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REVIEW

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The signal attenuation rat model of obsessive–compulsive disorder: a review

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Abstract During the last 30 years, there have been many attempts to develop animal models of obsessive–compulsive disorder (OCD), in the hope that they may provide a route for furthering our understanding and treatment of this disorder. The present paper reviews a recently developed rat model of OCD, namely, signal attenuation. Results of pharmacological and lesion studies are presented and evaluated with respect to the pharmacology and pathophysiology of OCD. It is argued that signal attenuation is a rat model of OCD with construct (derived from similarity in the underlying mechanisms), predictive (derived from similarity in response to treatment), and face (derived from phenomenological similarity between "compulsive" behavior in the model and compulsions in OCD patients) validity.

Keywords Animal model · Compulsive lever-pressing

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 (4th edition; DSM IV) (American Psychiatric Association 1994), the essential features of OCD are recurrent obsessions or compulsions (e.g., doubting, checking, washing).

For obvious reasons, the understanding and treatment of diseases such as OCD must rely heavily on appropriate animal models that closely mimic their behavioral and, if possible, their neural manifestations. During the last 3 decades, several animal models of OCD have been developed (for comprehensive reviews of these models and an assessment of their validity, see Insel et al. 1994; Joel, in press; Man et al. 2004; Pitman 1989; Ricciardi and Hurley 1990; Stein et al. 1994; Winslow and Insel 1991). These models can be divided into three classes: ethological, pharmacological, and genetic.

Ethological models include naturally occurring repetitive or stereotypic behaviors, such as tail chasing, fur chewing and weaving (for review, see Insel et al. 1994; Stein et al. 1994; Winslow and Insel 1991); innate motor behaviors that occur during periods of conflict, frustration, or stress (displacement behaviors), such as grooming, cleaning, and pecking (for review, see Insel et al. 1994; Pitman 1991; Ricciardi and Hurley 1990; Winslow and Insel 1991); and natural behaviors that occur following some behavioral manipulation (adjunctive behaviors; for review, see Insel et al. 1994), such as schedule-induced polydipsia (Woods et al. 1993) and food-restriction-induced hyperactivity (Altemus et al. 1996). These models rest primarily on behavioral similarity between the behavior in the model and the clinical condition. The similarity may be evident at two levels: at the level of the specific behavior, e.g., grooming in animals and cleaning in patients; and at a more abstract level, e.g., the behavior induced in the model is repetitive as are compulsions. The effects of serotonin reuptake inhibitors (SRIs), currently the only efficient monotherapy for OCD, have been tested in some of these models (Altemus et al. 1996; Nurnberg et al. 1997; Rapoport et al. 1992; Szechtman et al. 1998; Winslow and Insel 1991; Woods et al. 1993), and in some models, the effects of SRIs have also been compared to the effects of drugs known not to be effective in OCD (Altemus et al. 1996—fluoxetine vs imipramine; Rapoport et al. 1992—clomipramine, sertraline, and fluoxetine vs desipramine and fenfluramine; Winslow and Insel 1991—clomipramine vs desipramine; Woods et al. 1993—fluvoxamine, fluoxetine, and clomipramine vs desipramine, haloperidol, and diazepam). Although some of these models have good predictive validity in addition to face validity, many have not been used since the original publications. To date, only three behavioral models of OCD are in use, namely, the barbering (Garner et al. 2004a,b), marble burying (Broekkamp et al. 1986; Broekkamp and Jenck 1989;

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Gyertyan 1995; Londei et al. 1998; Njung'e and Handley 1991), and signal attenuation models. Similar to earlier behavioral models, barbering and marble burying have been suggested as potential models of OCD on the basis of behavioral similarity. In contrast, the signal attenuation model, the focus of the present review, is a theory-driven model of OCD, in which a "compulsive"-like behavior is induced by simulating a deficient psychological mechanism hypothesized to underlie compulsive behaviors in OCD.

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, 2001). In addition to behavioral similarity, the relevant behavior in these models is induced by manipulations of a neurotransmitter system whose dysfunction has been implicated in OCD. Thus, in the model of Yadin et al. (1991), perseveration is induced by manipulations of the serotonergic system, whereas in the model of Szechtman and colleagues, compulsive checking is induced by manipulations of the dopaminergic system. Finally, in both models, drug-induced compulsive-like behavior has been shown to be reduced by administration of an SRI (fluoxetine and clomipramine in the model of Yadin et al. 1991 [Yadin et al. 1991 and Fernandez-Guasti et al. 2003, respectively], and clomipramine in the model of Szechtman et al. 1998). Recently, *meta*-chlorophenylpiperazine (mCPP)-induced position preference in a T-maze has been suggested to provide a model of compulsive behavior, as it has been demonstrated that mCPP-induced position preference is blocked by chronic treatment with fluoxetine but not with diazepam or desipramine (Tsaltas et al. 2005).

