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Research report

Strain differences in 'compulsive' lever-pressing

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Abstract

In the signal attenuation rat model of obsessive-compulsive disorder, 'compulsive' behavior is induced by attenuating a signal indicating that a lever-press response was effective in producing food. In recent years several studies have reported that Lewis rats, an inbred strain derived from the Sprague Dawley strain, exhibit addictive and/or compulsive tendencies. The aim of the present study was thus to test whether Lewis rats will also show increased compulsivity in the signal attenuation model. Because the model has been developed and validated using Wistar rats only, the present study compared the behavioral response to signal attenuation of Lewis, Sprague Dawley and Wistar rats, and assessed the effects of the anti-compulsive drug paroxetine on compulsive behavior in Lewis and Sprague Dawley rats. The results show that Lewis rats are more 'compulsive' than Sprague Dawley and Wistar rats in terms of both higher levels of compulsive lever-pressing and higher resistance to the anti-compulsive effect of paroxetine. The possibility that these strain differences are related to strain differences in the serotonergic and dopaminergic systems are discussed in light of current knowledge of the pathophysiology and pharmacotherapy of OCD.

Keywords: Animal model; Obsessive–compulsive disorder (OCD); Post-training signal attenuation; Paroxetine; Lewis; Rat

1. Introduction

Rats undergoing extinction of lever-pressing after an external feedback for this behavior was attenuated by extinguishing its Pavlovian association with the reward (a procedure termed post-training signal attenuation, PTSA), exhibit excessive lever-pressing unaccompanied by an attempt to collect a reward (ELP-U). This behavior has been named 'compulsive' lever-pressing, because it may be analogous to the excessive and unreasonable behavior seen in obsessive–compulsive disorder (OCD, [10,12], for a recent review see [9]). 'Compulsive' lever-pressing is abolished by the selective serotonin reuptake inhibitors fluoxetine, paroxetine and fluvoxamine, but not by the anxiolytic drug diazepam, the tricyclic antidepressant desipramine, or the antipsychotic haloperidol [11–13], in accordance with the differential efficacy of these drugs in alleviating obsessions and compulsions in OCD patients (e.g., [3,24,34]). Moreover, compulsive lever-pressing is enhanced following lesions to the orbital cortex [14,15a], in line with neuroimaging studies in OCD patients which consistently implicate the orbitofrontal cortex in this disorder (for review see [26,30]), and is sensitive to dopaminergic manipulations [11,14], in line with clinical evidence implicating this system in OCD (for review see [7,21]). (For an extensive review of the signal attenuation model of OCD see [9].)

All the studies reported above have been carried out using male Wistar rats. In recent years several studies have reported that Lewis rats, an inbred strain derived from the Sprague Dawley (SD) strain, exhibit addictive and/or compulsive tendencies [17,20,23,32]. The aim of the present study was therefore to test whether Lewis rats will also show increased compulsivity compared to SD rats in the signal attenuation model, and whether they will differ in their response to the anti-compulsive drug paroxetine. In preliminary experiments (unpublished data) we found that the behavioral response to signal attenuation in Lewis and SD rats is qualitatively similar to that seen in Wistar rats. Specifically, rats that underwent an extinction session of lever-press responding that was preceded by signal attenuation

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(the PTSA procedure), exhibited a high number of excessive lever-presses that were *not* followed by magazine entry (i.e., ELP-U) and a high number of excessive lever-presses that were followed by magazine entry (i.e., ELP-C). In contrast, rats that underwent a control procedure (termed "Regular extinction") that is identical to the PTSA procedure but does not include a signal attenuation stage, showed mainly the latter type of behavior. (Because the effects of signal attenuation are assessed under extinction conditions, the comparison of rats' behavior in the PTSA and RE procedures enables the differentiation between the effects of signal attenuation and the effects of extinction per se. For a detailed discussion see [9]). The present study tested the effects of the selective serotonin reuptake inhibitor (SSRI) paroxetine on compulsive behavior in SD and Lewis rats. Experiments 1 and 3 assessed the effects of several doses of paroxetine on the behavior of SD and Lewis rats (respectively) in the PTSA procedure. Experiments 2 and 4 tested the effects of an effective paroxetine dose in both the PTSA and regular extinction procedures, to demonstrate that paroxetine effects are specific to compulsive lever-pressing (i.e., signal attenuation-induced ELP-U). In addition, because the results of Experiments 1–4 indeed suggested that Lewis rats are more 'compulsive' than SD and Wistar rats in terms of both higher levels of compulsive lever-pressing and higher resistance to the anti-compulsive effect of paroxetine, this possibility was further assessed by pooling together data obtained in different experiments in our laboratory and comparing the behavior of the three strains over the pooled data (Experiment 5–meta-analysis, for details see Section 3.5 below).

2. Methods

2.1. Subjects

Male Sprague Dawley and Lewis rats (Harlen, Jerusalem, Israel) 2–3 months old, were housed 4 to a cage under a reversed 12-h light–dark cycle (lights on 19:00–07:00). 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.

2.2. Apparatus and behavioral procedure

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 a 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.

Prior to the beginning of the experiment, rats were handled for about 2 min daily for 5 days. A 22-h food restriction schedule began simultaneously with handling and continued throughout behavioral testing. Food was provided in the home cage 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 2 pellets.

2.3. Post-training signal attenuation

The PTSA procedure included four stages.[2]

2.3.1. 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, simultaneous 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.

