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Alcohol seeking by rats becomes habitual after prolonged training

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Abstract

Background: This study examines the effect of the amount of training on alcohol seeking behavior in rats. Contemporary theories of instrumental learning suggest that habit learning processes are involved in the development of the compulsive drug seeking that characterizes addiction. **Method:** Wistar rats were trained to perform an instrumental response for a solution of ethanol. In Experiment 1, the rats received 2 instrumental training sessions, whereas animals in Experiment 2 received 2, 8, or 16 sessions. An aversion was then conditioned to ethanol by pairing it with LiCl, and the performance in extinction was subsequently tested. **Results:** Instrumental responding showed variable sensitivity to outcome devaluation as a function of the length of training. After 2 and 8 training sessions, but not after 16 sessions, drug seeking was influenced by a change in the value of ethanol. **Conclusions:** The results suggest that alcohol seeking is more flexible and goal-directed in early stages of training, but it becomes habitual and less governed by its consequences with more extended training.

Keywords: Alcohol seeking, instrumental learning, habit, reinforcer devaluation, rats.

Resumen

La búsqueda de alcohol en ratas se convierte en un hábito con la práctica reforzada. **Antecedentes:** en este estudio se evaluó el efecto de la duración del entrenamiento instrumental sobre la conducta de búsqueda de alcohol en ratas. La investigación actual sugiere que la formación de hábitos E-R es responsable de la búsqueda compulsiva de la droga que caracteriza a las conductas adictivas. **Método:** se entrenó a las ratas a realizar una respuesta instrumental con etanol como recompensa. Los sujetos recibieron 2 sesiones de entrenamiento en el primer experimento y 2, 8 o 16 sesiones en el segundo estudio. Tras devaluar el etanol con LiCl se estimó la tasa de respuesta de los animales en extinción. **Resultados:** el efecto de la devaluación del reforzador sobre la conducta instrumental dependió del número de sesiones de entrenamiento recibidas; la tasa de respuesta disminuyó tras un entrenamiento moderado (2 y 8 sesiones) pero no se vio afectada con un entrenamiento más prolongado (16 sesiones). **Conclusiones:** los resultados sugieren que la búsqueda de alcohol depende del valor reforzante de la droga en la fase inicial de desarrollo de la adicción pero se vuelve rígida y automática (hábito) con la experiencia repetida.

Palabras clave: adicción al alcohol, conducta instrumental, hábito, devaluación, ratas.

Drug addiction in humans often is characterized by a transition from controlled to uncontrolled drug consumption which occurs after prolonged drug experience. A variety of animal models have been proposed to study aspects of drug addiction in humans, such as compulsion to seek and take the drug, relapse, and loss of control over drug consumption (for reviews, see Olmstead, 2006; Panlilio & Goldberg, 2007; Sanchís-Segura & Spanagel, 2006; Shaham, Shalev, Lu, De Wit, & Stewart, 2003). For example, drug self-administration procedures (by oral, intragastric, intravenous, or intracranial routes) have been widely used to assess different behavioral and neurobiological aspects of drug reinforcement in rodents (Cardinal & Everitt, 2004; Koob & Le Moal, 2006; Robinson & Berridge, 2003; Shalev, Grimm, & Shaham, 2002). Specifically, in the operant drug self-administration method, animals are required to learn a response (for example, to press a lever) which results in a drug delivery, such as cocaine or heroin, and the ability of the drug delivered to act as a reinforcer can be assessed on subsequent performance. Operant self-administration of ethanol represents an obvious analog of alcohol consumption in humans, and it provides an opportunity to examine the factors that control the appetitive (seeking behavior) and consummatory (drug intake) components of alcohol addiction (see Cunningham, Fidler, & Hill, 2000; Koob, 2000; Spanagel, 2000; Tabakoff & Hoffman, 2000). A crucial issue is whether or not the use of addictive drugs such as alcohol by individuals may become a habitual behavior following repeated experience with the drug. Compulsive responding has been considered to reflect the development of a habit or stimulus-response (S-R) association (for reviews, see Everitt & Robbins, 2005; Hogarth, Dickinson, & Duka, 2010; Vanderschuren & Everitt, 2005).

For natural rewards, considerable evidence supports the view that instrumental behaviors in rats are originally acquired as goal-directed acts, which are based upon knowledge of their consequences (for reviews, see de Wit & Dickinson, 2009; Dickinson, 1995; Dickinson & Balleine, 1994). For example, it has been demonstrated by using the reinforcer devaluation paradigm that changing the value of a reward, such as food or sucrose, by

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pairing it with lithium chloride after training produces a decrease in the subsequent performance of the instrumental response, indicating that responding depends on the current value of the reinforcer (e.g., Adams & Dickinson, 1981; Colwill & Rescorla, 1985). In addition, it has been suggested that, with sufficient training, responding becomes habitual; that is, under the control of an S-R association, and insensitive to outcome devaluation (e.g., Adams, 1982; but see Colwill & Triola, 2002).

