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EFFECTS OF REINFORCEMENT SCHEDULE ON FACILITATION OF OPERANT EXTINCTION BY CHLORDIAZEPOXIDE

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Learning and memory are central topics in behavioral neuroscience, and inbred mice strains are widely investigated. However, operant conditioning techniques are not as extensively used in this field as they should be, given the effectiveness of the methodology of the experimental analysis of behavior. In the present study, male C57Bl/6 mice, widely used as background for transgenic studies, were trained to lever press on discrete-trial fixed-ratio 5 or fixed-interval (11 s or 31 s) schedules of food reinforcement and then exposed to 15 extinction sessions following vehicle or chlordiazepoxide injections (15 mg/kg i.p., administered either prior to all extinction sessions, or prior to the final 10 extinction sessions). Extinction of operant behavior was facilitated by drug administration following training on either schedule, but this facilitation only occurred once a number of extinction sessions had taken place. The extinction process proceeded more rapidly following fixed-interval training. Resistance to extinction was equally high following training with either schedule type, and was reduced by drug administration in both cases. These phenomena were evident in individual cumulative records and in analyses of group data. Results are interpreted in terms of phenomena of operant extinction identified in Skinner's (1938) *Behavior of Organisms*, and by behavioral momentum theory. These procedures could be used to extend the contribution of operant conditioning to contemporary behavioral neuroscience.

Key words: extinction, fixed ratio, fixed interval, chlordiazepoxide, memory, lever press, mouse

Early investigators of operant conditioning provided experimental analyses of the extinction process. Skinner (1938) examined extinction of lever pressing in rats following delivery of around 100 food reinforcements on a continuous reinforcement (fixed-ratio [FR] 1) schedule. From inspection of cumulative records, he concluded that response frequency declines with time following an approximately logarithmic curve, that initially there is an additional emotional effect of the transition to extinction which also depresses response frequency, that these two effects combine to produce a wave-like fluctuation from the logarithmic curve, and that the emotional effect habituates and thus is not evident later in extinction. Ferster and Skinner (1957) provided many data on the operant extinction process of key pecking in pigeons following a variety of reinforcement schedules. For one of the simplest cases, the FR schedule, they concluded that in extinction pigeons continue to respond predominantly at the high rate typical of reinforced FR performance, and overall decline in rate occurs because increasingly long pauses alternate with increasingly short runs. They also reported the effects of extinction following a variety of more complex schedules and concluded that there are specific relations between the preceding schedule of reinforcement and the subsequent pattern of behavior during the operant extinction process. In recent years, however, the contingencies of operant extinction have been extensively employed (for example, in the study of behavioral momentum, see Nevin & Grace, 2000), but the operant extinction process per se has rarely been the focus of attention.

Following progress in understanding the neural mechanisms of learning and memory, extinction is currently researched extensively in behavioral neuroscience (see Myers & Davis, 2002, for a review). However, operant techniques and operant methodology are little in evidence. Instead, extinction following Pavlov-

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ian conditioning is studied. Most studies use between-group designs in which a conditioned stimulus (CS) is followed by presentation of an aversive unconditioned stimulus (US). On later trials, the CS is presented without the US, an extinction procedure, and the conditioned response to the CS is examined. Specific procedures used include conditioned freezing (Ledgerwood, Richardson, & Cranney, 2004) and the fear-potentiated startle (Davis, Walker, & Myers, 2003). There seems to be a role for GABAergic neural processes during extinction of conditioned fear responses (Harris & Westbrook, 1998; Marsicano et al., 2002; Shumyatsky et al., 2002; Stowell, Berntson, & Sarter, 2000). It is not clear, however, whether these GABAergic effects are on conditioned fear per se or extinction processes in general.

In many cases where a Pavlovian conditioning procedure is used, the findings are offered as a model of, or as analogous to, situations in which humans show persistent fears. The analogy between aversive Pavlovian conditioning processes and human behavioral problems of the type described is plausible but is not directly tested within the experiments. It also is possible that persistent (unwanted) human behavior occurs when previously positively reinforced operant behavior persists despite the presence of an extinction contingency (''stalking'' and other forms of obsessional behavior may fall into this category). Thus the behavioral and neural basis of operant extinction may be of applied importance as well as being of basic scientific interest.

We have sought to provide information on operant extinction by carrying out a series of studies of extinction processes and their modification by GABAergic drugs in inbred (C57Bl/6) mice (Leslie, Shaw, McCabe, Reynolds, & Dawson, 2004; McCabe et al., 2004; Shaw, Dawson, Reynolds, McCabe, & Leslie, 2004). We used this strain of mice because it is widely employed as the background strain for gene manipulation studies. These include studies where the gene in question is thought to affect behavior, although little is known about the operant behavior of this strain. We used an AB design in which training sessions requiring lever pressing for a food reinforcer on a discrete-trial fixed-ratio (FR) schedule are followed by a number of sessions of extinction in which no food is presented. With this procedure, Williams, Gray, Sinden, Buckland, and Rawlins (1990) found that administration of chlordiazepoxide (CDP), a benzodiazepine which has been used widely for the clinical treatment of anxiety, facilitated the extinction process: on later extinction sessions, rats given the drug responded slower than control-treatment rats. Williams et al. also reported that septal or hippocampal lesions, both treatments believed to have similar effects to those of benzodiazepine drugs on the behavioral inhibition system in the brain (Gray & McNaughton, 2000), had similar effects to those of CDP. We followed Williams et al. in using a between-groups design because we wanted to investigate drug effects on extinction, which is difficult with a single-subject design, and because we had observed a considerable degree of within- and between-subject variability in pilot studies with mice.