2.3.2. Stage 2: Lever-press training

On Day 4, rats received a session of pre-training using a free-operant schedule. The houselight was on and one lever was present in the operant box throughout the entire session. Responding on this lever (reinforced lever, RL) resulted in the delivery of a single food pellet into the magazine, accompanied by the presentation of the compound stimulus (magazine light and tone). The stimulus was turned off after the rat's head entered the food magazine or after 15-s from the rat's first lever-press had elapsed. The lever designated as RL was counterbalanced over subjects and remained the same for each rat over the entire experimental procedure. Each rat was trained until it completed 30 trials, that is, pressed the lever and inserted its head into the food magazine during stimulus presentation. Rats that failed to attain 30 completed trials within 30 min, were returned to the test chamber at the end of the day for an additional session. On Days 5–7, rats were trained to lever-press in a discrete-trial procedure. On each trial, both levers were inserted into the chamber. Responding on the 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 from the rat's first lever-press had elapsed (see Fig. 1). Further lever-presses on the RL as well as responding on the other lever (nonreinforced lever, NRL) had no programmed consequences. Each trial was followed by a 30-s intertrial interval. Each rat was trained until it completed 40 trials, that is, pressed the lever and inserted its head into the food magazine during stimulus presentation, 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 rats' 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 during stimulus presentation; ELP-U), and ELP in completed trials (ELP-C). Rats were randomly assigned to the different experimental groups at the end of this stage.

2.3.3. Stage 3: Signal attenuation

On Days 8–10, 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 14 collected trials on

[2] The different parameters of the PTSA procedure used in the present study are identical to those used in previous publications from this laboratory. The only difference is that the lever-press training stage (Stage 2) in the present experiments (as well as in experiments described in [15b]) included one session of pre-training followed by three sessions of lever-press training, whereas in earlier publications [10,12–15a] this stage included only three sessions of lever-press training.

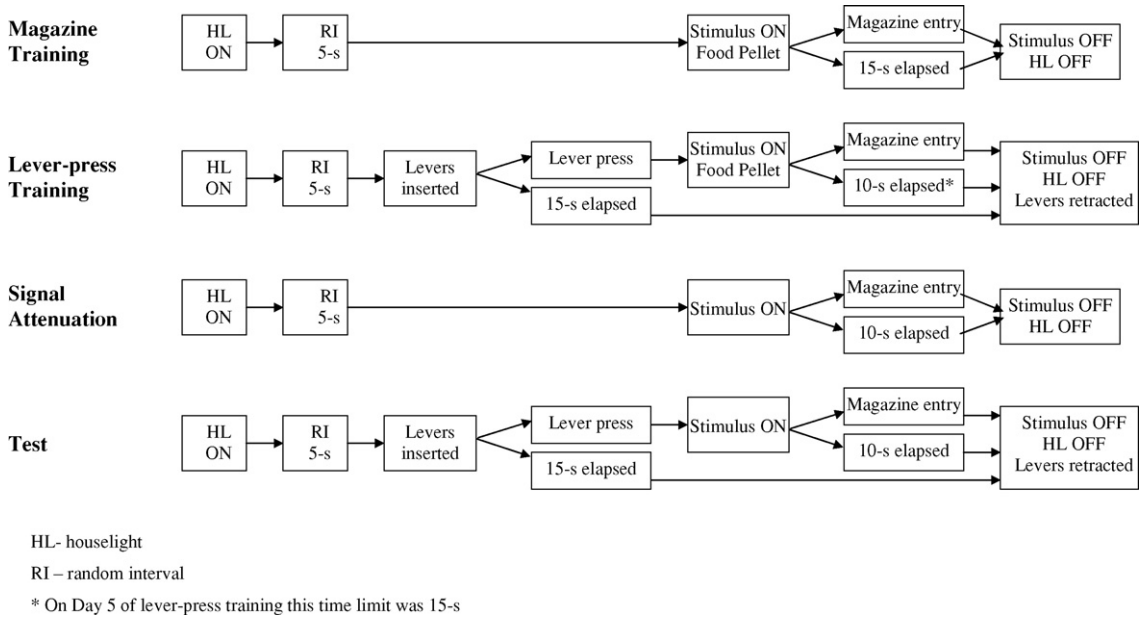

Fig. 1. A schematic diagram of the organization of a trial in each of the different stages of the PTSA procedure.

Day 10 were returned to the test chamber at the end of the day for an additional session.

2.3.4. Stage 4: Test

On Day 11, 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 PTSA procedure.

2.4. Regular extinction

Rats were run exactly as in the PTSA procedure, with the exception that they did not undergo the signal attenuation stage on Days 8–10. 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.

2.5. Drug administration

On the basis of our previous results with Wistar rats [12], the effects of several doses of paroxetine, ranging from low doses which had no effect on behavior, to high doses which almost abolished lever-press responding, were tested. Paroxetine (Unipharm, Ramat Gan) was dissolved in distilled water to the appropriate dose and administered intraperitoneally in a volume of 1 ml/kg 30 min before the beginning of the test stage. No-drug controls received an equivalent volume of distilled water.

2.6. Statistical analysis

Experiments 1 and 3: Rats' performance on the test stage was analyzed using analyses of variance (ANOVAs) with a main factor of Dose performed on the number of ELP-C and ELP-U. *Experiments 2 and 4:* Rats' performance on the test stage was analyzed using ANOVAs with main factors of Procedure (Signal attenuation/Regular extinction) and Drug (paroxetine/vehicle) performed on the number of ELP-C and ELP-U.

Although drugs were administered only prior to the test stage, rats' performance on 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. For the former, the number of ELP-C in the last day of lever-press training was analyzed (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 on the signal attenuation stage was analyzed using a mixed ANOVA performed on the number of collected trials (i.e., trials on which the rat performed magazine entry during stimulus presentation) on the three sessions of the signal attenuation stage.

3. 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 (where relevant), and the final number of rats in each group.

3.1. Experiment 1: The effects of paroxetine on SD rats undergoing the PTSA procedure

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 of ELP-U (Fig. 2b). ANOVAs yielded a significant main effect of Dose on the two measures (ELP-C, $F(3,22) = 5.15$, $p < 0.01$, ELP-U, $F(3,22) = 7.99$, $p < 0.001$) as well as a significant linear trend of Dose (ELP-C, $F(1,22) = 13.04$, $p < 0.005$, ELP-U, $F(1,22) = 21.58$, $p < 0.001$).