Because the reinforcer devaluation method may provide some information on the distinction between actions (goal-directed) and habits (S-R) in instrumental behavior, we use this procedure to assess whether or not the addictive drug, ethanol, has the propensity to establish automatic patterns of behavior. To our knowlge, only a few studies have examined the effects of outcome devaluation on ethanol-seeking behavior in rats. For example, Dickinson, Wood, and Smith (2002) using the operant self-administration procedure reported no effect of LiCl-induced devaluation of ethanol after training, suggesting that alcohol seeking by rats is a habitual response which is not mediated by the value of its consequences. The same conclusion is supported by other studies using a Pavlovian-instrumental transfer procedure (e.g., Corbit & Janak, 2007; Glasner, Overmier, & Balleine, 2005).

The insensitivity of alcohol seeking to outcome devaluation observed in the above mentioned studies contrasts, however, with the results of other study by Samson, Cunningham, Czachowski, Chappell, Legg, & Shannon (2004). In their experiments, after initial oral ethanol self-administration training, the aversive conditioning to the ethanol was induced by pairing passive infusion of ethanol directly into the stomach with an injection of LiCl. The devaluation procedure had an impact on the ethanol seeking behavior when the rats were again allowed to perform the instrumental response in the subsequent extinction test. Therefore, alcohol seeking by rats in this study appears to be mediated by the value of its consequences. One factor might to explain this discrepancy is the devaluation method, i.e., passive infusion of ethanol followed by the lithium, employed by Samson et al. (2004), a method which was specifically designed to devalue the postingestive pharmacologic effects of ethanol, rather than its taste.

At present, the precise factors that determine whether alcohol seeking by rats is habitual or goal directed have not been clearly determined. One of these factors might be the amount of instrumental training. In a recent study by Mangieri, Cofresí, and Gonzales (2012), these authors found that after limited, but not extended instrumental training, ethanol seeking was sensitive to outcome devaluation in rats trained under either variable ratio (VR) or variable interval (VI) schedules of reinforcement; in contrast, responding after both limited and extended training was not sensitive to outcome devaluation when a VI schedule was used. In order to better elucidate the conditions under which alcohol seeking can become habitual, our study explored this possibility by examining the effects of ethanol devaluation on instrumental lever pressing that was trained under a random interval (RI) schedule of reinforcement. Specifically, Experiment 1 evaluated the sensitivity of instrumental responding for oral ethanol to outcome devaluation in rats receiving 2 instrumental training sessions. Experiment 2 then compared the effect of minimal (2 sessions) and more extended (8 or 16 sessions) training on the susceptibility of alcohol-seeking behavior to become habitual.

Method

Participants

Subjects in Experiment 1 were 20 adult, drug-naive male Wistar rats weighing approximately 309 to 430 g at the start of the experiment. Subjects in Experiment 2 were 48 adult, drug-naive male Wistar rats with weights ranging from 315 to 453 g. The rats were housed in groups of four in standard plastic cages (size 27 × 42 × 16 cm) in a colony room maintained on a 12-h light/dark cycle (lights on at 0800 h) and at an ambient temperature of 23 º C. Behavioral procedures took place during the light phase. The rats were provided with free access to food and water until the start of the experiments, after which daily food and water were limited, as described in the procedure section. All behavioral procedures were conducted in accordance with guidelines of the European Council Directive (86/609/EEC) and Spanish regulation RD-1201/2005 regarding the care and use of animals.

Instruments

Instrumental training and testing took place in rodent operant chambers (Letica, S.A., Spain) housed in sound-and-light resistant shells. Each chamber was equipped with a retractable lever, a food dispenser that delivered 45-mg Noyes pellets (improved Formula A) into a recesses magazine, and a fluid dispenser that delivered 0.1-ml of an ethanol solution into a well in the same magazine. Each chamber was iluminated by a 3-W, 24-V house light mounted on the front wall above the magazine. A computer located in an adjoining room controlled the equipment and recorded the lever press and magazine entry responses during training and testing.

Absolute ethanol (Prolabo) was diluted to a concentration of 6% (v/v) with tap water. The lithium chloride was an intraperitoneal (i.p.) injection of 0.15 M LiCl administered at 20 ml/kg of body weight. The physiological saline was an intraperitoneal injection of 20ml/kg of an isotonic 0.15 M solution of NaCl.

Procedure

Experimental procedure for both experiments consisted of four phases: pretraining, instrumental training, devaluation, and testing. Sessions were usually 30 minutes in length.

