'Compulsive' lever-pressing in rats is attenuated by the serotonin re-uptake inhibitors paroxetine and fluvoxamine but not by the tricyclic antidepressant desipramine or the anxiolytic diazepam

D. Joel, E. Ben-Amir, J. Doljansky and S. Flaisher

Rats undergoing extinction of lever-pressing for food after the attenuation of an external feedback for this behavior, exhibit excessive lever-pressing unaccompanied by an attempt to collect a reward, which may be analogous to the excessive and unreasonable behavior seen in obsessive–compulsive disorder (OCD). Given that one of the most salient features of OCD is its selective response to treatment with serotonin re-uptake inhibitors (SRIs), the present study compared the effects of the SRIs paroxetine and fluvoxamine on compulsive lever-pressing, with those of the tricyclic antidepressant, desipramine, and the benzodiazepine, diazepam, which are not effective in the treatment of OCD. Paroxetine (1–15 mg/kg) and fluvoxamine (10–20 mg/kg) dose-dependently reduced the number of compulsive lever-presses and the number of lever-presses followed by an attempt to collect a reward; desipramine (5–15 mg/kg) dose-dependently reduced only the number of lever-presses followed by an attempt to collect a reward; diazepam (2–10 mg/kg) did not affect either type of lever-pressing, except for the highest dose (10 mg/kg), which almost completely abolished lever-press responding. When administered in an extinction session not preceded by signal attenuation, paroxetine, fluvoxamine and desipramine affected only the number of lever-presses followed by an attempt to collect a reward, whereas diazepam (4–8 mg/kg) decreased both types of lever-presses. The present findings strengthen the suggestion that compulsive lever-pressing may serve to model compulsive behavior in OCD, and lends the model predictive validity. *Behavioural Pharmacology* 15:241–252 © 2004 Lippincott Williams & Wilkins.

Behavioural Pharmacology 2004, **15**:241–252

Keywords: animal model, OCD (obsessive–compulsive disorder), post-training signal attenuation, extinction, lever-press, rat

Department of Psychology, Tel Aviv University, Tel Aviv, Israel.

Sponsorship: This research was supported by the Israel Science Foundation (grant No. 942/01-1).

Correspondence and requests for reprints to D. Joel, Department of Psychology, Tel Aviv University, Ramat-Aviv, Tel Aviv 69978, Israel.
E-mail: djoel@post.tau.ac.il

Received 25 November 2003 **Accepted as revised** 25 April 2004

Introduction

Obsessive–compulsive disorder (OCD) is a psychiatric affliction with a lifetime prevalence of 1–3% (Rasmussen and Eisen, 1992; Sasson *et al.*, 1997). According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV) (American Psychiatric Association, 1994), the essential features of OCD are recurrent obsessions or compulsions (e.g. doubting, checking, washing).

Most current animal models of OCD can be divided into two classes, ethological and pharmacological. The former includes naturally occurring repetitive or stereotypic behaviors, such as tail chasing, fur chewing, weaving, etc. (reviewed by Winslow and Insel, 1991; Stein *et al.*, 1994); innate motor behaviors that occur during periods of conflict or stress (displacement behaviors), such as grooming, cleaning and pecking (reviewed by Ricciardi and Hurley, 1990; Pitman, 1991; Winslow and Insel, 1991); and natural behaviors that occur following some behavioral manipulations, such as schedule-induced polydipsia (Woods *et al.*, 1993) and food restriction-induced hyperactivity (Altemus *et al.*, 1996). Pharmacological models are based on drug-induced behavioral alterations which bear similarity to some specific characteristics of the behavior of humans diagnosed with OCD, such as perseveration and indecision (Yadin *et al.*, 1991), or compulsive checking (Eilam and Szechtman, 1995; Szechtman *et al.*, 1998).

We (Joel and Avisar, 2001) have recently developed a new animal model of OCD, the signal attenuation model, on the basis of the theoretical proposition that compulsive behaviors result from a deficit in the feedback associated with the performance of normal goal-directed responses (e.g. Reed, 1977; Gray, 1982; Malloy, 1987; Pitman, 1987, 1991; Baxter, 1999; Szechtman and Woody, 2004; reviewed by Otto, 1992). In the model, the goal-directed behavior is lever-pressing for food. We utilize the following strategy to manipulate the feedback associated with making a response. Rats are first trained to lever-press for food, delivery of which is accompanied by a stimulus that previously had been paired with food. In

0955-8810 © 2004 Lippincott Williams & Wilkins DOI: 10.1097/01.fbp.0000132925.81402.0a

this manner the stimulus is established as a feedback cue which signals that the lever-press response was effective in producing food. The 'signaling' property of the stimulus is then attenuated by repeatedly presenting the stimulus without food (without the rat emitting the lever-press response). Finally, the effects of signal attenuation on lever-press responding are assessed under extinction conditions, that is, pressing the lever results in the presentation of the stimulus but no food is delivered.

We showed that during this last, test, stage, rats exhibit a period of excessive lever-pressing which is not accompanied by an attempt to collect a reward. The cessation of the attempts to collect a reward, which indicates that the rat detected the change in response consequences, combined with the increased emission of the lever-press response, makes the operant behavior both excessive and 'inappropriate' or 'unreasonable', thus fulfilling two important criteria of compulsive behavior (Reed, 1985; Rapoport, 1989; American Psychiatric Association, 1994). In our first paper (Joel and Avisar, 2001), compulsive responding was assessed indirectly using the correlation between the number of excessive lever-presses and the number of trials in which no attempt was made to collect a reward (uncompleted trials). In later studies (Joel and Doljansky, 2003; Joel *et al.*, 2004), as well as in the present study, we measured compulsive lever-pressing directly by scoring the number of excessive lever-presses that are not followed by an attempt to collect a reward, i.e. the number of excessive lever-presses in uncompleted trials (ELP-U).

Since one of the most salient features of OCD is its selective response to treatment with serotonin re-uptake inhibitors (SRIs) (Zohar *et al.*, 1992; Piccinelli *et al.*, 1995; Stein *et al.*, 1995; Masand and Gupta, 1999; Pigott and Seay, 1999), animal models of this disorder should show the same selective pharmacological response. We have shown previously that compulsive responding is abolished by the SRI fluoxetine but not by the anxiolytic drug, diazepam (Joel and Avisar, 2001), which has been shown not to be effective in alleviating obsessions and compulsions in OCD patients (Cassano *et al.*, 1975; Waxman, 1977; Montgomery, 1993; Kim *et al.*, 1997; Argyropoulos *et al.*, 2000; Stein, 2002). The aim of the present study was to further establish the pharmacological selectivity of the model by testing the effects of two additional SRIs routinely used for the treatment of OCD, namely, paroxetine and fluvoxamine (reviewed by Piccinelli *et al.*, 1995; Stein *et al.*, 1995; Goodman *et al.*, 1997; Gunasekara *et al.*, 1998; Masand and Gupta, 1999; Pigott and Seay, 1999; Figgitt and McClellan, 2000; Bourin *et al.*, 2001; Cheer and Figgitt, 2001), a tricyclic antidepressant, desipramine, a noradrenaline reuptake inhibitor which has been shown not to be effective in treating OCD patients (Leonard and Rapoport, 1989; Leonard *et al.*, 1989; Goodman *et al.*, 1990b; Piccinelli *et al.*, 1995; Hoehn-Saric *et al.*, 2000), and additional doses of diazepam.