In recent years, four genetic mice models of OCD have been presented: the D1CT-7 transgenic mouse model of comorbid Tourette's syndrome and OCD (Campbell et al. 1999a–c; McGrath et al. 1999a,b; Nordstrom and Burton 2002), the Hoxb8 mutants as a model of the OC-spectrum disorder trichotillomania (Greer and Capecchi 2002), the 5-HT2c receptor knockout mouse as a model of compulsive

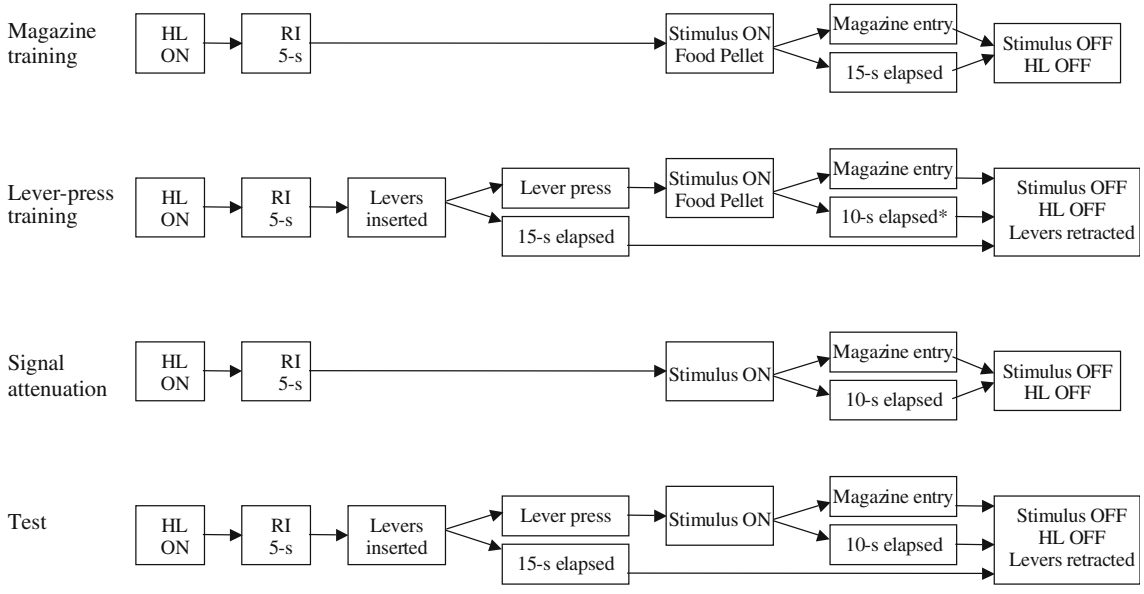

Fig. 1 A schematic diagram of the organization of a trial in each of the different training stages of the post-training signal attenuation procedure. In the magazine training stage (days 1–3), rats are trained to collect food pellets from the food magazine in the operant chamber, with the levers retracted. On each trial, a single food pellet is dropped into the food magazine, simultaneous with the onset of a compound stimulus (an 80-dB, 2.8-kHz tone and the magazine light). The stimulus is turned off after the rat's head enters the food magazine or after 15 s has elapsed, and a 30-s intertrial interval begins. In the lever-press training stage (days 4–6), rats are trained to lever-press in a discrete-trial procedure. On each trial, both levers are inserted into the chamber. Responding on one of the levers (reinforced lever; RL) results in the delivery of a single food pellet into the magazine, accompanied by the presentation of the compound stimulus. The levers are retracted and the compound stimulus is turned off after the rat's head enters the food magazine or after 10 s from the rat's first lever-press has elapsed. Further lever-presses on the RL as well as responding on the other lever (nonreinforced lever) are recorded, but have no programmed consequences. In the signal attenuation stage (days 7–9), with the levers retracted, rats are exposed to the presentation of the compound stimulus as on days 1–3, but no food is delivered to the food magazine (it should be noted that the pellet dispenser is activated as in previous stages, producing its typical noise, but no pellet is delivered because the pellet dispenser is empty at this stage). In the test (day 10), rats are trained as in the lever-press training stage, except that no food is delivered to the food magazine, i.e., pressing the lever results in the presentation of the compound stimulus only (again, the pellet dispenser is activated, but is empty). To assess rats' tendency for excessive lever-pressing, the number of lever-presses on the nonreinforced lever and the number of lever-presses on the reinforced lever after the first response (extra lever-presses; ELP) are recorded. The latter measure is further subdivided into ELP that are not followed by insertion of the head into the food magazine during stimulus presentation (ELP-U) and ELP that are followed by insertion of the head into the food magazine during stimulus presentation (ELP-C). *HL* houselight, *RI* random interval, *Lever press* a press on the reinforced lever. *On the first day of lever-press training, this time limit is 15 s

