



Roles of nucleus accumbens and basolateral amygdala in autoshaped lever pressing

Stephen E. Chang, Daniel S. Wheeler¹, Peter C. Holland*

Department of Psychological and Brain Sciences, 3400 North Charles Street, Baltimore, MD 21218, USA

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ABSTRACT

Initially-neutral cues paired with rewards are thought to acquire motivational significance, as if the incentive motivational value of the reward is transferred to the cue. Such cues may serve as secondary reinforcers to establish new learning, modulate the performance of instrumental action (Pavlovian-instrumental transfer, PIT), and be the targets of approach and other cue-directed behaviors. Here we examined the effects of lesions of the ventral striatal nucleus accumbens (ACb) and the basolateral amygdala (BLA) on the acquisition of discriminative autoshaped lever-pressing in rats. Insertion of one lever into the experimental chamber was reinforced by sucrose delivery, but insertion of another lever was not reinforced. Although sucrose was delivered independently of the rats' behavior, sham-lesioned rats rapidly came to press the reinforced but not the nonreinforced lever. Bilateral ACb lesions impaired the initial acquisition of sign-tracking but not its terminal levels. In contrast, BLA lesions produced substantial deficits in terminal levels of sign-tracking. Furthermore, whereas ACb lesions primarily affected the probability of lever press responses, BLA lesions mostly affected the rate of responding once it occurred. Finally, disconnection lesions that disrupted communication between ACb and BLA produced both sets of deficits. We suggest that ACb is important for initial acquisition of consummatory-like responses that incorporate hedonic aspects of the reward, while BLA serves to enhance such incentive salience once it is acquired.

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1. Introduction

An important consequence of associative learning is the acquisition of emotional and motivational responses (LeDoux, 2000; Rescorla & Holland, 1982; Rescorla & Solomon, 1967). For example, many investigators have asserted that Pavlovian conditioned stimuli (CSs) that predict food unconditioned stimuli (USs) acquire "incentive salience" reflecting the transfer of incentive motivational value from the US to the CS (Berridge, 2001, 2004). Such CSs can reinforce new learning, as rats will learn to press a lever to receive CS presentations in the absence of the US (conditioned reinforcement; Mackintosh, 1974), and can modulate the performance of previously-rewarded instrumental responses (Pavlovian-instrumental transfer, PIT; Estes, 1948; Lovibond, 1983). Furthermore, certain food-paired cues can elicit approach and consummatory behaviors directed towards that CS, sometimes called "sign-tracking" (Boakes, 1977; Brown & Jenkins, 1968; Jenkins & Moore, 1973). For example, rats will approach visual cues paired with food delivery (Cardinal, Parkinson, Hall, & Everitt, 2002; Holland, 1977), and will approach and contact a lever whose

insertion into the chamber signals food (Boakes, 1977; Flagel, Akil, & Robinson, 2009; Flagel, Watson, Akil, & Robinson, 2008; Kearns & Weiss, 2004). In contrast, rats may also direct their behavior toward the site of US delivery upon CS presentation, otherwise known as "goal-tracking" (Boakes, 1977; Flagel et al., 2008, 2009).

Considerable attention has recently been focused on rats' sign-tracking in an autoshaping (Brown & Jenkins, 1968) paradigm, in which the insertion of a lever into the experimental chamber is paired with the delivery of sucrose, regardless of the rats' behavior. After repeated Pavlovian lever-sucrose pairings, rats come to press, grasp, and bite the lever as if it were sucrose itself (sign-tracking), despite the absence of any response-reward contingency (e.g., Tomie, 1996; Tomie, Grimes, & Pohorecky, 2008). Although repeated CS-US pairings can result in both sign-tracking and goal-tracking CRs, some investigators have asserted that the sign-tracking (lever-directed) responses directly index the extent to which the lever CS becomes endowed with incentive salience (e.g., Flagel et al., 2009). For example, Robinson and Flagel (2009) reported that a lever insertion CS is more effective as a conditioned reinforcer in rats that showed high levels of sign-tracking responses during prior lever-food pairings than in rats that had primarily approached the food cup during lever insertions.

Many researchers have suggested that this paradigm may provide a valuable model for the study of incentive learning in drug addiction (e.g., Flagel et al., 2010; Mahler & Berridge, 2009; Tomie,

* Corresponding author. Fax: +1 410 516 0494.

E-mail address: pch@jhu.edu (P.C. Holland).

¹ Present address: Biomedical Sciences, PO Box 1881, Marquette University, Milwaukee, WI 3201, USA.

1996; Tomie et al., 2008). Autoshaping shares many of the behavioral characteristics associated with drug addiction such as persistence and relapse (Tomie et al., 2008), and high levels of sign-tracking responses have been associated with impulsivity, drug sensitization and other traits associated with addiction vulnerability (Flagel et al., 2010; Tomie et al., 2008). Furthermore, Flagel et al. (2011) found that sign-trackers but not goal-trackers showed increased phasic dopamine release in the nucleus accumbens (ACb) core in response to CS presentations, thus relating the sign-tracking response to brain systems frequently implicated in drug abuse and addiction (e.g., Everitt & Robbins, 2005; Robinson & Berridge, 2003).