3.2. Experiment 2: The effects of 5 mg/kg paroxetine on SD rats undergoing the PTSA or the regular extinction procedure

Because Experiment 1 revealed that at 5 mg/kg paroxetine significantly decreased compulsive lever-pressing, Experiment 2 tested the effects of this dose in both the PTSA and regular extinction procedures. There were no differences between the groups at the lever-press training and signal attenuation

Table 1
Summary of experiments

Experiment	Strain and drug	Procedure	Number of rats in experiment	Number of rats excluded	Group	Final *n* per group
1	SD and Paroxetine	SA	30	3—Illness 1—Partial injection	Vehicle 1 mg/kg 5 mg/kg 10 mg/kg	5 6 8 7
2	SD and Paroxetine	SA and RE	39	3—Statistical[a]	SA-Vehicle SA-Paroxetine RE-Vehicle RE-Paroxetine	10 8 8 10
3	Lewis and Paroxetine	SA	50	3—Computer failure	Vehicle 3 mg/kg 7 mg/kg 8.5 mg/kg 10 mg/kg	16 7 8 8 8
4	Lewis and Paroxetine	SA and RE	32	1—Statistical[a]	SA-Vehicle SA-Paroxetine RE-Vehicle RE-Paroxetine	9 8 7 7

RE, regular extinction procedure; SA, post-training signal attenuation procedure; SD, Sprague Dawley.
[a] Rats were excluded if their score on at least one variable was more than four standard deviations above their group mean.

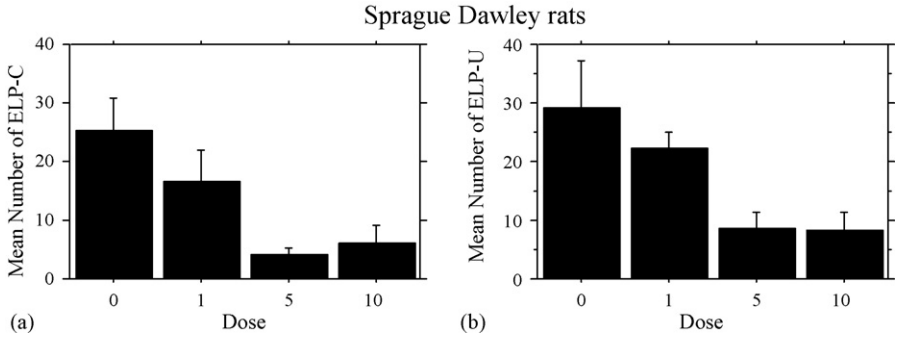

Fig. 2. Mean and standard error of the mean number of extra lever-presses that (a) were followed by magazine entry (ELP-C) and (b) that were not followed by magazine entry (ELP-U) of SD rats treated with vehicle, 1, 5 or 10 mg/kg paroxetine on the test day of the PTSA procedure (Experiment 1).

stages (data not shown). In the test, paroxetine decreased the number of ELP-C of rats undergoing regular extinction as well as of rats undergoing PTSA (Fig. 3a, main effect of Procedure, $F(1,32) = 6.50$, $p < 0.05$, main effect of Drug, $F(1,32) = 8.69$, $p < 0.01$, Procedure × Drug interaction, $F(1,32) = 0.43$, $p = 0.52$). In contrast, paroxetine decreased the number of ELP-U only in rats undergoing PTSA (Fig. 3b, main effect of Procedure, $F(1,32) = 9.60$, $p < 0.005$, main effect of Drug, $F(1,32) = 5.75$, $p < 0.05$, Procedure × Drug interaction, $F(1,32) = 4.83$, $p < 0.05$).

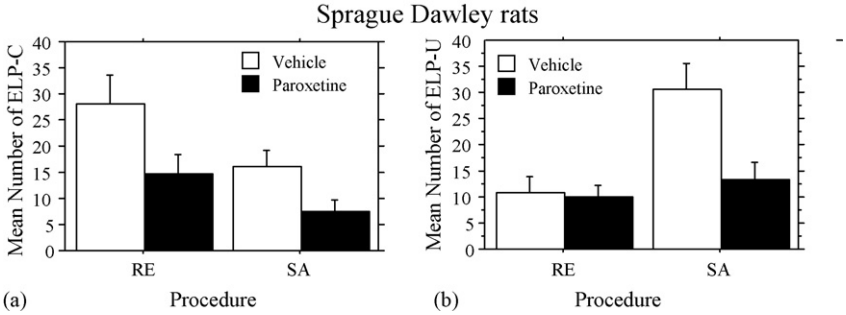

Fig. 3. Mean and standard error of the mean number of extra lever-presses that (a) were followed by magazine entry (ELP-C) and (b) that were not followed by magazine entry (ELP-U) of SD rats treated with 5 mg/kg paroxetine on the test day of the PTSA and the regular extinction procedures (Experiment 2).

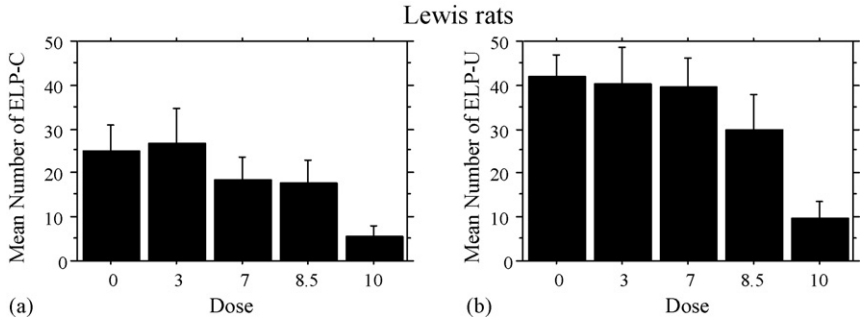

Fig. 4. Mean and standard error of the mean number of extra lever-presses that (a) were followed by magazine entry (ELP-C) and (b) that were not followed by magazine entry (ELP-U) of Lewis rats treated with vehicle, 3, 7, 8.5 or 10 mg/kg paroxetine on the test day of the PTSA procedure (Experiment 3).