Pretraining. Rats were first food deprived for 4 days, receiving free access to food in their home cages for 1.5-h each day. After magazine training in which food pellets were delivered on a random time (RT) 30-s schedule with the lever retracted, the rats received a single instrumental training session in which lever pressing was reinforced with the food pellets on a fixed ratio (FR) 1 schedule of reinforcement until 30 reinforcers had been earned. After acquiring the lever press response, rats were no longer food deprived and placed on a 22.5-h water-deprivation schedule with access to water in the home cage for 1.5-h following each daily session. Animals then received a single instrumental session in which lever pressing was reinforced with water on the FR-1 schedule. Over the next five days the rats were trained to press the lever for the ethanol solution on a random interval (RI) 5-s schedule, receiving one 30-min instrumental session per day. The concentration of ethanol was 2% for the first session, 4% for the next two sessions, and 6% for the remaining two sessions. The purpose of this procedure was to ensure that animals press the lever for the opportunity to drink the ethanol solution.

Instrumental training. After pretraining, the rats received four daily sessions of instrumental training in which lever pressing was reinforced with 6% ethanol on a random interval (RI) schedule whose parameter was increased from 5 to 10 and 15 to 30 s across successive sessions. After one additional session on the RI 30-s schedule, instrumental training concluded for the subjects in Experiment 1. Thus, these rats received 2 training sessions with ethanol on the RI 30-s schedule. For their part, the subjects in Experiment 2 received minimal (2 sessions) or more extended (8 or 16) training sessions with ethanol on the RI 30-s schedule. On average, the rats drank 6 ml of ethanol solution on each of the instrumental training sessions under the RI 30-s schedule of reinforcement. All the sessions started with the insertion of the lever and ended with its retraction 30 minutes later.

Devaluation. After instrumental training, ethanol was devalued by pairing it with LiCl in some rats (DEV; devalued) but not others (NON; nondevalued). An aversion was conditioned to the ethanol solution by pairing consumption with illness induced by intraperitoneal injections of 20 ml/kg of an isotonic 0.15 M solution of LiCl. To this end, the rats received two devaluation cycles, each of which consisted of 3 days. On the first day, the rats were placed in the operant chambers where they received the ethanol solution on a random time (RT) 30-s schedule for 30 minutes. The levers were withdrawn throughout devaluation phase. Upon removal from the operant chamber, the rats in the devalued condition were given the LiCl injection before being returned to their home cages. The animals in the nondevalued condition received an injection of 20 ml/kg of 0.15 M NaCl solution, and were then returned to their home cages. On the second day of each cycle, the rats in the devalued condition were removed from their home cage and immediately given an i.p. injection of isotonic saline before being returned to the home cages, while those in the nondevalued condition were injected with the LiCl solution. The third trial of each cycle was a recovery day in which all the animals received free access to water in the home cages for 90 min.

The rats in Experiment 1 were randomly assigned to one of two groups based upon the devaluation treatment (n=10/group): Group DEV and Group NON. The rats in Experiment 2 were assigned to one of six groups (n = 8/group) on the basis of the devaluation (devalued or nondevalued) and the number of instrumental training sessions (2, 8 or 16); that is, rats that had ethanol-LiCl pairings (groups DEV-2, DEV-8, and DEV-16), and rats that received explicitly unpaired presentations of these substances (groups NON-2, NON-8, and NON-16).

Extinction and reacquisition tests. The effect of the devaluation treatment on instrumental performance was then assessed on the next day in an extinction session, in which no reinforcers were presented. The test session started with the insertion of the levers and ended with their retraction after 30 min. Finally, in order to assess the effectiveness of the devaluation procedure on instrumental performance, over the next two days lever pressing was first re-established using water as the reinforcer on an RI 30-sec schedule before the reinforcer was switched to ethanol on the final reacquisition session.

Data analysis

In Experiment 1, the total number of lever presses during the last session of instrumental training and the extinction test was analyzed by a one-way analysis of variance (ANOVA) with group as between-subjects factor. The performance during the reacquisition sessions with water and ethanol as reinforcers was analysed in repeated-measures ANOVA with a between-subjects factor of group and a within-subjects factor of 10-min period within the session (session blocks). In Experiment 2, instrumental performance during the last day of training with ethanol and the extinction test was analysed by means of a 2 × 3 two-way ANOVA with devaluation (devalued vs. nondevalued) and training sessions (2, 8 or 16) as the between-subjects factors. The performance during the reacquisition session with ethanol was assessed by a 2 × 3 × 3 repeated measures ANOVA, with two between-subjects factors (devaluation and sessions) and one within-subjects factor (10-min block). Post hoc tests (Student-Newman-Keuls) were used to assess group differences when ANOVA indicated significant overall differences. Values are expressed as mean ± S.E.M., and $p<0.05$ was considered significant in this study.