A range of GABAergic agents including CDP have been found to facilitate operant extinction following reinforcement of lever pressing with food in C57Bl/6 mice (Leslie et al., 2004; McCabe et al., 2004; Shaw et al., 2004). Zolpidem (Leslie et al., 2004) and two subtype-selective benzodiazepines (McCabe et al., 2004) have the same effect. This facilitation is not due to sedative or cumulative effects of the drugs, but occurs only after several extinction sessions have occurred. Facilitation is never seen in the first four extinction sessions (when six discrete trials occur in each session), but can be seen immediately, for example, if the drug is only administered from the 11th extinction session onwards (McCabe et al., 2004; Shaw et al., 2004).

These findings raise the possibility that a GABAergic neural process may be involved in extinction of operant behavior following positive reinforcement, but only in a second phase that occurs following an initial period of extinction that does not appear to be mediated by GABA. This is consistent with suggestions arising from the studies of extinction following aversive Pavlovian conditioning that the early stages of extinction involve processes in the brain mediated by NMDA, but that GABA is involved at a later stage (Myers & Davis, 2002).

We appear to have been studying a behavioral process which is neurally mediated in similar fashion to extinction following Pavlovian aversive conditioning, but it is important to

establish the generality of the findings we have obtained with operant conditioning. To this end, the experiment reported here compared the effects of CDP on the extinction process following training on a standard discrete-trial FR 5 schedule with its effects following training on either fixed-interval (FI) 11 s or FI 31 s, again using discrete-trial procedures. As well as providing some information as to whether the effects observed following FR 5 training are schedule-dependent, we sought, by using two different interval schedules, to find out whether the effects depended on the rate of responding or the rate of reinforcement maintained by the schedule prior to the transition to extinction. The shorter FI value was selected to provide a reinforcement rate similar to that typically obtained with an FR 5 schedule (see, for example, Shaw et al., 2004). The longer FI value was chosen to provide a lower rate of reinforcement. A 3 × 3 between-groups design was employed, which varied the schedule across groups (discrete-trial FR 5, FI 11 s, or FI 31 s), and the drug administration regime. The drug administered prior to each extinction session was either vehicle (isotonic saline) throughout, CDP throughout, or vehicle for the first five extinction sessions and CDP for the last ten of the 15 extinction sessions. This enabled us to examine the effects of CDP across schedules, and to see whether the finding that CDP will facilitate extinction even when only administered on later extinction sessions can be found with both ratio and interval schedules. Data from individual mice, as well as group data, will be presented.

METHOD

Subjects

Adult male mice of the C57Bl/6 inbred strain (supplied by Harland UK Ltd., Bicester, England) were used. They weighed 25–30 g and were at least 11 weeks old at the start of the experiment. They were singly housed under temperature-controlled conditions and an alternating light/dark cycle (lights on from 8:00 A.M. to 8:00 P.M.). The mice were fed a cereal-based chow (Dixon's Formula FFG (M)), and were given *ad libitum* access to water. They were maintained at between 80 and 90% of their free-feeding weight by providing 4–8 g of laboratory chow once daily. In the training phase, sessions were only conducted five days a week and *ad libitum* food was available at the weekends. This procedure was followed to prevent the mice from becoming ill through prolonged food deprivation. Subsequent to the training phase, sessions were conducted seven days a week and 4–8 g chow was provided daily. All animal procedures were carried out in accordance with the UK Animals (Scientific Procedures) Act (1986) and its associated guidelines.

Apparatus

Operant chambers for mice (MED Associates model No. ENV 307A, length 21.6 cm, width 17.8 cm, height 12.7 cm) were enclosed in sound-attenuating boxes with electric fans. Chambers consisted of translucent side panels and aluminum instrument and rear panels. Instrument panels were equipped with two retractable response levers and a houselight located at the center top of the panel. Only the left levers were used. Reinforcers (20-mg Noyes food pellets) were delivered by a 28-V DC pellet dispenser to a recessed tray located at the bottom of the panel between the two levers. A computer programmed in MED-PC, which also recorded presses on the retractable levers, controlled all events in the chambers.

Procedure

Initially, daily free-operant acquisition sessions continued until 20–30 reinforcers were obtained. During these sessions the retractable lever was permanently extended and the houselight was on. Pressing the lever caused food pellet delivery. Following acquisition of lever pressing, groups of mice were trained on a discrete-trial FR 5, FI 11-s or FI 31-s schedule of food reinforcement. On the FR 5 schedule, completion of the lever-pressing requirement caused pellet delivery, lever retraction and a buzzer to sound. The inter-trial interval (ITI) prior to lever re-insertion was 60 s, and each experimental session had six discrete trials. FI 11-s and FI 31-s sessions were identical, except that the response requirement once the lever had been presented was to make one press after 11 or 31 s had elapsed from lever insertion. Sessions were run five days per week until the mice reached asymptotic performance, assessed by measuring the time taken to complete a session on the FR 5 schedule,

and by measuring the overall response rate on the FI schedules. This took between 20 and 25 sessions. Mice then received eight further sessions of reinforced training. The last two sessions of this training are referred to as the final training sessions of the experiment, and vehicle injections (0.9% saline solution) were given prior to these sessions. All injections were by the intraperitoneal route, the injected volume was 4 ml/kg, and injections were carried out 30 min before the session. Mice were returned to their home cage between drug administration and the beginning of the session.

