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Enhancement of Excessive Lever-Pressing After Post-Training Signal Attenuation in Rats by Repeated Administration of the D_1 Antagonist SCH 23390 or the D_2 Agonist Quinpirole, but Not the D_1 Agonist SKF 38393 or the D_2 Antagonist Haloperidol

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The authors have recently shown that attenuation of an external response feedback leads to excessive lever-pressing that is not associated with attempts to collect reward, and they have suggested that this may be an analogue to "unreasonable" excessive behavior characteristic of obsessive–compulsive disorder. The present study shows that repeated administration of SCH 23390 or quinpirole, but not SKF 38393 or haloperidol, enhances this behavioral pattern. On the basis of data regarding the enduring effects of chronic treatment with dopaminergic agents, these results suggest that overstimulation of striatal D_1 receptors underlies enhanced response to signal attenuation. These results may link the hypothesis that obsessions and compulsions result from a deficient response feedback mechanism with findings implicating dopaminergic abnormalities in the production of obsessions and compulsions.

Obsessive–compulsive disorder (OCD) is a psychiatric affliction with a lifetime prevalence of 1–3% (Rasmussen & Eisen, 1992). The *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., American Psychiatric Association, 1994) classifies OCD as an anxiety disorder characterized by obsessive thinking and compulsive behavior. A major characteristic of obsessions and compulsions is that they are excessive and unreasonable. However, both obsessions and compulsions (e.g., doubting, checking, or washing) may be viewed as an exaggeration of normal thoughts and behaviors (Pitman, 1989; Rasmussen & Eisen, 1992; Reed, 1985).

It has been suggested that obsessions and compulsions result from a deficient response feedback mechanism or a deficient signaling that the conditions have changed after the subject's response. As a result, the successful completion of an action does not lead to the cessation of that action, as would normally occur (e.g., Gray, 1982; Malloy, 1987; Pitman, 1991; Reed, 1977; for review, see Otto, 1990, 1992). We have recently shown that, after attenuation of an external feedback for operant behavior, rats excessively emit this behavior without attempting to collect a reward, and we have suggested that this may provide an analogue to the "unreasonable" excessive behavior in OCD patients. Our procedure included four stages. In Stage 1 (magazine training), a compound stimulus (light + tone) was established as a signal for the delivery of food by classically conditioning it with food. In Stage 2 (lever-press training), rats were trained to lever-press for food in a discrete-trial procedure (i.e., the levers were introduced into the operant box at the beginning of each trial and retracted from the box after the rat inserted its head into the food magazine to collect the food reward). The stimulus was presented as a feedback after the lever-press response, accompanying the delivery of food. In Stage 3 (signal attenuation), rats underwent extinction of the classical contingency between the stimulus and food. We hypothesized that the extinction of the stimulus–food contingency in this stage would attenuate the feedback provided by the stimulus on the effectiveness of the lever-press response. In Stage 4 (test), rats' lever-press behavior was assessed under extinction conditions (i.e., pressing the lever resulted in the presentation of the stimulus, but no food was delivered). As in Stage 2, the levers were retracted from the operant box only after the rat inserted its head into the food magazine, thus allowing the rat to make more than one lever-press response per trial. We found that, during the test stage, rats pressed the lever excessively without attempting to collect food from the food magazine. It is important to note that this behavioral pattern was not seen in an extinction test not preceded by signal attenuation. We have also shown that the behavioral pattern induced by signal attenuation was abolished by the serotonin reuptake inhibitor (SSRI), fluoxetine, but not by the anxiolytic drug, diazepam, in accordance with the differential efficacy of these drugs in treating OCD patients (Joel & Avisar, 2001).

The present study sought to investigate the involvement of the dopaminergic system in these behavioral phenomena because abnormalities of the dopaminergic system have been increasingly implicated in the pathophysiology of OCD, on the basis of surplus therapeutic benefits obtained with coadministration of SSRIs and dopamine (DA) blockers (McDougle, Goodman, Leckman, et al., 1994; McDougle, Goodman, Price, et al. 1990; Sasson & Zohar, 1996), as well as on clinical observations of obsessions and compulsions in basal ganglia-related disorders such as Tourette's syndrome (Frankel et al., 1986; Grad, Pelcovitz, Olson, Matthews, & Grad, 1987; Pitman, Green, Jenike, & Mesulam, 1987), and because this system has long been known to play an important role

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in the acquisition and execution of normal behavior by providing a reinforcement signal during learning and by energizing already learned behaviors (e.g., Berridge & Robinson, 1998; Graybiel, Aosaki, Flaherty, & Kimura, 1994; Le Moal & Simon, 1991; Miller & Wickens, 1991; Robbins & Everitt, 1992; Salamone, Cousins, & Snyder, 1997; Schultz, 1998). Because these two functions have been claimed to be mediated by the D_1 and D_2 dopamine receptors, respectively (Beninger & Miller, 1998), the present study tested the effects of stimulation and blockade of D_1 and D_2 receptors during lever-press training (Stage 2). Experiment 1 assessed the effects of the D_2 agonist quinpirole (0.05 mg/kg) and the D_2 antagonist haloperidol (0.05 mg/kg), and Experiment 2 assessed the effects of the D_1 agonist SKF 38393 (10.00 mg/kg) and the D_1 antagonist SCH 23390 (0.05 mg/kg). Because repeated administration of quinpirole and SCH 23390 has been found to enhance "compulsive-like" lever-pressing, Experiments 3 and 4 tested whether this effect is specific to the signal attenuation procedure or whether it would also be obtained in "regular" extinction of the lever-press response, that is, without the signal attenuation stage preceding the test stage.

