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Perirhinal Cortex Lesions Impair Simultaneous but Not Serial Feature-Positive Discrimination Learning

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Abstract

The role of the perirhinal cortex in discriminative eyeblink conditioning was examined by means of feature-positive discrimination procedures with simultaneous (A-/XA+) and serial (A-/X→A+) stimulus compounds. Lesions of the perirhinal cortex severely impaired acquisition of simultaneous feature-positive discrimination but produced no impairment in serial feature-positive discrimination. The results suggest that the perirhinal cortex plays a role in discriminative eyeblink conditioning by resolving ambiguity in discriminations with overlapping stimulus elements.

Keywords

eyeblink; eyelid; conditioning; learning; cerebellum

In a typical Pavlovian discrimination procedure, two conditioned stimuli (CSs) are presented separately, where one CS is paired with an unconditioned stimulus (CS+) and the other is not (CS-). Responding to the CS+ increases as training proceeds, whereas responding to the CS- does not (Hilgard, Campbell, & Sears, 1938; Rescorla, 1969). Conditioning procedures used to establish more complex discriminations often use compound stimuli. In feature-positive discrimination, for example, a compound stimulus is reinforced (XA+), whereas one of its elements is not reinforced (A-). The X stimulus serves as a reliable signal that A will be reinforced (Holland, 1989b; Holland & Hass, 1993; Ross & Holland, 1981). It has also been argued that the compound stimulus may form a configural stimulus (Kehoe & Gormezano, 1980; Pearce & Wilson, 1990; Razran, 1939). The associations underlying feature-positive discrimination, therefore, may involve more than one type of associative relationship.

The perirhinal cortex receives information from numerous sensory areas that are important for discrimination learning (Buckley & Gaffan, 1997; Burwell & Amaral, 1998a, 1998b; Eacott, 1998; Wiig & Burwell, 1998). Lesions of the perirhinal cortex have been shown to impair sensory preconditioning (Nicholson & Freeman, 2000) and temporal order discrimination (Hannesson, Howland, & Phillips, 2004). Perirhinal cortex lesions also disrupt performance on discrimination tasks with rats and nonhuman primates when there is mnemonic interference or perceptual overlap between stimulus items (Buckley, Booth, Rolls, & Gaffan 2001; Buckley & Gaffan, 1998; Bussey, Saksida, & Murray, 2002; 2003; Gilbert & Kesner, 2003). Campolattaro and Freeman (2006), for example, found that feature-negative discrimination learning (A+/XA-) with a simultaneous compound stimulus was impaired by perirhinal cortex lesions. The interpretation of this finding was that perirhinal cortex lesions impaired feature-negative discrimination because the procedure involves presentation of a common stimulus for both types of trials (A). A preliminary report by Burwell, Lester-Coll, and Jutras (2004)

demonstrated that combined damage to perirhinal and postrhinal cortices produce differential effects on serial and simultaneous feature-positive and feature-negative discrimination learning using an appetitive conditioning paradigm. The lesions facilitated simultaneous discriminations and impaired serial discriminations.

The neural substrates of short delay eyeblink conditioning have been localized to the cerebellum and interconnected brain stem nuclei (Thompson, 2005). However, a distributed network of forebrain areas, including areas of the limbic system, is involved in more complex eyeblink conditioning procedures such as blocking, discrimination reversal, feature-negative discrimination, feature-positive discrimination, latent inhibition, sensory preconditioning, and trace conditioning (Berger & Orr, 1983; Berger, Weikart, Bassett, & Orr, 1986; Kim, Clark, & Thompson, 1995; Loechner & Weisz, 1987; Moyer, Deyo, & Disterhoft, 1990; Moyer, Thompson, & Disterhoft, 1996; Nicholson & Freeman, 2002a; Port, Beggs, & Patterson, 1987; Port & Patterson, 1984; Solomon, 1977, 1987; Solomon & Moore, 1975; Solomon, Vander Schaaf, Thompson, & Weisz, 1986). Perirhinal cortical neurons might play a role in discrimination learning in eyeblink conditioning by influencing the pathway that provides CS input to the cerebellum (Campolattaro & Freeman, 2006). The CS pathway in eyeblink conditioning includes the basal pontine nuclei and their mossy fiber projection to the cerebellar nuclei and cortex (Hesslow, Svensson & Ivarsson, 1999; Lewis, LoTurco, & Solomon, 1987; Steinmetz, Lavond, & Thompson, 1989; Steinmetz et al., 1987; Steinmetz, Rosen, Chapman, Lavond, & Thompson, 1986). The perirhinal cortex has a monosynaptic projection to the basal pontine nuclei (Legg, Mercier, & Glickstein, 1989; R. D. Burwell, personal communication, January 6, 2006), indicating that it can directly influence CS input to the cerebellum.