Results

Experiment 1. Impact of outcome devaluation on alcohol seeking after limited training

By the last day of instrumental training, the rates of responding for ethanol of the two groups did not significantly differ ($F<1$). The mean number of lever presses during this session for the two groups were: Group DEV, 326 ± 23.9; Group NON, 303 ± 31.7.

The results of prime interest in this experiment are those of the extinction test after the devaluation of ethanol. The top panel of Figure 1 shows the mean number of lever presses in each group during this test. This figure suggests that subjects in Group DEV, which received LiCl injections immediately after exposure to the ethanol, pressed the lever less than animals in Group NON, which also received ethanol and LiCl injections, but separated by 24 h. This description was confirmed by the one-way ANOVA conducted on lever presses during the extinction test. This analysis revealed a significant effect of group, $F(1,18) = 14.189$, $p = .001$, showing evidence for a devaluation effect for alcohol-seeking behavior in the devalued group.

The analysis of the performance during the second session of reacquisition with water as reinforcer revealed that the two groups pressed at similar rates at the end of this session. This analysis revealed a significant effect of session blocks, $F(2,36) = 5.156$, $p = .011$, but no effect of group, $F(1,18) = 1.478$, $p = .224$, nor a significant interaction between these factors ($F<1$). The mean number of lever presses during this session for the two groups were: Group DEV, 313 ± 13.2; Group NON, 298 ± 21.3.

Performance during the reacquisition test in which the ethanol was presented contingent upon lever pressing was also analyzed to confirm that the devaluation treatment was effective in depressing instrumental response in the LiCl-paired group. As illustrated in the bottom panel of Figure 1, throughout the session the subjects in Group NON showed a higher response rate than those in Group DEV. The analysis of performance during this session, using group and 10-min block as the factors, yielded a significant effect of group, $F(1,18) = 21.480$, $p<.001$, and session blocks, $F(2,36) = 5.133$, $p = .011$, and no interaction between these factors, $F(2,36) = 2.091$, $p = .138$.

In conclusion, this experiment showed that instrumental behavior was sensitive to outcome devaluation after limited training. This finding supports the view that alcohol-seeking

behavior in rats can be goal-directed action; that is, controlled by outcome expectancies. Experiment 2 was designed to assess whether alcohol seeking depends on the status of the response as a habit after more extended training.

Experiment 2. Effect of outcome devaluation on drug seeking after extended training

Analysis of performance during the last day of instrumental training with ethanol as reinforcer found no significant main effects of devaluation or amount of training, and no significant interaction between these factors (*Fs* < 1). The mean (± SEM) numbers of lever presses during this session for the various groups were: DEV-2, 353 (± 22.44); NON-2, 372 (± 16.13); DEV-8, 406 (± 28.61); NON-8, 371 (± 27.90); DEV-16, 435 (± 18.68); NON-16, 439 (± 27.95).

The top panel of Figure 2 displays the mean number of lever presses during the extinction test session. A reinforcer devaluation effect was observed in that the animals that received ethanol-LiCl pairings (DEV; devalued) pressed less than those receiving delayed LiCl injections (NON; nondevalued). It is clear, however, that this effect did depend upon the amount of instrumental training. In accordance with this description, the analysis of