3.3. Experiment 3: The effects of paroxetine on Lewis rats undergoing the PTSA procedure

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. 4a) and of ELP-U (Fig. 4b), although the former effect did not reach statistical significance (Fig. 4, ELP-C, main effect of Dose, $F(4,42) = 1.76$, $p = 0.16$; ELP-U, main effect of Dose, $F(4,42) = 4.33$, $p < 0.01$, linear trend of Dose, $F(1,42) = 10.01$, $p < 0.005$). However, in both measures, the effect of dose was mainly attributed to the effects of the highest dose of paroxetine (i.e., 10 mg/kg).

3.4. Experiment 4: The effects of 9.25 mg/kg paroxetine on Lewis rats undergoing the post-training signal attenuation or the regular extinction procedure

Because Experiment 3 revealed that at 8.5 mg/kg paroxetine had no effect on rats' behavior, whereas at 10 mg/kg this drug almost completely abolished responding, Experiment 4 tested the effects of an intermediate dose, namely, 9.25 mg/kg, in both the PTSA and regular extinction procedures. There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown). In the test, paroxetine decreased the number of ELP-C of rats undergoing regular extinction as well as of rats undergoing PTSA (Fig. 5a, main effect of Procedure, $F(1,27) = 9.05$, $p < 0.01$, main effect of Drug, $F(1,27) = 13.54$, $p < 0.001$, Procedure × Drug interaction, $F(1,27) = 0.64$, $p = 0.43$). In contrast, paroxetine decreased the number of ELP-U only in rats undergoing PTSA (Fig. 5b, main effect of Procedure, $F(1,27) = 4.06$, $p = 0.054$, main effect of Drug, $F(1,27) = 7.00$, $p < 0.05$, Procedure × Drug interaction, $F(1,27) = 5.27$, $p < 0.05$).

3.5. Experiment 5—meta-analysis: Comparing the effects of signal attenuation in the three stains

Because the results of Experiments 1–4 suggest that Lewis rats exhibit a higher number of compulsive lever-presses (i.e., ∼50) compared to SD rats (∼30) and also compared to Wistar rats (e.g., Joel et al. [12]), Experiment 5 tested this difference using data from different experiments that were carried out in our laboratory (including Experiments 1–4 reported here). Table 2 presents the details of the different vehicle groups that were included in the analysis. For each strain and each procedure, separate ANOVAs with a main factor of Experiment were performed on the number of ELP-C and ELP-U in the test. In 11 of the 12 analyses (Signal attenuation/Regular extinction × Wistar/Sprague Dawley/Lewis × ELP-C/ELP-U) the effect of Experiment was not significant ($p > 0.05$), and therefore the data from the different experiments were combined. The analysis of the number of ELP-C in Wistar rats undergoing regular extinction yielded a significant effect of Experiment. Post hoc tests revealed a significant difference between the vehicle groups in the paroxetine and fluvoxamine/desipramine experiments (Lines 9 and 10 in Table 2). Because these two groups did not differ significantly from the other two Wistar-regular extinction groups, all four groups were included in the analysis. The meta-analysis included 94 and 36

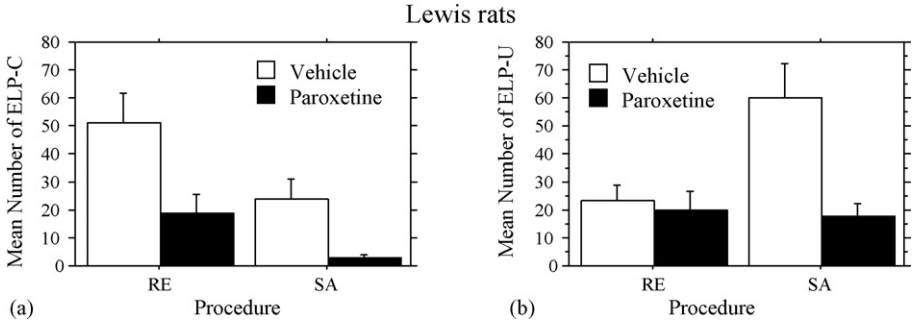

Fig. 5. Mean and standard error of the mean number of extra lever-presses that (a) were followed by magazine entry (ELP-C) and (b) that were not followed by magazine entry (ELP-U) of Lewis rats treated with 9.25 mg/kg paroxetine on the test day of the PTSA and the regular extinction procedures (Experiment 4).

Table 2
Details of vehicle groups included in the meta-analysis (Experiment 5)

