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Isolation rearing enhances the locomotor response to cocaine and a novel environment, but impairs the intravenous self-administration of cocaine

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Abstract. Male Lister hooded rats were raised from weaning either alone (isolation reared) or in groups of five (socially reared controls). At 5 months of age, experiments began. Experiment 1 examined the effect of isolation rearing upon the locomotor response to a novel environment, and the locomotor stimulant effect of an injection of cocaine (10 mg/kg). Isolation reared animals were more active in a novel environment, and were more responsive to the locomotor stimulant action of cocaine. In succeeding experiments, the effects of isolation rearing on the reinforcing efficacy of intravenous cocaine were assessed. Animals were never "primed" with noncontingent infusions of cocaine at any time during these experiments. In experiment 2, the effect of isolation rearing upon the acquisition of the intravenous self-administration of cocaine was examined. Two levers were present in the operant chambers. Depression of one lever resulted in the intravenous delivery of a 1.5 mg/kg infusion of cocaine, responses on the second, control lever were recorded but had no programmed consequences. Isolation reared animals acquired a selective response on the drug lever at a slower rate than socially reared controls. In experiment 3, a full cocaine dose-response function was examined. Isolation rearing shifted the cocaine dose-response function to the right. In addition, isolation rearing impaired the selectivity of the response on the drug lever at lower doses of cocaine. In experiment 4, the effect of isolation rearing upon the response to a conditioned reinforcer associated previously with cocaine delivery was observed. In the absence of cocaine, the contingent presentation of the conditioned reinforcer enhanced selectively the rate of response by socially reared controls. However, isolation reared animals were unresponsive to this manipulation. These data are discussed with reference to dysfunctional cortico-limbic-striatal systems, and their interactions with the mesoaccumbens dopamine projection.

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There is growing evidence that susceptibility to drug effects can be influenced by previous experience, such as drug or reinforcement history (Barrett and Witkin 1986; Nader et al. 1992), and stress, including early social experience (Piazza et al. 1989, 1990; Schenk et al. 1987a, b). Social isolation at weaning has profound consequences for behaviour in later life. In particular, isolation rearing of rats has been reported to enhance the propensity to self-administer drugs of abuse (e.g. Katz and Steinberg 1972; Kostowski and Czlondowski 1973; Kostowski et al. 1977; Alexander et al. 1978), and hence to have important implications for the aetiology of human drug addiction. By contrast, isolation housing in adulthood has been reported not to affect the self-administration of cocaine (Bozarth et al. 1989). Thus, in this paper the term "isolation rearing" implies a continuous period of social isolation, beginning at weaning. Animals may be able to smell, hear and even see other conspecifics, but are not able to interact physically. A cardinal trait of this isolation syndrome (Hatch et al. 1963; Valzelli 1973) is an enhanced locomotor response to a novel environment (Morgan 1973; Weinstock and Speiser 1973; Sahakian et al. 1975, Einon and Morgan 1978; Garzon et al. 1979; Guisado et al. 1980; Garzon and Del Rio 1981; Gentsch et al. 1981a,b; Jones et al. 1990). Isolation reared rats also show elevated levels of food consumption and concomitant weight gain (Morgan and Einon 1975), enhanced tail pinch-induced oral behaviours (Sahakian and Robbins 1977), and a consistently "anxiogenic" profile (Morinan and Parker 1985; Wright et al. 1991). A number of studies suggest that isolation reared animals show deficits in response inhibition (Morgan 1973; Morgan and Einon 1975; Morgan et al. 1977).

Isolation rearing also enhances the unconditioned behavioural response to psychomotor-stimulant drugs. For

example, isolation reared animals have been reported to show an enhanced locomotor response to *d*-amphetamine (Garzon et al. 1979; Jones et al. 1990, 1992). They are also more susceptible to the sedative effect of low doses of apomorphine (Wilmot et al. 1986; Jones et al. 1992), and exhibit a greater degree of stereotypy following administration of *d*-amphetamine (Kostowski and Czlondowski 1973; Sahakian et al. 1975; Einon and Sahakian 1979). Similarly, conditioned locomotor activity was potentiated by *d*-amphetamine to a greater extent in isolation reared rats (Jones et al. 1990), the dose-effect curve being shifted to the left compared with socially reared rats. The efficacy of *d*-amphetamine to increase the control over behaviour exerted by a conditioned reinforcer was also enhanced by isolation rearing (Jones et al. 1990; but see Schenk et al. 1986). Isolation rearing has yielded a similarly consistent effect upon responsivity to the noncontingent administration of opiate receptor agonists. However, in contrast to their reactivity to psychomotor stimulants, isolation reared animals in general are less responsive to opiates. Thus, the symptoms of precipitated withdrawal in animals made dependent upon morphine are less marked in isolation reared animals (Adler et al. 1975; Marks-Kaufman and Lewis 1984), who also are less affected by the analgesic properties of morphine (Kostowski et al. 1977). Moreover, isolation rearing impairs severely the capacity of heroin to establish a conditioned place preference (Schenk et al. 1983, 1985), and impairs the establishment of a conditioned taste aversion to morphine (Schenk et al. 1987).

Isolation has also been reported to enhance the rate of the contingent self-administration of some classes of drugs of abuse (Alexander et al. 1978, 1981; Hadaway et al. 1979; Marks-Kaufman and Lewis 1984; Bozarth et al. 1989; Schenk et al. 1990). By contrast, the effects of isolation rearing on the contingent self-administration of psychomotor stimulant drugs are less clear. Thus, it has been reported to have no effect on the self-administration of *d*-amphetamine (Schenk et al. 1988) or cocaine (Boyle et al. 1991). However, others have found the rate of self-administration of cocaine was enhanced (Schenk et al. 1987).

Hence, the effect of isolation rearing on the reinforcing action of psychomotor stimulant drugs remains unclear. Accordingly, the present study examined in detail the effect of isolation rearing on the response to cocaine. The responsivity of isolation reared rats to a novel environment, and to the locomotor stimulant properties of a noncontingent injection of cocaine was assessed initially (experiment 1). Then, the effect of isolation rearing on the acquisition of the self-administration of cocaine was examined, and also its maintenance by a range of doses of cocaine (experiments 2 and 3, respectively). Finally, the responsivity of isolation reared animals to a conditioned reinforcer, associated previously with the contingent presentation of cocaine was investigated (experiment 4).