Our main prediction was that paroxetine and fluvoxamine, but not desipramine and diazepam, would reduce compulsive responding seen after signal attenuation. However, since the effects of signal attenuation on rats' lever-press responding are assessed under extinction conditions, drug manipulations may be expected to affect other behaviors typical to extinction (e.g. extinction burst). This is certainly the case with regard to desipramine and diazepam, as tricyclics and benzodiazepines have been reported, respectively, to facilitate and retard extinction (Soubrie *et al.*, 1978; Feldon and Gray, 1981; Telegdy *et al.*, 1983; Thiebot *et al.*, 1983; McNaughton, 1984; Halevy *et al.*, 1986; Cowie *et al.*, 1987; Kikusui *et al.*, 2001). No comparable information is available for paroxetine and fluvoxamine, because, to the best of our knowledge, the effects of SRIs on extinction have not been investigated. In order to better differentiate between the effects of each drug on the behavioral response to signal attenuation and on extinction *per se*, drug doses that were effective in the post-training signal attenuation procedure were tested in an extinction session that was not preceded by signal attenuation (we refer to the behavioral procedure that is identical to the post-training signal attenuation procedure but does not include a signal attenuation stage, as 'regular extinction'). We expected that: (1) only the therapeutic drugs would affect 'compulsive' responding; and (2) drugs' effects on 'compulsive' responding would be apparent in the post-training signal attenuation procedure only, whereas drugs' effects on behavioral measures of extinction would be similar in the post-training signal attenuation and the regular extinction procedures.

Methods

Subjects

Male Wistar rats (Tel Aviv University, Sackler Faculty of Medicine, Israel), approximately 4 months old, weighing 400–500 g, were housed four to a cage under a reversed 12-h light-dark cycle (lights on 19.00 to 07.00 hours). Rats were maintained on a 22-h 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%. All experimental protocols were carried out according to the guidelines of the Institutional Animal Care and Use Committee of Tel Aviv University.

Apparatus

The apparatus and behavioral procedure have been described in detail elsewhere (Joel and Doljansky, 2003). Behavioral testing was conducted in four operant

chambers (Campden Instruments, Loughborough, UK), housed in sound-attenuated boxes and equipped with a 3 W house light, a Sonalert module (Model SC 628) that could produce an 80 dB, 2.8 kHz tone, and two retractable levers on either side of a food magazine (fitted with a 3 W magazine light), into which 45 mg Noyes precision food pellets (Noyes, Sandown Chemical Limited, Hampton, England) could be delivered. Access to the food magazine was through a hinged panel, the opening of which activated a micro-switch. Equipment programming and data recording were computer controlled.

Procedure

Prior to the beginning of the experiment, rats were handled for about 2 min daily for 5 days. A 22-hour food restriction schedule began simultaneously with handling and continued throughout behavioral testing. Food was provided in the home cage between 14.00 and 16.00 hours, 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 after each rat was observed to consume at least two pellets.

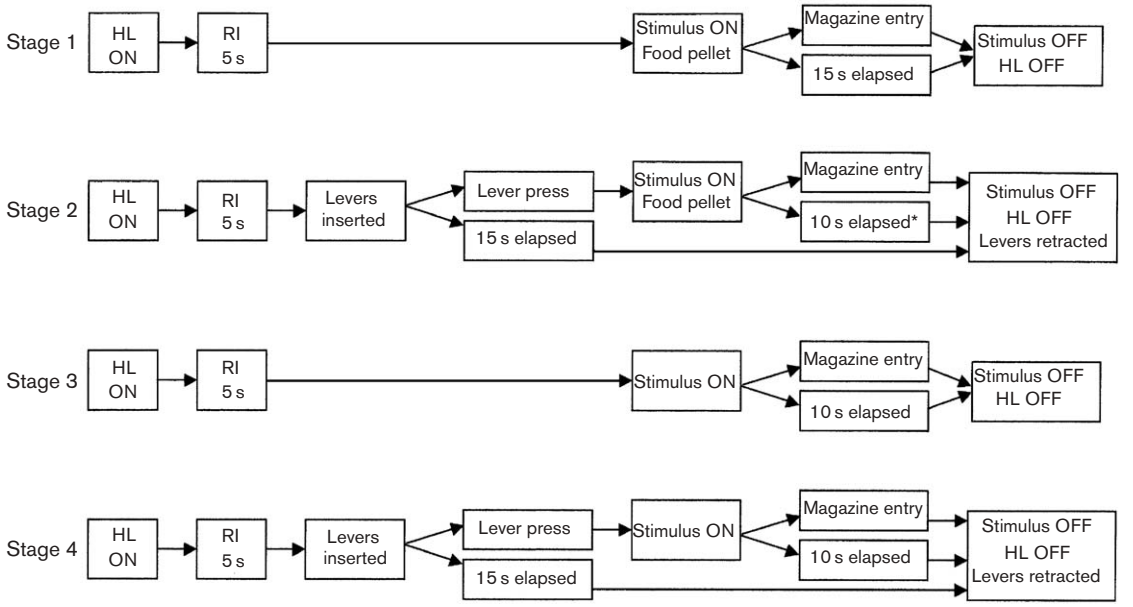
Post-training signal attenuation

The post-training signal attenuation procedure included four stages:

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 each trial, a single food pellet was dropped into the food magazine, simultaneously with the onset of a compound stimulus consisting of the magazine light and the tone. The compound stimulus was turned off after the rat's head entered the food magazine or after 15-s had elapsed, and a 30-s intertrial interval began (for more details see Fig. 1). On each day, each rat was trained until it completed 30 trials in which it inserted its head into the food magazine during stimulus presentation (collected trials), or until a total of 40 trials was reached. The number of collected trials and the total number of trials were recorded.

Stage 2: Lever-press training. On Days 4–6, rats were trained to lever-press in a discrete-trial procedure. On each trial, both levers were inserted into the chamber. Responding on one of the levers (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 was turned off, after the rat's head entered the food magazine or after 15-s had elapsed from the rat's first lever-press (see Fig. 1). Further lever-presses on the RL as well as 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

Fig. 1



A schematic diagram of the organization of a trial in each of the different training stages of the post-training signal attenuation procedure. HL, houselight; RI, random interval; * on the first day of lever-press training (Day 4) this time limit was 15 s.

the lever and inserted its head into the food magazine during stimulus presentation, or for a total of 60 trials. 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. Those that did not attain at least 20 completed trials in the second session were excluded from the experiment. On Days 5 and 6, all rats were trained as on Day 4, except that the compound stimulus was turned off after 10 s instead of after 15-s and training ended when the rat had attained 40 completed trials or for a total of 60 trials.

In order to assess acquisition of the lever-press response, the number of trials on which the rat did not press the RL (unpressed trials) and the number of trials on which the rat pressed the RL without inserting its head into the food magazine (uncompleted trials) were recorded, in addition to the number of completed trials. In order to assess the rat's tendency for excessive lever-pressing, the number of lever-presses on the NRL, and the number of lever-presses on the RL after the first response (extra lever-presses, ELP) were recorded. The latter measure was further subdivided into ELP in uncompleted trials (that is, ELP not followed by insertion of the head into the food magazine; ELP-U), and ELP in completed trials (ELP-C).

Stage 3: Signal attenuation. On Days 7–9, 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 (see Fig. 1). Rats received 30 such trials on each day, and the number of collected trials was recorded. Rats that had more than 15 collected trials on Day 9 were returned to the test chamber at the end of the day for an additional session. Rats were randomly assigned to the different experimental groups at the end of this stage.

Stage 4: Test. On Day 10, rats were trained as in the lever-press training stage, except that no food was delivered to the food magazine, that is, pressing the lever resulted in the presentation of the compound stimulus only (see Fig. 1). The session lasted for 50 trials. The behavioral measures recorded were the same as in the lever-press training stage. Compulsive lever-pressing is operationally defined as the number of ELP-U in the test stage of the post-training signal attenuation procedure.