The present experiment used eyeblink conditioning procedures to assess the effects of lesions of the perirhinal cortex on feature-positive discrimination in rats. It was hypothesized that the perirhinal cortex is involved in feature-positive discrimination learning because the standard feature-positive discrimination procedure uses a common stimulus element during both trial types (A-/XA+) (Buckley et al., 2001; Buckley & Gaffan, 1998; Bussey et al., 2002; 2003; Campolattaro & Freeman, 2006). The effects of perirhinal cortex lesions on feature-positive discrimination were examined by means of serial and simultaneous stimulus compounds to determine whether the lesions would produce differential effects on these discrimination paradigms, as seen with appetitive conditioning (Burwell et al., 2004).

Method

Subjects

Subjects were 30 male Long-Evans rats (200–250 g; Harlan, Indianapolis, IN), approximately 150 days old at the beginning of the experiment. The rats were housed in Spence Laboratories of Psychology at the University of Iowa with a 12-hr light–dark cycle, with light onset at 7 a.m.

Surgery

One week prior to training, rats were removed from their home cage and anesthetized by an intraperitoneal injection of sodium pentobarbital (80 mg/kg). An intraperitoneal injection of atropine sulfate (0.45 mg/kg) was administered to reduce respiratory tract secretions. After onset of anesthesia, the rats received either perirhinal cortex lesions or control surgery. Perirhinal cortex lesions were made by passing 2 mA of DC current for 10 s at three sites in each hemisphere. The stereotaxic coordinates were 3.3, 4.8, and 6.3 mm posterior to bregma and ± 5.0 mm lateral to midline. An insect pin insulated with epoxy, except for 1.0 mm at the tip, was lowered at each skull hole 8.5–9.0 mm below the skull surface and angled at 15° from vertical. Skull holes were sealed with bonewax. The same procedure was used for making

control lesions, except that no current was applied during surgery. Rats were then fitted with differential EMG electrodes that were implanted in the left upper eyelid muscles (orbicularis oculi), and a ground electrode was attached to a stainless steel skull screw. The EMG electrode leads terminated in gold pins held in a plastic connector, which was secured to the skull with dental acrylic. A bipolar stimulating electrode (for delivering the shock unconditioned stimulus; US) was implanted in a plastic connector immediately caudal to the left eye. The bipolar electrode terminated in a plastic connector that was secured to the skull with dental acrylic.

Groups

Perirhinal-lesioned and control rats were randomly assigned to either simultaneous or serial feature-positive discrimination groups. One group of rats received perirhinal cortex lesions and simultaneous feature-positive discrimination ($n = 8$), a second group received control surgery and simultaneous feature-positive discrimination ($n = 8$), a third group received perirhinal cortex lesions and serial feature-positive discrimination ($n = 8$), and a fourth group received control surgery and serial feature-positive discrimination ($n = 6$).

Conditioning Apparatus

The conditioning apparatus consisted of four small-animal sound attenuation chambers (BRS/LVE, Laurel, MD). Within each sound attenuation chamber was a small-animal operant chamber (BRS/LVE, Laurel, MD) where the rats were kept during conditioning. One wall of the operant chamber was fitted with two speakers. The back wall of the sound attenuating chamber was equipped with a small house light and an exhaust fan. A light bulb (for delivering the light CS) was located on the back wall of the sound attenuating chamber, positioned behind and to the right of the operant chamber. The electrode leads from the rat's head stage were connected to peripheral equipment and a desktop computer. Computer software controlled the delivery of stimuli and the recording of eyelid EMG activity (JSA Designs, Raleigh, NC). One circuit permitted the delivery of a shock stimulus (1–2 mA, DC constant current) through a stimulus isolator (Model number 365A, World Precision Instruments, Sarasota, FL). EMG activity was recorded differentially, filtered (500–5,000 Hz) and integrated by equipment (JSA Designs, Raleigh, NC) described in other reports (Nicholson & Freeman, 2002b; Nicholson, Sweet, & Freeman, 2003; Nolan & Freeman, 2005).