General Method

Subjects

Male Wistar rats (Tel Aviv University Medical School, Tel Aviv, Israel) approximately 3 months old, weighing 300–420 g, were housed 4 to a cage under a reversed 12-hr light–dark cycle (lights on 1900–0700). Rats were maintained on a 22-hr food restriction schedule (see below), with water freely available. They were weighed twice a week to ensure that their body weight was not reduced to below 90%.

Apparatus

Behavioral testing was conducted in four operant chambers (Campden Instruments, Loughborough, UK) fitted with a food magazine and two retractable levers. The levers were 4 cm wide and were positioned 2.8 cm from the side walls, 7.5 cm from either side of the food magazine, and 5 cm from the grid floor. The chambers could be illuminated by a houselight located at the ceiling. Access to the food magazine was through a hinged Perspex panel, the opening of which activated a microswitch. The food magazine could be illuminated by a 3-W light. An 80-dB, 2.8-kHz tone was produced by a Sonalert module (Model SC 628, Campden Instruments, Loughborough, UK). A food dispenser delivered 45-mg, "dust-free" sucrose pellets (P. J. Noyes, Sandown Scientific, London, UK). The operant chambers were housed in sound-attenuating boxes, and ventilating fans were mounted on the side of each box. Equipment programming and data recording were computer controlled.

Procedure

Handling. Before the beginning of the experiment, rats were handled for about 2 min daily for 5 days. A 22-hr food restriction schedule began simultaneously with handling and continued throughout behavioral testing. Food in the home cage was given between 1400–1600, at least half an hour after the end of the session. On the last 2 days, after handling, 20–30 food pellets used as reinforcement for operant training were introduced into the home cages on a tray. The tray was removed from the cage only after each rat was observed to consume at least 2 pellets.

Stage 1: Magazine training. On Days 1–3, rats were trained to collect food pellets from the food magazine in the operant chamber, with the levers retracted. On the 1st day of magazine training, six food pellets were placed in the food magazine, and training began only after each of the 4 rats had collected its food pellets. At the start of each trial, the houselight was turned on. After a 5-s variable delay, a single food pellet was dropped into the food magazine, simultaneous with the onset of a compound stimulus consisting of the magazine light and a tone. The compound stimulus and houselight were turned off after the rat's head entered the food magazine or after 15 s had elapsed. Each trial was followed by a 30-s intertrial interval. Each rat was trained until it completed 30 trials in which it inserted its head into the food magazine during stimulus presentation, or until a total of 40 trials was reached.

Stage 2: Lever-press training. Rats were trained to lever-press in a discrete-trial procedure. The start of each trial was signaled by the onset of the houselight. Five seconds later, both levers were introduced into the chamber; responding on one of them (reinforced lever, RL) resulted in the delivery of a single food pellet into the magazine, accompanied by the presentation of the compound stimulus. The levers were retracted, and the compound stimulus and houselight turned off, only after the rat's head entered the food magazine or after 15 s had elapsed. Responding on the other lever (nonreinforced lever, NRL) had no programmed consequences. The lever designated as RL was counterbalanced over subjects and remained the same for each rat over the entire experimental procedure. Each trial was followed by a 30-s intertrial interval. On Day 4, each rat was trained until it completed 24 trials, that is, pressed the lever and inserted its head into the food magazine (see below), or until a total of 60 trials was reached. Rats that failed to attain at least 20 completed trials were returned to the test chamber at the end of the day for an additional session. Rats that did not attain at least 20 completed trials in the second session were excluded from the experiment. On the following days, all rats were trained as on Day 4, except that they were treated with drug or vehicle before the beginning of the session and training ended when the rat had attained 44 completed trials, or when a total of 60 trials was reached. The following measures were recorded: the number of unrewarded lever-presses on the RL and on the NRL on each trial, that is, (a) the number of presses after the first response on the RL (extra lever-presses) and (b) the number of lever-presses on the NRL, (c) the number of trials on which the rat did not press the lever (unpressed trials), (d) the number of trials on which the rat pressed the lever and inserted its head into the food magazine to collect the food reward (completed trials), and (e) the number of trials on which the rat pressed the lever without inserting its head into the food magazine (uncompleted trials).

Lever-press training continued for 16 days in Experiments 1 and 3 (Days 4–19) and for 10 days in Experiments 2 and 4 (Days 4–13). In Experiments 2 and 4, on Days 5–13, the compound stimulus was turned off after 10 s instead of 15 s.

Stage 3: Signal attenuation. On the following days (Experiments 1 and 3: Days 20–21, Experiments 2 and 4: Days 14–16), with the levers retracted, rats were exposed to the presentation of the compound stimulus as on Days 1–3, but no food was delivered to the food magazine. Rats received 40 such trials on each day. In Experiments 3 and 4, rats were brought to the laboratory and left in their home cages for a period equivalent to the average duration of the signal attenuation stage.

Test. On the next day (Experiments 1 and 3: Day 22, Experiments 2 and 4: Day 17), rats were trained as in the lever-press training stage, except that no food was delivered to the food magazine (i.e., pressing the lever resulted in the presentation of the compound stimulus only) and training lasted for 44 trials.