Regular extinction

Rats were run exactly as in the post-training signal attenuation procedure, with the exception that they did not undergo the signal attenuation stage on Days 7–9. On these days, 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.

Drug administration

In order to assess systematically the effects of paroxetine, fluvoxamine, desipramine and diazepam on compulsive lever-pressing, several doses were tested for each drug, ranging from low doses that had no effect on behavior, to high doses that almost abolished lever-press responding. Doses were selected on the basis of previous studies that tested the behavioral effects of these drugs (e.g. Thiebot *et al.*, 1983; Sanchez and Meier, 1997; Cryan *et al.*, 1998; Sokolowski and Seiden, 1999). However, when, at such doses, a drug was found to have no effect on responding in the test stage (diazepam) or to almost completely abolish lever-pressing (paroxetine), additional doses were tested. For assessing drug effects in regular extinction, drug doses that were effective in the post-training signal attenuation procedure without completely abolishing lever-press responding were selected. Drugs were administered i.p. in a volume of 2 ml/kg (fluvoxamine, desipramine, diazepam) or 1 ml/kg (paroxetine), 30 min (paroxetine, fluvoxamine, diazepam) or 60 min (desipramine) before the beginning of the test stage. Paroxetine (Unipharm, Ramat-Gan, Israel) was dissolved in distilled water to a dose of 1, 3, 5, 7, 10 and 15 mg/kg. Fluvoxamine (Agis, Israel) was dissolved in distilled water to a dose of 10, 15 and 20 mg/kg. Desipramine (Sigma, Israel) was dissolved in saline to a dose of 5, 10 and 15 mg/kg. Diazepam (Tiferet Hacarmel, Israel) was diluted in saline with a few drops of Tween 80 to a dose of 2, 3, 4, 6, 8 and 10 mg/kg. No-drug controls received an equivalent volume of the corresponding vehicle.

Statistical analysis

Rats' performance in the test stage was analyzed using analysis of variance (ANOVA), with a main factor of Dose, performed on the number of ELP-C and ELP-U. Significant Dose effects were followed by analysis of the linear trend component of the ANOVA and by *post-hoc* least significant difference (LSD) comparisons comparing each of the drug-treated groups with the vehicle group. For all comparisons, significance was assumed at $P < 0.05$. For experiments run in several replications (Experiments 1, 3, 4 and 7 were run in two partially or completely overlapping replications each; Experiment 6 was run in three partially overlapping replications), data of the overlapping groups were analyzed using ANOVAs with Replication and Dose as main factors. Because in the five experiments, the effect of Replication and the Replication $\times$ Dose interaction in these analyses were not significant, data from different replications were combined.

Although drugs were administered only prior to the test stage, performance in the lever-press training and signal attenuation stages was also analyzed, to ensure that differences in performance at the test stage were not a result of an earlier difference. The former was analyzed using ANOVA, with a main factor of Dose, performed on

the number of ELP-C during the last day of lever-press training (the variability of the other variables was too low to enable statistical analysis, as all rats achieved 40 completed trials with no uncompleted trials and therefore with no ELP-U, and most rats had no unpressed trials). Performance in the signal attenuation stage was analyzed using ANOVA, with a main factor of Dose, performed on the number of collected trials (i.e. a trial on which the rat performed magazine entry during stimulus presentation) during the last session of the signal attenuation stage.

Results

Table 1 presents the number of rats allocated to each experiment, the number of rats that were excluded from each experiment, the doses used, and the final number of rats in each group.

Experiment 1: The effects of 1, 3, 5, 7, 10 and 15 mg/kg paroxetine in post-training signal attenuation

There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown). In the test, paroxetine dose-dependently decreased the number of ELP-C (Fig. 2A) and ELP-U (Fig. 2B), with 1 mg/kg paroxetine having no effect; 3, 5 and 7 mg/kg paroxetine decreasing the number of ELP-C and of ELP-U; and 10 and 15 mg/kg almost completely abolishing extra lever-presses. ANOVAs yielded a significant main effect of Dose on the two measures [ELP-C, $F(6,66) = 7.69$, $P < 0.001$; ELP-U, $F(6,66) = 4.40$, $P < 0.001$] as well as a significant linear trend of Dose [ELP-C, $F(1,66) = 36.05$, $P < 0.001$; ELP-U, $F(1,66) = 18.36$, $P < 0.001$] (see Fig. 2 for results of *post-hoc* comparisons).

Experiment 2: The effects of 3 and 7 mg/kg paroxetine in regular extinction

Of the doses of paroxetine tested in the post-training signal attenuation procedure, three (3, 5 and 7 mg/kg) were effective in reducing ELP-U, without completely abolishing lever-press responding. As the three doses had a similar effect in post-training signal attenuation, the effects of only the highest (7 mg/kg) and the lowest (3 mg/kg) dose were assessed in regular extinction.

There were no differences between the groups at the lever-press training stage (data not shown). In the test, the lower dose of paroxetine was without effect, whereas the higher dose reduced the number of ELP-C (Fig. 3A) without affecting the number of ELP-U (Fig. 3B). ANOVAs indicated a significant main effect of Dose

Table 1 Summary of experiments

Exp	Drug	Procedure	Number of rats in experiment	Number of rats excluded[a]	Dose (mg/kg)	Final *n* per group
1	Paroxetine	Signal attenuation	80	6, acquisition failure; 1, statistical	Vehicle	20
					1	7
					3	8
					5	15
					7	8
					10	7
					15	8
2	Paroxetine	Regular extinction	24	3, acquisition failure; 1, statistical	Vehicle	6
					3	7
					7	7
3	Fluvoxamine	Signal attenuation	59	1, acquisition failure; 4, statistical	Vehicle	13
					10	13
					15	14
					20	14
4	Desipramine	Signal attenuation	65	4, acquisition failure; 2, illness; 2, statistical	Vehicle	17
					5	13
					10	13
					15	14
5	Fluvoxamine, desipramine	Regular extinction	32	1, statistical	Vehicle	10
					Fluvoxamine	11
					Desipramine	10
6	Diazepam	Signal attenuation	84	5, acquisition failure; 2, illness; 6, statistical	Vehicle	16
					2	9
					3	10
					4	13
					6	9
					8	7
					10	7
7	Diazepam	Regular extinction	49	1, acquisition failure; 1, illness; 2, computer failure; 3, statistical	Vehicle	14
					2	6
					4	7
					6	8
					8	7

[a]Acquisition failure: rats were excluded if they needed another session on the first day of lever-press training (Day 4) and did not attain the criterion of 20 completed trails in the second session.
Statistical: rats were excluded if their score on at least one variable was more than 4 standard deviations above their group mean.

and a significant linear trend of Dose on the number of ELP-C [$F(2,17) = 4.55$, $P < 0.05$; $F(1,17) = 5.43$, $P < 0.05$, respectively], whereas the effect of Dose on the number of ELP-U was not significant [$F(2,17) = 0.837$, NS].