behavior in OCD (Chou-Green et al. 2003), and the dopamine transporter knockdown mouse as a model of OCD and Tourette's syndrome (Berridge et al. 2004). It is important to note that the above models were not created on the basis of a known mutation in humans that was found to be related to OCD. Rather, these models are based on behavioral similarity, i.e., the behavior of genetically modified mice was found to be similar in specific respects to that of OCD patients (e.g., excessive), and this is the main basis for the claim that they may serve as animal models of this disorder. Regretfully, to date there are no reports on the effects of different pharmacological treatments in these models, which could have strengthened their relevance to OCD.

The signal attenuation rat model of OCD

The signal attenuation model has been developed 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., Baxter 1999; Gray 1982; Malloy 1987; Pitman 1991; Pitman et al. 1987, Reed 1977; Szechtman and Woody 2004; for review, see Otto 1992). In the model, the normal behavior is lever-pressing for food, and the feedback for the response is an external stimulus, which follows the lever-press response and is accompanied by the presentation of the food reward. Thus, the stimulus signals that the lever-press response was effective in producing food. The deficiency in response feedback is simulated by extinguishing the contingency between the stimulus and the reward ("signal attenuation"). The procedure used to establish a stimulus as a response feedback and to test the effects of signal attenuation on the performance of this response has been termed post-training signal attenuation.

The post-training signal attenuation procedure

The post-training signal attenuation procedure includes four stages. First, a stimulus (typically the magazine light and a tone) is established as a signal for the delivery of food by repeatedly pairing it with food (magazine training). Next, rats are trained to lever-press for food, whose delivery is accompanied by the presentation of the stimulus (lever-press training). Because rats experience the stimulus before they find the food, the stimulus comes to signal that the lever-press response was effective in producing food. In the third stage (signal attenuation), the stimulus is repeatedly presented without food (the levers are not present at this stage). It is hypothesized that the extinction of the stimulus–food contingency in this stage attenuates the "signaling" property of the stimulus. In the last stage (test), the effects of signal attenuation on rats' lever-press behavior are assessed under extinction conditions, i.e., pressing the lever results in the presentation of the stimulus but no food is delivered (see Fig. 1).

The assessment of the effects of signal attenuation on lever-press responding is performed under extinction conditions to prevent the fast relearning of the stimulus–food association, which would occur if the test is carried out under rewarded conditions. The fact that the test is carried out under extinction conditions may, however, confound the assessment of the effects of signal attenuation because an encounter of nonreward produces an increase in operant responding (i.e., an extinction burst). To better differentiate between the effects of signal attenuation and of extinction per se, the behavior of rats undergoing an extinction test preceded by a signal attenuation stage has been compared to that of rats 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").

The behavior

Figure 2 presents the results of an experiment comparing the behavior of rats that underwent the post-training signal attenuation procedure to that of rats that underwent the regular extinction procedure. As can be seen, the effect of nonreward is clearly seen in the regular extinction procedure in the form of a high number of excessive lever-presses that are followed by magazine entry (extra lever-presses in completed trials; ELP-C). Such a behavior is also exhibited by rats that underwent signal attenuation prior to the extinction test, but these rats show in addition an equally high number of lever-presses that are *not* followed by magazine entry (extra lever-presses in uncompleted trials; ELP-U). It should be noted that although the mean number of ELP-C and ELP-U may vary

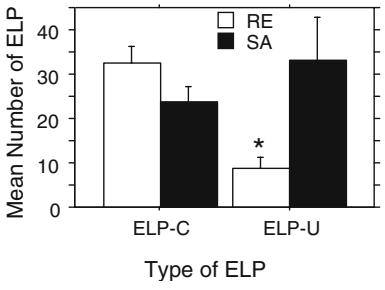

Fig. 2 The mean and standard error of the mean number of extra lever-presses that were followed by an attempt to collect a reward (*ELP-C*) and extra lever-presses that were not followed by an attempt to collect a reward (*ELP-U*) exhibited by intact rats (Wistar) undergoing the test of the post-training signal attenuation procedure (*SA*, n=12) or of the regular extinction procedure (*RE*, n=10). Mixed ANOVA with a main factor of procedure (SA, RE) and a repeated measurements factor of type of ELP (ELP-C, ELP-U) yielded a significant procedure × type of ELP interaction, $F(1,20)=6.93$, $p<0.02$ (the effect of procedure and of type of ELP was not significant, $F(1,20)=1.75$, $p=0.20$ and $F(1,20)=1.35$, $p=0.26$, respectively); post hoc least significant difference comparisons comparing the number of ELP-C and ELP-U between the two procedures yielded a significant difference between the number of ELP-U in the post-training signal attenuation and regular extinction procedures ($p<0.05$), but not in the number of ELP-C

considerably across experiments, the distribution of ELP-C and ELP-U in the two procedures is consistent. That is, in rats undergoing signal attenuation, the number of ELP-U is similar to or higher than the number of ELP-C, whereas in rats undergoing regular extinction, the number of ELP-U is much lower than the number of ELP-C (e.g., Fig. 2; Joel and Doljansky 2003; Joel et al. 2004).