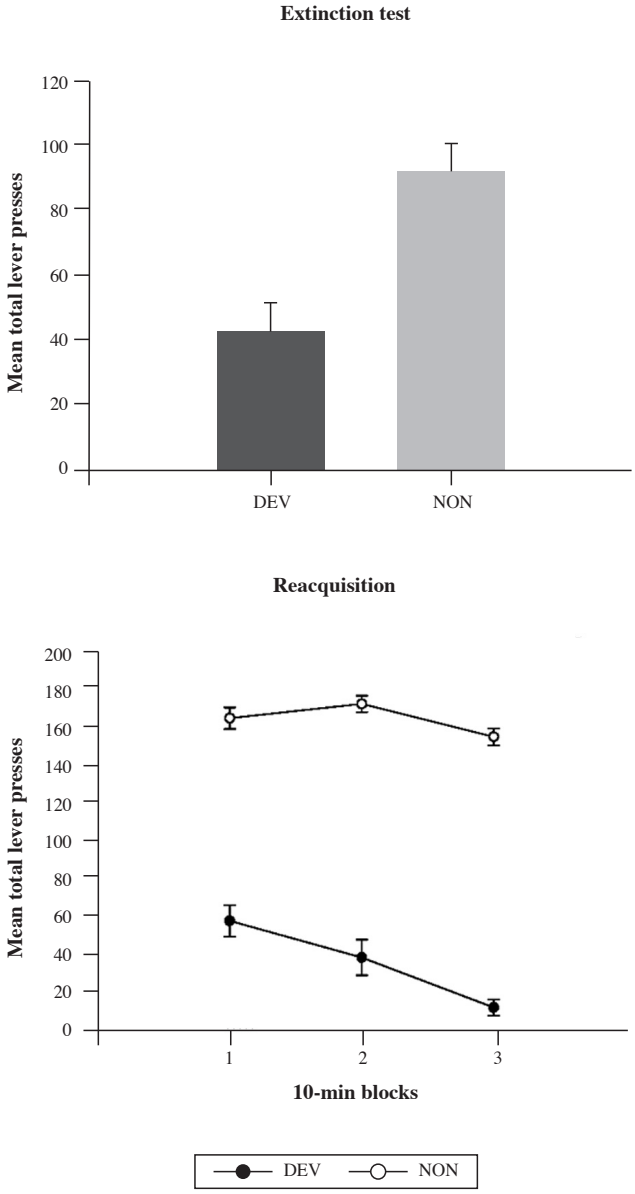

Figure 1. Experiment 1. *Mean number of lever presses during the extinction test (top panel), and during the reacquisition test in 10-min blocks (bottom panel), for the devalued group (Group DEV) and the nondevalued group (Group NON). Error bars represent the standard error of mean (SEMs)*

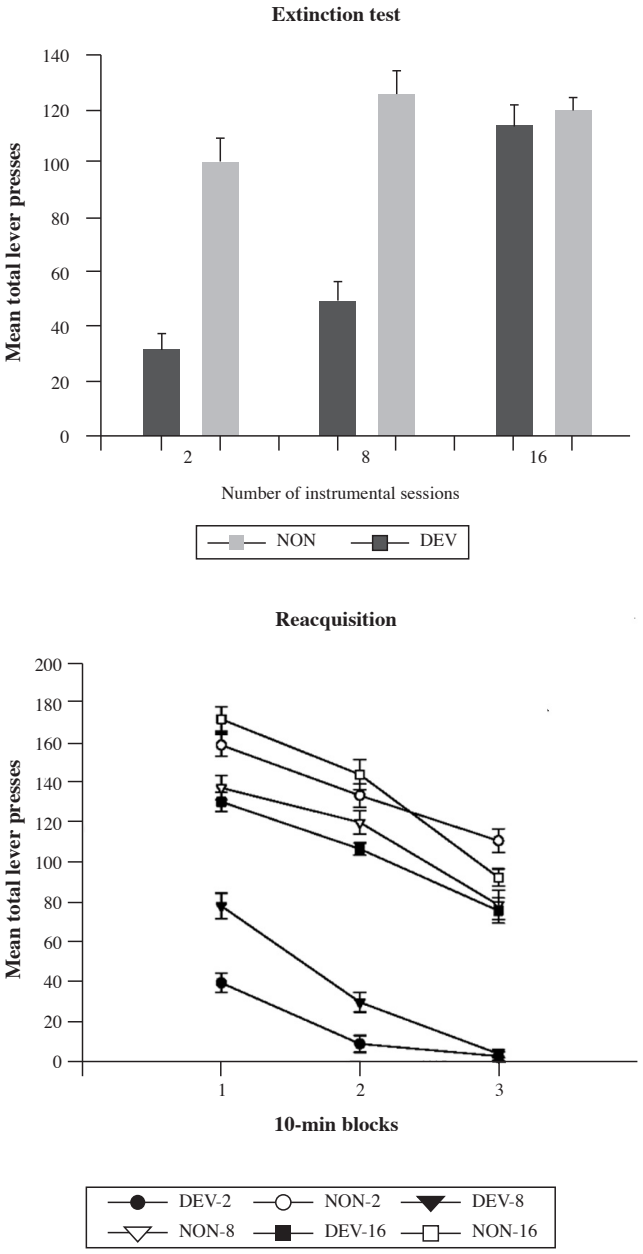

Figure 2. Experiment 2. *Mean number of lever presses during the extinction test (top panel), and during the reacquisition test in 10-min blocks (bottom panel), for each of the groups in Experiment 2. The groups are termed on the basis of the devaluation (DEV or NON) and the number of instrumental training sessions (2, 8 or 16). Error bars represent the standard error of mean (SEMs)*

performance during this session detected a significant effect of devaluation, $F(1,42) = 29.897$, $p<.001$, amount of training, $F(2,42) = 10.027$, $p < .001$, and a significant interaction between these two factors, $F(2,42) = 5.826$, $p = .006$. A comparison (Newman-Keuls) of performance by the devalued and nondevalued groups yielded reliable differences among the rats that received two instrumental sessions, and eight sessions, but not among rats that received sixteen training sessions. Also, the Newman-Keuls procedure showed that the group DEV-16 responded significantly more than the groups DEV-2 and DEV-8, which did not differ reliably.