Group no.	Paper	Experiment	Number of rats in group	Mean (S.E.) number of ELP-C	Mean (S.E.) number of ELP-U
Wistar—SA					
1	Joel and Doljansky [13]	Acute administration of SCH23390	7	15.7 (5.7)	31.3 (8.4)
2	Joel and Doljansky [13]	Acute administration of haloperidol	13	26.7 (4.7)	25.3 (7.4)
3	Joel et al. [12]	Acute administration of paroxetine	20	32.1 (5.9)	33.7 (6.3)
4	Joel et al. [12]	Acute administration of fluvoxamine	13	16.0 (3.8)	20.2 (4.9)
5	Joel et al. [12]	Acute administration of desipramine	17	28.2 (5.7)	26.9 (3.0)
6	Joel et al. [12]	Acute administration of diazepam	16	15.8 (3.9)	20.4 (4.1)
7	Unpublished observations		8	17.5 (6.3)	15.2 (4.7)
Wistar—RE					
8	Joel and Doljansky [13]	Acute administration of SCH23390 or haloperidol	6	41.2 (12.5)	14.3 (4.4)
9	Joel et al. [12]	Acute administration of paroxetine	6	23.8 (6.9)	5.3 (2.4)
10	Joel et al. [12]	Acute administration of fluvoxamine or desipramine	10	64.2 (10.6)	11.1 (3.7)
11	Joel et al. [12]	Acute administration of diazepam	14	36.1 (5.4)	5.8 (2.0)
SD—SA					
12	Joel [9]	Acute administration of fluvoxamine	10	19.1 (3.2)	28.1 (6.9)
13	Present study	Experiment 1	5	26.2 (6.9)	34.0 (7.9)
14	Present study	Experiment 2	10	16.1 (3.1)	30.6 (5.1)
15	Unpublished observations		21	18.6 (3.3)	33.9 (5.8)
16	Unpublished observations		10	18.3 (2.1)	21.4 (6.3)
17	Unpublished observations		21	12.7 (1.7)	30.9 (5.2)
18	Unpublished observations		23	16.2 (3.2)	34.0 (4.3)
19	Unpublished observations		9	19.3 (4.9)	34.3 (4.5)
SD—RE					
20	Joel [9]	Acute administration of fluvoxamine	6	29.7 (5.4)	7.2 (3.0)
21	Present study	Experiment 2	8	28.1 (5.5)	10.7 (3.2)
22	Unpublished observations		20	32.3 (5.1)	25.0 (3.7)
23	Unpublished observations		8	38.7 (8.9)	23.0 (5.7)
24	Unpublished observations		9	21.4 (3.5)	34.4 (8.9)
25	Unpublished observations		10	38.8 (6.4)	29.6 (9.4)
Lewis—SA					
26	Present study	Experiment 3	16	25.1 (5.9)	42.0 (4.8)
27	Present study	Experiment 4	9	23.7 (7.5)	60.1 (12.3)
28	Unpublished observations		5	26.4 (5.5)	52.2 (14.9)
Lewis—RE					
29	Present study	Experiment 4	7	51.0 (10.6)	23.1 (5.6)
30	Unpublished observations		7	57.7 (11.7)	17.1 (6.7)
31	Unpublished observations		6	36.2 (10.0)	7.7 (3.3)

Wistar rats, 109 and 61 SD rats, and 30 and 20 Lewis rats, in the SA and RE procedures, respectively.

The mean number of ELP-C and ELP-U exhibited by Wistar, SD and Lewis rats in the PTSA and the regular extinction procedures is presented in Fig. 6a and b, respectively. As can be seen, in the three strains, rats undergoing regular extinction exhibited a higher number of ELP-C compared to rats undergoing PTSA. In addition, in the two procedures, Lewis and Wistar rats exhibited a higher number of ELP-C compared to SD rats (Fig. 6a, Strain: $F(2,344) = 9.82$, $p < 0.0001$, Procedure: $F(1,344) = 57.85$, $p < 0.0001$, Strain × Procedure interaction: $F(2,344) = 1.15$, $p = 0.32$. Tukey Honestly Significant Difference (HSD) post hoc comparisons between the number of ELP-C exhibited by the three strains revealed significant differences between SD and Lewis rats ($p < 0.0005$) and between SD and Wistar rats, $p < 0.05$).

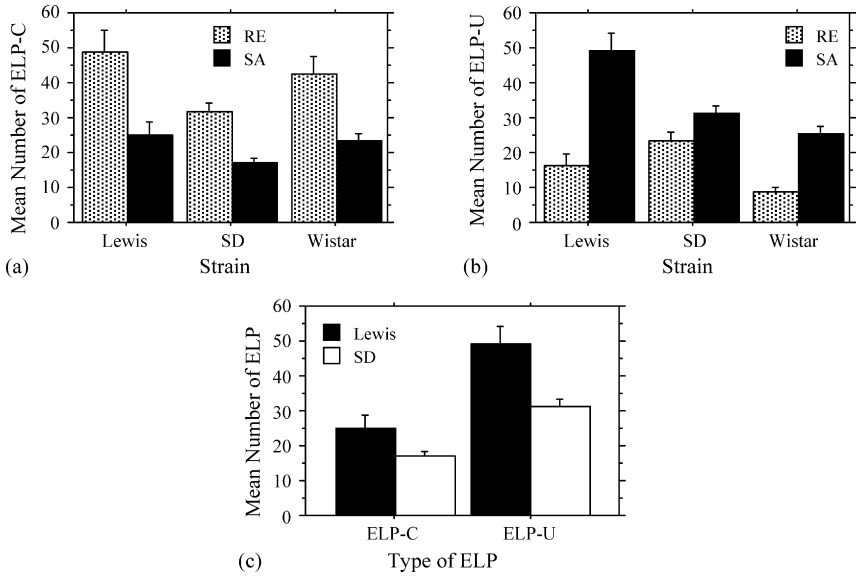

Fig. 6. Mean and standard error of the mean number of extra lever-presses that (a) were followed by magazine entry (ELP-C) and (b) that were not followed by magazine entry (ELP-U) of Wistar, SD and Lewis rats on the test day of the PTSA and the regular extinction procedures. (c) Mean and standard error of the mean number of ELP-C and ELP-U of SD and Lewis rats on the test day of the PTSA procedure (Experiment 5, meta-analysis).

In the three strains, the effect of procedure on the number of ELP-U was opposite to its effect on ELP-C, with the number of ELP-U being higher in rats undergoing PTSA than in rats undergoing regular extinction. This difference, however, was very different in the three strains, being highest in Lewis rats and lowest in SD rats (Fig. 6b, Strain: $F(2,344) = 12.11$, $p < 0.0001$, Procedure: $F(1,344) = 52.80$, $p < 0.0001$, Strain × Procedure interaction: $F(2,344) = 6.70$, $p < 0.005$; Tukey HSD post hoc comparisons between the number of ELP-U in the two procedures within each strain revealed a significant difference for the Lewis and Wistar strains only (Lewis, $p < 0.0001$; Wistar, $p < 0.0005$; SD, $p = 0.14$).