Prior to each of the ensuing 15 extinction sessions, vehicle (0.9% saline solution) or CDP injections (15 mg/kg in 0.9% saline solution) were given. For different groups of mice, saline injections were given prior to every extinction session, CDP injections were given prior to every extinction session, or saline injections were given prior to the first five extinction sessions and CDP injections were given thereafter. There were thus nine groups altogether: FR 5 Saline (n=9), FR 5 CDP1-15 (n=10), FR 5 CDP6-15 (n=10), FI 11 s Saline (n=9), FI 11 s CDP1-15 (n=8), FI 11 s CDP6-15 (n=9), FI 31 s Saline (n=8), FI 31 s CDP1-15 (n=9), and FI 31 s CDP6-15 (n=9).

When extinction was in effect, the lever was withdrawn on each occasion that the schedule requirement was completed, but no buzzer sounded and no pellet was presented. In these sessions, if a mouse failed to press the lever within the preset extinction criterion of 600 s, then its current trial and session were terminated. When session average data were calculated (see below), all uncompleted schedule-response requirements were allocated a time of 600 s. This had the effect of allocating a weighted average response latency or inter-response time (IRT), with a maximum value of 600 s, to sessions in which the extinction criterion was met. All mice were tested in all 15 extinction sessions, even if the extinction criterion was met on one or more sessions.

For each session, individual IRTs were recorded and later used to construct cumulative records for each mouse. For these purposes, the latency to the first response after lever presentation was treated as an IRT. The average overall IRTs for each group of mice for each session were calculated and log-transformed, to improve homogeneity of variance. The log-transformed IRT group data were submitted to statistical analysis using a general statistical package (SPSS 11).

RESULTS

Cumulative records for mice trained under the FR 5 schedule of reinforcement are shown in Figure 1 (upper panels). Note that the records are continued across sessions and include the final two training sessions and all 15 extinction sessions (a possible maximum of 510 responses). Under saline, all mice completed the response requirement on every session. Slowing of responding by extinction was not evident until about 250 responses had been completed; this would have occurred on Extinction session 7. Under CDP, whether administered from Extinction sessions 1 or 6, slowing of responding occurred at around the same time as under saline, but the reduction thereafter was more marked. No mice in either of the CDP groups completed more than 400 responses. In both groups, all mice slowed their responding markedly, with some stopping altogether and others resuming responding and then stopping again. Visual inspection suggests that when responding resumed, it was at a rate similar to that seen before the initial cessation of responding. The lower panels of Figure 1 show cumulative records for responses 30–90, from the final training session and Extinction session 1. On these magnified records it is clear that following lever presentation there was typically a pause, of varying duration, followed by rapid responding until reinforcer delivery. The same pattern is seen for all groups for responses 31–60 (reinforcement) and responses 61–90 (extinction).

Cumulative records for the mice trained under the FI 11-s schedule are shown in Figures 2 and 3. Prior to the transition to extinction, all mice under the FI 11-s schedule made many more responses per session than seen under FR 5 for the same number of reinforcers. Consequently, records are shown for selected sessions. Upper panels of Figure 2 show records from the final two training sessions when no drug was administered (overall mean = 75 responses per session). Although some records show fluctuations in rate (and occasional long pauses), compared with the FR 5 records in Figure 1, overall rates were similar to those seen under FR 5. Lower

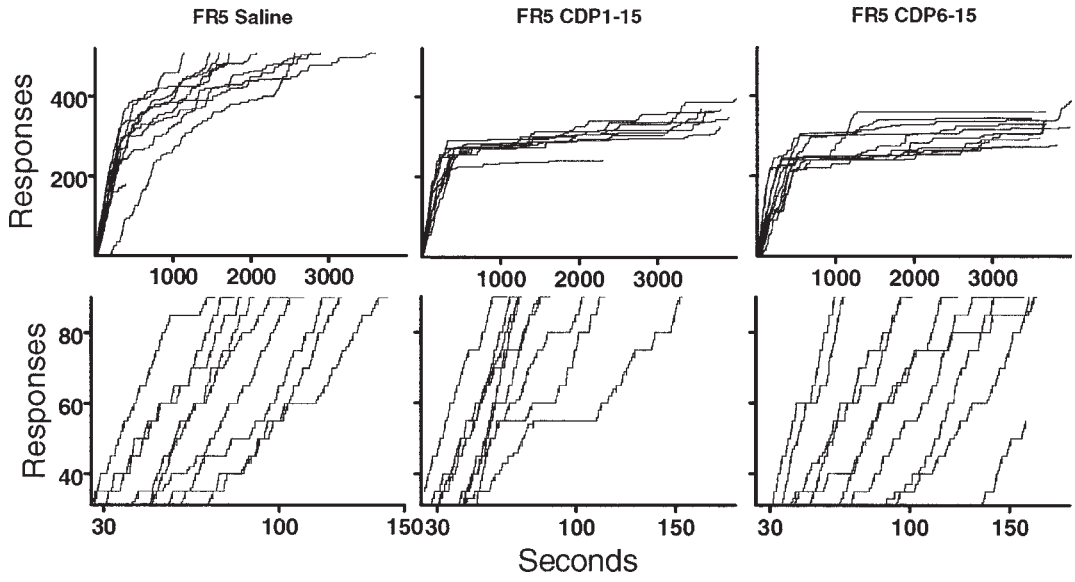

Fig. 1. Upper panels: Cumulative records for all mice trained on FR 5. Records include final two training sessions (cumulative responses 1–60) and all responses during 15 sessions of extinction. Lower panels: Magnified cumulative records for the same mice for the final training session (responses 31–60) and for the first extinction session (responses 61–90). Vertical marks indicate lever removal (accompanied by food presentation during training) that was followed by a 1-min intertrial interval.