ELP-C and ELP-U are operationally defined according to the presence or absence, respectively, of a nose-poke during stimulus presentation. To better understand the behavioral differences between ELP-C and ELP-U, we have looked at two measures of rats' behavior: the rate of lever-presses (stated in terms of inter-response intervals between successive lever-presses), and the latency between the last lever-press and the first nose-poke. We have calculated these measures for each trial and then compared these measures between trials in which a nose-poke was made during stimulus presentation (i.e., completed trials) and trials in which a nose-poke was not made during stimulus presentation (i.e., uncompleted trials). In addition, we compared the rats' behavior in the last session of lever-press training, in an extinction test preceded by signal attenuation and in regular extinction, using these measures (Figs. 3 and 4; please note that because in the last session of lever-press training rats never failed to collect the food during stimulus presentation, there were no uncompleted trials and no ELP-U at this stage). Figure 3 presents the proportion of inter-response intervals in 0.25-s time bins. As can be seen, in the last session of lever-press training, when more than one lever-press was made in a single trial, the inter-response interval was very short (typically less than 1 s; Fig. 3a). Inter-response intervals of successive lever-presses performed at the extinction test were somewhat longer than those made during the last session of lever-press training (Fig. 3b–e). However, there were no differences in the distribution of inter-response intervals performed in completed vs uncompleted trials, or in an extinction test preceded or not preceded by signal attenuation. Thus, there seems to be no difference between ELP-C and ELP-U in terms of the intervals between successive lever-presses.