Materials and methods

Subjects

A total of 28 male Lister hooded rats was used (Olac, Bicester, UK). Animals were obtained at 21 days of age as a single cohort, and immediately were divided equally into two groups (matched by body weight) and housed either in groups of five (Socially reared condition), or one (Isolation reared condition). Sixteen animals took part in experiment 1 (eight socially reared, eight isolation reared), and the remaining 12 animals took part in experiments 2, 3 and 4. The rats in experiment 1 were isolated for an identical period of time to that of rats in experiments 2, 3 and 4, but were not catheterised and did not have the opportunity to self-administer cocaine. Experiment 1 was run concurrently with experiments 2, 3 and 4. Due to catheter-related attrition of subject numbers, while all 12 animals took part in experiment 2 (6 socially reared, 6 isolation reared), 10 animals took part in experiment 3 (5 socially reared, 5 isolation reared) and 9 animals took part in experiment 4 (5 socially reared, 4 isolation reared). Socially reared animals were maintained in cages 51 × 32 × 19 cm high. Isolation reared animals were housed individually in cages 33 × 21 × 19 cm high, and could hear and smell other rats. Housing conditions consisted of a 12 h:12 h reversed light:dark cycle (lights off 0900 hours) at a constant temperature of 22° C. Animals were aged 20 weeks at the start of experiments, and body weights ranged from 300 to 350 g. All socially reared animals were housed separately prior to the catheterisation of animals in experiments 2, 3 and 4. This procedure has been shown previously not to affect the self-administration of cocaine (Bozarth et al. 1989). Experiments were carried out between 1300 and 1600 hours. Sufficient food to maintain body weight at 95% free feeding weight was made available at 1700 hours. Access to water was unrestricted.

Apparatus

For experiment 1, locomotor activity was monitored in a bank of wire mesh photocell cages (40 × 25 × 18 cm). Each cage was fitted with two parallel horizontal infrared beams, 1 cm above the floor, spaced equally along the long axis of the cage. Interruption of either beam resulted in an incremental count for that cage, registered by on-line input to a BBC Master microcomputer, housed in an adjacent room. Beam breaks were recorded in 15-min bins, and as the total number per session.

Experiments 2, 3 and 4 were carried out in four operant chambers (28 × 26 × 28 cm; Gerbrands Corporation, Arlington, Mass., USA). Each chamber contained two retractable levers each 3.8 cm wide, positioned symmetrically upon one wall 17.5 cm apart and 9 cm from the grid floor. The force required to produce switch closure by each lever was approximately 0.118 N. The operant chamber could be illuminated by a 2.5 W, 24 V houselight in the centre of the ceiling, painted with red enamel. Translucent round discs (3.5 cm diameter) situated 10 cm above each lever could also be illuminated by 2.5 W, 24 V light sources. Each chamber was fitted with an infusion pump (Model 56–8816: Harvard Apparatus Ltd, Edenbridge, UK) which could be activated by computer command. Intravenous infusions of cocaine were carried out through a single-channel liquid swivel (Stoelting, Wood Dale, Ill., USA) with connector attachment (Plastics One, Roanoke, Va., USA). Depression of the left lever by the experimenter turned the houselight on, extended the levers and began the session. Subsequent depression of one lever (the drug lever) caused the houselight to extinguish and the lever light to turn on. After a period of 1 s, the levers retracted and the infusion pump was activated for 4 s, and a 0.2 ml intravenous infusion of cocaine solution was delivered. After a further period of 16 s, the levers again were extended into the operant chamber (total retraction time: 20 s), the lever light was extinguished and the houselight turned on. Depression of the drug lever again would result in an infusion of cocaine. Depression of the

second lever (the control lever) was recorded but had no programmed consequences at any time. The operant chambers were housed in sound-attenuating boxes and external noise was masked by ventilating fans mounted on the side of each box. The apparatus was controlled, and the data collected, by an Acorn System 3 microcomputer (Acorn Computers Ltd, Cambridge, UK), running with the control language ONLIBASIC. Total responses upon each lever were recorded.

Drug

Cocaine hydrochloride (Rhone-Poulenc-Rorer, Dagenham, UK) was dissolved in sterile 0.9% saline (Animalcare Ltd, Dunnington, UK). All doses of cocaine were calculated as the salt. For experiment 1b, cocaine (10 mg/kg) was injected intraperitoneally in a volume of 1 ml/kg 30 min before each session, saline served as vehicle (see Procedure below).

Surgery

Rats were anaesthetised with an injection IP of a solution containing 2,2,2-tribromoethanol in tertiary amyl alcohol (Avertin: volume injected, 10 ml/kg; for method of preparation, see Phillips et al. 1993a). Following anaesthesia, animals were prepared, and maintained with chronic jugular catheters according to standard procedures (see Caine et al. 1992). Streptokinase (825 IU/day; Hoechst UK, Hounslow, UK) was used routinely to flush catheters in order to maintain patency.

Procedure

Experiment 1: *locomotor response to a novel environment, and to cocaine IP.* Each animal was allocated randomly to one of eight photocell cages, with the sole constraint that the eight cages should contain equal numbers of socially reared, and isolation reared animals at any one time. Then, the effect of isolation rearing upon the locomotor response to the novel environment was recorded during daily 2-h sessions (experiment 1a). Three consecutive daily sessions were found to be sufficient for the isolation reared group to exhibit an habituated locomotor response, by comparison with socially reared controls. Two sessions subsequent to experiment 1a assessed the effect of isolation rearing upon the locomotor response to cocaine (10 mg/kg; experiment 1b). Drug and saline administration was counterbalanced across subjects. The two sessions were separated by a washout period of 48 h.

Experiment 2: *acquisition of cocaine self-administration.* Following surgery and a period of recovery of 1 week, the remaining animals of the original cohort of 28 (see Subjects above) were each allocated randomly to an operant chamber for the duration of the experiments, with the sole constraint that the four operant chambers should contain equal numbers of socially reared, and isolated animals at any one time. The active drug lever (left or right) was fully counterbalanced across subjects. The effect of isolation rearing upon the acquisition of cocaine self-administration behaviour was then assessed. Each animal was placed in its designated operant chamber and attached to the connector for the delivery of cocaine. The experimenter then started the session by a single press of the left lever. The operant chamber was then closed. Depression of the drug lever by the animal resulted in a delivery of 1.5 mg/kg cocaine (see also Apparatus). Non-contingent "priming" infusions of cocaine were not delivered at any time during these experiments. After 3 h, each animal was removed from the operant chamber and returned to the home cage. Five consecutive daily sessions were required for the two groups to achieve asymptotic performance levels.

Experiment 3: *cocaine dose-response function.* Three days after the completion of experiment 2, animals were exposed to a sixth session with cocaine available at the training dose of 1.5 mg/kg per infusion. The two groups exhibited a similar rate of response. The dose of cocaine subsequently was halved repeatedly over the following six 3-h sessions. Thus, the doses of cocaine available during experiment 3 were: 1.5, 0.75, 0.375, 0.1875, 0.0938, 0.0469 and 0.0234 mg/kg per infusion.

Experiment 4: *influence of the conditioned reinforcer on the rate of response.* Following the completion of experiment 3, all animals were re-baselined for at least seven sessions at 1.5 mg/kg per infusion (see Phillips et al. 1993b). During this time, response rates by the two groups were entirely comparable. Throughout experiments 2 and 3, a "leverlight on, houselight off" compound stimulus immediately preceded, and was paired directly with, the delivery of cocaine (see Apparatus). However, during the two 30-min sessions which comprised experiment 4, cocaine was not available at any time. Instead, during one session depression of the active lever (previously the drug lever) resulted in the presentation of the compound stimulus (schedule of contingency: FR2). Depression of the control lever remained without programmed consequence. During the second session, both levers were inactive. The order of exposure to these two conditions was counterbalanced across subjects.