In SD rats, the small difference between the number of ELP-U in the PTSA and regular extinction procedures is attributed to the relatively high number of ELP-U exhibited by these rats in the latter procedure. This number is high not only with respect to the number of ELP-U exhibited by the other two strains in regular extinction, but also with respect to the number of ELP-C exhibited by SD rats in this procedure. Thus, whereas in Wistar and Lewis rats the number of ELP-C in the regular extinction procedure was much higher than the number of ELP-U, this difference was small and not significant in SD rats (a mixed ANOVA with Strain as a between-subject factor and Type-of-ELP (ELP-C/ELP-U) as a within-subject factor: Strain, $F(2,114) = 1.14$, $p = 0.32$; Type-of-ELP, $F(1,114) = 92.71$, $p < 0.0001$; Strain × Type-of-ELP interaction, $F(2,114) = 14.11$, $p < 0.0001$; Tukey HSD post hoc comparisons of the number of ELP-U versus the number of ELP-C within each strain revealed a significant difference in Lewis and Wistar rats, p's < 0.0005, but not in SD rats, $p = 0.1$).

In contrast, in Lewis rats, the large difference between the number of ELP-U in the PTSA and regular extinction procedures is attributed solely to the high number of signal attenuation-induced ELP-U exhibited by the Lewis rats (Tukey HSD post hoc comparisons of the number of ELP-U in the PTSA procedure between the three strains revealed significant differences between Lewis and SD rats, $p < 0.0005$, and between Lewis and Wistar rats, $p < 0.0001$). This is because the number of ELP-U in the regular extinction procedure was lower in Lewis rats compared to SD rats, and because although this number was higher (although not significantly, $p = 0.76$) in Lewis compared to Wistar rats, this difference cannot account for the difference between these strains in the number of ELP-U in the PTSA procedure. Specifically, a two-way ANOVA comparing the number of ELP-U in Wistar and Lewis rats in the PTSA and regular extinction procedures revealed a significant Strain × Procedure interaction ($F(1,176) = 5.12$, $p < 0.05$), in addition to the significant main effects of Strain ($F(1,176) = 20.04$, $p < 0.0001$) and Procedure ($F(1,176) = 49.60$, $p < 0.0001$).

The finding that Lewis rats exhibited a higher number of ELP-U in the PTSA procedure but not in the regular extinction procedure supports the hypothesis that these rats are more compulsive. However, because Lewis rats undergoing PTSA emitted also more ELP-C compared to SD rats (though not compared to Wistar rats), it is possible that the strain difference in the number of ELP-U reflects a more general strain difference in the response to signal attenuation (i.e., in the number of both ELP-U and ELP-C) rather than a selective strain difference in compulsivity. We have therefore analyzed the performance of SD and Lewis rats in the PTSA procedure using a mixed ANOVA with Strain as a between-subject factor and Type-of-ELP (ELP-C/ELP-U) as a within-subject factor (Fig. 6c). This analysis supported the claim that the higher number of ELP-U exhibited by Lewis rats in the PTSA procedure cannot be attributed solely to a higher number of ELP-C (Strain, $F(1,137) = 17.33$, $p < 0.0001$, Type-of-ELP, $F(1,137) = 57.39$, $p < 0.0001$, Strain × Type-of-ELP interaction, $F(1,127) = 3.87$, $p = 0.051$. Tukey HSD post hoc comparisons revealed a significant difference between Lewis and SD rats

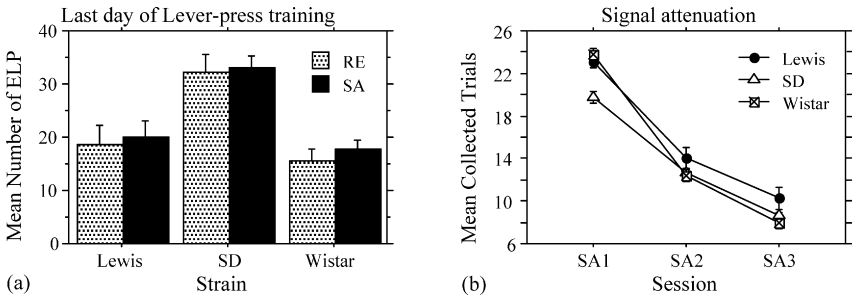

Fig. 7. (a) Mean and standard error of the mean number of extra lever-presses that were followed by magazine entry (ELP-C) of Wistar, SD and Lewis rats on the last session of the lever-press training stage. (b) Mean and standard error of the mean number of collected trials of Wistar, SD and Lewis rats on the 3 days of the signal attenuation stage (Experiment 5, meta-analysis).

in the number of ELP-U, $p < 0.0005$, but not in the number of ELP-C, $p = 0.28$).

In order to check whether strain differences at the test stage were a result of differences at earlier stages of the task, the performance of rats in the lever-press training and signal attenuation stages was also analyzed. Fig. 7a presents the mean number of extra lever-presses on the last day of lever-press training in the three strains (the data of one Lewis rat and of Wistar rats from Experiments 4, 8, 9 and 10 (in Table 2) are missing). As can be seen, SD rats exhibited a higher number of extra lever-presses compared with the other two strains, which performed similarly (Strain: $F(2,302) = 15.63$, $p < 0.0001$, the effect of Procedure and the Strain × Procedure interaction were not significant, F's < 1; Tukey HSD post hoc analysis yielded a significant difference between SD and Lewis rats ($p < 0.0005$) and between SD and Wistar rats ($p < 0.0001$).