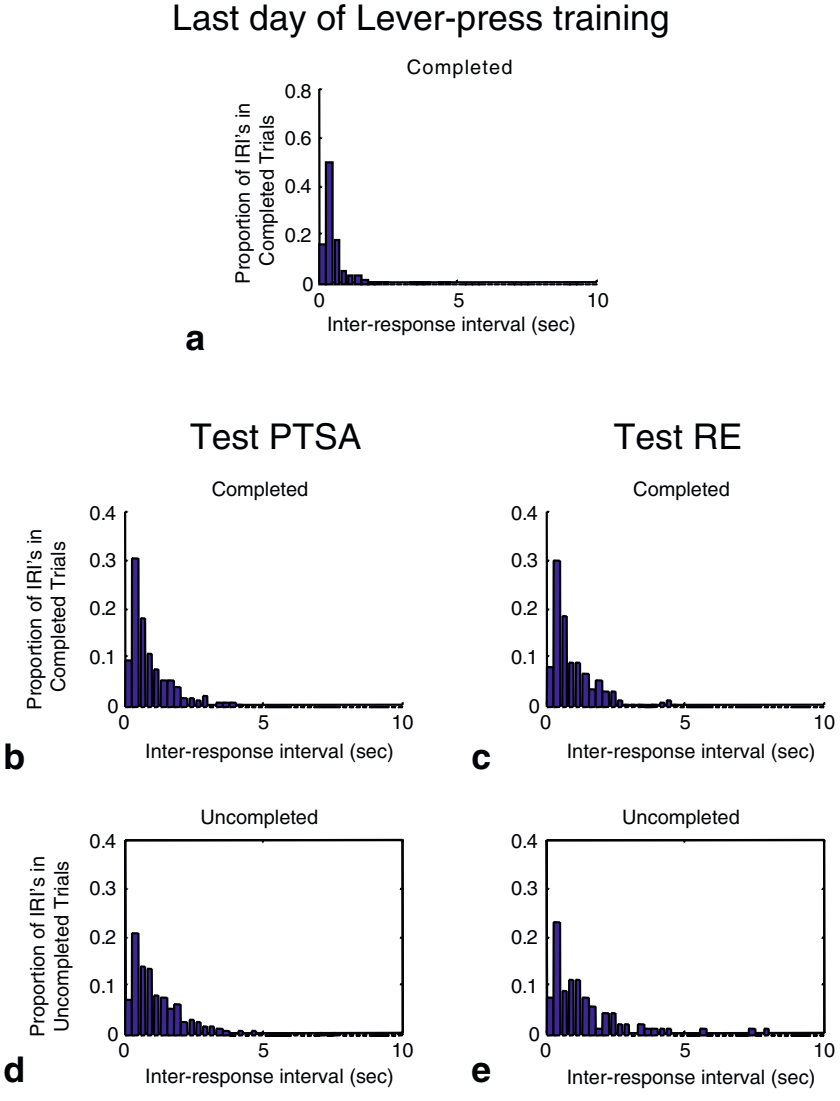

Fig. 3 The proportion of inter-response intervals in 0.25-s time bins of successive lever-presses performed on completed trials in the last day of lever-press training (**a**), the test stage of the post-training signal attenuation procedure (**b**), and the test stage of the regular extinction procedure (**c**), as well as on uncompleted trials in the test stage of the post-training signal attenuation procedure (**d**) and the test stage of the regular extinction procedure (**e**)

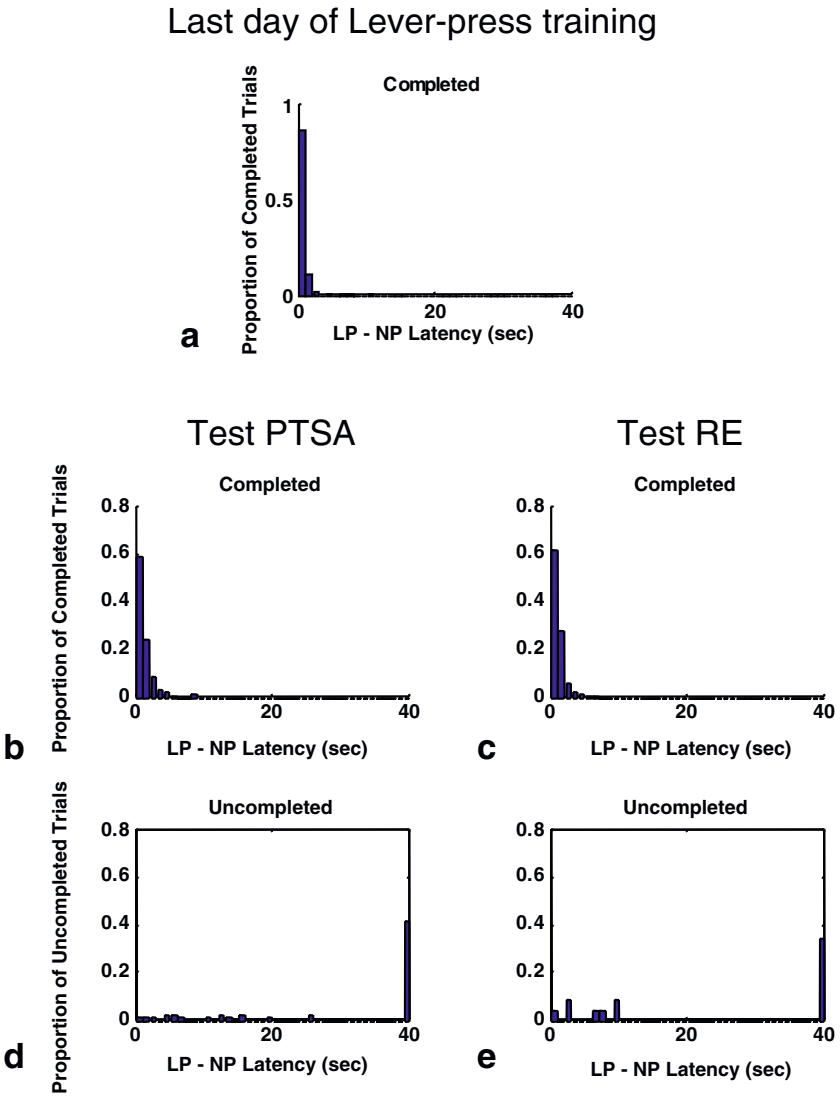

Fig. 4 The proportion of last lever-press to first nose-poke intervals in 1-s time bins on completed trials in the last session of lever-press training (**a**), the test stage of the post-training signal attenuation procedure (**b**), and the test stage of the regular extinction procedure (**c**), as well as on uncompleted trials in the test stage of the post-training signal attenuation procedure (**d**) and the test stage of the regular extinction procedure (**e**). In trials in which a nose-poke was not performed until the end of the intertrial interval, the lever-press–nose-poke interval was scored as 40 s, which is the maximum interval between a lever-press and a nose-poke in a single trial