The mean rates of lever pressing on the second day of reacquisition with water as the reinforcer were similar for all groups. The analysis of these data showed that was a significant effect of blocks, $F(2,84) = 25.469$, $p<.001$, but no effect of devaluation, $F(1,42) = 1.363$, $p = .250$, or effect of amount of training, $F(2,42) = 2.431$, $p = .100$. Additionally, none of the interactions between blocks and the between-subjects factors reached significance ($Fs \leq 1.081$, $ps \geq .349$). The mean numbers of lever presses during this session for the various groups were: DEV-2, 315 (± 17.13); NON-2, 321 (± 12.15); DEV-8, 351 (± 18.32); NON-8, 307 (± 18.89); DEV-16, 357 (± 21.5); NON-16, 337 (± 17.64).

The results from the reacquisition session in which the ethanol was again presented contingent upon lever pressing showed that this solution was equally ineffective as a reinforcer in the devalued groups given 2 or 8 training sessions, but the ethanol solution sustained performance in the devalued group that received sixteen sessions. The bottom panel of Figure 2 shows that pressing declined at a comparable rate in the groups DEV-2 and DEV-8. Confirming this description, the statistical analysis found a significant effect of devaluation, $F(1,42) = 40.299$, $p<.001$, amount of training, $F(1,42) = 6.517$, $p = .003$, and a significant interaction between these two factors, $F(2,42) = 4.411$, $p = .018$. The analysis also found a significant effect of session blocks, $F(2,84) = 53.472$, $p<.001$. Furthemore, none of the interactions between session blocks and the between-subjects factors reached significance ($Fs \leq 1.390$, $ps \geq .244$). Subsequent pairwise comparisons (Newman-Keuls) confirmed that the groups DEV-2 and DEV-8 responded significantly less than the remaining groups.

In conclusion, this experiment yielded two main findings. First, the result obtained in Experiment 1—that alcohol-seeking behavior was decreased by reinforcer devaluation after limited training—was replicated. More importantly, this experiment offers support for the proposal that drug seeking becomes increasingly independent of consequent outcomes with extended training; that is, under the control of a stimulus-response association, and insensitive to changes in reward value.

Discussion

The experiments described in this article demonstrated that devaluing the value of the ethanol by pairing it with LiCl produces a depression of the alcohol-seeking behavior depending on the length of instrumental training. Specifically, Experiment 1 showed that drug seeking was decreased significantly greater in one group that received pairings of the ethanol solution with LiCl than in another group that received unpaired LiCl injections. This pattern replicates the standard outcome devaluation effect obtained with natural rewards (e.g., Adams & Dickinson, 1981; Colwill & Rescorla, 1985). Experiment 2 found evidence that extended training (16 sessions) was accompanied by a shift from the control of drug seeking by the value of its consequences (goal-directed) to control by a stimulus-response mechanism. According the dual-process theories of instrumental lerning, this study supports the conclusion that alcohol-seeking behavior becomes increasingly automatic and less governed by its consequences after prolonged training.

The present results serve to extend previous studies examining the effect of outcome devaluation on alcohol-seeking behavior by rats. As mentioned above, Samson et al. (2004) found that alcohol seeking may be affected directly by a change in the value of the instrumental outcome. In our study, however, the effect of the devaluation on drug seeking was obtained after limited but not extended instrumental training. There are some procedural differences that might explain this discrepancy such as the sucrose substitution method employed for the initiation of ethanol self-administration (i.e., the concentration of the sucrose in the reinforcer is progressively decreased as the concentration of the ethanol is increased across the training), and that their rats were maintained on a food deprivation schedule. In addition, these authors used a procedure, —passive infusion of ethanol directly in the stomach, to devalue the postingestive effects of ethanol—, while in our study, the self-administered ethanol during devaluation presumably altered the hedonic taste value of ethanol by its association with illness. On the other hand, our results are in accordance with those reported by Dickinson et al. (2002), who found that alcohol seeking was not affected directly by a change in the value of the reinforcer. However, there are also some procedural differences between the present experiments and those by Dickinson et al. (2002) that preclude us from determining the source of the resistance to ethanol devaluation observed in their study. One major difference is that they used the sucrose-substitution procedure during training and, as a consequence, their rats had only reduced exposure to the drug.