panels of Figure 2 show magnified records for a sample of behavior during training, responses 11–60. Following lever presentation there was typically a pause, of varying duration, followed by responding at varying rates until reinforcer delivery. Figure 3 shows records from Extinction sessions 4–6 (upper panels) and extinction sessions 13–15 (lower panels). In Extinction sessions 4–6, all groups show lower response rates than seen in training,

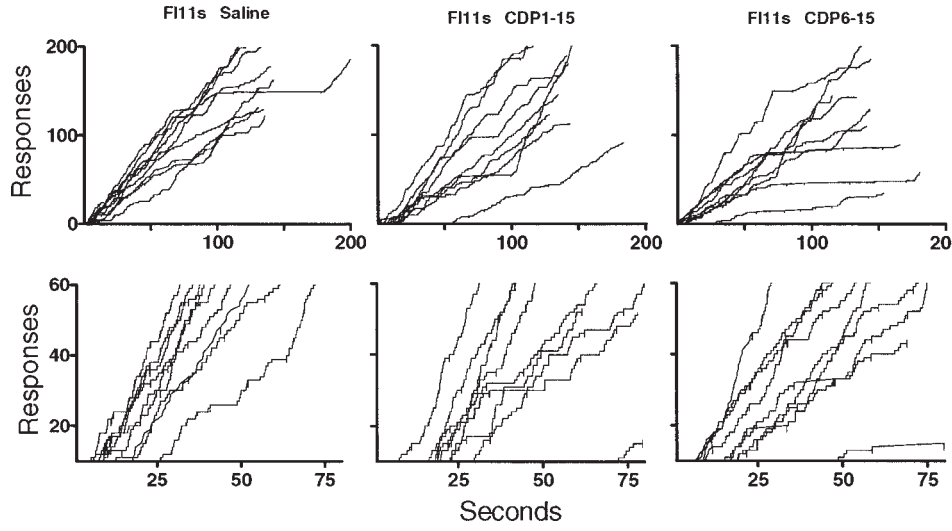

Fig. 2. Upper panels: Cumulative records for the final two training sessions for all mice trained on FI 11 s. Lower panels: Magnified cumulative records for the same mice for cumulated responses 11–60 from the final two training sessions. Vertical marks indicate lever removal (accompanied by food presentation) that was followed by a 1-min intertrial interval.

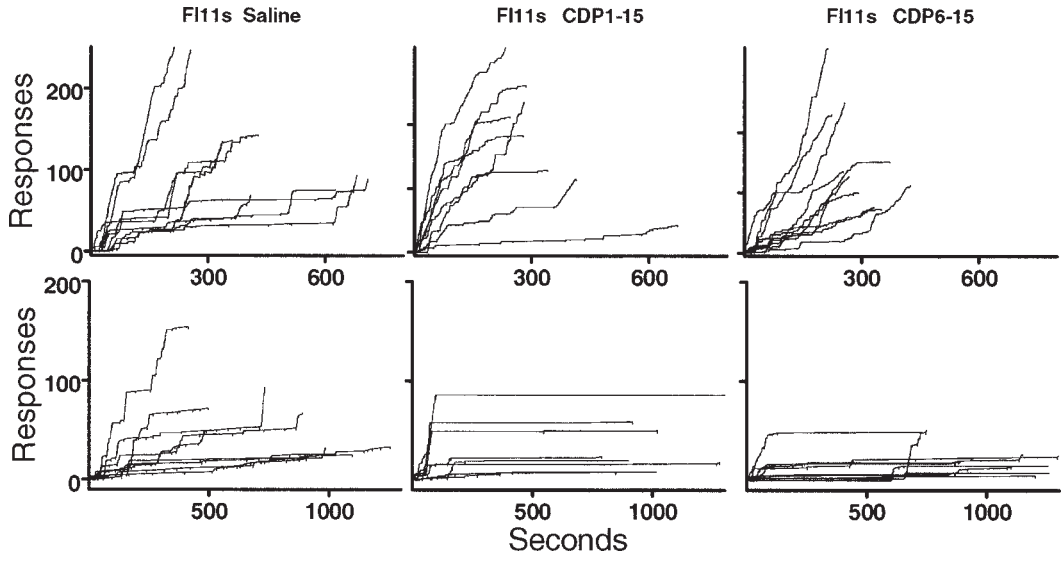

Fig. 3. Cumulative records for all mice trained on FI 11 s for Extinction sessions 4–6 (upper panels) and Extinction sessions 13–15 (lower panels).

with a lot of variability among subjects but no clear differences between groups. Where longer pauses occurred, they were often followed by resumption of responding at a fairly high rate. Over Extinction sessions 13–15, in contrast, most mice in the CDP groups stopped altogether, whereas all mice in the Saline group continued to respond, albeit at lower rates than earlier in extinction.