Fig. 7b presents the mean number of collected trials on the three sessions of signal attenuation in the three strains (data of the first session of one Lewis rat and of the three sessions of one Wistar rat are missing). As can be seen, on the first session of the signal attenuation stage Lewis and Wistar rats exhibited more collected trials than SD rats. This difference became smaller for Lewis rats and completely disappeared for Wistar rats already at the second session of signal attenuation (Strain: $F(2,228) = 4.20$, $p < 0.05$, Session: $F(2,456) = 513.24$, $p < 0.0001$, Strain × Session interaction: $F(4,456) = 11.28$, $p < 0.0001$). As detailed in Section 2.3.3, rats that perform more than 14 collected trials on the third session of the signal attenuation stage receive an additional session of extinction. Analysis of the mean number of collected trials on the last session of signal attenuation (i.e., the third or fourth session for each rat), did not reveal a significant difference between the three strains (mean (standard error) number of collected trials of Wistar: 7.12 (0.40); SD: 7.35 (0.29); Lewis: 8.73 (0.71), main effect of Strain: $F(2,229) = 2.51$, $p = 0.084$), further confirming that the three strains achieved a similar level of extinction by the end of the signal attenuation stage.

4. Discussion

We have previously demonstrated that Wistar rats undergoing the PTSA procedure exhibit a high number of excessive lever-presses that are *not* followed by magazine entry (i.e., ELP-U) and a high number of excessive lever-presses that are followed by magazine entry (i.e., ELP-C). In contrast, Wistar rats undergoing a control procedure in which an extinction test is not preceded by signal attenuation (i.e., regular extinction) show mainly the latter type of behavior [9]. In view of these differences we have suggested that in an extinction test conducted after signal attenuation, ELP-U reflect rats' response to the encounter of an attenuated signal, whereas ELP-C reflect rats' response to the encounter of non-reward. Thus, ELP-U in the PTSA procedure are emitted in response to an attenuated feedback, as has been hypothesized for compulsions in OCD patients. Moreover, this behavior bears some face similarity to compulsive behaviors in OCD, because 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 (Diagnostic and Statistical Manual of Mental Disorders, 4th edition, DSM-IV). Therefore, *signal attenuation-induced ELP-U* has been suggested to provide the measure of 'compulsive' responding in the model. This hypothesis, derived at the behavioral level, has been supported by the pattern of drug and lesion effects on ELP-C and on ELP-U in the two procedures (see Section 1, for a detailed review and discussion see [9]).

Experiments 1–4 revealed that SD and Lewis rats that were tested in the PTSA and regular extinction procedures also exhibited high levels of ELP-C and ELP-U in the PTSA procedure, but mainly ELP-C in the regular extinction procedure. These experiments demonstrated in addition that the effects of systemic administration of the SSRI paroxetine are also similar in the three strains. Thus, when administered to SD and Lewis rats prior to the test stage of the PTSA procedure, paroxetine dose-dependently decreased the number of ELP-U and the number of ELP-C (Experiments 1 and 3), whereas when administered prior to regular extinction, paroxetine decreased the number of ELP-C only (Experiments 2 and 4). This pattern of results is very similar to that obtained previously with Wistar rats [12]. The only notable difference is the finding that whereas in SD rats the anti-compulsive effect of paroxetine was obtained at a dose (5 mg/kg, Experiments 1 and 2) similar to that needed

in Wistar rats (3–7 mg/kg, [12]), Lewis rats required a higher paroxetine dose (9.25 mg/kg, Experiments 3 and 4) to obtain the same effect.

Taken together, the results of Experiments 1–4 show that the response of SD and Lewis rats to signal attenuation is qualitatively similar to that of Wistar rats, both behaviorally and pharmacologically, but also point to a quantitative difference between Lewis rats and rats of the other two strains. The meta-analysis of data of Wistar, SD and Lewis rats from different experiments (Experiment 5) supports this observation and reveals additional differences between the strains.

The most important result of the meta-analysis is that Lewis rats exhibited a much higher number of compulsive lever-presses, that is, signal attenuation-induced ELP-U, compared to Wistar and SD rats. This difference is particularly striking when Lewis rats are compared only to Wistar rats, because these two strains were very similar on all measures except for the number of compulsive lever-presses. Thus, the higher 'compulsivity' of Lewis rats cannot be attributed to non-specific differences in lever-press responding or in extinction between Lewis and Wistar rats. In this sense, Lewis rats can be said to truly be more 'compulsive' than Wistar rats.

Several observations support this conclusion also with regard to the different levels of compulsivity in Lewis and SD rats. Thus, the higher number of compulsive lever-presses emitted by Lewis compared to SD rats, cannot be attributed to (1) a non-specific tendency to emit excessive lever-presses that are not followed by magazine entry, because Lewis rats did not exhibit more ELP-U compared to SD rats in the regular extinction procedure; (2) a general tendency to emit more excessive lever-presses in the PTSA procedure, because although Lewis rats emitted more ELP-C compared to SD rats, this difference cannot account for the higher number of ELP-U exhibited by Lewis rats in the PTSA procedure; (3) a general tendency to press the lever excessively, because in the last session of the lever-press training stage the number of excessive lever-presses exhibited by Lewis rats was actually lower than that exhibited by SD rats; (4) strain differences in the extinction of the stimulus-food contingency at the signal attenuation stage, because SD and Lewis rats performed similarly on the second and last sessions of signal attenuation.

The finding that Lewis rats show a high level of compulsivity in the signal attenuation model is in line with previous findings suggesting that this strain exhibits compulsive tendencies. Thus, Lewis rats have been reported to run excessively in a running wheel [32] and to perform inefficiently on a variable interval free operant lever-pressing task due to excessive lever-pressing [20] (it should be noted that in both studies the performance of Lewis rats was compared to that of Fischer 344 rats, another inbred strain derived from SD, and not to SD or Wistar rats, as has been done in the present study). The novel aspect of the present finding is that compulsive behavior was demonstrated using an established animal model of OCD, in which pharmacological and neural relevance to the modeled disorder have been demonstrated (for review see [9]).