Drugs

Drugs were administered during the lever-press training stage (Stage 2) only (i.e., Days 5–19 in Experiments 1 and 3 and Days 5–13 in Experiments 2 and 4), before the beginning of each daily session. All the drugs were administered intraperitoneally in a volume of 1 ml/kg. Haloperidol—prepared from an ampoule containing 5 mg haloperidol in 1 ml of solvent that contained 6 mg lactic acid (Abic Ltd., Bet Shemesh, Israel), and

diluted with saline—was administered 60 min before the daily session, at a dose of 0.05 mg/kg. Quinpirole (Sigma Chemical, Rehovot, Israel), dissolved in saline, was administered 30 min before the daily session, at a dose of 0.05 mg/kg. SCH 23390 (Sigma), dissolved in 0.3% tartaric acid and diluted with saline, was administered 60 min before the daily session, at a dose of 0.05 mg/kg. SKF 38393 (Sigma), dissolved in distilled water, was administered 15 min prior to the daily session, at a dose of 10.00 mg/kg. The doses used were selected on the basis of previous studies that showed disruption of lever-press behavior by these drugs (haloperidol: Fowler & Liou, 1998; Salamone et al., 1996; quinpirole: Hoffman & Beninger, 1989; SCH 23390: Beninger et al., 1987; Cousins et al., 1994; Fowler & Liou, 1998; SKF 38393: Hoffman & Beninger, 1989; Rusk & Cooper, 1989). In addition, in a preliminary study, we found that 0.10 mg/kg haloperidol abolished responding in lever-press training sessions. No-drug controls received an equivalent volume of the corresponding vehicle, administered at the corresponding time before the behavioral sessions.

Statistical Analysis

Rats' behavior during lever-press training was analyzed by multivariate analyses of variance (MANOVAs), with a main factor of drug and a repeated measures factor of days, performed on the number of completed trials, unpressed trials, and extra lever-presses (the number of uncompleted trials was not analyzed because none of the rats had uncompleted trials on any of the days). Rats' behavior during signal attenuation was assessed with two analyses: (a) The rate of extinction of the classical contingency between the stimulus and food was assessed by MANOVA, with a main factor of drug and a repeated measures factor of days, performed on the number of trials per day on which the rat inserted its head into the food magazine during stimulus presentation. (b) The level of extinction at the end of the signal attenuation stage was assessed by one-way ANOVA, with a main factor of drug, performed on the number of such trials on the last extinction day only. Rats' behavior in the test was analyzed by one-way ANOVAs, with a main factor of drug, performed on the number of completed, uncompleted, and unpressed trials; and by a MANOVA, with a main factor of drug and a repeated measures factor of days, performed on the number of extra lever-presses on the last training session and on the test. When significant drug effects were obtained, post hoc comparisons of each of the drug-treated groups with the vehicle group were performed.

Experiment 1: The Effects of Repeated Administration of Quinpirole and Haloperidol in the Post-Training Signal Attenuation Procedure

Method

Twenty-four rats were randomly assigned to three groups (vehicle, quinpirole, and haloperidol). Five rats needed an additional session on Day 4; 3 of these rats did not attain the criterion of 20 completed trials in the second session and were excluded from the experiment. The test data of 3 vehicle-treated rats and 1 haloperidol-treated rat were lost as a result of computer failure. Thus, the final analysis included 4 vehicle-, 6 haloperidol-, and 7 quinpirole-treated rats.

Results

During lever-press training, there were no differences between the three groups on any of the four measures (number of completed, uncompleted, and unpressed trials, and number of extra lever-presses; $ps > .5$). There was no difference between the three groups in the extinction of the compound stimulus, either in the rate of extinction ($p > .7$) or in the performance level at the end of this stage ($p > .9$). From the 2nd day of lever-press training, rats rarely pressed the NRL. In the three groups, there was no increase in lever-presses on the NRL in the test stage.

Figures 1a–1c present the total number of completed, uncompleted, and unpressed trials, respectively, by the three groups on the test day. As can be seen, there were no differences between the groups in the number of completed trials, $F(2, 17) = 0.22$, $p > .8$, or in the number of unpressed trials, $F(2, 17) = 0.77$, $p > .4$. However, quinpirole-treated rats had more uncompleted trials compared with the vehicle- and haloperidol-treated rats, which had a similar number of uncompleted trials, $F(2, 17) = 3.44$, $p = .0557$. Post hoc least significant difference comparisons yielded a significant difference between the quinpirole and vehicle groups ($p < .05$), but not between the haloperidol and vehicle groups ($p > .7$).

Figure 1d presents the number of extra lever-presses by the three groups on the last training session and on the test. As can be seen, the three groups had a higher number of lever-presses during the test compared with the last session, but this increase was most pronounced in the quinpirole group: significant effects of drug, $F(2, 14) = 9.73$, $p < .01$, and day, $F(1, 14) = 48.18$, $p < .0001$, as well as a significant Drug × Day interaction, $F(2, 14) = 7.71$ $p < .01$. Post hoc one-tailed t tests using the error term derived from the MANOVA that compared the number of extra lever-presses on the test day yielded a significant difference between the quinpirole and vehicle groups, $t(9) = 5.05$, $p < .05$, but not between the haloperidol and vehicle groups, $t(8) = 1.17$, *ns*.

Experiment 2: The Effects of Repeated Administration of SKF 38393 and SCH 23390 in the Post-Training Signal Attenuation Procedure

Method

Twenty-four rats were randomly assigned to three groups (vehicle, SKF 38393, and SCH 23390). Four rats needed an additional session on Day 4; 2 of these rats did not attain the criterion of 20 completed trials in the second session and were excluded from the experiment. Thus, the final analysis included 8 vehicle-, 8 SKF 38393-, and 6 SCH 23390-treated rats.