Cumulative records for the mice trained under FI 31-s schedule are shown in Figures 4 and 5, and display broadly similar patterns to those seen with FI 11 s. Very high numbers of responses per session occurred in the final

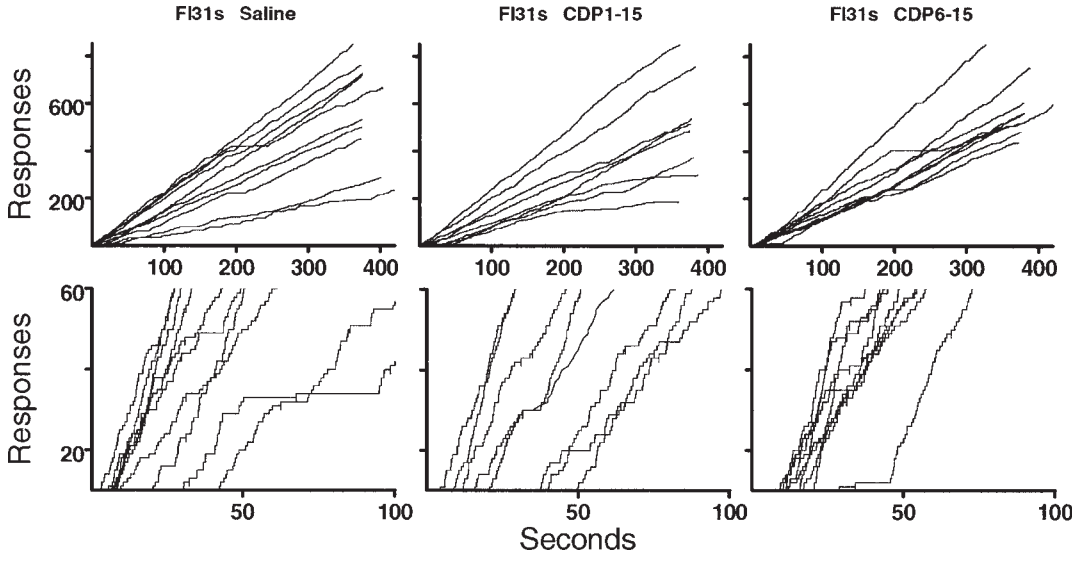

Fig. 4. Upper panels: Cumulative records for the final two training sessions for all mice trained on FI 31 s. Lower panels: Magnified cumulative records for the same mice for cumulated responses 11–60 from the penultimate training session. Vertical marks indicate lever removal (accompanied by food presentation) that was followed by a 1-min intertrial interval.

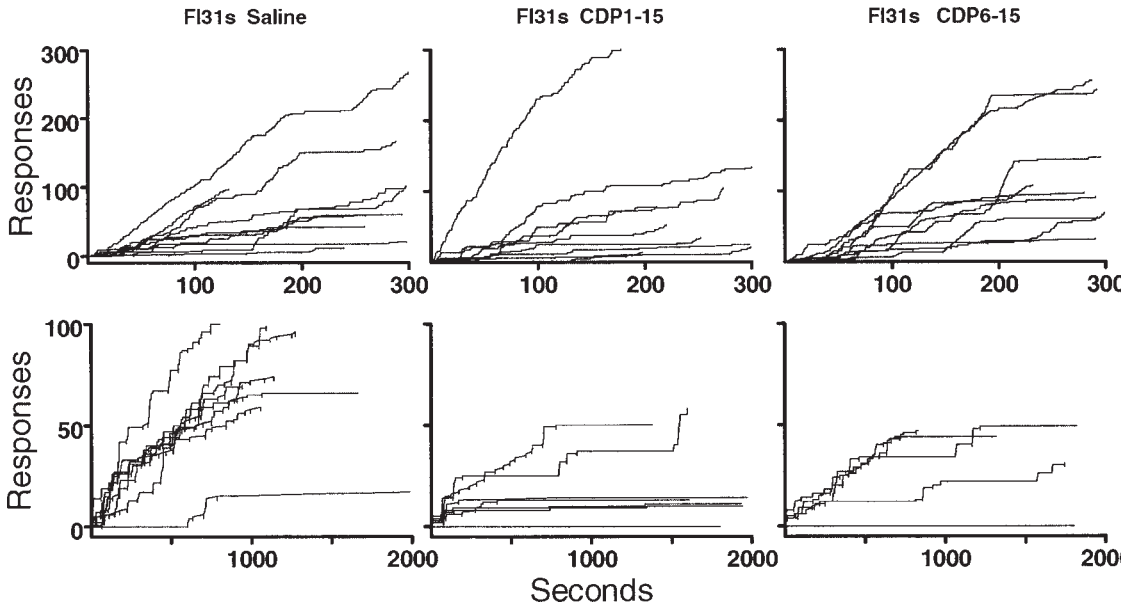

Fig. 5. Cumulative records for all mice trained on FI 11 s for Extinction sessions 4–6 (upper panels) and Extinction sessions 13–15 (lower panels).

training sessions with this schedule (overall mean = 301 responses per session). Upper panels of Figure 4 indicate the high rate of responding in the final two training sessions, slightly higher than seen with FR 5 or FI 11-s schedules (cf. Figures 1 and 2). Lower panels of Figure 4 show magnified records for a sample of behavior during training, responses 11–60. Following lever presentation there typically was a pause, of varying duration, followed by responding at varying rates until reinforcer delivery. Figure 5 shows records from Extinction sessions 4–6 (upper panels) and extinction sessions 13–15 (lower panels). All groups had lower rates of responding in Extinction sessions 4–6 than during training, with a lot of variability among subjects but no clear differences between groups. Where longer pauses occurred, they often were followed by resumption of responding at a fairly high rate. Over Extinction sessions 13–15 there was a marked drug effect: most mice in the Saline group responded through all the sessions, but in contrast most mice in the CDP groups stopped altogether. Three and four mice respectively from CDP1-15 and CDP 6-15 groups did not respond at all over the last three extinction sessions.