Statistical analyses

Within-session data from experiments 1a and 1b, and data from experiments 2, 3 and 4 were subjected initially to three-factor parametric analyses of variance [experiment 1a, Group (Social, Isolate); Time (15, 30, 45, 60, 75, 90, 105, 120 min); Session (1,2,3): experiment 1b, Group (Social, Isolate); Time (15, 30, 45, 60, 75, 90, 105, 120 min); Drug (Vehicle, Cocaine): experiment 2, Group (Social, Isolate); Lever (Active, Control); Days (1, 2, 3, 4, 5): experiment 3, Group (Social, Isolate); Lever (Active, Control); Dose (1.5, 0.75, 0.375, 0.1875, 0.0938, 0.0469, 0.0234 mg/kg per infusion): experiment 4, Group (Social, Isolate); Lever (Active, Control); Conditioned Stimulus (Presence, Absence)]. The factor "Group", and the factor "Drug" in experiment 1b represent nested factors. Total beam breaks from experiments 1a and 1b were subjected to two-factor parametric analyses of variance [Group (Social, Isolate); Drug (Vehicle, Cocaine)].

Statistically significant main effects ($P < 0.05$) were analysed further. Within-factor comparisons for factors containing two levels were made using simple main effects parametric analyses of variance (Winer 1971). Within-factor comparisons with the baseline condition (factors containing more than two levels) were also analysed initially using simple main effects analysis of variance, but then were completed post hoc using Dunnett's t test (D-t; Winer 1971).

Results

Experiment 1a: effect of isolation rearing upon the locomotor response to a novel environment

Isolation reared animals were more active than socially reared animals during the first exposure to the novel environment [Fig. 1, upper right panel; $F(1,14) = 15.3$, $P < 0.01$]. Further, this difference in response was evident from the start of the session, and isolation reared animals continued to show more activity almost for the entire 2-h session [Fig. 1, upper central panel; $F(1,14) = 15.4$, $P < 0.01$]. However, the level of activity of isolation reared animals declined to levels comparable with the socially reared group by the second and third

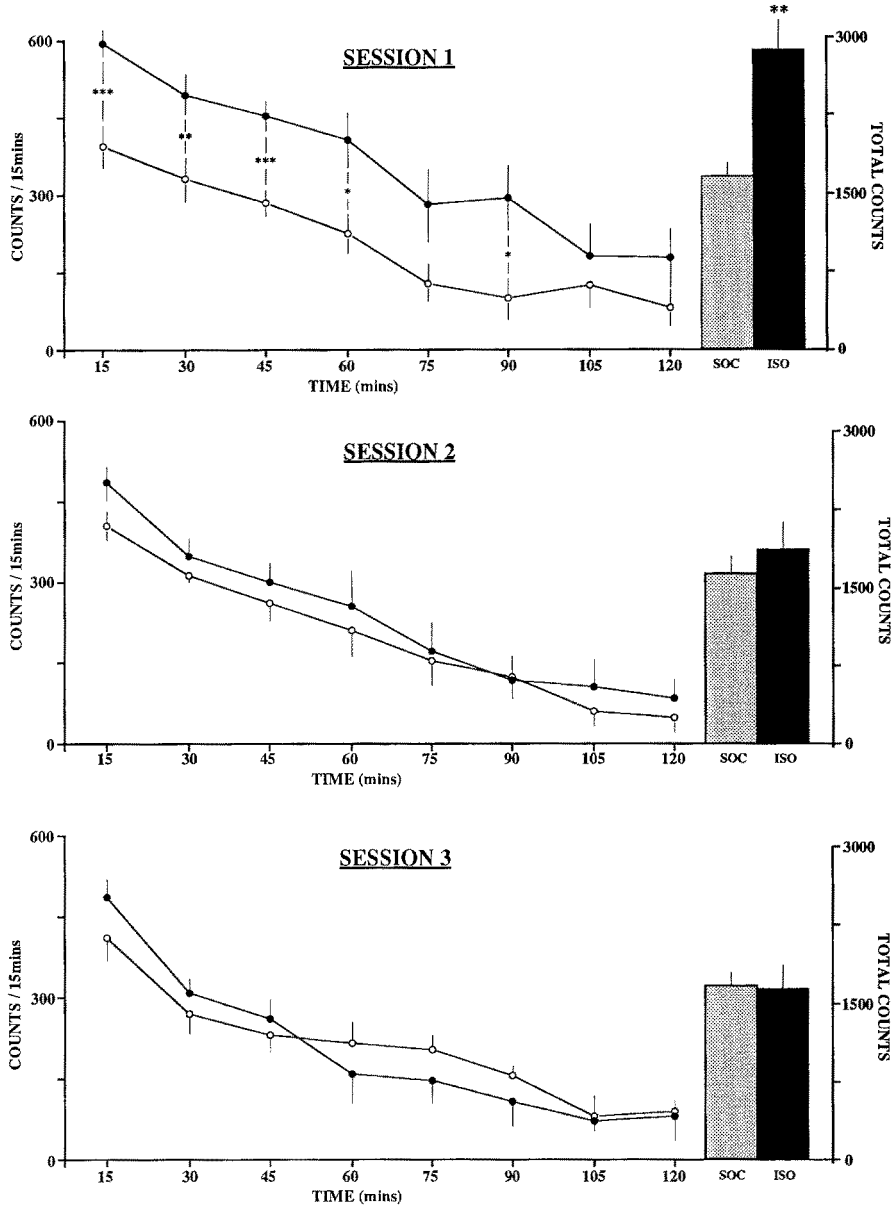

Fig. 1. Effect of isolation rearing upon the locomotor response to a novel environment. *Upper panel*, first exposure to the novel environment; *middle panel*, second exposure to the novel environment; *bottom panel*, third exposure to the novel environment. *Right panels*, total activity counts per 2-h session, *left panels*, within-session activity counts per 15 min. *SOC*, socially reared control animals; *ISO*, isolation reared animals. Values represent means ± SEM. *Stars* represent statistical significance of comparisons indicated; $*P < 0.05$; $**P < 0.01$; $***P < 0.001$. ○, socials; ●, isolates

locomotor sessions [Total activity, social versus isolate, run 2: $F(1,14) = 0.6$, NS; run 3: $F(1,14) = 0.1$, NS]. Thus, isolation rearing resulted in a higher level of activity upon exposure to a novel environment, but did not affect the level of activity when the same environment was no longer novel.

