhinal/parahippocampal cortex, are more involved in the processing of visuo-spatial characteristics of the stimuli (Malkova and Mishkin 2003, Norman and Eacott 2005, Mullally and Maguire 2011, Ramos 2013b).

Finally, in concordance with anatomical studies showing that the higher-order cortical areas of different sensory systems project to the Prh (Suzuki and Amaral 1994, Burwell and Amaral 1998, Kealy and Commins 2011), our data suggest that the Prh might represent a common mechanism for perceptual disambiguation of complex representations of different modalities (Lindquist et al. 2004, Bartko et al. 2007, Feinberg et al. 2012). Specifically, here, in agreement with a previous study performed in our lab (Ramos 2013a), the present data suggest that the Prh may be necessary for representing ambiguous somatosensory/tactual information in rats.

CONCLUSION

In conclusion, the deficit in generalization observed in the present study is coherent with perceptual interpretation of the function of the perirhinal cortex.

ACKNOWLEDGEMENTS

This work was supported by a grant from the Spanish Science and Innovation Ministry (General Office for Research, Ministerio de Economía y Competitividad, Spain) and the European Regional Development Fund-ERDF (PSI2010-14979). The author declares no conflict of interest.

REFERENCES

Abe H, Ishida Y, Nonaka H, Iwasaki T (2009) Functional difference between rat perirhinal cortex and hippocampus in object and place discrimin ation tasks. Behav Brain Res 197: 388–397.

Aggleton JP, Albasser MM, Aggleton DJ, Poirier GL, Pearce JM (2010) Lesions of the rat perirhinal cortex spare the acquisition of a complex configural visual discrimination yet impair object recognition. Behav Neurosci 124: 55–68.

Agster KL, Burwell RD (2009) Cortical efferents of the perirhinal, postrhinal, and entorhinal cortices of the rat. Hippocampus 19: 1159–1186.

Barense MD, Groen IIA, Lee ACH, Yeung L-K, Brady SM, Gregori M, Kapur N, Bussey TJ, Saksida LM, Henson RNA (2012) Intact memory for irrelevant information impairs perception in amnesia. Neuron 75: 157–167.

Bartko SJ, Winters BD, Cowell RA, Saksida LM, Bussey TJ (2007) Perceptual functions of perirhinal cortex in rats: zero-delay object recognition and simultaneous oddity discriminations. J Neurosci 27: 2548–2559.

Baxter M (2009) Involvement of medial temporal lobe structures in memory and perception. Neuron 61: 667–677.

Brown MW, Warburton EC, Aggleton JP (2010) Recognition memory: Material, processes, and substrates. Hippocampus 20: 1228–1244.

Buckley MJ, Gaffan D (1998) Perirhinal cortex ablation impairs visual object identification. J Neurosci 18: 2268–2275.

Buckley MJ, Gaffan D (2006) Perirhinal cortical contributions to object perception. Trends Cogn Sci 10: 100–107.

Buckley MJ, Gaffan D, Murray EA (1997) Functional double dissociation between two inferior temporal cortical areas: Perirhinal cortex versus middle temporal gyrus. J Neurophysiol 77: 587–598.

Buckley MJ, Booth MC, Rolls ET, Gaffan D (2001) Selective perceptual impairments after perirhinal cortex ablation. J Neurosci 21: 9824–9836.

Burwell RD (2001) Borders and cytoarchitecture of the perirhinal and postrhinal cortices in the rat. J Comp Neurol 437: 17–41.

Burwell RD, Amaral DC (1998) Cortical afferents of the perirhinal, postrhinal and entorhinal cortices of the rat. J Comp Neurol 398: 179–205.

Burwell RD, Witter MP, Amaral DC (1995) Perirhinal and postrhinal cortices of the rat: A review of the neuroanatomical literature and comparison with findings from the monkey brain. Hippocampus 5: 390–408.

Bussey TJ, Saksida LM (2002) The organization of visual object representations: a connectionist model of effects of lesions in perirhinal cortex. Eur J Neurosci 15: 353–364.

Bussey TJ, Saksida LM (2005) Object memory and perception in the medial temporal lobe: An alternative approach. Curr Opin Neurobiol 15: 730–737.