Here we examined the roles of two brain regions known to be critical to incentive learning, ACb and the basolateral amygdala (BLA, Cador, Robbins, & Everitt, 1989; Cardinal et al., 2002; Everitt, Cardinal, Parkinson, & Robbins, 2003; Parkinson, Robbins, & Everitt, 2000; Parkinson, Willoughby, Robbins, & Everitt, 2000), in learning and performance of discriminative autoshaped lever pressing in rats. Because both ACb core and shell have been found to be important for various learned incentive functions (Cardinal et al., 2002; Corbit & Balleine, 2011), we elected to lesion the entire ACb as a first step in determining its role in autoshaped lever pressing. We found that ACb lesions impaired the initial acquisition of sign-tracking but not its terminal levels. In contrast, BLA lesions produced substantial deficits in terminal levels of sign-tracking. Furthermore, whereas ACb lesions primarily affected the probability of lever press responses, BLA lesions mostly affected the rate of responding once it occurred. Finally, disconnection lesions that disrupted communication between ACb and BLA produced both sets of deficits.

2. Materials and methods

2.1. Animals

The subjects were male Long-Evans rats (Charles River Laboratories, Raleigh, NC, USA), which weighed 300–325 g on arrival. Rats were individually housed in a climate controlled colony room that was illuminated from 7:00 A.M. to 7:00 P.M. Rats were given *ad libitum* access to food and water before and continuing two weeks after surgery. They were then placed on a food restriction schedule and maintained at 85% of their *ad libitum* weights throughout the autoshaping procedure.

2.2. Surgical procedures

Surgery was performed under aseptic conditions with isoflurane anesthesia, and all infusions were made with a Hamilton 2.0- μ l syringe equipped with a 26-gauge needle. ACb lesions were made with 20 mg/ml *N*-methyl-D-aspartate (NMDA; Sigma, St. Louis, MO, USA), 0.3 μ l/site, using the coordinates 2.1 mm anterior of bregma, 1.6 mm from the midline, and 7.2 mm ventral from the skull surface at the injection site. BLA lesions were made with NMDA (10 mg/ml in Dulbecco's PBS; Sigma) using the coordinates 2.8 mm posterior of bregma, 5.1 mm from the midline, and 8.7 mm (0.16 μ l/site) and 8.4 mm (0.08 μ l/site) ventral from the skull surface at the injection site.

In Experiment 1, bilateral ACb lesion surgery was performed on 31 rats, and bilateral sham lesion surgeries on 12 rats. In Experiment 2, bilateral BLA lesion surgery was performed on 15 rats, and bilateral sham lesion surgeries on 9 rats. In each of these experiments, rats that received sham lesions underwent the same surgical procedures as their lesioned cohort, but no infusions were made once the needle was in position.

In Experiment 3, all rats received both a unilateral lesion of ACb and a unilateral lesion of BLA. Rats in the Contra condition ($n = 12$) received these lesions in opposite hemispheres, whereas rats in the Ipsi condition ($n = 12$) received both lesions in the same hemisphere. Both contra- and ipsilateral lesions were completely counterbalanced by side. Because communication between these two regions is predominantly ipsilateral, the contralateral disconnection lesion impairs functions that require communication between ACb and BLA but leaves other functions unaffected, relative to the ipsilateral control lesion, which destroys equal amounts of tissue in each structure, but leaves communication between them intact in one hemisphere.

2.3. Apparatus

The behavioral training apparatus consisted of eight individual chambers (20.5 cm \times 22.0 cm \times 22.5 cm) with stainless steel front and back walls, clear acrylic sides, and a floor made of 0.48-cm stainless steel rods spaced 1.9 cm apart. An illuminated clear acrylic food cup was recessed in an opening of the front wall, and photocells at the front of the food cup recorded entries and time spent in the cup. Locally-fabricated retractable levers, which were operated nearly silently by pneumatic controls, were located on either side of the food cup. Each chamber was enclosed inside a sound attenuating shell. An infrared light was located outside of each chamber, and cameras mounted within the shell allowed for television viewing.

2.4. Behavioral training procedures

The behavioral training procedures were identical in all three experiments. Rats first received two 64-min sessions in which they were trained to eat from the food cups. In each of these sessions, rats were given 16 0.1-ml deliveries of 8% (w/v) sucrose solution, with a mean intertrial interval (ITI) of 240 s. Next, rats underwent 12 sessions of the autoshaping procedure. Within each 64-min session, there were 25 CS+ and 25 CS- trials (mean ITI = 77 s), ordered so that no more than two of same trial type occurred in sequence (after Bussey, Everitt, & Robbins, 1997). On CS+ trials, one lever was extended for 10 s and reinforced with 0.1 ml of 8% sucrose upon retraction and on CS- trials, the other lever was extended for 10 s, but no sucrose was delivered. For half the rats, the CS+ lever was the left lever and the CS- lever was the right lever and for the other half, the sides of the CS+ and CS- levers were reversed.

2.5. Data analysis

We analyzed two primary measures of autoshaping, the rate of lever pressing and the percentage of trials on which at least one lever press occurred, to permit distinguishing between lesion effects on the rate or persistence of responding and on the probability of an autoshaped response. We also analyzed the rate of responding on trials on which at least one response occurred, to provide additional information about response rate or persistence. Finally, we analyzed the percentage of time each rat spent with its head in the food cup during CS presentations.

To characterize the temporal distribution of responses during the CSs, we initially divided the 10-s lever presentations into two 5-s bins. Previous experiments in our laboratory (e.g., Holland, 1977) showed that when visual CSs were paired with food, cue-dependent conditioned orienting responses (ORs), such as rearing, occurred primarily in the first 5 s of a 10-s CS, whereas food cup behavior occurred more frequently during the last half of that interval. If autoshaped lever presses were an example of an OR, then rats might display peak levels of responding to the lever

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