Experiment 1b: effect of isolation rearing upon the locomotor response to cocaine

Prior administration of 10 mg/kg cocaine enhanced the level of activity exhibited by both socially reared, and isolation reared animals [Fig. 2, right panel; Total activity, vehicle versus cocaine, socially reared: $F(1,7) = 7.7$, $P<0.05$; isolation reared: $F(1,7) = 112$, $p<0.001$]. However, cocaine enhanced the level of activity of isolation reared animals to a larger extent than it did the socially reared group [Total activity, group × drug simple interaction effect: $F(1,14) = 5.7$, $p<0.05$]. The greater effect of cocaine upon the activity of isolation reared animals was evident from the session start, and continued for most of the duration of the session [Fig. 2, central panel; group × drug interaction: $F(1,12) = 11.1$, $p<0.01$].

Experiment 2: acquisition of cocaine self-administration

Socially reared animals acquired the cocaine self-administration response faster than isolation reared animals [Fig. 3; $F(1,10) = 5.1$, $p < 0.05$]. Hence, enhanced self-administration of cocaine by the socially reared group was most evident during the first day of acquisition. The difference between the two groups in the rate of infusion declined thereafter. Rates of response upon the control lever generally were low [drug lever versus control lever, socially reared: $F(1,5) = 127$, $P < 0.001$; isolation reared: $F(1,5) = 12.1$, $P < 0.05$]. Thus, the drug lever ex-

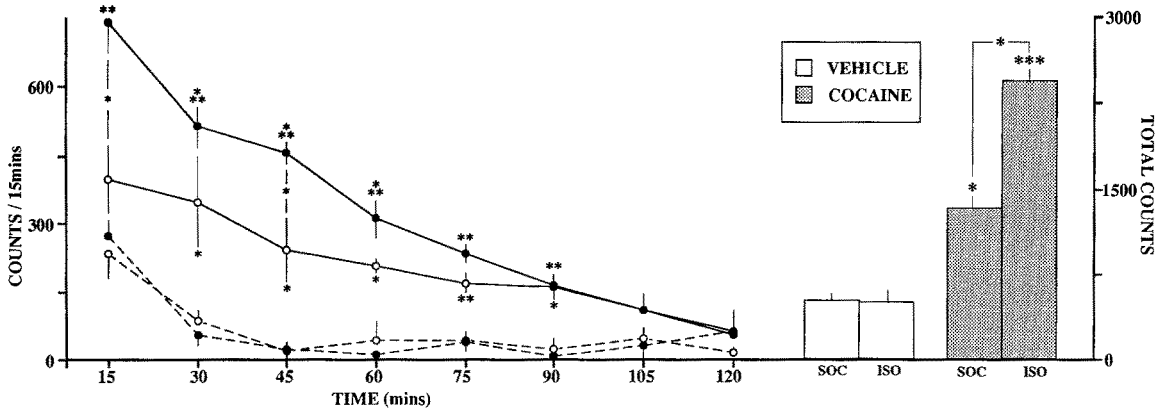

Fig. 2. Effect of isolation rearing upon the locomotor response to cocaine. *Right panel*, total counts per 2-h session, *left panel*, within-session activity counts per 15 min. *SOC*, socially reared control animals; *ISO*, isolation reared animals. Values represent means ± SEM. *Stars* adjacent to SEMs represent statistical significance of comparisons with the respective vehicle condition; $*P < 0.05$; $**P < 0.01$; $***P < 0.001$. ○, socials; ●, isolates; ----, vehicle; ——, 10 mg/kg cocaine

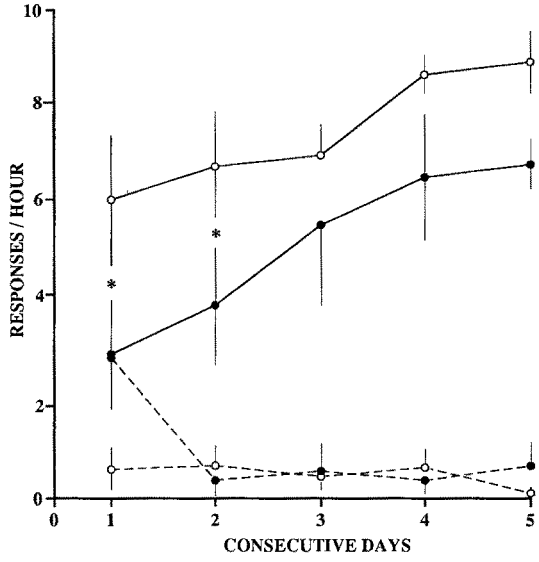

Fig. 3. Effect of isolation rearing upon the acquisition of cocaine self-administration. Schedule, FR1; dose, 1.5 mg/kg per infusion. *Solid lines*, drug lever; *dotted lines*, control lever. ●, isolation reared animals, ○, socially reared control animals. Values represent means ± SEM. *Stars* represent statistical significance of comparisons indicated; $*P < 0.05$

erted a high degree of control over behaviour within the operant chambers, by comparison with the control lever. Nonetheless, isolation reared animals failed to discriminate between the drug and control levers during the first day of acquisition [$F(1,5) = 0.0$, NS]. Inspection of individual event records for representative rats on the first day confirms these data (Fig. 4). Both rats pressed the drug lever early in the initial session. However, while the socially reared rat returned to the drug lever within a relatively short time, and continued to do so selectively thereafter, the isolation reared rat did not return to the drug lever until comparatively late in the session, and number of presses upon the control lever were also evident.

Experiment 3: effect of isolation on the dose-response function for the self-administration of cocaine

Both groups exhibited inverted U-shaped cocaine dose-response functions (Fig. 5, left panels). Responding increased initially as the concentration of cocaine available was lowered, before decreasing very steeply at the lowest doses of cocaine tested.

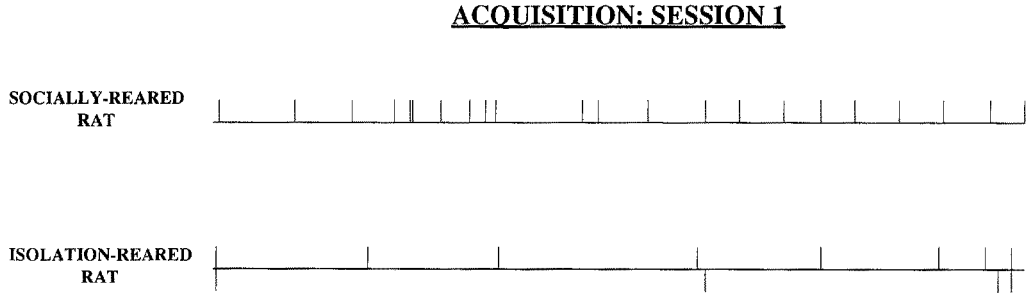

Fig. 4. Effect of isolation rearing upon the acquisition of cocaine self-administration. Schedule, FR1; dose, 1.5 mg/kg per infusion. Event records are shown for one representative socially reared rat (*upper record*), and one representative isolation reared rat (*lower record*). The total number of responses by representative rats was the closest to mean number of responses for their respective groups. Each horizontal line represents a single 3-h self-administration session. Each vertical stroke above the horizontal lines represents a response upon the drug lever and an intravenous infusion of cocaine. Each vertical stroke below the horizontal lines represents a response upon an inactive control lever