Another novel finding of the present study is that a higher dose of paroxetine was needed to obtain an anti-compulsive effect in Lewis rats compared to SD and Wistar rats. It could be argued that this difference is a result of the higher level of compulsive lever-presses exhibited by Lewis rats. Such a baseline-dependent account is not likely, however, because a higher dose of paroxetine was also needed to reduce the number of ELP-C in Lewis rats, although the number of ELP-C was almost identical in the Lewis and SD vehicle groups in the paroxetine dose-response experiments (compare Figs. 2 and 4). The strain difference in the response to paroxetine may reflect pharmacokinetic strain differences [2] and/or strain differences in the serotonergic system. Indeed, Lewis rats have been found to express less hippocampal and frontal cortical 5-HT1A receptor binding sites and mRNA than SD rats [1b]. It is not clear, however, whether the different sensitivity to paroxetine reported here is related to this difference, because although 5-HT1A receptors are thought to be involved in the mechanism of action of SSRIs [29,31], this function has been attributed to 5-HT1A somatodendritic autorecepots rather than to post-synaptic receptors (for a recent review see [5]). Similarly, although post-synaptic 5-HT1A receptors in the orbital cortex have been found to desensitize following repeated administration of paroxetine [4], this has been taken as evidence against their involvement in the anti-compulsive effects of this drug [4,5]. Because very little is currently known on the neurobiological differences between Lewis rats and SD or Wistar rats, it remains to be determined whether there are additional strain differences in the serotonergic system, and whether these are related to the different sensitivity to the anti-compulsive effects of paroxetine reported here. One plausible source of variation is in the expression and/or functioning of the serotonin transporter, as this transporter is the primary target of action of SSRIs. Although no study compared the functioning of the serotonin transporter in Lewis, SD and Wistar rats, Fernandez et al. [6] reported that the expression and function of this transporter was lower in Lewis compared to Fischer 344 rats. Moreover, these authors suggested that because there were no strain differences in the coding sequence of the serotonin transporter gene, the source of strain differences in the expression and functioning of the transporter may be the promoter region. This possibility is of special interest given that allelic variation in the human serotonin transporter gene promoter has been related to variation in the response to SSRIs [8,18,25,28].

Different sensitivity to paroxetine may be taken to suggest that strain differences in the serotonergic system also underlie strain differences in compulsive lever-pressing. This is not necessarily the case, however, especially as most current evidence point to the involvement of the serotonergic system in the pharmacotherapy of OCD rather than in its pathogenesis [5]. Thus, whereas strain differences in the serotonergic system may underlie strain differences in the response to paroxetine, differences in other neurotransmitter systems may underlie the observed difference in compulsive lever-pressing. One such system may be the dopaminergic system, which has been implicated in the pathophysiology of OCD (for review see [7,21]) and have been shown to play an important role in compulsive lever-pressing [11,13]. Interestingly, Nestler [23] reported differences in the mesolimbic dopamine pathway between Lewis and SD rats. Specifically, drug-naïve Lewis rats were found to display several features of the mesolimbic pathway that were similar to

those of morphine- and cocaine-treated SD rats [23]. This finding has been related to the observation that Lewis rats are more vulnerable to drug addiction compared to SD rats (for review see [17]). As has been noted by others, the fact that Lewis rats show both increased compulsivity and increased vulnerability to drug addiction suggests that compulsive behavior and drug addiction may share certain underlying molecular mechanisms [19,27,32], and the dopaminergic system is a possible candidate to serve both tendencies.

Finally, the finding that rats of the Lewis inbred strain exhibit compulsive tendencies compared to rats of the outbred strain from which the Lewis strain is derived, supports the possibility that genetic factors may influence the vulnerability to develop OCD. Indeed, variation in several genes related to serotonin and dopamine neurotransmission have been linked to OCD (for a recent review see [16]).

Another noteworthy finding of the meta-analysis is that SD rats exhibited a high number of ELP-U in the regular extinction procedure compared to Wistar and Lewis rats. This unexpected outcome may be related to the findings that SD rats showed higher levels of excessive lever-pressing at the end of the lever-press training stage and faster extinction on the first session of the signal attenuation stage compared to the other two strains. These latter two findings suggest that by the end of lever-press training, the tone + light stimulus was less effective in controlling the behavior of these rats compared to the other two strains. Whereas different mechanisms may account for this decreased efficacy, the possibility that it reflects a weaker stimulus-food association in SD rats is particularly intriguing because signal attenuation-induced ELP-U has been suggested to reflect the weakening of the stimulus-food contingency in the signal attenuation stage. Thus, it might be argued that high levels of ELP-U in regular extinction, high levels of excessive lever-pressing at the end of lever-press training and faster extinction on the first session of signal attenuation may all be a result of a weaker stimulus-food association. However, ELP-U in regular extinction in SD rats (like in Wistar and Lewis rats) are pharmacologically different from signal attenuation-induced ELP-U, in that only the latter type of ELP-U are reduced by the SSRIs paroxetine (present study) and fluvoxamine [9]. This differential drug response does not support the possibility that a similar mechanism underlies ELP-U in regular extinction and in PTSA in SD rats.

We have previously suggested that compulsive lever-pressing may provide an animal model of compulsive behavior in OCD with construct validity, which derives from similarities in the underlying inducing mechanism (i.e., attenuation of an external feedback and a deficient response feedback mechanism, respectively) and in the neural systems involved (the orbital cortex and the serotonergic and dopaminergic systems); face validity, that is, compulsive lever-presses are both excessive and unreasonable, as are compulsions; and predictive validity, that is, selectivity for anti-obsessional/anti-compulsive drugs (for a detailed review see [9]; the application of the terms construct, face and predictive validity to animal models of psychopathology is after [22,33]). The data from which these conclusions were drawn were all obtained in Wistar rats. The present findings that the behavioral effects of signal attenuation are evident also in SD and Lewis rats and that the anti-compulsive drug paroxetine exerts the same effect in SD and Lewis rats as it does in Wistar rats, demonstrate the generality of the signal attenuation model. Moreover, the present finding that rats from the Lewis strain, which has previously been suggested to exhibit compulsive tendencies, exhibit more signal attenuation-induced ELP-U compared to SD and Wistar rats, contributes to the model's validity and further strengthens our claim that signal attenuation-induced ELP-U provides the measure of compulsive behavior in the signal attenuation model.

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