In contrast, ELP-C and ELP-U differ markedly in terms of the latency between the last lever-press and the first nose-poke (Fig. 4). Whereas in completed trials the latency between the last lever-press and the first nose-poke is typically lower than 2 s (Fig. 4b and c), similar to the lever-press–nose-poke latency during the last session of lever-press training (Fig. 4a), in uncompleted trials there is no clear relation between the last lever-press and the first nose-poke, and on about 40% of uncompleted trials, no nose-poke is performed during the intertrial interval (Fig. 4d and e). This pattern suggests that although in both ELP-C and ELP-U the lever-press response is emitted excessively, in ELP-C the behavioral sequence of a lever-press and a nose-poke is completed, whereas in ELP-U this sequence is disrupted. It is of interest to note that an inability to inhibit a response in a learned behavioral sequence so that the next response in the sequence can be performed has been related to compulsive behaviors (Chudasama et al. 2003; Robbins 2002).

The above analysis suggests that ELP-C and ELP-U are qualitatively different, irrespective of the procedure used to induce these types of excessive lever-presses (i.e., post-training signal attenuation or regular extinction). However, there are quantitative differences between ELP-C and ELP-U in the two procedures, whereby ELP-U are induced to a much larger extent after signal attenuation, whereas the number of ELP-C in the two procedures is quite similar. In view of these differences, we have suggested that in a test stage conducted after signal attenuation, ELP-U reflect the rats' response to the encounter of an attenuated signal, whereas ELP-C reflect the rats' response to the encounter of nonreward. In addition, we argued that signal-attenuation-induced ELP-U bear some 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 (DSM-IV; Rapoport 1989; Reed 1985). These hypotheses, derived at the behavioral level, are supported by the different patterns of drug and lesion effects on ELP-C and on ELP-U in the two procedures (see succeeding sections).

Pharmacology of compulsive lever-pressing (i.e., signal-attenuation-induced ELP-U)

Since one of the most salient features of OCD is its selective response to treatment with SRIs (Masand and Gupta 1999; Piccinelli et al. 1995; Pigott and Seay 1999; Stein et al. 1995; Zohar et al. 1992), we have tested whether compulsive lever-pressing shows a similar pharmacological selectivity. The effects of drugs that are known to be effective in OCD as well as drugs that were found not to be effective in this disorder were assessed (Table 1). First, the effects of each drug were tested in the post-training signal attenuation procedure using several doses, ranging from a dose that had no effect on rats' behavior to a dose that abolished responding altogether. Next, to better differentiate between the drug's effects on the behavioral response to signal attenuation and on extinction per se, drug doses that were effective in the post-training signal attenuation procedure without completely abolishing responding were tested in an extinction test not preceded by signal attenuation (i.e., regular extinction of the lever-press response). All the experiments described below employed acute administration of drugs prior to the test stage.

The effects of selective serotonin reuptake inhibitors

The effects of acute administration of three selective serotonin reuptake inhibitors (SSRIs), paroxetine, fluvoxamine (Joel et al. 2004), and fluoxetine (Joel and Avisar 2001), were assessed in the post-training signal attenuation procedure. We refer here only to the results obtained with the first two drugs because the effects of fluoxetine were assessed using an older version of the software which did not enable the separate recording of ELP-C and ELP-U (Joel and Avisar 2001). Paroxetine and fluvoxamine exerted very similar effects. When administered prior to an extinction session of lever-press responding that was preceded by signal attenuation, paroxetine (1, 3, 5, 7, and 10 mg/kg, administered i.p. 30 min before the test) and fluvoxamine (10, 15, and 20 mg/kg, administered i.p. 30 min before the test) dose-dependently decreased the number of ELP-U and 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 (7 mg/kg) and fluvoxamine (15 mg/kg) decreased the number of ELP-C without affecting the number of ELP-U (Joel et al. 2004).

Figure 5 presents the results of an experiment which assessed the effects of a single dose of fluvoxamine (15 mg/kg) in both the post-training signal attenuation and the regular extinction procedures. It is clearly seen that fluvoxamine decreased ELP-C in the two procedures (Fig. 5a) but decreased ELP-U only in the post-training signal attenuation procedure (Fig. 5b; although fluvoxamine tended to increase the number of ELP-U in rats undergoing regular extinction, this increase, which was not observed in a previous experiment [Joel et al. 2004], was not significant).

Table 1 Summary of drugs' effects on ELP-C and ELP-U in the post-training signal attenuation and regular extinction procedures

	ELP-C		ELP-U	
	SA	RE	SA	RE
Paroxetine	↓	↓	↓	–
Fluvoxamine	↓	↓	↓	–
Desipramine	↓	↓	–	–
Diazepam	(↓)	↓	(↓)	↓
Haloperidol	↓	↓	↓	↓

SA post-training signal attenuation, *RE* regular extinction

The effects of drugs that are not effective in the treatment of OCD

We also tested the effects of three drugs that are known not to be effective in the treatment of OCD when given as monotherapy, namely, the anxiolytic drug diazepam (Cassano et al. 1975; Waxman 1977, see also Argyropoulos et al. 2000; Kim et al. 1997; Montgomery 1993; Stein 2002), the tricyclic antidepressant desipramine (Goodman et al. 1990; Hoehn-Saric et al. 2000; Leonard and Rapoport 1989; Leonard et al. 1989; Piccinelli et al. 1995), and the antipsychotic haloperidol (e.g., McDougle et al. 1990, 1994).