Results

During lever-press training, there were no differences between the three groups on any of the four measures (number of completed, uncompleted, and unpressed trials, and number of extra lever-presses; $ps > .4$). There was no difference between the three groups in the extinction of the compound stimulus, either in the rate of extinction ($p > .25$) or in the performance level at the end of this stage ($p > .45$). From the 2nd day of lever-press training, rats rarely pressed the NRL. In the three groups, there was no increase in lever-presses on the NRL in the test stage.

Figures 2a–2c present the total number of completed, uncompleted, and unpressed trials, respectively, by the three groups on the test day. As can be seen, there were no differences between the groups in the number of completed trials, $F(2, 19) = 0.40$, $p > .6$, or in the number of unpressed trials, $F(2, 19) = 1.09$, $p > .3$. However, SCH 23390-treated rats had more uncompleted trials compared with the vehicle- and SKF 38393-treated rats, which had a similar number of uncompleted trials, $F(2, 19) = 3.77$, $p < .05$. Post hoc least significant difference comparisons yielded a signif-

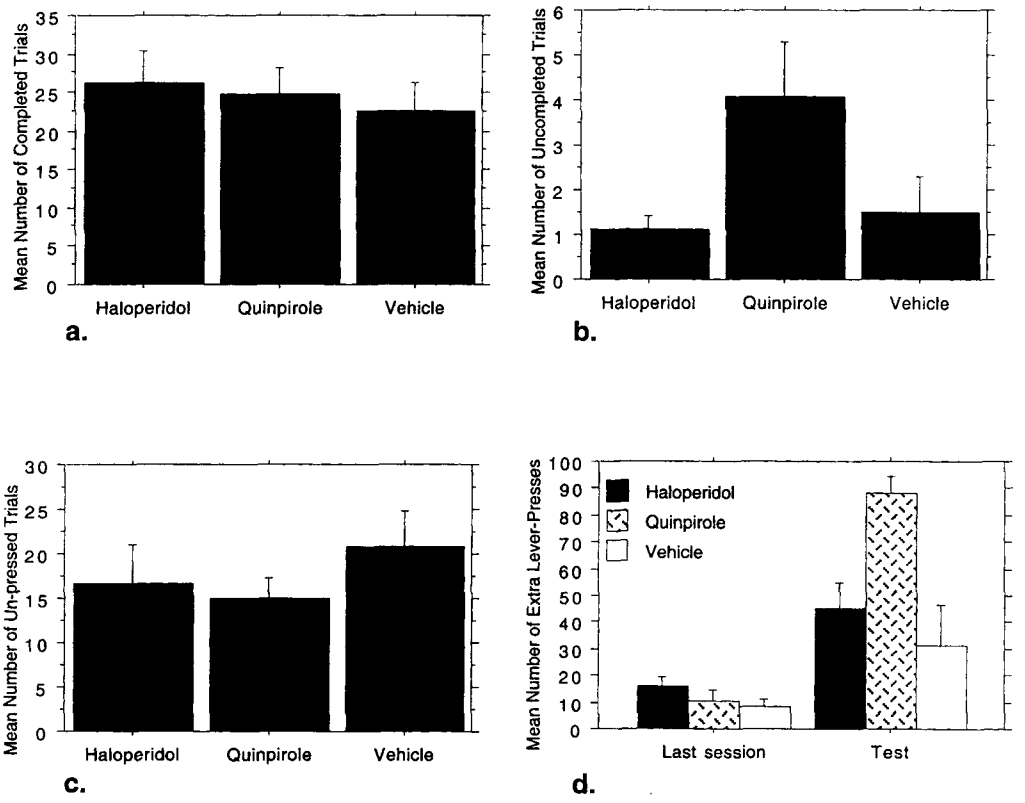

Figure 1. Mean (± *SEM*) number of completed trials (a), uncompleted trials (b), unpressed trials on the test day (c), and extra lever-presses on the last training session and on the test (d) by rats in the vehicle, haloperidol, and quinpirole groups, in the post-training signal attenuation procedure.

icant difference between the SCH 23390 and vehicle groups ($p < .05$), but not between the SKF 38393 and vehicle groups ($p > .8$).

Figure 2d presents the number of extra lever-presses by the three groups on the last training session and on the test. As can be seen, the three groups had a higher number of lever-presses during the test compared with the last session, but this increase was most pronounced in the SCH 23390 group and was slightly reduced in the SKF 38393 group: significant effect of day, $F(1, 19) = 30.23$, $p < .0001$, and a nearly significant Drug × Day interaction, $F(2, 19) = 3.27$, $p = .06$. Post hoc one-tailed t tests using the error term derived from the MANOVA that compared the number of extra lever-presses on the test day yielded a significant difference between the SCH 23390 and vehicle groups, $t(12) = 1.95$, $p < .05$, but not between the SKF 38393 and vehicle groups, $t(14) = -1.53$, $p < .1$.

Experiment 3: The Effects of Repeated Administration of Quinpirole on Regular Extinction

Method

Fourteen rats were randomly assigned to two groups (vehicle and quinpirole). Five rats needed an additional session on Day 4.

Results

During lever-press training, there were no differences between the two groups on any of the four measures (number of completed, uncompleted, and unpressed trials, and number of extra lever-presses; $ps > .1$). From the 2nd day of lever-press training, rats rarely pressed the NRL. In the two groups, there was no increase in lever-presses on the NRL in the test stage.