Group data, log-transformed mean IRTs, for all sessions on which injections occurred are shown in Figure 6. Following FR 5 training (top panel), mean IRT did not increase for any group before Extinction session 6. Thereafter, mean IRT increased slowly for the Saline group, and much more rapidly for groups CDP1-15 and CDP6-15. There are no apparent differences between these two groups. There is evidence, therefore, of facilitation of extinction from Extinction session 7 whether CDP was administered throughout extinction or from Extinction session 6 onwards. Following FI 11-s training (center panel), mean IRT increased slowly for the Saline group across all extinction sessions. Mean IRT increased more rapidly for the CDP1-15 group from Extinction session 7 and for the CDP6-15 group from Extinction session 10. There is evidence, therefore, of facilitation of extinction from Extinction session 7 when CDP was administered throughout extinction, and rather later when CDP was administered from Extinction session 6 onwards. Following FI 31-s training (bottom panel), mean IRT increased steadily for the Saline group across all extinction sessions. For the CDP1-15 group, mean IRT was higher than for the Saline group (but

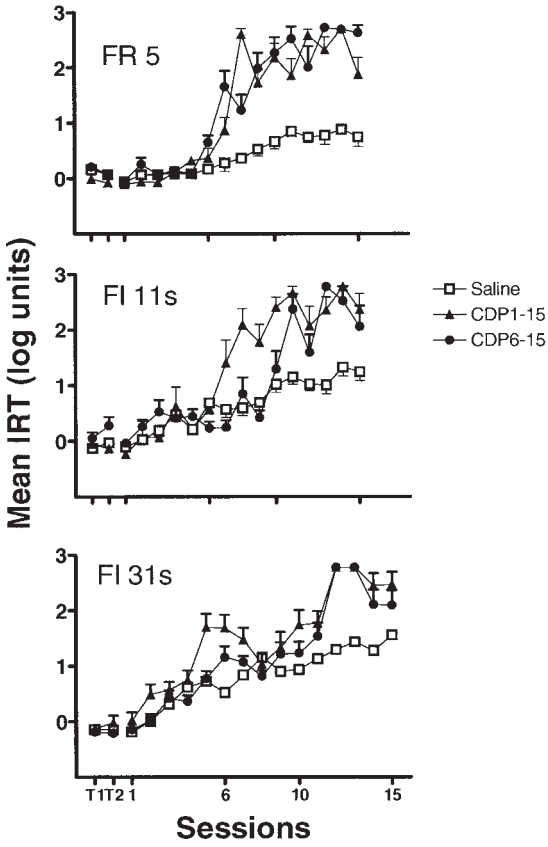

Fig. 6. Mean IRTs (bars indicate standard errors) for the two final training sessions (T1, T2) and the subsequent 15 extinction sessions for groups of mice trained on FR 5, FI 11 s, or FI 31 s. Note that 1 log unit = 10 s.

increased erratically) from Extinction session 5, and for the CDP6-15 group, mean IRT was higher from Extinction session 9. Therefore, there is evidence of facilitation of extinction whether CDP was administered throughout extinction or from Extinction session 6 onwards.

The account given above of the group data in Figure 6 is supported by statistical analyses summarized in Table 1. There was a statistically significant effect on mean IRT of drug treatment, extinction sessions, and an interaction between these two factors. Saline groups responded faster than other groups on later, but not earlier, extinction sessions. Table 1 also shows a measure of resistance to extinction, the average percentage of trials completed by each group over the final three extinction sessions. Saline groups completed 100% of trials, but much lower percentages (13.6–55.9) were obtained by the drug-treatment groups. (These percentages were not subjected to statistical comparisons because of the large number of zero scores.) Thus, there is evidence of high resistance to extinction under all schedule conditions with saline treatment and a marked reduction in resistance to extinction with CDP treatment, whether throughout extinction or from Extinction session 6 onwards.

DISCUSSION

The main finding of the present study was that facilitation of operant extinction by the GABAergic drug CDP occurred following prior training under an FI 11-s or an FI 31-s as well as an FR 5 schedule of food reinforcement. This finding extends the generality of the extinction-facilitation effect, which has previously been reported only following discrete-trial FR 5 training (Leslie et al., 2004; McCabe et al., 2004; Shaw et al., 2004). The present study

Table 1

Statistical summary. Top three rows: Results of repeated measure ANOVAs conducted separately for mice trained on the three schedules of reinforcement. Rows 4 and 5: Results from subsequent *t*-tests noting sessions where Saline groups had shorter IRTs than corresponding CDP1-15 or CDP6-15 groups ($p < .05$ in each case). Bottom three rows: Percentage of trials completed by each group over the final three extinction sessions.