Desipramine (5–15 mg/kg, administered i.p. 60 min before the test) and haloperidol (0.005–0.05 mg/kg, administered i.p. 60 min before the test) had a similar effect on rats' lever-press responding regardless of whether lever-press extinction was preceded by a signal attenuation stage or not. Desipramine decreased the number of ELP-C, while having no effect on the number of ELP-U in both procedures (Joel et al. 2004), whereas haloperidol decreased both ELP-C and ELP-U in the two procedures (Joel and Doljansky 2003).

Diazepam (2–10 mg/kg, administered i.p. 30 min before the test) 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). In contrast, when administered prior to an extinction session not preceded by signal attenuation, diazepam significantly decreased the number of ELP-C already at a dose of 4 mg/kg and almost completely abolished ELP-U at all doses tested (2, 4, 6, and 8 mg/kg) (Joel et al. 2004).

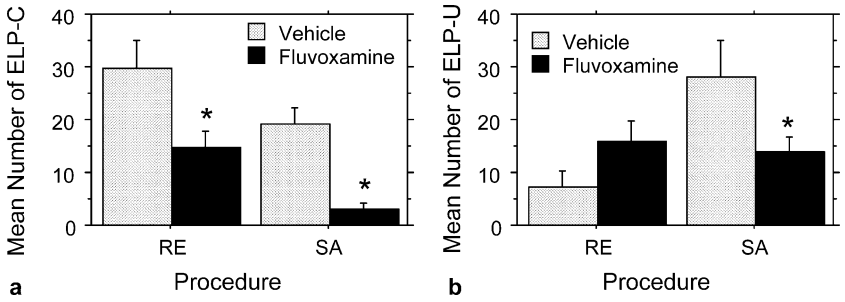

Fig. 5 The mean and standard error of the mean number of extra lever-presses that were followed by an attempt to collect a reward (*ELP-C*) (**a**) and extra lever-presses that were not followed by an attempt to collect a reward (*ELP-U*) (**b**) exhibited by vehicle-treated and fluvoxamine-treated rats (Sprague Dawley, n=32) undergoing the test of the post-training signal attenuation procedure (*SA*) or of the regular extinction procedure (*RE*). Two-way ANOVAs with main factors of procedure (SA, RE) and drug (fluvoxamine, vehicle) were conducted on the number of ELP-C and ELP-U. ELP-C: significant main effects of procedure, $F(1,28)=10.87$, $p<0.005$, and drug, $F(1,28)=21.40$, $p<0.0001$ [the procedure × drug interaction was not significant, $F(11,28)<1$]. ELP-U: a significant procedure × drug interaction, $F(1,28)=4.77$, $p<0.05$ [the effect of procedure approached significance, $F(1,28)=3.33$, $p=0.078$; the effect of drug was not significant, $F(1,28)<1$]; post hoc least significant difference comparisons comparing fluvoxamine- and vehicle-treated groups in each procedure yielded a significant difference between these groups in the post-training signal attenuation procedure ($p<0.05$), but not in the regular extinction group

Summary and interpretation of the pharmacological studies

Table 1 presents a summary of drugs' effects on ELP-C and ELP-U in the two procedures (post-training signal attenuation and regular extinction). As can be seen, all drugs decreased the number of ELP-C in both procedures. In contrast, the different drugs exerted different effects on the number of ELP-U, depending on the procedure used. Specifically, the two SSRIs 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; diazepam had no effect on signal-attenuation-induced ELP-U at doses that markedly reduced ELP-U in regular extinction; and haloperidol decreased the number of ELP-U in both procedures. 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 nor ELP-C in the two procedures 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.