Our results are in line with those recently reported by Mangieri, Cofresí, and Gonzales (2012), who found that after limited but not extended training, ethanol-seeking behavior was sensitive to outcome devaluation, suggesting that drug seeking is not always a goal-directed behavior. It is important to note, however, that in this study, the impact of ethanol devaluation on drug seeking was influenced by the schedule of reinforcement used during training. As previously mentioned, after limited but not extended training, alcohol seeking was sensitive to outcome devaluation when rats were trained under either VI or VR schedules of reinforcement; in contrast, responding after both limited and extended training was not sensitive to ethanol devaluation when a variable interval (VI) schedule was used. Thus, while it is possible that the schedule of reinforcement influences the instrumental reinforcer devaluation effect, the results by Mangieri et al. (2012) support the view that overtraining produces habitual behavior. Also, Thrailkill and Bouton (2015) have reported a similar finding when training was conducted with food pellets. Devaluation of the reinforcer suppressed responding after relatively minimal, but not more extensive, training, a result consistent with the view that action becomes habitual after extended training. Interestingly, these authors also found that after extensive training, a habit that was insensitive to reinforcer devaluation was still decremented by a context shift, which suggests that context primary control habitual responding rather than goal-directed actions (see also Ostlund, Maidment, & Balleine, 2010).

Relative to the generality of the associative mechanisms controlling drug seeking in rats, the findings from the current study

with ethanol are consistent with the results of similar studies with other addictive drugs. For example, in a recent study by Zapata, Minney, and Shippenberg (2010), these authors used a chained schedule of intravenous cocaine administration to examine whether cocaine seeking becomes habitual after prolonged experience. In this procedure, pressing a lever (drug-seeking response) provided access to a second lever (drug-taking response) that resulted in a cocaine infusion. After training, the value of the drug-taking response was reduced by extinction, and the influence of this manipulation was then estimated in an extinction test. The finding was that extinction of drug-taking response reduced the performance of the drug seeking response, indicating that drug seeking is goal-directed rather than habitual. With, however, more prolonged drug experience, cocaine seeking was insensitive to outcome devaluation, indicating that animals transitioned to habitual cocaine seeking. By contrast, Olmstead, Lafond, Everitt, and Dickinson (2001) found that extinction of drug taking response reduced the performance of the drug seeking response, indicating that drug seeking was mediated by the expectancy of taking the drug (but see Miles, Everitt, & Dickinson, 2003). A similar finding has been reported by Hutcheson, Everitt, Robbins, and Dickinson (2001) with heroin.

In conclusion, it remains to be definitively established whether compulsive or habitual responding for addictive drugs, such as ethanol, develops as a consequence of substantially greater practice. In this study, we have examined the effect of the amount of training but other factors such as the motivation for the drug or the drug-associated context might well determine that drug seeking and drug taking in alcoholic individuals may become habitual. As demonstrated in studies with other drugs such as cocaine and amphetamine (Deroche-Gamonet et al., 2004; Nelson & Killcross, 2006; Vanderschuren & Everitt, 2004), chronic drug exposure increases the motivation for the drug and leads to impulsive behavior no longer controlled by the current value of the drug. Future research will provide us new information on the behavioral and neural mechanisms that control compulsive drug seeking.

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References

Adams, C. D. (1982). Variations in the sensitivity of instrumental responding to reinforcer devaluation. *Quarterly Journal of Experimental Psychology*, *34B*, 77-98.

Adams, C. D., & Dickinson, A. (1981). Instrumental responding following reinforcer devaluation. *Quarterly Journal of Experimental Psychology*, *33B*, 109-121.

Cardinal, R. N., & Everitt, B. J. (2004). Neural and psychological mechanisms underlying links to drug addiction. *Current Opinion in Neurobiology*, *14*, 156-162.

Colwill, R. M., & Rescorla, R. A. (1985). Post-conditioning devaluation of a reinforcer affects instrumental responding. *Journal of Experimental Psychology: Animal Behavior Processes*, *11*, 120-132.

Colwill, R. M., & Triola, S. M. (2002). Instrumental reesponding remains under the control of the consequent outcome after extended training. *Behavioural Processes*, *57*, 51-64.

Corbit, L-H., & Janak, P. H. (2007). Ethanol-associated cues produce general Pavlovian-instrumental transfer. *Alcoholism: Clinical and Experimental Research*, *31*, 766-774.

Cunningham, C. L., Fidler, T. L., & Hill, K. G. (2000). Animal models of alcohol's motivational effects. *Alcohol Research & Health*, *24*, 85-92.

de Wit, S., & Dickinson, A. (2009). Associative theories of goal-directed behaviour: A case for animal-human translational models. *Psychological Research*, *73*, 463-476.

Deroche-Gamonet, V., Belin, D., & Piazza, P. V. (2004). Evidence for addiction-like behavior in the rat. *Science*, *305*, 1014-1017.