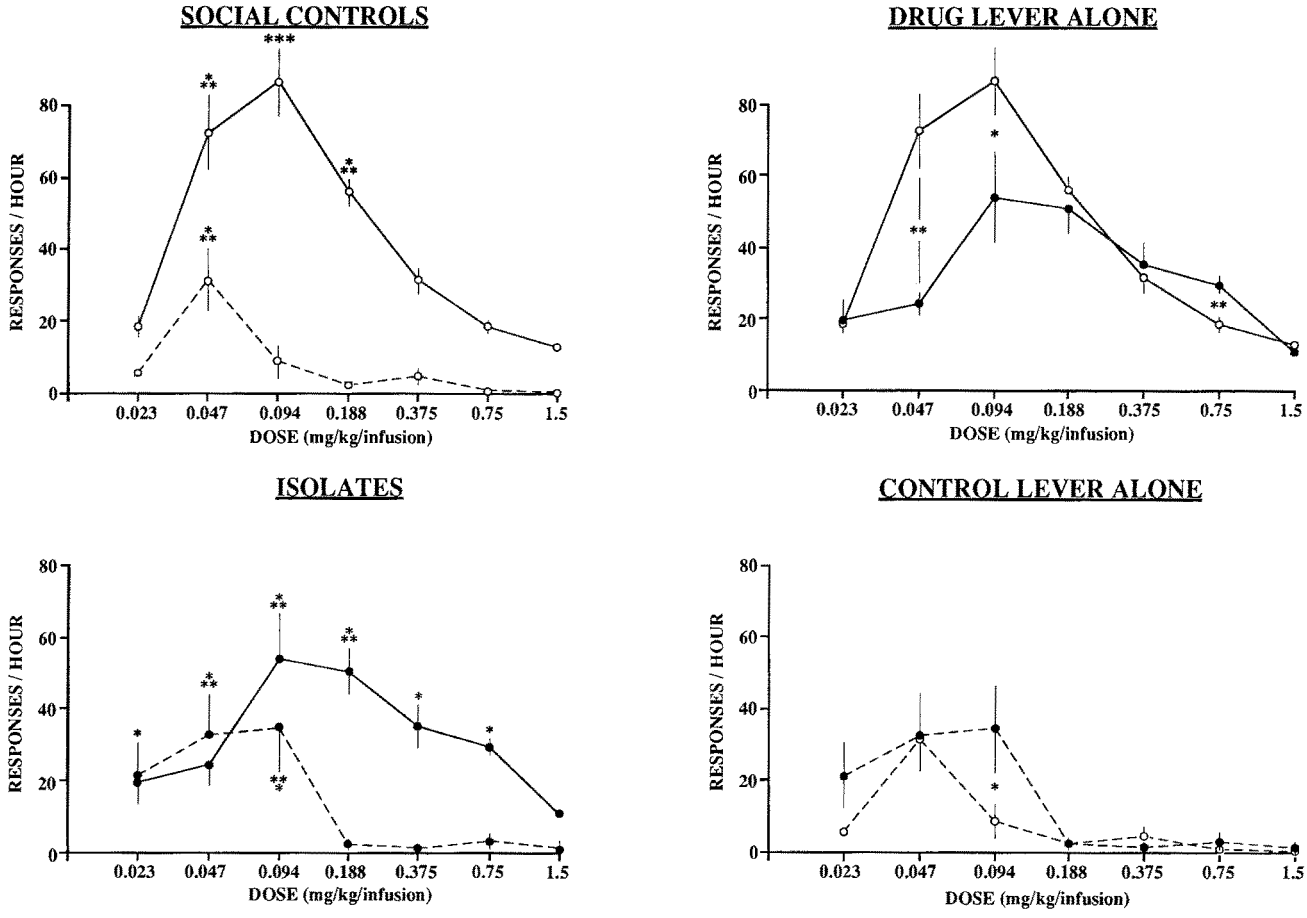

Fig. 5. Effect of isolation rearing upon the cocaine dose-response function. Schedule, FR1; baseline dose, 1.5 mg/kg per infusion. *Solid lines*, drug lever; *dotted lines*, control lever. ●, isolation reared animals, ○, socially reared control animals. Values represent means ± SEM. Unless indicated otherwise, *stars* represent statistical significance of comparisons with the baseline dose of 1.5 mg/kg per infusion; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

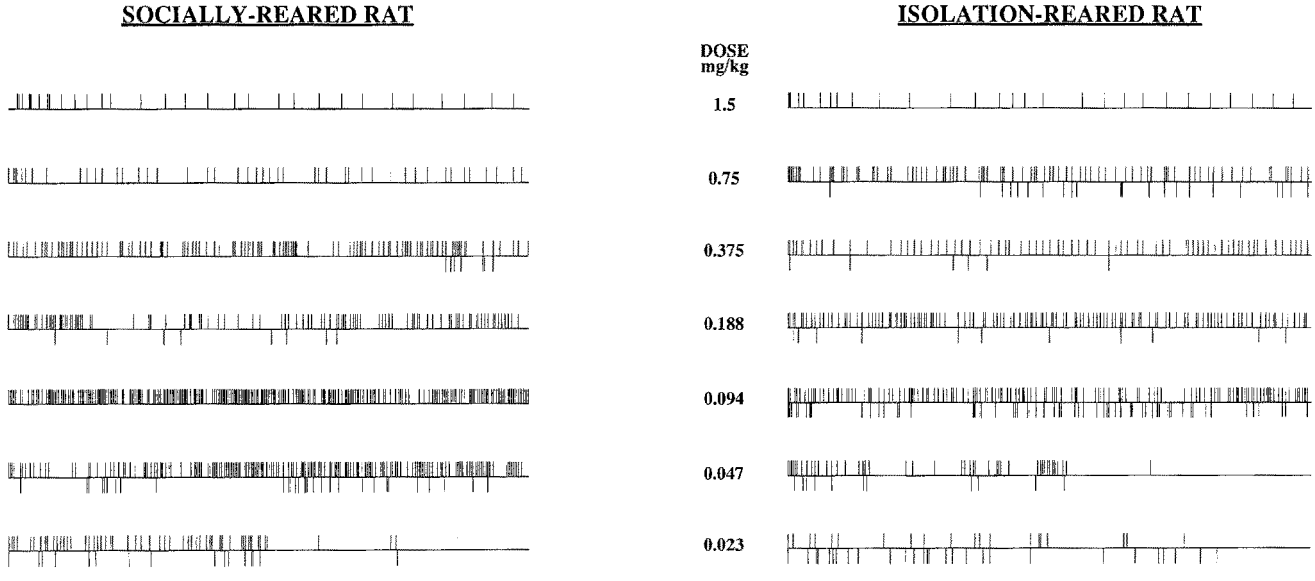

Fig. 6. Effect of isolation rearing upon the cocaine dose-response function. Schedule, FR1; baseline dose, 1.5 mg/kg per infusion. Event records are shown for one representative socially reared rat (*left panel*), and one representative isolation reared rat (*right panel*). The total number of responses by representative rats were the closest to mean number of responses for their respective groups. Each horizontal line represents a single 3-h self-administration session. Each vertical stroke above the horizontal lines represents a response upon the drug lever and an intravenous infusion of cocaine. Each vertical stroke below the horizontal lines represents a response upon an inactive control lever