Bussey TJ, Saksida LM, Murray EA (2002) Perirhinal cortex resolves feature ambiguity in complex visual discriminations. Eur J Neurosci 15: 365–374.

Bussey TJ, Saksida LM, Murray EA (2003) Impairments in visual discrimination after perirhinal cortex lesions: Testing 'declarative' vs. 'perceptual-mnemonic' views of perirhinal cortex function. Eur J Neurosci 17: 649–660.

Campolattaro MM, Freeman JH (2006) Perirhinal cortex lesions impair feature-negative discrimination. Neurobiol Learn Mem 86: 205–213.

Clark RE, Reinagel P, Broadbent NJ, Flister ED, Squire LR (2011) Intact performance on feature-ambiguous discriminations in rats with lesions of the perirhinal cortex. Neuron 70: 132–140.

Cowell RA, Bussey TJ, Saksida LM (2006) Why does brain damage impair memory? A connectionist model of object recognition memory in perirhinal cortex. J Neurosci 26: 12186–12197.

Eacott MJ, Gaffan EA (2005) The roles of perirhinal cortex, postrhinal cortex, and the fornix in memory for objects, contexts, and events in the rat. Q J Exp Psychol 58B: 202–217.

Eacott MJ, Gaffan D, Murray EA (1994) Preserved recognition memory for small sets, and impaired stimulus identification for large sets, following rhinal cortex ablations in monkeys. Eur J Neurosci 6: 1466–1478.

Eacott MJ, Machin PE, Gaffan EA (2001) Elemental and configural visual discrimination learning following lesions to perirhinal cortex in the rat. Behav Brain Res 124: 55–70.

Eichenbaum H, Yonelinas AP, Ranganath C (2007) The medial temporal lobe and recognition memory. Annu Rev Neurosci 30: 123–152.

Feinberg LM, Allen TA, Ly D, Fortin NJ (2012) Recognition memory for social and non-social odors: Differential effects of neurotoxic lesions to the hippocampus and perirhinal cortex. Neurobiol Learn Mem 97: 7–16.

Gilbert PE, Kesner RP (2003) Recognition memory for complex visual discriminations is influenced by stimulus interference in rodents with perirhinal cortex damage. Learn Mem 10: 525–530.

Goulet S, Murray EA (2001) Neural substrates of crossmodal association memory in monkeys: The amygdala versus the anterior rhinal cortex. Behav Neurosci 115: 271–284.

Hampton RR, Murray EA (2002) Learning of discriminations is impaired, but generalization to altered views is intact, in monkeys (*Macaca mulatta*) with perirhinal cortex removal. Behav Neurosci 116: 363–377.

Harris JA (2006) Elemental representations of stimuli in associative learning. Psychol Rev 113: 584–605.

Holdstock JS, Hocking J, Notley P, Devlin JT, Price CJ (2009) Integrating visual and tactile information in the perirhinal cortex. Cereb Cortex 29: 2993–3000.

Hunsaker MR, Kesner RP (2013) The operation of pattern separation and pattern completion processes associated with different attributes or domains of memory. Neurosci Biobehav Rev 37: 36–58.

Johnson KO (2001) The roles and functions of cutaneous mechanoreceptors. Curr Opin Neurobiol 11: 455–461.

Kealy J, Commins S (2011) The rat perirhinal cortex: A review of anatomy, physiology, plasticity and function. Prog Neurobiol 93: 522–548.

Kholodar-Smith DB, Allen TA, Brown TH (2008) Fear conditioning to discontinuous auditory cues requires perirhinal cortical function. Behav Neurosci 122: 1178–1185.

Kim S, Jeneson A, van der Horst A, Frascino J, Hopkins RO, Squire LR (2011) Memory, visual discrimination performance and the human hippocampus. J Neurosci 31: 2624–2629.

Kivisaari SL, Tyler LK, Monsch AU, Taylor KI (2012) Medial perirhinal cortex disambiguates confusable objects. Brain 135: 3757–3769.

Lindquist DH, Jarrard LE, Brown TH (2004) Perirhinal cortex supports delay fear conditioning to rat ultrasonic social signals. J Neurosci 24: 3610–3617.