Dickinson, A. (1995). Actions and habits: the development of behavioral autonomy. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *308*, 67-78.

Dickinson, A., Balleine, B. W. (1994). Motivational control of goal-directed action. *Animal Learning & Behavior*, *22*, 1-18.

Dickinson, A., Wood, N., & Smith, J. W. (2002). Alcohol seeking by rats: Action or habit? *Quarterly Journal of Experimental Psychology*, *55B*, 331-348.

Everitt, B. J, & Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: from action to habits to compulsion. *Nature Neuroscience*, *8*, 1481-1489.

Glasner, S. V., Overmier, J. B., & Balleine B. W. (2005). The role of Pavlovian cues in alcohol seeking in dependent and nondependent rats. *Journal of Studies on Alcohol*, *66*, 53-61.

Hogarth, L., Dickinson, A., & Duka, T. (2010). The associative basis of cue elicited drug taking in humans. *Psychopharmacology*, *208*, 337-351.

Hutcheson, D. M., Everitt, B. J., Robbins, T. W., & Dickinson, A. (2001). The role of withdrawal in heroin addiction: Enhances reward or promotes avoidance? *Nature Neuroscience*, *4*, 943-947.

Koob, G. F. (2000). Animal models of craving for ethanol. *Addiction*, *95*, 73-81.

Koob, G. F., & Le Moal, M. (2006). *Neurobiology of addiction*. London: Academic Press.

Mangieri, R. A., Cofresí, U., & Gonzales, R. A. (2012). Ethanol seeking by Long Evans rats is not always a goal-directed behavior. *PloS One*, *7*, 1-13.

Miles, F. J., Everitt, B. J., & Dickinson, A. (2003). Oral cocaine seeking by rats: Action or habit? *Behavioral Neuroscience*, *117*, 927-938.

Nelson, A., & Killcross, S. (2006). Amphetamine exposure enhances habit formation. *Journal of Neuroscience*, *26*, 3805-3812.

Olmstead, M. C. (2006). Animal models of drug addiction: Where do we go from here? *Quarterly Journal of Experimental Psychology*, *59*, 625-653.

Olmstead, M. C., Lafond, M. V., Everitt, B. J., & Dickinson, A. (2001). Cocaine seeking by rats is a goal-directed action. *Behavioral Neuroscience*, *115*, 394-402.

Ostlund, S. B., Maidment, N. T., & Balleine, B. W. (2010). Alcohol-paired contextual cues produce an immediate and selective loss of goal-directed action in rats. *Frontiers in Integrative Neuroscience, 4*, 1-8.

Panlilio, L. V., & Goldberg, S. R. (2007). Self-administration of drugs in animals and humans as a model and a investigative tool. *Addiction*, *102*, 1863-1870.

Robinson, T. E., & Berridge, K. C. (2003). Addiction. *Annual Review of Psychology*, *54*, 25-53.

Samson, H. H., Cunningham, C. L., Czachowski, C. L., Chappell, A., Legg, B., & Shannon, E. (2004). Devaluation and ethanol reinforcement. *Alcohol*, *32*, 203-212.

Sanchis-Segura, C., & Spanagel, R. (2006). Behavioural assessment of drug reinforcement and addictive features in rodents: An overview. *Addiction Biology*, *11*, 2-38.

Shaham, Y., Shalev, U., Lu, L., De Wit, H., & Stewart, J. (2003). The reinstatement model of drug relapse: History, methodology and major findings. *Psychopharmacology*, *168*, 3-20.

Shalev, U., Grimm J. W., & Shaham, Y. (2002) Neurobiology of relapse to heroin and cocaine seeking: A review. *Pharmacological Reviews*, *54*, 1-42.

Spanagel, R. (2000). Recent animal models of alcoholism. *Alcohol Research & Health*, *24*, 124-131.

Tabakoff, B., & Hoffman, P. L. (2000). Animal models in alcohol research. *Alcohol Research & Health*, *24*, 77-84.

Thrailkill, E. A., & Bouton, M. E. (2015). Contextual control of instrumental actions and habits. *Journal of Experimental Psychology: Animal Learning and Cognition, 41*, 69-80.

Vanderschuren, L. J., & Everitt, B. J. (2004). Drug seeking becomes compulsive after prolonged cocaine self-administrationr. *Science*, *305*, 1017-1019.

Vanderschuren, L. J., & Everitt, B. J. (2005). Behavioral and neural mechanisms of compulsive drug seeking. *European Journal of Pharmacology*, *526*, 77-88.

Zapata, A., Minney, V. L., & Shippenberg, T. S. (2010). Shift from goal-directed to habitual cocaine seeking after prolonged experience in rats. *Journal of Neuroscience, 30*, 15457-15463.