The dose-response function for the isolation reared group was shifted to the right of the socially reared animals [Fig. 5, top right panel; group concentration simple interaction effect: $F(6,48) = 6.1$, $P < 0.001$]. Thus, isolation reared animals increased responding to a greater degree than socially reared animals when the dose of cocaine was initially halved [$F(1,8) = 13.0$, $P < 0.01$]. However, while socially reared animals maintained responding at asymptotic rates at a dose as low as 0.047 mg/kg per infusion, this dose was insufficient to maintain responding by isolation reared animals [socially reared versus isolation reared: $F(1,8) = 19.4$, $P < 0.01$]. Twice this dose (0.094 mg/kg per infusion) was required to maintain asymptotic responding by isolation reared animals; an asymptote lower than that of socially reared controls [$F(1,8) = 5.6$, $P < 0.05$].

Both groups increased responding on the control lever at the lowest doses of cocaine required to maintain asymptotic responding (Fig. 5, bottom right panel). Isolation reared animals first increased responding on the control lever at 0.094 mg/kg per infusion (0.094 mg/kg per infusion versus 1.5 mg/kg per infusion, D-t: $P < 0.001$). At this dose responding on the two levers by this group did not differ [$F(1,4) = 1.0$, NS]. Socially reared controls first increased responding on the control lever at half this dose (0.047 mg/kg per infusion, D-t: $P < 0.001$). Drug lever responding by socially reared animals remained higher than on the control lever [$F(1,4) = 8.5$, $P < 0.05$]. Thus, cocaine dose-response functions for the drug lever, and the control lever suggest that isolation reared animals were less sensitive to the reinforcing properties of cocaine.

Individual event records taken from representative rats for each group lend credence to these data (Fig. 6). Event records also indicate that while higher doses of cocaine maintained a constant rate of responding throughout sessions, isolation reared rats failed to maintain responding at 0.047 mg/kg per infusion, while socially reared controls continued to maintain responding at this low dose. However, socially reared animals also failed to maintain responding at 0.023 mg/kg per infusion.

Experiment 4: *effect of the cocaine-paired conditioned reinforcer*

In the absence of the availability of a conditioned reinforcer associated previously with cocaine reinforcement, both groups demonstrated a preference for responding on the active lever, designated previously as the "drug" lever [Fig. 7; active lever versus control lever, socially reared: $F(1,4) = 9.0$, $P < 0.05$; isolation reared: $F(1,4) = 8.2$, $P < 0.05$]. Moreover, both groups responded at similar rates on both the active lever and control lever under these conditions [socially reared versus isolation reared, active lever: $F(1,7) = 0.3$, NS; control lever: $F(1,7) = 0.2$, NS]. Thus, the behaviour of the two groups in the absence of conditioned reinforcement was very similar. However, the addition of the contingency of a conditioned reinforcer increased strikingly, and selectively the rate of response on the active lever by socially reared animals [socially reared, lever × stimulus condition simple interaction effect: $F(1,4) = 8.1$, $P < 0.05$]. In contrast, isolation reared animals were wholly unaffected by the addition of the contingency of a conditioned reinforcer [isolation reared, lever × stimulus interaction: $F(1,3) = 0.0$, NS; absence versus presence of conditioned reinforcer, active lever: $F(1,3) = 0.0$, NS; control lever: $F(1,3) = 0.0$, NS]. Thus, the addition of the contingency of a conditioned reinforcer associated previously with cocaine reinforcement increased markedly, and selectively the rates of response emitted by the socially reared group, but had no effect whatever upon the rates of response exhibited by isolation reared animals.

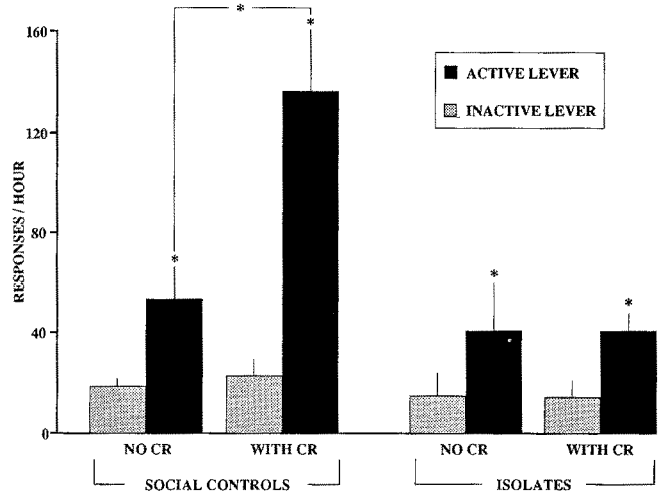

Fig. 7. Effect of isolation rearing upon the response to a conditioned reinforcer. The stimulus was paired previously with the contingent availability of cocaine (schedule: FR1; baseline dose of cocaine: 1.5 mg/kg per infusion; cocaine:stimulus correlation, 1:1). Assessment of the reinforcing efficacy of the stimulus was carried out in the absence of cocaine. Active lever, previously the drug lever; inactive lever, previously the control lever. Sessions were carried out both in the presence of the conditioned reinforcer (*CR*), and with no conditioned reinforcement available (*NO CR*). Values represent means ± SEM. *Stars* directly above SEMs represent statistical significance of comparisons with inactive lever; *$P < 0.05$

Discussion

Isolation rearing enhanced the locomotor response to a novel environment, and also enhanced the locomotor response to the noncontingent administration of cocaine. By contrast, isolation rearing retarded the acquisition of the self-administration of cocaine, and shifted to the right a cocaine dose-response function. These results have two important sets of implications. First, they suggest that elevated levels of spontaneous, or psychomotor stimulant-induced, locomotor activity are not necessarily predictive of the reinforcing effects of such drugs. This is important in the light of recent findings relating individual differences in socially reared populations of rats, to subsequent susceptibility to drugs such as *d*-amphetamine, and also of psychomotor stimulant-induced drug sensitisation which customarily measures sensitisa-

tion in terms of heightened locomotor responses (Robinson et al. 1988; Piazza et al. 1990). Second, the enhanced locomotor response to cocaine seen here, which is in agreement with earlier demonstrations of a leftward shift in the dose-effect curve with *d*-amphetamine (Jones et al. 1992) and cocaine (Sahakian et al. 1975), occurs in rats who show apparently rightward shifts in the reinforcing efficacy of the drug. It is important to note that although different subjects were utilised for locomotor and self-administration experiments, all animals were derived from the same cohort. Thus, all animals were obtained together at weaning, and reared either in isolation or as groups in adjacent cages. Further, locomotor and self-administration studies were conducted concurrently. This paradox strongly suggests that the effect of contingent and noncontingent administration of drugs can be qualitatively different, in this study having been revealed in rats with restricted early social experience. However, the underlying mechanisms for these differences may require further characterisation.