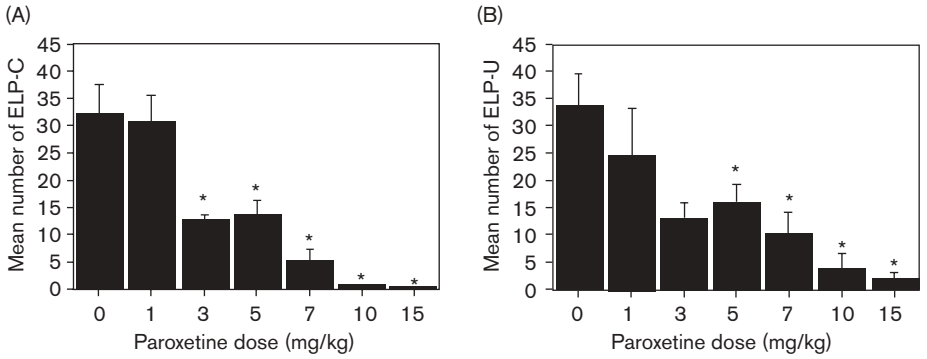
Experiment 3: The effects of 10, 15 and 20 mg/kg fluvoxamine in post-training signal attenuation

There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown). In the test, fluvoxamine dose-dependently decreased the number of ELP-C (Fig. 4A) and the number of ELP-U (Fig. 4B), with 10 mg/kg fluvoxamine having no effect, 15 mg/kg fluvoxamine decreasing the number of ELP-C and of ELP-U, and 20 mg/kg almost completely abolishing extra lever-presses. ANOVAs yielded a significant Dose effect on the two measures [ELP-C, $F(3,50) = 4.68$, $P < 0.01$; ELP-U, $F(3,50) = 3.50$, $P < 0.05$], as well as a significant linear trend of Dose [ELP-C, $F(1,50) = 14.02$, $P < 0.001$; ELP-U, $F(1,50) = 10.48$, $P < 0.005$) (see Fig. 4 for results of *post-hoc* comparisons).

Experiment 4: The effects of 5, 10 and 15 mg/kg desipramine in post-training signal attenuation

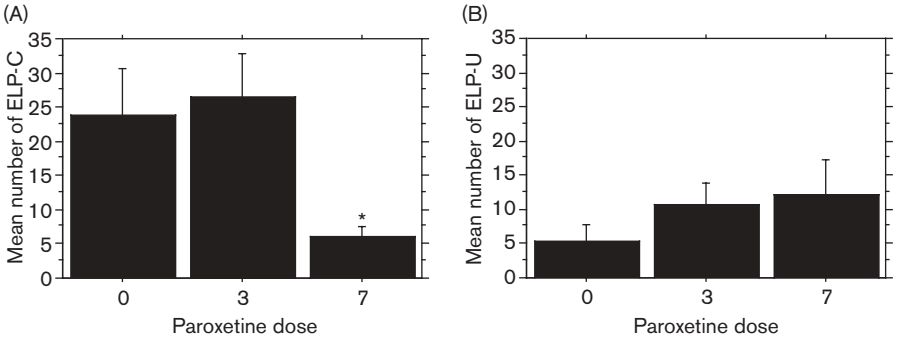
There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown). In the test, desipramine dose-dependently decreased the number of ELP-C [Fig. 5A; main effect of Dose, $F(3,53) = 6.73$, $P < 0.001$; linear trend of Dose,

Fig. 2



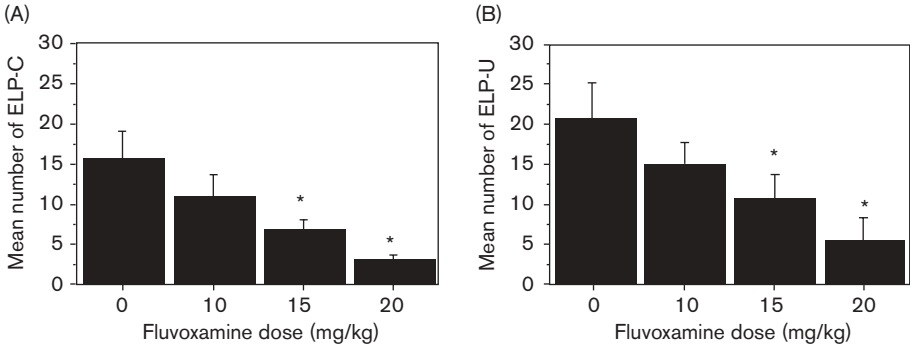
Mean and standard error of the mean number of extra lever-presses that (A) were followed by magazine entry (extra lever-presses in completed trials; ELP-C) and (B) that were not followed by magazine entry (extra lever-presses in uncompleted trials; ELP-U) of rats treated with vehicle or 1, 3, 5, 7, 10 or 15 mg/kg paroxetine on the test day of the post-training signal attenuation procedure (Experiment 1). *, Significantly different from the vehicle group ($P < 0.05$).

Fig. 3



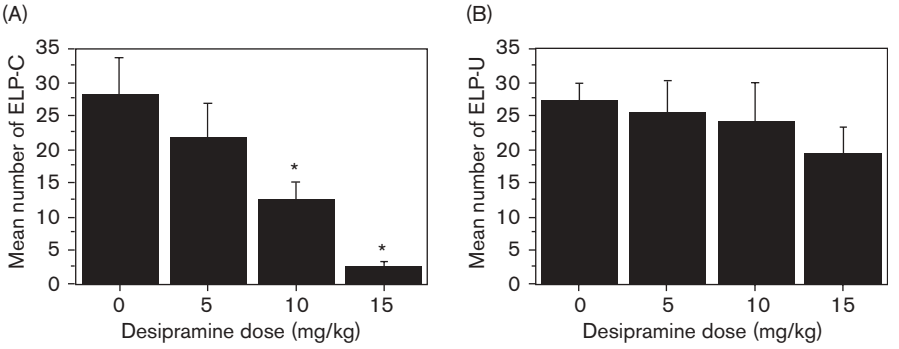
Mean and standard error of the mean number of (A) extra lever-presses in completed trials (ELP-C) and (B) extra lever-presses in uncompleted trials (ELP-U) of rats treated with vehicle or 3 or 7 mg/kg paroxetine on the test day of the regular extinction procedure (Experiment 2). *, Significantly different from the vehicle group ($P < 0.05$).

Fig. 4



Mean and standard error of the mean number of (A) extra lever-presses in completed trials (ELP-C) and (B) extra lever-presses in uncompleted trials (ELP-U) of rats treated with vehicle, 10, 15 or 20 mg/kg fluvoxamine on the test day of the post-training signal attenuation procedure (Experiment 3). *, Significantly different from the vehicle group ($P<0.05$).

Fig. 5



Mean and standard error of the mean number of (A) extra lever-presses in completed trials (ELP-C) and (B) extra lever-presses in uncompleted trials (ELP-U) of rats treated with vehicle, 5, 10 or 15 mg/kg desipramine on the test day of the post-training signal attenuation procedure (Experiment 4). *, Significantly different from the vehicle group ($P<0.05$).

$F(1,53) = 20.15$, $P < 0.001$; see Fig. 5 for results of *post-hoc* comparisons), but had no effect on the number of ELP-U (Fig. 5B; $F < 1$).

Experiment 5: The effects of 15 mg/kg fluvoxamine and 10 mg/kg desipramine in regular extinction

Of the doses of fluvoxamine and desipramine tested in the post-training signal attenuation procedure, the lowest dose tested had only a mild effect whereas the highest dose tested greatly reduced lever-pressing in general. We therefore assessed the effects of the intermediate dose of each drug in regular extinction.

There were no differences between the groups at the lever-press training stage (data not shown). In the test, both fluvoxamine and desipramine significantly reduced the number of ELP-C [Fig. 6A; $F(2,28) = 5.43$, $P < 0.05$, see Fig. 6 for results of *post-hoc* comparisons], while having no effect on the number of ELP-U (Fig. 6B; $F < 1$), although desipramine tended to increase this measure.