Figures 3a–3c present the total number of completed, uncompleted, and unpressed trials, respectively, by the two groups on the test day. As can be seen, there were no differences between the groups in the number of completed, uncompleted, and unpressed trials, $F(1, 12) = 0.65$, $p > .8$; $F(1, 12) = 0.67$, $p > .4$; and $F(1, 12) = 0.45$, $p > .5$, respectively.

Figure 3d presents the number of extra lever-presses by the two groups on the last training session and on the test. As can be seen, both groups had a higher number of lever-presses during the test compared with the last training session and did not differ from each other: significant effect of day only, $F(1, 12) = 43.13$, $p < .0001$.

Experiment 4: The Effects of Repeated Administration of SCH 23390 on Regular Extinction

Method

Fourteen rats were randomly assigned to two groups (vehicle and SCH 23390). Seven rats needed an additional session on Day 4.

Results

During lever-press training, there were no differences between the two groups on any of the four measures (number of completed,

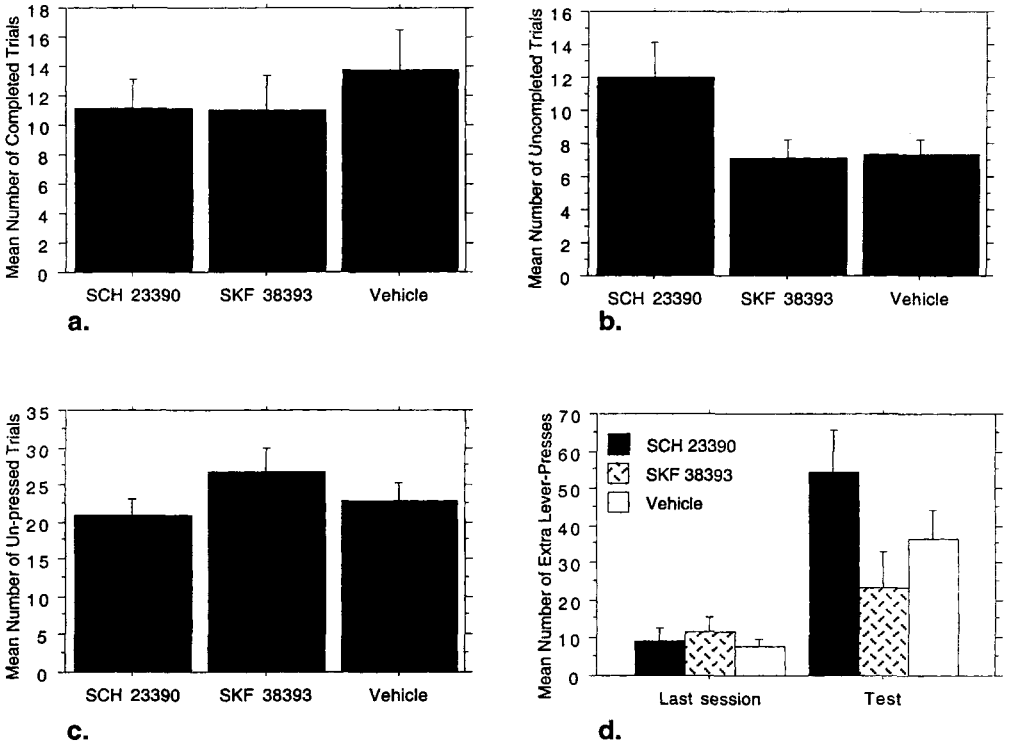

Figure 2. Mean (± *SEM*) number of completed trials (a), uncompleted trials (b), unpressed trials on the test day (c), and extra lever-presses on the last training session and on the test (d) by rats in the vehicle, SCH 23390, and SKF 38393 groups, in the post-training signal attenuation procedure.

uncompleted, and unpressed trials, and number of extra lever-presses; *p*s > .1). From the 2nd day of lever-press training, rats rarely pressed the NRL. In the two groups, there was no increase in lever-presses on the NRL in the test stage.

Figures 4a–4c present the total number of completed, uncompleted, and unpressed trials, respectively, by the two groups on the test day. As can be seen, although the SCH 23390-treated rats extinguished the lever-press response faster than did the vehicle-treated rats, as manifested in their reduced number of completed trials and increased number of unpressed trials, $F(1, 12) = 4.10$, $p = .06$, and $F(1, 12) = 5.97$, $p < .05$, respectively, there was no difference between the groups in the number of uncompleted trials, $F(1, 12) = 0.01$, $p > .9$.

Figure 4d presents the number of extra lever-presses by the two groups on the last training session and on the test. As can be seen, both groups had a higher number of lever-presses during the test compared with the last session and did not differ from each other: significant effect of day only, $F(1, 12) = 44.68$, $p < .0001$.

General Discussion

Repeated administration of the D_1 agonist, SKF 38393, the D_1 antagonist, SCH 23390, the D_2 agonist, quinpirole, or the D_2 antagonist, haloperidol, during lever-press training had no effect on rats' behavior in the lever-press training (Experiments 1–4) and signal attenuation (Experiments 1 and 2) stages. The lack of effect of the four drugs on lever-press during the training stage is surprising given that D_1 and D_2 antagonists such as SCH 23390 and haloperidol, as well as D_1 and D_2 agonists such as SKF 38393 and quinpirole, have been previously shown to reduce lever-pressing for food (for a review, see Beninger & Miller, 1998) at doses and delays between drug administration and training comparable to those used in the present study (SKF 38393: Hoffman & Beninger, 1989; Rusk & Cooper, 1989; SCH 23390: Beninger et al., 1987; Cousins et al., 1994; Fowler & Liou, 1998; quinpirole: Hoffman & Beninger, 1989; haloperidol: Fowler & Liou, 1998, Salamone et al., 1996; but see Cousins et al., 1994, who found no effect of acute administration of 0.05 mg/kg haloperidol). This inconsistency may be due to the fact that the present experiments used a discrete-trial procedure, whereas previous studies used free-operant schedules. It has been suggested that DA manipulations reduce response rates (Salamone, Kurth, McCullough, Sokolowski, & Cousins, 1993). Such a reduction could be expected to be manifested in free-operant schedules, in which the session ends after a predetermined time has elapsed, but to be less evident in discrete-trial procedures, in which the session ends after a predetermined number of trials have been completed.