Conditioning Procedure

All rats received 10 sessions of feature-positive discrimination, which consisted of 50 A– and 50 XA+ trials. For simultaneous feature-positive discrimination, the compound stimulus was presented simultaneously, where onset and offsets for A and X occurred simultaneously. For serial feature-positive discrimination, the compound stimulus was presented serially, such that the onset of A coincided with the offset of X. The stimuli (X and A) were a 2-kHz tone CS or 4-W light CS. The modality of the CSs was counterbalanced. The US was a 1–2-mA periorbital shock. The duration of each CS was 400 ms, where the onset of the US coincided with the offset of a CS. On each of the 10 days of training, all rats received a 100-trial session of feature-positive discrimination. Trials were separated by a variable intertrial interval that averaged 30 s (range = 18–42 s).

Conditioned responses (CRs) were defined as EMG activity that exceeded a threshold of 0.4 units (amplified and integrated units in volts) above the baseline mean during the CS period after 80 ms. CRs during CS– and compound stimulus trials were defined as responses that occurred between CS onset (after the baseline period) and the end of the stimulus.

Histology

After training, rats given the perirhinal cortex lesion surgery were deeply anesthetized with an overdose of sodium pentobarbital (90 mg/kg) and transcardially perfused with 0.9% saline, followed by 3.0% formalin. The brains were removed from the skull and post-fixed in 30% sucrose in 0.1 M phosphate buffered saline, and subsequently sectioned at 50 μ m on a sliding microtome (American Optical, Buffalo, NY). Every fifth section was mounted on a slide, stained with thionin, and examined for lesion placement.

Results

There were no statistical effects of stimulus type (i.e., tone or light) for rats that received simultaneous or serial feature-positive discrimination. The data were, therefore, collapsed across stimulus type for further analysis.

Simultaneous Feature-Positive Discrimination

Simultaneous feature-positive discrimination was impaired in rats that were given perirhinal cortex lesions (see Figure 1A, 1B). Rats given perirhinal cortex lesions exhibited a lower overall percentage of CRs during XA+ trials relative to the control group (Figure 1A). Discriminative responding emerged earlier in training in the control group, but the magnitude of discrimination was similar between the groups by the end of training (see Figure 1B).

These observations were confirmed by an analysis of variance (ANOVA) that revealed a significant interaction of the trial-type and lesion-type factors, $F(1, 14) = 7.03, p < .02$, which was due to a higher percentage of CRs on XA+ trials in the control group ($p < .05$). There were no significant group differences in the CR percentage data during A- trials. Figure 1B shows that control rats acquired feature-positive discrimination during the 10 sessions of training more quickly than perirhinal-lesioned rats. This finding was confirmed by an ANOVA of CR percentage data, which revealed a marginally significant interaction of lesion-type, trial-type, and session factors, $F(9, 126) = 1.91, p < .056$. Follow-up tests that used the Scheffe procedure showed that control rats discriminated between A- and XA+ trials during Sessions 3–10 ($p < .05$), whereas rats given the perirhinal lesions discriminated only during Sessions 8–10 ($p < .05$). Five of the 8 control rats reached a discrimination criterion defined as a 40% difference in percentage of CRs between the A- and XA+ trial types, whereas only 2 of the 8 rats that received the perirhinal cortex lesion were able to meet this criterion. It is notable, however, that there was no systematic relationship between size of lesion and degree of impairment.

Serial Feature-Positive Discrimination

Feature-positive discrimination for rats given perirhinal cortex lesions did not differ from the controls. The mean percentage of CRs to the serial compound stimulus (X→A+) and target stimulus (A) for rats with perirhinal cortex lesions did not differ significantly from the CR percentages of the control group (see Figure 1C). Acquisition of CRs to X→A+ and A- during the 10 sessions of feature-positive discrimination training also did not differ between the two groups (see Figure 1D). All control rats, as well as 5 of the 8 rats with perirhinal lesions, achieved the discrimination criterion specified above. The only significant interaction found by an ANOVA was for the trial-type and sessions factors, $F(9, 108) = 7.02, p < .001$, which was due to the development of a significantly greater percentage of CRs during X→A+ trials compared with A- trials in both groups.

Lesions

Electrolytic lesions produced bilateral damage in the perirhinal cortex in all rats. In some rats, damage also extended bilaterally to the lateral entorhinal cortex. Lesions were transcribed onto stereotaxic figures from the stereotaxic atlas of Paxinos and Watson (1998). The largest and smallest lesions are shown in Figure 2. There were no group differences observed for the size or location of lesions between rats that received simultaneous and serial feature-positive discrimination training.

