Neuroscience 196 (2011) 80–96

A FOOD PREDICTIVE CUE MUST BE ATTRIBUTED WITH INCENTIVE SALIENCE FOR IT TO INDUCE c-FOS mRNA EXPRESSION IN CORTICO-STRIATAL-THALAMIC BRAIN REGIONS

S. B. FLAGEL,[a]* C. M. CAMERON,[b] K. N. PICKUP,[c] S. J. WATSON,[d] H. AKIL[d] AND T. E. ROBINSON[c]

[a]*Department of Psychiatry, University of Michigan, USA*

[b]*Department of Psychology, University of North Carolina, USA*

[c]*Department of Psychology and Neuroscience Program, University of Michigan, USA*

[d]*Molecular and Behavioral Neuroscience Institute, University of Michigan, USA*

Abstract—Cues associated with rewards acquire the ability to engage the same brain systems as rewards themselves. However, reward cues have multiple properties. For example, they not only act as predictors of reward capable of evoking conditional responses (CRs), but they may also acquire incentive motivational properties. As incentive stimuli they can evoke complex emotional and motivational states. Here we sought to determine whether the predictive value of a reward cue is sufficient to engage brain reward systems, or whether the cue must also be attributed with incentive salience. We took advantage of the fact that there are large individual differences in the extent to which reward cues are attributed with incentive salience. When a cue (conditional stimulus, CS) is paired with delivery of food (unconditional stimulus, US), the cue acquires the ability to evoke a CR in all rats; that is, it is equally predictive and supports learning the CS–US association in all. However, only in a subset of rats is the cue attributed with incentive salience, becoming an attractive and desirable incentive stimulus. We used *in situ* hybridization histochemistry to quantify the ability of a food cue to induce c-fos mRNA expression in rats that varied in the extent to which they attributed incentive salience to the cue. We found that a food cue induced c-fos mRNA in the orbitofrontal cortex, striatum (caudate and nucleus accumbens), thalamus (paraventricular, intermediodorsal and central medial nuclei), and lateral habenula, only in rats that attributed incentive salience to the cue. Furthermore, patterns of "connectivity" between these brain regions differed markedly between rats that did or did not attribute incentive salience to the food cue. These data suggest that the predictive value of a reward cue is not sufficient to engage brain reward systems—the cue must also be attributed with incentive salience. **© 2011 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: sign-trackers, goal-trackers, incentive salience, c-fos, mesocorticolimbic, motive circuit.

*Correspondence to: S. B. Flagel, Molecular and Behavioral Neuroscience Institute, University of Michigan, 205 Zina Pitcher Place, Ann Arbor, MI 48109, USA. Tel: +1-734-936-2033; fax: +1-734-647-4130. E-mail address: sflagel@umich.edu (S. B. Flagel).

Abbreviations: CRs, conditional responses; CS, conditional stimulus; GTs, goal-trackers; ITI, inter-trial interval; PCA, Pavlovian Conditional Approach; STs, sign-trackers; UN, unpaired group; US, unconditional stimulus.

Cues in the environment (conditional stimuli, CSs) associated with rewards (unconditional stimuli, USs) can come to influence behavior in a number of different ways. Perhaps best known is the ability of a CS to evoke simple conditional responses (CRs) that often prepare an organism for consumption of the US, such as salivation or conditioned insulin release, in the case of a food reward (Pavlov, 1927; Woods et al., 1970; Zener, 1937). But cues predictive of an outcome also play an important role in learning and making decisions about what actions are most advantageous in a given situation (Bindra, 1974; Toates, 1998; Dickinson and Balleine, 2002). Furthermore, such cues can come to act as incentive stimuli and become attractive and desired in their own right, if they are attributed with incentive salience (Berridge, 2001; Cardinal et al., 2002). If reward cues are attributed with incentive salience they may be especially effective in motivating maladaptive behaviors, including overeating (Schachter, 1968; Grilo et al., 1989; Sobik et al., 2005), gambling (Potenza et al., 2003; Kushner et al., 2007), risky sexual behavior (for review see O'Donohue and Plaud, 1994), and drug abuse (for reviews see Childress et al., 1993; O'Brien, 2005). There has been considerable interest, therefore, in identifying brain systems that mediate the effects of reward cues on behavior.