Mackintosh NJ (1974) The Psychology of Animal Learning. Academic Press, London, UK.

Malkova L, Mishkin M (2003) One-trial memory for object-place associations after separate lesions of hippocampus and posterior parahippocampal region in the monkey J Neurosci 23: 1956–1965.

Maricich SM, Morrison KM, Mathes EL, Brewer BM (2012) Rodents rely on merkel cells for texture discrimination tasks. J Neurosci 32: 3296–3300.

Mullally SL, Maguire EA (2011) A new role for parahippocampal cortex in representing space. J Neurosci 31: 7441–7449.

Murray EA, Bussey TJ, Hampton RR, Saksida LM (2000) The parahippocampal region and object identification. Ann N Y Acad Sci 911: 166–174.

Murray EA, Bussey TJ, Saksida LM (2007) Visual perception and memory: A new view of medial temporal lobe function in primates and rodents. Annu Rev Neurosci 30: 99–122.

Norman G, Eacott MJ (2004) Impaired object recognition with increasing levels of feature ambiguity in rats with perirhinal cortex lesions. Behav Brain Res 148: 79–91.

Norman G, Eacott MJ (2005) Dissociable effects of lesions to the perirhinal cortex and the postrhinal cortex on memory for context and objects in rats. Behav Neurosci 119: 557–566.

Paxinos G, Watson C (1998) The Rat Brain in Stereotaxic Coordinates (4th ed.). Academic Press, New York, NY.

Ramos JMJ (2013a) Essential role of the perirhinal cortex in complex tactual discrimination tasks in rats. Cereb Cortex (E-pub ahead of Print). [doi: 10.1093/cercor/bht054.]

Ramos JMJ (2013b) Differential contribution of hippocampus, perirhinal cortex and postrhinal cortex to allocentric spatial memory in the radial maze. Behav Brain Res 247: 59–64.

Robinson J, Whitt EJ, Horsley RR, Jones PM (2010) Familiarity-based stimulus generalization of conditioned supression in rats is dependent on the perirhinal cortex. Behav Neurosci 124: 587–599.

Saksida LM, Bussey TJ (2010) The representational-hierarchical view of amnesia: Translation from animal to human. Neuropsychologia 48: 2370–2384.

Shrager Y, Gold JJ, Hopkins RO, Squire LR (2006) Intact visual perception in memory-impaired patients with medial temporal lobe lesions. J Neurosci 26: 2235–2240.

Squire LR, Zola-Morgan S (1991) The medial temporal lobe memory system. Science 253: 1380–1386.

Suzuki WA (2009) Perception and the medial temporal lobe: Evaluating the current evidence. Neuron 61: 657–666.

Suzuki WA (2010) Untangling memory from perception in the medial temporal lobe. Trends Cogn Sci 14: 195–200.

Suzuki WA, Amaral DG (1994) Perirhinal and parahippocampal cortices of the macaque monkey: Cortical afferents. J Comp Neurol 350: 497–533.

Suzuki WA, Baxter MG (2009) Memory, perception, and the medial temporal lobe: A synthesis of opinions. Neuron 61: 678–679.

Taylor KI, Moss HE, Stamatakis EA, Tyler LK (2006) Binding crossmodal object features in perirhinal cortex. Proc Natl Acad Sci U S A 103: 8239–8244.

Wagner AR (2003) Context-sensitive elemental theory. Q J Exp Psychol B 56: 7–29.

Watson HC, Lee ACH (2013) The perirhinal cortex and recognition memory interference. J Neurosci 33: 4192–4200.

Winters BD, Reid JM (2010) A distributed cortical representation underlies crossmodal object recognition in rats. J Neurosci 30: 6253–6261.

Wu HPP, Ioffe JC, Iverson MM, Boon JM, Dyck RH (2013) Novel, whisker-dependent texture discrimination task for mice. Behav Brain Res 237: 238–242.

Yonelinas AP, Aly M, Wang WC, Koen JD (2010) Recollection and familiarity: examining controversial assumptions and new directions. Hippocampus 20: 1178–1194.