An enhanced locomotor response to a novel environment represents a cardinal trait of the isolation-syndrome (Morgan 1973; Weinstock and Speiser 1973; Sahakian et al. 1975; Einon and Morgan 1978; Garzon et al. 1979; Guisado et al. 1980; Garzon and Del Rio 1981; Gentsch et al. 1981a,b; Jones et al. 1990), and the findings of the present work are in agreement with these earlier reports. However, animals predisposed to exhibit an enhanced locomotor response to a novel environment are reported to acquire the intravenous self-administration of *d*-amphetamine at a relatively rapid rate (Piazza et al. 1990). The present data show that this hyper-reactivity does not necessarily predict an enhanced propensity to self-administer cocaine. Of course, it is possible that the mechanisms underlying the hyper-reactivity of rats selected for this trait from a socially reared population are not the same as those responsible for the isolation syndrome. Other evidence from a variety of sources also suggests that hyperactivity or hyper-reactivity does not necessarily predict the response to reinforcing agents. For example, repeated intra-ventral tegmental area infusions of opiate receptor agonists have been shown to result in a sensitised locomotor response (Kalivas et al. 1985; Vezina et al. 1987; Kalivas et al. 1988; Kalivas and Duffy 1990), but an impaired ability of *d*-amphetamine to enhance the control over behaviour exerted by a conditioned reinforcer (Phillips et al. 1993a). In addition, others have shown that high levels of basal, or *d*-amphetamine-induced locomotor activity corresponded with a reduced responsivity to a *d*-amphetamine cue in a drug discrimination procedure (Exner and Clark 1993). In this context, it is worthy of note that isolation rearing impaired the control over behaviour exerted by the drug lever at low doses of cocaine.

The reduction in reinforcing effect of cocaine by isolation is supported by three distinct pieces of evidence in this study. First, the isolates acquired the discriminative continuous-reinforcement procedure more slowly than socially reared rats. This deficit was evident both across acquisition sessions, and upon inspection of individual event records for the initial session, during which isolation reared animals failed to return to the drug lever following an initial response until relatively late in the session, and responded to a relatively high degree upon the control lever. This deficit is unlikely to have resulted indirectly from more general effects of isolation rearing. For example, it is possible that the heightened locomotor activity of the isolates competed behaviourally with lever pressing. However, this seems unlikely for two reasons: (i) the rates of lever pressing were low and thus unlikely to suffer from behavioural competition; (ii) other work has reported enhanced operant response rates in isolated rats maintained with other reinforcers (Jones et al. 1990). These observations suggest that reduced lever pressing in isolates does not arise from low operant baselines or from a general deficit in associative learning. They also underline the specificity of the reduced reinforcing effect of cocaine. Second, while it is possible that the impaired acquisition is a function of the large unit training dose of cocaine and consequent enhanced stereotypical responses (Sahakian et al. 1975; see below), the results of experiment 3 refute this argument. Thus, it was shown that systemic variation of the dose-effect function produced a significant rightward shift in isolates relative to controls, who displayed a characteristic inverted U-shaped dose-response function with an intermediate dose supporting higher rates of responding by isolates, and lower doses supporting reduced rates of response. The latter were coincident with increased rates of response on the control lever, suggesting a loss of the discriminative stimulus properties of the drug. Both of these effects occurred at relatively high doses of cocaine in isolation reared animals. Hence, an enhanced degree of competing behaviours induced by isolation rearing, including stereotypy cannot account for enhanced rates of response which were integral to an overall shift to the right of the cocaine dose- response function.

A third important piece of evidence was the abolition of the conditioned reinforcing effect of stimuli paired with cocaine in isolates. In the absence of cocaine itself, the availability of a stimulus paired previously with cocaine reinforcement enhanced greatly the rates of response of socially reared controls. By contrast, the conditioned stimulus had no effect upon the rate of response of isolation reared animals. Again, this is most unlikely to reflect a general associative deficit, because isolation rearing has been shown to enhance the conditioned reinforcing effect of previously neutral stimuli paired with food (Jones et al. 1990). However, high rates of responding upon the control lever during the first day of acquisition suggest that a deficit in associative learning in relation to cocaine cannot be ruled out. Socially reared controls responded at relatively high rates with availability of the conditioned reinforcer, by comparison with relatively low rates maintained by the training dose of cocaine. This does not indicate that the conditioned reinforcer, associated previously with cocaine, was more reinforcing than cocaine itself. The majority of classes of reinforcers follow an inverted U-shaped function. Thus, the training dose of cocaine used in the present study (1.5 mg/kg per infusion) lay low on the "descending limb" of this function (experiment 3). When provided with a choice between two val-

ues of a reinforcer (e.g. dose), animals have been shown consistently to prefer the reinforcer with higher value. This remains true even when the preferred reinforcer value in itself supports only a low rate of response on the "descending limb" of function, and is preferred even over a value of reinforcer which of itself supports an asymptotic rate of response. This has been shown using "natural" reinforcers (Young 1949; Young and Greene 1953; Hammer 1968; Flaherty et al. 1979; Phillips et al. 1991a), intracranial self-stimulation (Hodos and Valenstein 1962), and intravenous drug self-administration (Pickens and Thompson 1968; Iglauer and Woods 1974; Johanson and Schuster 1975; Llewellyn et al. 1976). In a chained schedule, animals will also work at a higher rate to gain access to a "descending limb" value of intracranial self-stimulation (Hawkins and Pliskoff 1964), and exhibit a greater degree of "frustrative" responding during extinction following training with a "descending limb" value of a reinforcer, compared even with a reinforcer value supporting previously asymptotic rates of response (Guttman 1953; Phillips et al. 1991b).

Accounting for the "descending limb" of reward functions is a controversial issue (cf. Herrnstein 1970 versus Baum 1981). Certainly, low rates of response engendered by high doses of drugs of abuse do not indicate a side-effect-induced inability to respond (Wise et al. 1977; Gerber et al. 1985). Rather, it has been suggested that the marked efficacy of a highly preferred, "descending limb" reinforcer value is such as to render higher rates of presentation superfluous (Miliaressis and Malette 1987; Waraczynski et al. 1987; Phillips et al. 1991a,b,c,d). Indeed, animals appear to titrate the blood levels of drug such that regardless of the dose available, the actual quantity of drug in the bloodstream remains remarkably constant (Yokel and Pickens 1974).