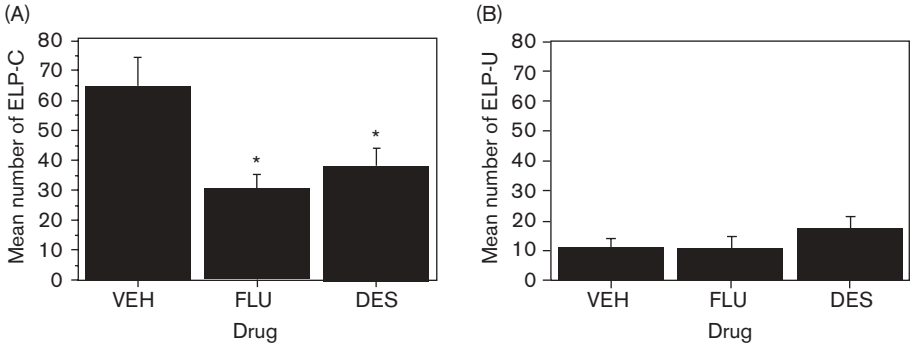
Experiment 6: The effects of 2, 3, 4, 6, 8 and 10 mg/kg diazepam in post-training signal attenuation

There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown). In the test, diazepam dose-dependently decreased the number of ELP-C (Fig. 7A), and the number of ELP-U (Fig. 7B), although the latter effect did not reach statistical significance [ELP-C, main effect of Dose, $F(6,64) = 2.36$, $P < 0.05$, linear trend of Dose, $F(1,64) = 9.16$, $P < 0.005$; ELP-U, main effect of Dose, $F(6,64) = 2.02$, $P = 0.075$).

Experiment 7: The effects of 2, 4, 6 and 8 mg/kg diazepam in regular extinction

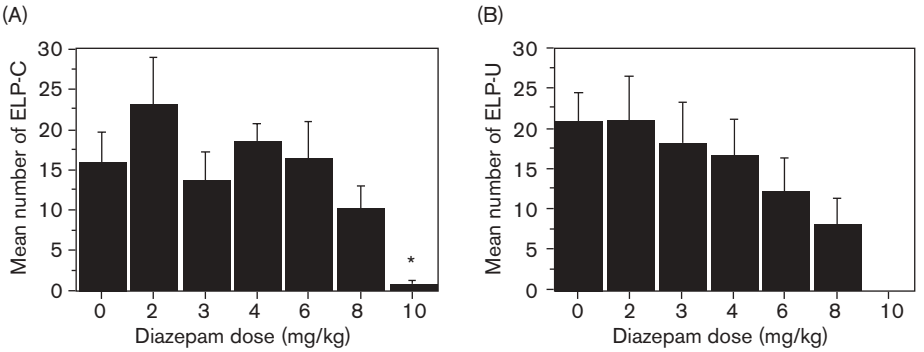
In contrast to reports in the literature on the effects of diazepam on extinction (see Discussion), only the highest doses (8 and 10 mg/kg) of this drug affected performance in post-training signal attenuation. We therefore tested the effects of diazepam on regular extinction using a range of doses (2–8 mg/kg).

Fig. 6



Mean and standard error of the mean number of (A) extra lever-presses in completed trials (ELP-C) and (B) extra lever-presses in uncompleted trials (ELP-U) of rats treated with vehicle (VEH), 15 mg/kg fluvoxamine (FLU) or 10 mg/kg desipramine (DES) on the test day of the regular extinction procedure (Experiment 5). *, Significantly different from the vehicle group ($P<0.05$).

Fig. 7



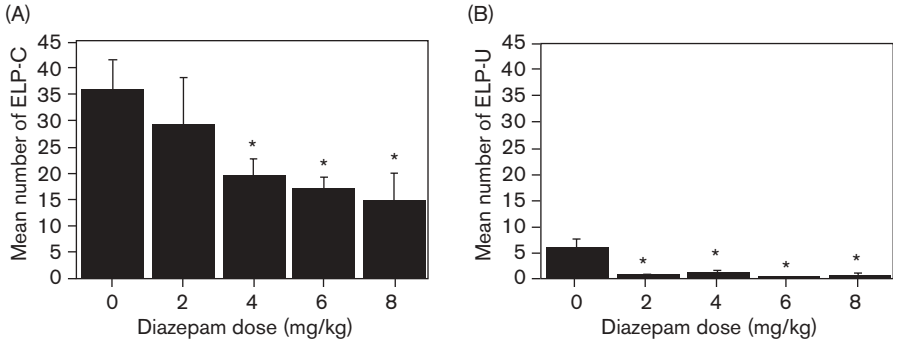
Mean and standard error of the mean number of (A) extra lever-presses in completed trials (ELP-C) and (B) extra lever-presses in uncompleted trials (ELP-U) of rats treated with vehicle or 2, 3, 4, 6, 8 or 10 mg/kg diazepam on the test day of the post-training signal attenuation procedure (Experiment 6). *, Significantly different from the vehicle group ($P<0.05$).

There were no differences between the groups at the lever-press training stage (data not shown). In the test, diazepam decreased the number of ELP-C and of ELP-U (Fig. 8). ANOVAs indicated a significant main effect of Dose on the number of ELP-C [$F(4,37) = 3.05$, $P < 0.05$], and on the number of ELP-U [$F(4,37) = 3.05$, $P < 0.05$], as well as a significant linear trend of Dose on these measures [ELP-C, $F(1,37) = 9.75$, $P < 0.005$; ELP-U, $F(1,37) = 5.01$, $P < 0.05$] (see Fig. 8 for results *of post-hoc* comparisons).

Discussion

The aim of the present study was to test whether the behavior induced by signal attenuation is affected by drugs that are effective, but not by drugs that are ineffective, in the treatment of OCD. As noted in the Introduction, the fact that the effects of signal attenuation on lever-press responding are assessed under extinction conditions may confound the assessment of the effects of signal attenuation, because an encounter of non-reward produces an increase in operant responding (i.e. an extinction burst). This effect of non-reward was indeed seen in an extinction session not preceded by signal attenuation, namely, in the test stage of the 'regular extinction' procedure (Experiments 2, 5 and 7), in the form of a high number of excessive lever-presses that were followed by magazine entry (ELP-C). Such a behavior was also exhibited by rats that underwent signal attenuation prior to the extinction test (Experiments 1, 3, 4 and 6), but these rats showed in addition an equally high number of lever-presses that were not followed by magazine entry (i.e. ELP-U). The different patterns of lever-presses displayed in the two procedures suggest

Fig. 8



Mean and standard error of the mean number of (A) extra lever-presses in completed trials (ELP-C) and (B) extra lever-presses in uncompleted trials (ELP-U) of rats treated with vehicle or 2, 4, 6 or 8 mg/kg diazepam on the test day of the regular extinction procedure (Experiment 7). *, Significantly different from the vehicle group ($P<0.05$).

that in a test stage conducted after signal attenuation, ELP-C reflect rats' response to encountering non-reward, whereas ELP-U reflect rats' response to encountering an attenuated signal.

This hypothesis, derived at the behavioral level, seems to be supported by the different patterns of drug effects on ELP-C and on ELP-U in the two procedures. Administration of the SRIs paroxetine (1, 3, 5, 7, 10 and 15 mg/kg) and fluvoxamine (10, 15 and 20 mg/kg), prior to an extinction session of lever-press responding that was preceded by signal attenuation, resulted in a dose-dependent decrease in the number of ELP-U as well as in the number of ELP-C. When administered prior to an extinction session not preceded by signal attenuation (i.e. regular extinction of lever-press responding), paroxetine and fluvoxamine decreased the number of ELP-C without affecting the number of ELP-U.