There is now abundant evidence in both humans and non-human animals that different classes of reward cues (e.g. food, sex, or drug cues) engage highly overlapping brain systems. This reward or "motive circuit" includes mesocorticolimbic dopamine pathways as well as other cortico-striatal-thalamic loops (Childress et al., 1999; Ikemoto, 2010; Jentsch and Taylor, 1999; Kalivas and Volkow, 2005; Kelley et al., 2005a; Weiss, 2005; Schiltz et al., 2007; Zellner and Ranaldi, 2010). However, it is not clear from previous studies exactly what properties of a reward cue are responsible for activating these brain regions. Is the predictive relationship with a US, which supports the ability of a CS to evoke a CR, sufficient to engage this system? Or, must the CS also be attributed with incentive salience? It is not easy to parse these different properties of reward cues because they are usually acquired together (Berridge and Robinson, 2003; Berridge, 2007). Nevertheless, in a series of recent studies using rats, we have shown that it is possible to dissociate the predictive and incentive motivational properties of reward cues through the study of individual differences (Flagel et al., 2007; Flagel et al., 2008b; Flagel et al., 2011; Robinson and Flagel, 2009).

When a spatially discrete CS is presented before food delivery the CS comes to evoke a CR in all rats—that is, it

0306-4522/11 $ - see front matter © 2011 IBRO. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuroscience.2011.09.004

is equally predictive and supports learning the CS–US association in all. However, the CS is attributed with incentive salience only in a subset of rats. This is indicated by the observation that only in some rats does the CS itself (1) become attractive, eliciting approach toward it (Flagel et al., 2007, 2008a), (2) desired, in that animals will work to get it (Flagel et al., 2011; Robinson and Flagel, 2009), and (3) effective in motivating renewed seeking for the reward after extinction of an instrumental response (Saunders and Robinson, 2010; Yager and Robinson, 2010). Animals prone to attribute incentive salience to a reward cue are called "sign-trackers" (STs), a term derived from their propensity to approach the cue or "sign" that signals impending reward delivery (Brown and Jenkins, 1968; Hearst and Jenkins, 1974). In other individuals a food cue is equally predictive and equally effective in evoking a CR, but in these animals the CR is not directed towards the cue itself, but to the location of impending reward delivery, and in these rats the cue is also not a very effective conditioned reinforcer (Flagel et al., 2011; Robinson and Flagel, 2009). These animals are called "goal-trackers" (GTs), a term derived from their propensity to approach the location of reward delivery (Boakes, 1977). Thus, the cue (CS) serves as an equally effective predictor in STs and GTs, and both STs and GTs learn the CS–US association, but only in STs does it function as a potent incentive stimulus (Flagel et al., 2011; Robinson and Flagel, 2009).

We have taken advantage of this natural individual variation in the propensity to attribute incentive salience to a reward cue to parse the psychological and neurobiological processes underlying stimulus-reward learning and motivated behavior (Flagel et al., 2007, 2011; Robinson and Flagel, 2009). Most recently, we utilized this model to study the role of dopamine in stimulus-reward learning (Flagel et al., 2011). We demonstrated that learning a sign-tracking CR requires dopamine but learning a goal-tracking CR does not (also see Danna and Elmer, 2010). Furthermore, the acquisition of a sign-tracking CR is associated with the transfer of a phasic dopamine response from the US to the CS, whereas learning a goal-tracking CR is not (Flagel et al., 2011). Thus, dopamine is not required for all forms of learning in which reward cues become effective predictors (Schultz et al., 1997; Waelti et al., 2001), but acts selectively in a form of stimulus-reward learning in which incentive salience is attributed to reward cues (Flagel et al., 2011). Here, we used the same logic to examine more broadly, what brain regions are "engaged" when the cue has predictive value (i.e. as in GTs and STs) relative to when it also has incentive value (i.e. only for STs). To do this we used *in situ* hybridization histochemistry to quantify the ability of a food cue to induce c-fos mRNA expression in rats classed as STs or GTs, and in a control group that received unpaired presentations of the CS and US. We focused on those brain regions previously reported to be "engaged" by reward cues—the so-called "motive circuit" that includes the prefrontal cortex, dorsal and ventral striatum, thalamus, habenula, and amygdala (Cardinal et al., 2002; Ikemoto, 2010; Kalivas and Volkow, 2005; Weiss, 2005; Schiltz et al., 2007). We report that a food cue induced c-fos mRNA expression in these brain regions only in rats that attributed incentive salience to the cue.