Thus, a high rate of response maintained by a conditioned reinforcer in experiment 4 does not indicate that this reinforcer was more valued than cocaine itself in experiments 2 and 3. It is far more likely that the high rates of response engendered by the conditioned reinforcer actually indicate it was less reinforcing.

The evidence presented here that isolation rearing blunts the reinforcing effect of cocaine is also supplemented by two further points provided in a companion paper (Phillips et al. 1993b) that (i) isolates also showed impairments in the self-administration of *d*-amphetamine directly into the nucleus accumbens, and thus, these effects generalise to other psychomotor stimulants and are not limited to cocaine; and (ii) isolates showed a reduced response to dopamine D_1 and D_2 receptor antagonists when administered intra-accumbens (Phillips et al. 1993b). Overall, these five pieces of evidence strongly indicate a reduced responsivity of isolates to the reinforcing effects of psychomotor stimulants. At present we do not know if the effect is developmentally specific, but in this context it is of significance that other investigators (e.g. Bozarth et al. 1989) have found that isolating rats in adulthood does not alter the propensity to self-administer psychomotor stimulants, and so this may suggest that the effects of isolation reported here indeed are specific to early social isolation. Variations in methods for manipulating the social experience of the animals, as well as the means for assessing the reinforcing effects of drugs, may also explain some of the apparent discrepancies in the literature.

Thus, in apparent contrast with the present study, isolation rearing has been reported to enhance consistently the rate of self-administration of both morphine and heroin (Alexander et al. 1978; Hadaway et al. 1979; Alexander et al. 1981; Marks-Kaufman and Lewis 1984), and also to enhance the rate of self-administration of ethanol (Schenk et al. 1990), and cocaine (Schenk et al. 1987b). However, Schenk et al. (1988) have also reported no effect of isolation rearing on the self-administration of *d*-amphetamine. Hence, isolation rearing in the main has been reported to enhance the self-administration of drugs of abuse, in apparent contrast with the results of the present study. In general, enhanced rates of self-administration have been suggested to indicate that isolation rearing enhances responsivity to the reinforcing drug. However, it is important to note that the rate of response maintained by reinforcing drugs is inversely proportional to the concentration of drug available (Koob and Goeders 1989). Hence, an increase in the rate of self-administration in point of fact may represent a reduction in reinforcer efficacy. In addition, in the present study depression of the drug lever resulted in the presentation of the leverlight, extinction of the houselight and retraction of the levers. By contrast, depression of the control lever had no programmed consequences. It is possible therefore that cocaine exerted a reinforcing action by enhancing the incentive properties of the above stimuli, rather than through a "primary" reinforcing property. This would also be true of all self-administration studies in which lever retraction following an infusion is used to prevent overdose. However, animals have no difficulty in acquiring the self-administration response in the complete absence of the stimulus changes listed above (personal observations). It is also important to note that in all previous studies of the effects of isolation rearing upon the intravenous self-administration of drugs of abuse, noncontingent "priming" infusions apparently were administered at the beginning of every session. This practice commonly is considered necessary in order to establish self-administration behaviour at the beginning of each session. However, such behaviour is therefore drug-driven, and not drug-seeking as presumably intended in studies of the acquisition of drug self-administration. At no time in the present experiments were noncontingent infusions of cocaine provided at the start of the session to "prime" responding. This was possible in part because of the use of relatively large, contingent unit doses (1.5 mg/kg per infusion) of cocaine. The importance of this omission of priming can be appreciated from the fact that isolates tend to show enhanced responses to non-contingent administration of psychomotor stimulant drugs. Clearly, this would have confounded the assessment of the reinforcing efficacy of the drug. However, it remains a possibility that the results reported here arose specifically through the use of a relatively high dose of cocaine, which may have resulted in a greater degree of tolerance in isolation reared animals (Emmett-Oglesby, personal

communication; see below). Parametric investigation of the effects of isolation rearing upon acquisition at a range of doses of cocaine are underway in order to assess this hypothesis.

In considering the mechanism for altered responding to psychomotor stimulant drugs, it is apparent that isolation rearing has a range of neurochemical effects, including alterations in dopamine and serotonergic function within the ventral striatum (Jones et al. 1992). Thus, isolation leads to enhanced levels of dopamine in response to *d*-amphetamine, in both the dorsal and ventral striatum as measured by in vivo microdialysis; an effect shown recently to be dose dependent, with isolates exhibiting a leftward shift in the dose-effect function (L.S. Wilkinson, T.W. Robbins, F.S. Hall, unpublished observations). These effects, together with reduced serotonin function (Jones et al. 1992) may explain the heightened response to non-contingently administered psychomotor stimulants, but they do not explain the apparent effect of contingent administration.

One important consideration is the regulation of presynaptic dopamine activity perhaps by afferent influences (Grace 1991). Lesions of two sources of limbic afferents to the nucleus accumbens have differential effects on the response to amphetamine; thus, basolateral amygdala lesions impair the control over behaviour by conditioned reinforcers and thereby diminish the potentiation of such control by *d*-amphetamine, without affecting the locomotor response to the drug (Cador et al. 1989; Burns et al. 1993). By contrast, lesions of the ventral subiculum block both the rate-increasing effects of *d*-amphetamine with conditioned reinforcement and the locomotor response (Burns et al. 1993). Thus, it is possible that the influence of conditioned stimuli, including those controlling the instrumental contingency of cocaine self-administration, are mediated in part by limbic afferents to the ventral striatum. This hypothesis might predict that isolated rats may exhibit altered functioning of the afferent regulation of dopamine release, possibly resulting from changes in limbic forebrain structures, and is supported by some evidence of neurochemical effects of isolation in the amygdala (Thoa et al. 1977) and hippocampus (Bickerdike et al. 1993). Of possible significance are recent data showing that isolation *reduces* dopamine release in response to a potassium pulse (L.S. Wilkinson, T.W. Robbins, F.S. Hall, unpublished observations). Potassium-stimulated release of dopamine in the nucleus accumbens is controlled both by presynaptic autoreceptors, and by serotonin receptors (Hetey and Dreschler 1986). Thus, a reduced response to potassium suggests an additional dysfunction of systems other than the dopaminergic innervation of the nucleus accumbens. Moreover, these results emphasise previous demonstrations in socially reared rats of differences in neurochemical effects between contingently and non-contingently administered drugs (Hemby et al. 1992).

While it seems likely that isolation rearing engenders an overresponsive mesoaccumbens dopamine system under certain conditions, there may also be compensatory adjustments in postsynaptic dopamine receptor function. This is supported by evidence of downregulation of postsynaptic D_2 receptors in the ventral striatum of isolates (L.S. Wilkinson, T.W. Robbins, F.S. Hall, unpublished observations). This possibility is explored further in the context of the self-administration of psychomotor stimulants in the companion paper that follows (Phillips et al. 1993b).

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