The tricyclic antidepressant desipramine had a similar effect on rats' lever-press responding, regardless of whether lever-press extinction was preceded by a signal attenuation stage or not: in both procedures, the drug decreased the number of ELP-C, while having no effect on the number of ELP-U.

Diazepam affected rats' behavior in the post-training signal attenuation procedure only at the highest doses tested, with 8 mg/kg tending to decrease the number of ELP-C and of ELP-U, and 10 mg/kg almost completely abolishing lever-press responding (doses between 2 and 6 mg/kg had no effect on ELP-C and ELP-U). Diazepam exerted similar effects when administered prior to an extinction session not preceded by signal attenuation, albeit at lower doses. Thus, already diazepam significantly decreased the number of ELP-C at a dose of 4 mg/kg, and almost completely abolished ELP-U at all doses tested.

The finding that each of the four drugs decreased the number of ELP-C in both procedures (post-training signal attenuation and regular extinction), supports the suggestion that ELP-C reflect rats' response to encountering non-reward in the extinction test. To the best of our knowledge, there have been no studies on the effects of SRIs on extinction. Similarly, there have been no studies on the effects of acute administration of desipramine on extinction, and studies using chronic regimens of desipramine administration have reported conflicting effects on the extinction of lever-press responding (Willner *et al.*, 1981; Willner and Towell, 1982; Lucki and Frazer, 1985). Other tricyclic antidepressants have been reported to facilitate extinction of active avoidance and of fear-induced ultrasonic vocalization following acute administration (Telegdy *et al.*, 1983; Kikusui *et al.*, 2001). It may therefore be speculated that the decrease in ELP-C following administration of the three antidepressants (paroxetine, fluvoxamine and desipramine) may reflect facilitated extinction of lever-press responding or attenuated extinction burst. It is less clear whether the decrease in ELP-C following diazepam administration also reflects facilitated extinction, because diazepam at low doses (2–4 mg/kg), as well as other anxiolytic drugs, has been typically reported to retard, rather than facilitate, the extinction of a variety of Pavlovian and operant behaviors (e.g. Soubrie *et al.*, 1978; Feldon and Gray, 1981; McNaughton, 1984; Halevy *et al.*, 1986; Cowie *et al.*, 1987), including lever-pressing for a food reward (Thiebot *et al.*, 1983). It is possible that the reduction in ELP-C obtained in the present study with higher diazepam doses (not previously tested in extinction), reflects the sedative effects of the drug (Giorgetti

et al., 1998; Griebel *et al.*, 1999; Rimondini *et al.*, 2002), which include decreasing the rate of reinforced operant behavior (Shannon and Katzman, 1986; Yang *et al.*, 1988). This may also account for the lack of effect of 2–4 mg/kg diazepam in the present study, as procedural differences may have made our task more sensitive to its sedative effects.

In contrast to the similar pattern of drug effects on ELP-C in the two procedures, the different drugs exerted different effects on the number of ELP-U, depending on the procedure used. Specifically, the two SRIs reduced the number of ELP-U in post-training signal attenuation but not in regular extinction; desipramine did not affect ELP-U in either procedure; and diazepam had no effect on signal attenuation-induced ELP-U at doses that markedly reduced ELP-U in regular extinction (i.e. 2, 4, 6 mg/kg). It should be noted that because the number of ELP-U in regular extinction in the control groups was very low, the lack of effect of paroxetine, fluvoxamine and desipramine on this measure may reflect a floor effect. Although the finding that diazepam significantly reduced ELP-U in regular extinction at doses that did not affect ELP-U in signal attenuation, or ELP-C in either procedure, makes this possibility less likely, the problem of confounding drug effects on ELP-U in regular extinction with a floor effect may be inherent to the regular extinction procedure, because the number of ELP-U in this procedure is spontaneously low (see also Joel and Doljansky, 2003).

The finding that ELP-U in post-training signal attenuation and ELP-U in regular extinction are affected differently by the three classes of drugs may thus suggest that ELP-U induced by signal attenuation are both quantitatively and qualitatively different from ELP-U in regular extinction (see also Joel and Doljansky, 2003). Moreover, the finding that only the two SRIs reduced the number of ELP-U in post-training signal attenuation, at doses that did not affect ELP-U in regular extinction, supports our hypothesis that ELP-U may provide a measure of 'compulsive' responding in the signal attenuation model. However, it should be noted, that whereas, ideally, an anti-compulsive drug should reduce the incidence of the measure of 'compulsive' responding in the model without affecting other measures of performance, paroxetine and fluvoxamine also affected the number of ELP-C in the post-training signal attenuation procedure. Although, as discussed above, the pattern of drug effects on ELP-C in the two procedures suggests that the effect of the two SRIs on this response measure reflects their effect on extinction, rather than on the response to signal attenuation, this is clearly a shortcoming of the post-training signal attenuation procedure. Until a procedure is developed that measures the effects of signal attenuation under rewarded conditions, the only way to deal with the confounding effects of extinction in the test stage is to compare the pattern of drug effects in the post-training signal attenuation procedure to that in a regular extinction procedure, as has been done here.

We have suggested previously that the extinction of the classical contingency between the stimulus and food in the signal attenuation stage, alters the ability of the stimulus to provide feedback that the response was effective in producing food, and that this alteration leads, in the subsequent test stage, to repeated emission of the lever-press response that is not followed by an attempt to collect a reward (Joel and Avisar, 2001; Joel and Doljansky, 2003). We have further speculated that signal attenuation may simulate a deficient response feedback or a deficient signaling that the conditions have changed following the organism's response; a deficit hypothesized to underlie obsessions and compulsions in patients (e.g. Reed, 1977; Pitman, 1987, 1991; Baxter, 1999; Szechtman and Woody, 2004; for a review see Otto, 1992). The possibility that ELP-U induced by signal attenuation may provide an animal model of compulsive behavior in OCD is further supported by preliminary evidence of common neural substrates. Thus, we have shown that compulsive lever-pressing is increased following lesions to the orbital cortex (Joel *et al.*, 2004), dysfunction of which has been implicated in the production of obsessions and compulsions in OCD patients (reviewed by Saxena *et al.*, 1998), and is sensitive to dopaminergic manipulations (Joel *et al.*, 2001; Joel and Doljansky, 2003), in accordance with several lines of clinical and preclinical evidence implicating abnormalities of the dopaminergic system in OCD (reviewed by Goodman *et al.*, 1990a; McDougle *et al.*, 1993). The present finding that the two selective serotonin reuptake inhibitors reduce compulsive lever-pressing, implicates the serotonergic system in the production of compulsive lever-pressing, in line with the prevailing view that dysregulation of this neurotransmitter system plays an essential role in the pathophysiology of OCD (for a recent review see Stein, 2002). Finally, the latter finding, combined with the findings that compulsive lever-pressing is not affected by desipramine, diazepam and the antipsychotic haloperidol (Joel and Doljanski, 2003), strengthens the suggestion that compulsive lever-pressing may serve to model compulsive behavior in OCD, and lends the model predictive validity.