	FR 5	FI 11 s	FI 31 s
Extinction sessions	$F_{14,364} = 76.08$, $p < 0.001$	$F_{14,322} = 53.63$, $p < 0.001$	$F_{14,322} = 58.67$, $p < 0.001$
Drug treatment	$F_{2,26} = 40.54$., $p < 0.001$	$F_{2,23} = 16.47$, $p < 0.001$	$F_{2,23} = 15.00$, $p < 0.001$
Interaction	$F_{28,364} = 9.50$, $p < 0.001$	$F_{28,322} = 5.83$, $p < 0.001$	$F_{28,322} = 3.67$, $p < .001$
Saline < CDP1-15	Ext. sessions 7-15	Ext. sessions 7-15	Ext. sessions 5-7, 10, & 12-14
Saline < CDP6-15	Ext. sessions 7-15	Ext. sessions 11,13, & 14	Ext. sessions 6 & 12–14
Saline	100%	100%	100%
CDP1-15	40.5%	48.1%	19.2%
CDP6-15	13.6%	55.9%	34.6%

utilized both single-subject and group-data presentation, enabling a fuller account of the behavioral phenomena to be specified and revealing similarities and differences following training on different schedules. The data have implications for behavioral accounts of operant extinction. The study further demonstrates the utility of the operant conditioning procedure used for investigation of complex behavioral phenomena in C57Bl/6 mice, a strain widely used as background for gene manipulation studies which seek to identify the genetic bases of psychological processes.

The individual cumulative records of mice lever pressing in extinction following discrete-trial FR 5 food-reinforced training enable the pattern of behavior maintained by the schedule, the extinction process, and the effects of CDP, to be observed directly rather than inferred from group data as in previous studies (Leslie et al., 2004; McCabe et al., 2004; Shaw et al., 2004). Cumulative records from training and the beginning of extinction show pause–respond patterns of behavior typical of FR schedules (Leslie, 1996), although in the present procedure there was a 1-min interval of lever withdrawal following each ratio completion. Records during extinction are as would be predicted from previous studies (e.g., McCabe et al., 2004): mice given only vehicle injections were highly resistant to extinction and slowed down only slightly during 15 brief extinction sessions, whereas those given CDP at the dose previously found to be effective slowed down markedly, but only from Extinction session 7 onwards. The performance of mice given CDP throughout extinction was indistinguishable from that of mice given CDP only from Extinction session 6. This is further evidence that the extinction-facilitating effect of CDP does not occur in this procedure until several extinction sessions have elapsed, but does not depend on repeated drug administration during those first extinction sessions. It is not, for example, a chronic effect of drug administration. Exactly the same conclusions were reached based on group data and following slightly different drug administration regimes by McCabe et al. (2004) and Shaw et al. (2004). The drug (which had no sedative effects in this or the previous studies using this procedure with C57Bl/6 mice) also had the effect of reducing resistance to extinction, as measured by the number of times the response requirement was met over the last three extinction sessions.

The two other schedules employed, discrete-trial FI 11 s and FI 31 s, provided training with either a similar (FI 11 s) or lower (FI 31 s) rate of reinforcement to that obtained on the FR 5. Both yielded similar (or slightly shorter) mean IRTs as compared to the FR 5 schedule and thus more (for FI 11 s) or considerably more (for FI 31 s) responding in baseline sessions. Individual cumulative records were more variable and showed more fluctuations in rate during FI training, especially under the lower schedule value. Pausing was evident from cumulative records but scalloping typical of FI performance in other species (Ferster & Skinner, 1957; Leslie, 1996) was not seen. This may be because training did not continue for long enough. In the present study training ended once there was no systematic change in overall response rates to ensure that the total number of training sessions was not much greater than occurred in other studies in this series using only FR schedules (Leslie et al., 2004; McCabe et al., 2004; Shaw et al., 2004) and that findings could be validly compared across studies. Following training on either FI schedule, it is quite clear that administration of CDP again had the effect of facilitating extinction on later sessions. However, interpretation of this observation is more complex because, following FI rather than FR training, responding declined sooner in mice given only vehicle injections. The group data presentation makes it clear that the effect of CDP was again delayed (and thus was not a direct effect of the drug) but now it appears that (for both schedules) the effect was seen earlier in the CDP1-15 group than in the CDP6-15 group. However, this conclusion should be interpreted with caution; this is the first time data from FI schedules have been reported and it proved relatively difficult to establish stable responding. Mice were trained for longer than in the earlier experiments in which only FR schedules were employed (e.g., McCabe et al., 2004), but more variability in performance occurred within and between subjects in the FI groups than in the FR groups. Variability in performance under FI schedules has been reported often with other species (e.g., Gentry, Weiss, & Laties, 1983).

Comparison of the data following FI training with that following FR 5 training shows two further similarities and one major difference. One similarity is that under both types of schedule, there was high resistance to extinction, as indexed by the proportion of trials completed on later extinction sessions, and a marked reduction in resistance to extinction when CDP was administered. A second similarity is that there were some instances of pausing on both types of schedule on later extinction sessions followed by resumption of responding at a rate and pattern typical of that schedule. The difference is that under the FI schedules the rate and number of responses declined over early sessions when no drug effect was seen. On early extinction sessions following FR training, in contrast, there was no reduction in responding with or without drug treatment, replicating previous findings with this procedure with various GABAergic drugs (Leslie et al., 2004; McCabe et al., 2004).