Discussion

Perirhinal cortex lesions impaired feature-positive discrimination learning when the stimulus elements in the compound occurred simultaneously ($A-/XA+$). However, rats with perirhinal cortex lesions were not impaired on feature-positive discrimination learning when the stimulus elements were presented serially ($A-/X \rightarrow A+$). These findings are consistent with results of a previous study that demonstrated that rats with perirhinal cortex lesions were impaired on acquisition of simultaneous feature-negative discrimination learning ($A+/XA-$; Campolattaro & Freeman, 2006). That study also showed that perirhinal cortex lesions have no effect on acquisition of excitatory conditioning ($A+$) or simple discrimination learning ($A+/X-$). Together, these results suggest that perirhinal cortex lesions produce deficits in discriminative eyeblink conditioning when the procedure involves presentations of simultaneous stimulus compounds. The perirhinal cortex may play a role in simultaneous feature-positive discrimination learning by helping to resolve ambiguity when there are trials with overlapping stimuli. This interpretation is consistent with the idea that the perirhinal cortex helps to resolve ambiguity in discriminations that use stimulus elements with overlapping features (Buckley et al., 2001; Buckley & Gaffan, 1998; Bussey et al., 2002; 2003; Gilbert & Kesner, 2003).

Discrimination learning with a simultaneous compound is thought to be accomplished by the feature stimulus acting directly on a representation of the US, whereas serial discriminations are thought to be established by occasion setting (Holland, 1984; Holland & Lamarre, 1984; Ross & Holland, 1981). The present study showed that perirhinal cortex lesions only impair acquisition of simultaneous feature-positive discrimination. The findings are not consistent with Burwell et al.'s (2004) results, which suggested that the perirhinal cortex contributes primarily to occasion setting. However, this difference may be attributed to different experimental paradigms and/or stimulus parameters that were used in these studies. Burwell et al.'s (2004) study used relatively long CSs (5,000 ms) to establish appetitive conditioning and also inserted a 5,000-ms gap between the stimuli in the serial compound stimulus, compared with the present study, which used short duration CSs (400 ms) to establish eyeblink conditioning and did not use a temporal gap in the serial compound. The perirhinal cortex might reduce stimulus interference between A and X when they are presented together in a short simultaneous stimulus compound ($XA+$). Damage to the perirhinal cortex could, therefore, impair acquisition of an X-US association during feature-positive discrimination training because of a deficit in stimulus differentiation. An alternative hypothesis is that the lesions could have impaired configural learning. However, there is evidence that perirhinal lesions do not impair configural learning in rats (Bussey et al., 2000).

The relative stimulus salience of each element has been shown to affect the acquisition of feature-positive discrimination (Holland, 1989a). For example, Loechner and Weisz (1987), using nictitating membrane conditioning with rabbits, showed that hippocampal lesions impair simultaneous feature-positive discrimination ($A-/XA+$), but only when A was more salient than X. It is unlikely that stimulus salience or overshadowing interfered with the lesion-induced deficit in the acquisition of simultaneous feature-positive discrimination in the present study because the stimulus modalities were counterbalanced and produced the same CR percentage when presented as the target stimulus (A).

In conclusion, perirhinal cortex lesions impair feature-positive discrimination learning with a simultaneous compound stimulus but not with a serial compound. The findings are consistent with a previous study that showed that perirhinal cortex lesions impair feature-negative discrimination with a simultaneous compound stimulus (Campolattaro & Freeman, 2006). The lesion-induced impairments in feature-positive and feature-negative discrimination learning suggest that the perirhinal cortex plays a role in discriminative eyeblink conditioning by resolving ambiguity in discriminations with overlapping stimulus elements.

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Figure 1.

A and C: Overall mean percentage of conditioned responses (CRs) during simultaneous (A) and serial (C) feature-positive discrimination learning for rats given the perirhinal cortex lesions or control surgery. Black bars show the percentage of CRs during presentations of the simultaneous (XA+) and serial (X→A+) stimulus compounds. Gray bars show the percentage of CRs during presentations of the target stimulus (A-). Error bars represent SEM. B and D: Mean percentage CRs across sessions of simultaneous (B) and serial (D) feature-positive discrimination learning. Black plots show the percentage of CRs during presentations of the simultaneous (XA+) and serial (X→A+) stimulus compounds. White plots show the percentage of CRs during presentations of the target stimulus (A-). Error bars represent SEM.

Figure 2.

Drawings of three coronal sections showing the smallest (gray regions) and largest lesions (black regions). The values to the right of each section indicate the stereotaxic coordinates relative to bregma. Arrows indicate the boundaries of the perirhinal cortex, composed of Areas 35 and 36 (adapted from Burwell & Amaral, 1998a; 1998b). Drawings are adapted from *The Rat Brain in Stereotaxic Coordinates* (4th ed.), by G. Paxinos and C. Watson, Figures 32, 36, and 40, Copyright 1998, with permission from Elsevier.