It should be pointed out, however, that our claim for predictive validity may be unwarranted because we have used acute drug administration, whereas SRIs require several weeks of treatment to produce beneficial effects in humans. Indeed, animal models of OCD have typically used chronic administration of SRIs to dissociate between SRIs and tricyclic antidepressants and benzodiazepines [fluoxetine versus imipramine (Altemus *et al.*, 1996); clomipramine, sertraline and fluoxetine versus

desipramine (Rapoport *et al.*, 1992); fluvoxamine, fluoxetine and clomipramine versus desipramine and diazepam (Woods *et al.*, 1993); but see Winslow and Insel (1991) who dissociated between clomipramine and desipramine using acute administration]. While it is the convention in the OCD field to use chronic administration, this is not a prevailing convention in other areas of animal modeling. For example, the two leading animal models of schizophrenia, namely, latent inhibition and prepulse inhibition, use acute drug administration to detect antipsychotic activity (for recent reviews see Moser *et al.*, 2000; Geyer *et al.*, 2001). As pointed out by Willner (1991), the demonstration of drug effects in the model after a period of chronic administration is important for establishing its face validity, but differences in treatment regime (acute versus chronic) between the animal model and the disease modeled do not undermine the model's predictive validity and its ability to serve as a screening test for treatments.

References

Altemus M, Glowa JR, Galliven E, Leong YM, Murphy DL (1996). Effects of serotonergic agents on food-restriction-induced hyperactivity. *Pharmacol Biochem Behav* **53**:123–131.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Press.

Argyropoulos SV, Sandford JJ, Nutt DJ (2000). The psychobiology of anxiolytic drug. Part 2: Pharmacological treatments of anxiety. *Pharmacol Ther* **88**: 213–227.

Baxter LR (1999). Functional imaging of brain systems mediating obsessive–compulsive disorder. In: Nestler CE, Bunney W (editors): *Neurobiology of Mental Illness*. New York: Oxford University Press; pp. 534–547.

Bourin M, Chue P, Guillon Y (2001). Paroxetine: a review. *CNS Drug Rev* **7**: 25-47.

Cassano GB, Carrara S, Castrogiovanni P (1975). Bromazepam versus diazepam in psychoneurotic inpatients. *Pharmakopsychiatr Neuropsychopharmakol* **8**:1–7.

Cheer SM, Figgitt DP (2001). Fluvoxamine: a review of its therapeutic potential in the management of anxiety disorders in children and adolescents. *Paediatr Drugs* **3**:763–781.

Cowie S, Quintero S, McNaughton N (1987). Home cage and test apparatus artefacts in assessing behavioral effects of diazepam in rats. *Psychopharmacology (Berl)* **91**:257–259.

Cryan JF, McGrath C, Leonard BE, Norman TR (1998). Combining pindolol and paroxetine in an animal model of chronic antidepressant action – can early onset of action be detected? *Eur J Pharmacol* **352**:23–28.

Eilam D, Szechtman H (1995). Towards an animal model of obsessive–compulsive disorder (OCD): Sensitization to dopamine agonist quinpirole. *Soc Neurosci Abstr* **21**:192.

Feldon J, Gray JA (1981). The partial reinforcement extinction effect after treatment with chlordiazepoxide. *Psychopharmacology (Berl)* **73**:269–275.

Figgitt DP, McClellan KJ (2000). Fluvoxamine. An updated review of its use in the management of adults with anxiety disorders. *Drugs* **60**:925–954.

Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR (2001). Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. *Psychopharmacology (Berl)* **156**: 117–154.

Giorgetti M, Javaid JI, Davis JM, Costa E, Guidotti A, Appel SB, *et al.* (1998). Imidazenil, a positive allosteric GABAA receptor modulator, inhibits the effects of cocaine on locomotor activity and extracellular dopamine in the nucleus accumbens shell without tolerance liability. *J Pharmacol Exp Ther* **287**:58–66.

Goodman WK, McDougle CJ, Price LH, Riddle MA, Pauls DL, Leckman JF (1990a). Beyond the serotonin hypothesis: A role for dopamine in some forms of obsessive–compulsive disorder. *J Clin Psychiatry* **51**:36–43.

Goodman WK, Price LH, Delgado PL, Palumbo J, Krystal JH, Nagy LM, *et al.* (1990b). Specificity of serotonin reuptake inhibitors in the treatment of obsessive–compulsive disorder. Comparison of fluvoxamine and desipramine. *Arch Gen Psychiatry* **47**:577–585.

Goodman WK, Ward H, Kablinger A, Murphy T (1997). Fluvoxamine in the treatment of obsessive–compulsive disorder and related conditions. *J Clin Psychiatry* **58**:32–49.

Gray JA (1982.) *The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-hippocampal System*. Oxford: Oxford University Press.

Griebel G, Perrault G, Tan S, Schoemaker H, Sanger DJ (1999). Comparison of the pharmacological properties of classical and novel BZ-omega receptor ligands. *Behav Pharmacol* **10**:483–495.

Gunasekara NS, Noble S, Benfield P (1998). Paroxetine. An update of its pharmacology and therapeutic use in depression and a review of its use in other disorders. *Drugs* **55**:85–120.

Halevy G, Feldon J, Weiner I (1986). The effects of clonidine on the partial reinforcement extinction effect (PREE). *Psychopharmacology (Berl)* **90**: 95–100.

Hoehn-Saric R, Ninan P, Black DW, Stahl S, Greist JH, Lydiard B, *et al.* (2000). Multicenter double-blind comparison of sertraline and desipramine for concurrent obsessive–compulsive and major depressive disorders. *Arch Gen Psychiatry* **57**:76–82.

Joel D, Avisar A (2001). Excessive lever pressing following post-training signal attenuation in rats: A possible animal model of obsessive compulsive disorder? *Behav Brain Res* **123**:77–87.

Joel D, Doljansky J (2003). Selective alleviation of compulsive lever-pressing in rats by D1, but not D2, blockade: possible implications for the involvement of D1 receptors in obsessive–compulsive disorder. *Neuropsychopharmacology* **28**:77–85.

Joel D, Avisar A, Doljansky J (2001). Enhancement of excessive lever-pressing after post-training signal attenuation in rats by repeated administration of the D1 antagonist SCH 23390 or the D2 agonist quinpirole but not of the D1 agonist SKF 38393 or the D2 antagonist haloperidol. *Behav Neurosci* **115**:1291–1300.

Joel D, Doljansky J, Roz N, Rehavi M (2004). Role of the orbital cortex and the serotonergic system in a rat model of obsessive compulsive disorder. Submitted for publication.

Kikusui T, Takeuchi Y, Mori Y (2001). Pharmacological manipulations of the extinction process of fear-induced ultrasonic vocalization in rats. *J Vet Med Sci* **63**:591–595.

Kim SW, Dysken MW, Kushner MG, Kuskowski MA, Hoover KM, Klein KW, *et al.* (1997). Phenomenological and pharmacological study of provoked obsessive/anxiety symptoms in obsessive–compulsive disorder: a preliminary study. *Biol Psychiatry* **42**:969–975.

Leonard HL, Rapoport JL (1989). Pharmacotherapy of childhood obsessive–compulsive disorder. *Psychiatr Clin North Am* **12**:963–970.

Leonard HL, Swedo SE, Rapoport JL, Koby EV, Lenane MC, Cheslow DL, *et al.* (1989). Treatment of obsessive–compulsive disorder with clomipramine and desipramine in children and adolescents. A double-blind crossover comparison. *Arch Gen Psychiatry* **46**:1088–1092.

Lucki I, Frazer A (1985). Performance and extinction of lever press behavior following chronic administration of desipramine to rats. *Psychopharmacology (Berl)* **85**:253–259.

Malloy P (1987). Frontal lobe dysfunction in obsessive compulsive disorder. In: Perecman E (editor): *The Frontal Lobes Revisited*. New York: IRBN Press.

Masand PS, Gupta S (1999). Selective serotonin-reuptake inhibitors: an update. *Harv Rev Psychiatry* **7**:69–84.

McDougle CJ, Goodman WK, Leckman JF, Price LH (1993). The psychopharmacology of obsessive–compulsive disorder. Implications for treatment and pathogenesis. *Psychopharmacology (Berl)* **16**:749–766.