Experiments 1 and 2 also show that repeated administration of SKF 38393 and haloperidol did not affect performance in the test stage of the post-training signal attenuation procedure, although there was a tendency for reduced extra lever-presses in the SKF 38393 group. In contrast, the repeated administration of SCH 23390 and quinpirole led to an increased number of extra lever-presses and an increased number of uncompleted trials in the test stage. These effects were specific in that there was no parallel

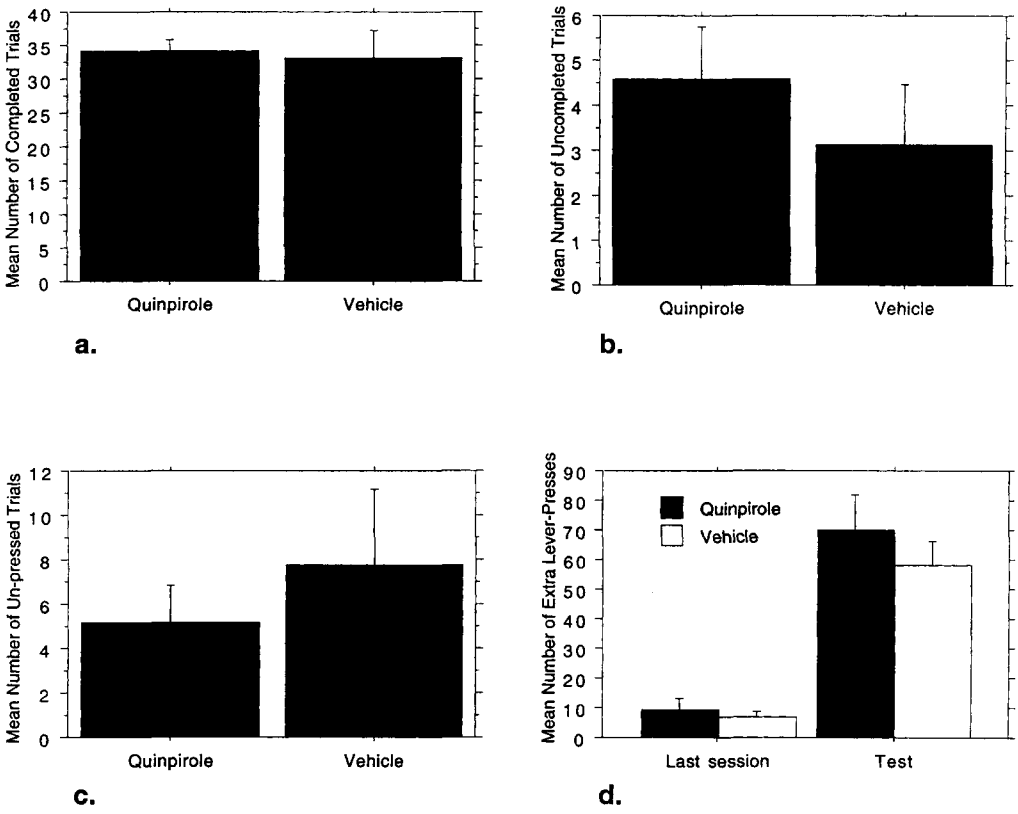

Figure 3. Mean (± *SEM*) number of completed trials (a), uncompleted trials (b), unpressed trials on the test day (c), and extra lever-presses on the last training session and on the test (d) by rats in the vehicle and quinpirole groups, in regular extinction.

increase in lever-pressing on the NRL, and there was no effect on the rate of extinction of the lever-press response (as reflected in the number of completed and unpressed trials). Experiments 3 and 4 show that these effects were not obtained in a regular extinction procedure; thus, neither SCH 23390 nor quinpirole induced an increased number of extra lever-presses or uncompleted trials when the test stage was not preceded by a signal attenuation stage. This suggests that quinpirole and SCH 23390 specifically affected rats' response to signal attenuation. As pointed out in the introduction section, an increased number of extra lever-presses and of uncompleted trials is obtained in intact rats in the test stage only if this stage is preceded by the signal attenuation stage (Joel & Avisar, 2001). Therefore, the exacerbation of this behavioral pattern in the quinpirole and SCH 23390 groups suggests that alteration of the DA system at the test stage, caused by the repeated administration of these drugs, enhanced the rats' reaction to signal attenuation.

We have previously suggested that signal attenuation may provide an analogue to a deficient response feedback mechanism hypothesized to underlie obsessions and compulsions in OCD (Joel & Avisar, 2001). The present findings of enhanced response to signal attenuation after alterations of the DA system may link this hypothesis to findings implicating abnormalities of the DA system in the production of obsessions and compulsions.