EXPERIMENTAL PROCEDURES

Subjects

Male Sprague–Dawley rats (Charles River, Wilmington, MA, USA) weighing 250–300 g upon arrival were used. Rats were housed individually in hanging acrylic cages ($8\times8\times9$ cm^3) and kept on a 12-h light/dark cycle (lights on at 0800 h) in a temperature- and humidity-controlled colony room. Food and water were available *ad libitum* for the duration of the study. Procedures were approved by the University Committee on the Use and Care of Animals.

Pavlovian conditioning

Pavlovian training was conducted using an autoshaping procedure described previously (Flagel et al., 2007). All training sessions were conducted between 1100 and 1600 h. Standard ($22\times18\times13$ cm^3) test chambers (Med Associates Inc., St. Albans, VT, USA) were located inside a sound-attenuating cabinet with a ventilating fan to mask background noise. For Pavlovian training, each chamber had a food cup located in the center of one wall, 3 cm above a stainless steel grid floor. A retractable lever was located 2.5 cm to the left of the food cup and a red house light located at the top of the wall opposite the food cup remained illuminated for the duration of each session.

Banana-flavored food pellets (Bio-Serv, Frenchtown, NJ, USA) were placed into the rats' home cages for 2 days before training to familiarize the animals with this food, which served as the US. Two pre-training sessions were conducted, consisting of the delivery of 50 food pellets on a variable time 30-s schedule (25-min session), and it was determined whether the rats reliably retrieved the food pellets. For rats in the Paired groups ($n=45$) each daily Pavlovian training session, which followed pre-training, consisted of 25 trials in which the lever (CS) was inserted into the chamber for 8 s and immediately following its retraction a 45-mg food pellet (US) was delivered into the food cup, using a variable time 90 s schedule (i.e. one presentation of the CS occurred on average every 90 s, but the actual time between CS presentations varied randomly between 30 and 150 s). When the lever was inserted, the slot through which it protruded was simultaneously illuminated by a LED located behind the slot. Note that no response was required for the rat to receive reward, and that the animals were not food deprived. Rats in the Unpaired Group (UN, $n=15$) received pseudorandom CS and US presentations during each session. Pavlovian training was conducted over seven consecutive days (days 1–7).

The following events were recorded using Med Associates software: (1) number of lever-CS contacts, (2) latency to the first lever-CS contact, (3) number of food cup entries during lever-CS presentation, (4) latency to the first food cup entry following lever-CS presentation, and (5) number of food cup entries during the inter-trial interval (ITI). From these measures a "Pavlovian Conditioned Approach" (PCA) score was calculated using the following formula: ((*Response Bias*+*Probability*+*Contact Latency*)/3). Where *Response Bias*=(lever contacts−magazine entries)/(lever contacts+magazine entries); *Probability*=(lever contact probability−magazine entry probability); and *Contact Latency*=(−(lever contact latency−magazine entry latency))/8 s. The final PCA score was obtained by averaging scores from sessions 6 and 7. With this index a score of +1 indicates that all responses were directed toward the lever-CS, a score of −1 indicates that all responses were directed toward the food cup, and a score of zero signifies that responses were directed equally to both places.

Download English Version:

https://daneshyari.com/en/article/6276217

Download Persian Version:

https://daneshyari.com/article/6276217

Daneshyari.com