McKinney WT (1988). Models of Mental Disorders. A New Comparative Psychiatry. New York: Plenum Medical Book Co.

McNaughton N (1984). Effects of anxiolytic drugs on the partial reinforcement extinction effect in runway and Skinner box. *Q J Exp Psychol B* **36**:319–330.

Montgomery SA (1993). Obsessive compulsive disorder is not an anxiety disorder. *Int Clin Psychopharmacol* **1** (**suppl 8**):57–62.

Moser PC, Hitchcock JM, Lister S, Moran PM (2000). The pharmacology of latent inhibition as an animal model of schizophrenia. *Brain Res Rev* **33**:275–307.

Otto MW (1992.) Normal and abnormal information processing: A neuropsychological perspective on obsessive–compulsive disorder. In: Jenike MA (editor): *The Psychiatric Clinics of North America. Obsessional Disorders*. Chicago: W.B. Saunders, Harcourt Brace Jovanovich; pp. 825–848.

Piccinelli M, Pini S, Bellantuono C, Wilkinson G (1995). Efficacy of drug treatment in obsessive–compulsive disorder. A meta-analytic review. *Br J Psychiatry* **166**:424–443.

Pigott TA, Seay SM (1999). A review of the efficacy of selective serotonin reuptake inhibitors in obsessive–compulsive disorder. *J Clin Psychiatry* **60**:101–106.

Pitman RK (1987). A cybernetic model of obsessive–compulsive psychopathology. *Compr Psychiatry* **28**:334–343.

Pitman RK (1991). Historical considerations. In: Zohar J, Insel T, Rasmussen S (editors): *The Psychobiology of Obsessive–compulsive Disorder*. New York: Springer Publishing; pp. 1–12.

Rapoport JL (1989). The biology of obsessions and compulsions [see comments]. *Sci Am* **260**:82–89.

Rapoport JL, Ryland DH, Kriete M (1992). Drug treatment of canine acral lick. An animal model of obsessive–compulsive disorder. *Arch Gen Psychiatry* **49**:517–521.

Rasmussen SA, Eisen JL (1992.) The epidemic logical and clinical features of obsessive–compulsive disorder. In: Jenike MA (editor): *The Psychiatric Clinics of North America. Obsessional Disorders*. Chicago: W.B. Saunders, Harcourt Brace Jovanovich; pp. 743–758.

Reed GF (1977). Obsessional personality disorder and remembering. *Br J Psychiatry* **130**:177–183.

Reed GF (1985). Obsessional Experience and Compulsive Behaviour: A Cognitive-structural Approach. London: Academic Press.

Ricciardi JN, Hurley J (1990.) Development of animal models of obsessive–compulsive disorders. In: Jenike MA, Baer L, Minichiello WE (editors): *Obsessive-compulsive Disorders: Theory and Management*. Chicago: Year Book Medical Publishers; pp. 189–199.

Rimondini R, Sommer W, Heilig M (2002). Effects of tiagabine and diazepam on operant ethanol self-administration in the rat. *J Stud Alcohol* **63**:100–106.

Sanchez C, Meier E (1997). Behavioral profiles of SSRIs in animal models of depression, anxiety and aggression. Are they all alike? *Psychopharmacology (Berl)* **129**:197–205.

Sasson Y, Zohar J, Chopra M, Lustig M, lancu I, Hendler T (1997). Epidemiology of obsessive–compulsive disorder: a world view. *J Clin Psychiatry* **58**: 7–10.

Saxena S, Brody AL, Schwartz JM, Baxter LR (1998). Neuroimaging and frontal-subcortical circuitry in obsessive–compulsive disorder. *Br J Psychiatry Suppl* **35**:26–37.

Shannon HE, Katzman NJ (1986). COS 8216: agonist and diazepam-antagonist effects in rodents. *J Pharmacol Exp Ther* **239**:166–173.

Sokolowski JD, Seiden LS (1999). The behavioral effects of sertraline, fluoxetine, and paroxetine differ on the differential-reinforcement-of-low-rate 72-second operant schedule in the rat. *Psychopharmacology (Berl)* **147**:153–161.

Soubrie P, Thiebot MH, Simon P, Boissier JR (1978). Benzodiazepines and behavioral effects of reward (water) omission in the rat. *Psychopharmacology (Berl)* **59**:95–100.

Stein DJ (2002). Obsessive–compulsive disorder. *Lancet* **360**:397–405.

Stein DJ, Dodman NH, Borchelt P, Hollander E (1994). Behavioral disorders in veterinary practice: relevance to psychiatry. *Compr Psychiatry* **35**: 275–285.

Stein DJ, Spadaccini E, Hollander E (1995). Meta-analysis of pharmacotherapy trials for obsessive–compulsive disorder. *Int Clin Psychopharmacol* **10**: 11–18.

Szechtman H, Woody E (2004). Obsessive-compulsive disorder as a disturbance of security motivation. *Psychol Rev* **111**:111–127.

Szechtman H, Sulis W, Eilam D (1998). Quinpirole induces compulsive checking behavior in rats: a potential animal model of obsessive–compulsive disorder (OCD). *Behav Neurosci* **112**:1475–1485.

Telegdy G, Fekete M, Balazs M, Kadar T (1983). Effects of a new antidepressant drug on active avoidance behavior in rats. Comparative study with tricyclic antidepressants. *Arch Int Pharmacodyn Ther* **266**:50–59.

Thiebot MH, Childs M, Soubrie P, Simon P (1983). Diazepam-induced release of behavior in an extinction procedure: its reversal by Ro 15-1788. *Eitr J Pharmacol* **88**:111–116.

Waxman D (1977). A clinical trial of clomipramine and diazepam in the treatment of phobic and obsessional illness. *J Int Med Res* **5** (**suppl 5**):99–110.

Willner P (1991.) Behavioural models in psychopharmacology. In: Willner P (editor): *Behavioural Models in Psychopharmacology: Theoretical, Industrial and Clinical Perspectives*. Cambridge: Cambridge University Press; pp. 3–18.

Willner P, Towell A (1982). Evidence suggesting that DMI-induced resistance to extinction is not mediated by the dorsal noradrenergic bundle. *Brain Res* **238**:251–253.

Willner P, Montgomery T, Bird D (1981). Behavioural changes during withdrawal from desmethylimipramine (DMI). II. Increased resistance to extinction. *Psychopharmacology (Berl)* **75**:60–64.

Winslow JT, Insel TR (1991.) Neuroethological models of obsessive–compulsive disorder. In: Zohar J, Insel T, Rasmussen S (editors): *The Psychobiology of Obsessive–Compulsive Disorder*. New York: Springer Publishing Company; pp. 208–226.

Woods A, Smith C, Szewczak M, Dunn RW, Cornfeldt M, Corbett R (1993). Selective serotonin re-uptake inhibitors decrease schedule-induced polydipsia in rats: a potential model for obsessive compulsive disorder. *Psychopharmacology (Berl)* **112**:195–198.

Yadin E, Friedman E, Bridger WH (1991). Spontaneous alternation behavior: an animal model for obsessive–compulsive disorder? *Pharmacol Biochem Behav* **40**:311–315.

Yang XM, Luo ZP, Zhou JH (1988). Behavioral evidence for the role of noradrenaline in putative anxiolytic and sedative effects of benzodiazepines. *Psychopharmacology (Berl)* **95**:280–286.

Zohar J, Zohar-Kadouch RC, Kindler S (1992). Current concepts in the pharmacological treatment of obsessive–compulsive disorder. *Drugs* **43**:210–218.