Repeated administration of quinpirole has been previously suggested to provide an animal model of the checking compulsions of OCD patients, as it has been shown to induce compulsive and rigid locomotion and repeating motor rituals (Eilam & Szechtman, 1995; Szechtman, Sulis, & Eilam, 1998). Although the dose (0.50 mg/kg sc vs. 0.05 mg/kg ip), treatment regime (twice a week, every day), and time of test relative to drug administration (immediately after quinpirole administration, 96 hr after last quinpirole administration) are different in Szechtman and colleagues' model and in the present procedure, our results combined with theirs suggest that manipulations of the DA system induce a group of compulsive-like behaviors.

The present experiments do not reveal the mechanisms underlying the enhanced response of the SCH 23390 and quinpirole groups to signal attenuation; however, results of studies that assessed alterations in DA function several days after the termination of chronic treatment with dopaminergic agents suggest that this enhanced response is mediated by D_1 rather than D_2 receptors.

Chronic SCH 23390 treatment has been found to increase the density of D_1, but not D_2, receptors in the striatum (Creese & Chen, 1985; Giorgi et al., 1993; Hess, Albers, Le, & Creese, 1986, Hess, Norman, & Creese, 1988; Lappalainen, Hietala, Pohjalainen, & Syvalahti, 1992; Memo et al., 1987; O'Boyle, Gavin, & Harrison, 1993; Porceddu, Ongini, & Biggio, 1985). The enduring effects of chronic treatment with SCH 23390 on striatal DA metabolism are less clear, as such a treatment was reported to decrease DA metabolism in the striatum 16 hr (Koulu, Lappalainen, Pesonen, Hietala, & Syvalahti, 1988; Lappalainen et al.,

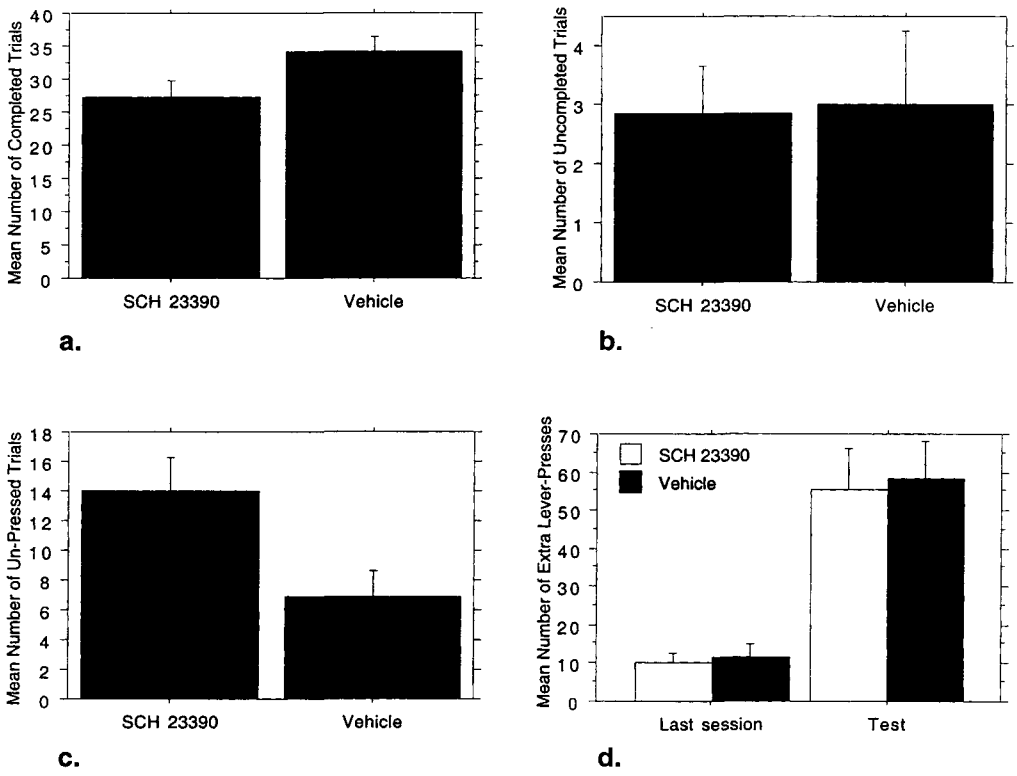

Figure 4. Mean (± *SEM*) number of completed trials (a), uncompleted trials (b), unpressed trials on the test day (c), and extra lever-presses on the last training session and on the test (d) by rats in the vehicle and SCH 23390 groups, in regular extinction.

1990), but not 24 hr (Rowlett, Mattingly, & Bardo, 1995), after the termination of chronic administration. Because the test stage in the present experiment was conducted 96 hr after the last SCH 23390 injection, DA metabolism at that time was probably normal. Therefore, the enhanced behavioral response of the SCH 23390 group may reflect the stimulation of an increased number of D_1 receptors. This is in line with studies demonstrating increased behavioral response to novelty, as well as potentiated behavioral response to a D_1 agonist, several days after the termination of chronic treatment with SCH 23390 (Bijak & Smialowski, 1989; Hess et al., 1986; Smialowski, 1989).

It should be noted that SCH 23390 binds with high affinity to 5-HT_{2A} receptors (Bischoff, Heinrich, Sonntag, & Krauss, 1986), and its chronic administration has been reported to lead to functional supersensitivity of these receptors (Bijak & Smialowski, 1989). However, the dose used in the present experiment (0.05 mg/kg) is thought to be selective for the D_1-class and to avoid the interactions with 5-HT_{2A} receptors found for higher doses (Bischoff et al., 1986; Hess et al., 1986). In addition, Lappalainen et al. (1990) found that chronic administration of SCH 23390 had no effect on serotonin synthesis and metabolism in the raphe nuclei.