Taken together, these findings may illustrate the effects of extinction reported by Skinner (1938) following FR 1 reinforcement of lever pressing by rats and the general finding reported by Ferster and Skinner (1957) with pigeons trained on a variety of schedules. Following FR training with C57Bl/6 mice, extinction sessions with restricted opportunities to respond (only 30 responses could be made per session) produced high resistance to extinction, and responding characteristic of the schedule continued to be shown. This may be evidence of strong stimulus control (by lever presentation) following FR training, such as has been reported previously with pigeons (Nevin, 1967; Zeiler, 1968), and the significance of stimulus control by lever presentation is discussed below. If, however, resistance to extinction was reduced by administration of CDP, then switching between pausing and high rate responding was seen. Following FI training, extinction sessions in which many more responses were made resulted in much earlier reductions in response rate, particularly following training on the FI 31-s schedule which produced the largest amount of responding. Resistance to extinction remained high, however, unless reduced by administration of CDP. In the later stages of extinction switching between pausing and FI-type behavior was seen.

One interpretation of these findings is that extinction produced a slow, long-term reduction in response strength, which could be facilitated by CDP once a number of extinction sessions had occurred. Alongside this, high levels of responding in extinction (following FI training) were followed by additional decrements in responding in early sessions without affecting resistance to extinction, as measured by the number of trials completed on later sessions. These two processes may correspond to the separate strength-reducing and emotional effects of extinction proposed by Skinner (1938). Once responding had declined substantially, there was evidence that behavior switched between pausing and the behavior pattern previously maintained by the schedule, as noticed by Skinner (1938) and Ferster and Skinner (1957).

The conditioned reinforcing properties of lever presentation and retraction are likely to have been high on all the schedules used, because lever presentation during training signaled a relatively brief delay until reinforcement of lever pressing with food and lever retraction was contiguous with food presentation (Fantino, 1977). The temporal proximity of these events to food makes it likely that they acted as CSs (and conditioned reinforcers) paired with an appetitive US, and engendered Pavlovian approach and contact conditioned responses (see Leslie, Boakes, Linaza, & Ridgers, 1979, for a demonstration of such ''autoshaped'' lever-contact responses with rats). The effects of CDP on extinction, therefore, may have been through neural processes that mediate Pavlovian as well as operant extinction, if these are different.

These findings can be interpreted within the framework of behavioral momentum theory (e.g., Nevin & Grace, 2000). Central tenets of this approach are that the rate of reinforcement associated with a particular context is a major determinant of response strength and thus resistance to change, but that current response rate in that context may not be a good predictor of response strength. Response rate, it is argued (e.g., Nevin, 2003), is readily shaped by contingencies on IRTs that do not change the underlying response strength. In the present case, the argument would be slightly different: all three schedules provided the same history of reinforcement in the sense that the same number of sessions

occurred with the same small number of reinforcers in each session. Thus response strength should be similar, although slightly lower in the FI 31-s condition where there is rather longer exposure to the response lever per reinforcer. However, within the discrete-trial procedure used the interval schedules provided more opportunities to respond than the FR 5 schedule. According to behavioral momentum theory this should not have changed response strength, as assessed by resistance to extinction. This proved to be the case. This speculative account could be tested directly. Although differences during extinction following FI or FR training were observed here, behavioral momentum theory would predict that, if equivalent exposure to the training context has occurred, then food-reinforced responding under either schedule would be similarly disrupted by other operations such as prefeeding.

We have suggested that response strength was initially similar following training on each of the three schedules, that it declined slowly during extinction, and that this reduction proceeded more rapidly under CDP. A slightly different account could be given, which is also derived from behavioral momentum theory. Ross and Schaal (2002) observed that cocaine administration suppressed food-reinforced responding of rats at a lower dose when supplemental feeding occurred immediately after test sessions than when it occurred 2 hr after test sessions (see also Schaal & Branch, 1992 for a related observation with pigeons). Consistent with behavioral momentum theory, they suggested that response suppression by cocaine occurred more readily when response strength was weaker because of the feeding regime. Applying the same argument to the present study, CDP may have had a disruptive (extinction-facilitating) effect only once exposure to extinction had reduced response strength somewhat.

Recent accounts of the neural basis of learning and extinction (e.g., Davidson & Jerrard, 2004; Myers & Davis, 2002) have concluded that different neural processes are brought into play that inhibit or counteract those mediating earlier learning, rather than dismantling of the brain processes established earlier. Those accounts are based very largely on studies of Pavlovian aversive conditioning procedures. We have argued elsewhere (Leslie et al., 2004) that the delayed effect of GABAergic drugs on operant extinction suggests that there are two successive neural processes involved, with the latter one being mediated by GABA. The findings reported here extend the generality of our earlier findings and indicate that the procedure employed may be a useful candidate for exploring the neural mediation of operant extinction (and possibly appetitive Pavlovian extinction) and its similarities and differences from extinction following Pavlovian aversive conditioning. Growing understanding of the neural basis of operant conditioning and extinction should lead to strong links between behavior theory (e.g., behavioral momentum theory) and neuroscience, and an integrated psychobiological account of both memory and extinction.

Because of observed variability in the behavior of C57Bl/6 mice in the operant procedure employed, and the inherent problems of implementing a single-subject design for the study of drug effects on extinction processes, the strategy used here involved examining data both at the level of individual participants and of groups. The strategy was successful in establishing that some phenomena observed in group data could be seen in the behavior of individual participants, and it therefore may be appropriate in other neuroscience research contexts where similar problems are encountered.

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