Chronic treatment with haloperidol leads to upregulation of striatal D_2, but not D_1, receptors that lasts for days after termination of the chronic treatment (e.g., Ishikane,Kusumi, Matsubara, Matsubara, & Koyama, 1997; Lappalainen et al., 1990; Laruelle et al., 1992; O'Boyle et al., 1993; Porceddu et al., 1985; Szczepanik & Wilmot, 1997). In addition, although chronic haloperidol treatment alters striatal DA release, such changes are not found several days after withdrawal from chronic haloperidol treatment (Wiedemann, Garris, Near, & Wightman, 1992). These findings suggest that the response to signal attenuation was not affected by D_2 receptor overstimulation. Clearly, this suggestion is restricted to the specific dose used here, although, as noted in the Method section, a higher dose of haloperidol abolished lever-pressing during training.

To the best of our knowledge, there are no studies assessing the density of D_1 and D_2 receptors after the termination of chronic quinpirole administration. Studies assessing the behavioral response to quinpirole challenge after such treatment are not conclusive, with some suggesting that chronic stimulation of D_2 receptors leads to behavioral supersensitivity (Sullivan, Talangbayan, Einat, & Szechtman, 1998), and others concluding that it leads to subsensitivity (Braun & Chase, 1988). However, chronic quinpirole treatment results in increased striatal DA release and turnover lasting for several days after drug withdrawal (Rowlett, Mattingly, & Bardo, 1995; Sullivan et al., 1998). Although it is not clear whether such an increase leads to overstimulation, understimulation, or normal stimulation of D_2 receptors, it is likely to result in overstimulation of D_1 receptors. The latter possibility is supported by the finding that chronic quinpirole treatment attenuated catalepsy induced by acute administration of SCH 23390 (Meller, Kuga, Friedhoff, & Goldstein, 1985).

Chronic treatment with SKF 38393 was found not to alter D_1 or D_2 receptor binding (Lappalainen et al., 1992). Such treatment was reported to lead to an initial subsensitivity of the behavioral and electrophysiological response to a challenge dose of SKF 38393, followed by the emergence of supersensitivity 7 days after withdrawal (Hu, Brooderson, & White, 1992; Kelland, Pitts, Freeman, & Chiodo, 1991; Neisewander, Lucki, & McGonigle, 1991; White, Hu, & Brooderson, 1990). As pointed out by Hu et al. (1992), both the dose used and the withdrawal period seem to be critical in determining whether the behavioral response to subsequent stimulation of D_1 receptors would be enhanced or depressed. The dose used in the present experiment (10 mg/kg daily) was lower and the withdrawal period (4 days) shorter than those reported to induce supersensitivity. The tendency toward reduction in extra lever-presses in the SKF 38393 group may even suggest subsensitivity of the behavioral response to D_1 stimulation at the test stage. It is clear that testing with additional doses of SKF 38393 is needed before firm conclusions regarding its effects in the signal-attenuation procedure can be reached.

The suggestion that the enhanced response to signal attenuation in the SCH 23390 and quinpirole groups is mediated by altered functioning of D_1 receptors, and specifically their overstimulation, is in line with the view that D_1 receptors play a more important role than D_2 receptors in the mechanisms by which unconditioned and conditioned rewards control behavior (for reviews, see Beninger & Miller, 1998; Sutton & Beninger, 1999). The present results point to another aspect of the involvement of dopaminergic mechanisms in the control of behavior by conditioned stimuli (CSs). Thus, whereas the involvement of D_1 receptors in mediating the effects of conditioned reinforcement was based on analysis of drug effects on the ability of CSs to support the acquisition of new operant responses (Sutton & Beninger, 1999), the post-training signal-attenuation procedure assesses the ability of CSs to inhibit the emission of already-learned responses once they have attained their goal, as signaled by the appearance of the CS. Viewed in this way, the present results suggest that, whereas learning of new responses depends on stimulation of D_1 receptors (Sutton & Beninger, 1999), such stimulation attenuates the ability of CSs to inhibit already-learned responses.

The latter suggestion is in line with Gratton and colleagues' (Kiyatkin & Gratton, 1994; Richardson & Gratton, 1996) conclusion that rewards produce some of their behavioral effects as a consequence of suppressing activation of DA neurons by conditioned incentives. It may therefore be suggested that mirror processes take place during the acquisition of a new response and the routine performance of a well-learned response. Although in both cases the successful completion of the response leads to the appearance of a CS, in the former case such appearance is accompanied by an increase in DA, and as a result, the preceding response is strengthened (i.e., is more likely to occur again under similar conditions), whereas in the latter case, the appearance of the CS is accompanied by a decrease in DA, and as a result, the emission of the preceding response is inhibited. Both the increase in DA and the resultant reinforcement of behavior, and the decrease in DA and the resultant inhibition of behavior, however, are mediated by D_1 receptors.

The present results may also shed light on the mechanism underlying the induction of excessive lever-pressing by signal attenuation in intact rats. It is possible that the signal attenuation stage reduces the ability of the CS to inhibit DA release. As a result, in the test stage, there is a smaller decrease in DA after the presentation of the stimulus, leading to reduced inhibition of the lever-press response and therefore to its excessive emission. Whether this is indeed the underlying mechanism, and whether a similar alteration contributes to the emission of excessive behaviors in OCD patients in the form of obsessions and compulsions, remains to be elucidated.

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