Drugs' effects on extinction The finding that the different drugs had a similar effect on ELP-C regardless of whether the test was preceded by signal attenuation or not supports the suggestion that ELP-C does not reflect rats' response to signal attenuation but rather their response to the encounter of nonreward in the extinction test. To the best of our knowledge, this is the first report on the effects of acute administration of SSRIs or desipramine on extinction. Our findings suggest that the three antidepressants may facilitate extinction of lever-press responding or attenuate the extinction burst, in agreement with previous reports that acute administration of tricyclic antidepressants facilitate extinction of active avoidance and of fear-induced ultrasonic vocalization (Kikusui et al. 2001; Telegdy et al. 1983). Our findings seem to contradict, however, previous reports that diazepam at low doses (2–4 mg/kg), as well as other anxiolytic drugs, retards rather than facilitates the extinction of a variety of pavlovian and operant behaviors (e.g., Cowie et al. 1987; Feldon and Gray 1981; Halevy et al. 1986; McNaughton 1984; Soubrie et al. 1978), including lever-pressing for a food reward (Thiebot et al. 1983). Two findings, therefore, require an explanation: the finding that low diazepam doses decreased the number of ELP-C and ELP-U in rats undergoing regular extinction, and the finding that at these doses, diazepam had no effect on ELP-C and ELP-U in rats undergoing post-training signal attenuation.

Although anxiolytic drugs such as diazepam are known to counteract the effects of nonreward (for review, see Gray 1982), it should be borne in mind that the encounter of nonreward elicits two responses: The initial encounter of nonreward elicits an increase in the rate of the previously reinforced behavior [e.g., the extinction burst observed at the early stages of extinction; the higher response rate after nonrewarded compared with rewarded responses (Manning and McDonough 1974; Wookey and Strongman 1974)], an effect often referred to as a "frustration effect" (Gray 1982; Mackintosh 1974), whereas repeated exposure to nonreward, as in extinction, typically results in the suppression of the previously rewarded behavior (Gray 1982; Mackintosh 1974). In agreement with the known effects of anxiolytics on the frustration effect, low doses of diazepam reduced the number of excessive lever-presses in our regular extinction procedure. At these doses, however, diazepam had no effect on the number of trials on which rats did not press the lever (unpressed trials), a behavioral measure which may reflect the suppressive effects of repeated exposure to nonreward in our procedure. The lack of effect of low diazepam doses on unpressed trials may be due to (1)

procedural differences, as drug effects are known to depend on the schedule of reinforcement and the type of reinforcer (Kelleher and Morse 1968). Specifically, the present procedure employs a discrete-trial lever-press procedure in which, to the best of our knowledge, the effects of benzodiazepines have never been tested. Another reason may be (2) insufficient sensitivity of the behavioral measure of unpressed trials. It is possible that a more sensitive measure (e.g., the latency to the first lever-press on each trial) could have detected diazepam's effects. However, such data were not available to us at the time of this study.

The lack of effect of low diazepam doses on ELP-C and ELP-U in rats undergoing post-training signal attenuation can be taken to suggest that in this procedure, excessive lever-presses reflect the unconditioned effects of nonreward, as these are known to be immune to the influence of anxiolytics (Gray 1982). An alternative explanation may be that in the post-training signal attenuation procedure, the encounter of nonreward in the test generates little frustration because this encounter occurs after three sessions of extinction of the stimulus–food contingency (in the signal attenuation stage). This suggestion is derived by analogy from the observation that anxiolytic drugs do not antagonize the suppressive effects of aversive stimuli (i.e., neutral stimuli that had been associated with an unconditioned aversive stimulus, such as shock) once behavioral suppression is well developed and the unconditioned aversive stimulus is no longer likely (as in a well-learned avoidance task; Gray and McNaughton 2000). Although there are no aversive stimuli in the post-training signal attenuation procedure, stimuli that signal no reward have, under many circumstances, similar effects to aversive stimuli (Gray 1982; Mackintosh 1974). It is therefore possible that diazepam does not affect excessive lever-pressing in the post-training signal attenuation procedure because encountering nonreward in the test after three sessions of extinction of the stimulus–food contingency does not result in a strong aversive response (or frustration).

Another mechanism that could be invoked to account for the finding that diazepam had no effect on excessive lever-pressing in post-training signal attenuation at doses that significantly decreased this behavior in regular extinction may be derived from the rate dependency hypothesis. Rate dependency refers to the observed relation between the behavioral effects of drugs and the level of responding before the drug was given (Kelleher and Morse 1968). Because most, if not all, of the work on rate dependency has been done using free operant schedules, it is not clear what is the appropriate measure of rate of responding in our discrete-trial procedure. However, rate dependency cannot account for the differences in diazepam effects in the post-training signal attenuation and regular extinction procedures regardless of whether rate of responding is assessed using inter-response intervals or the total number of responses because, using these measures, similar levels of responding are typically obtained in the two procedures. In contrast, the ELP-C–ELP-U distribution is markedly different in the two procedures, and this could account for the observed differences in diazepam effects. Specifically, in the experiments testing the effects of diazepam, the mean number of ELP-C and ELP-U of the vehicle group that underwent post-training signal attenuation was 15.8 [standard error (SE)=3.9] and 20.4 (SE=4.1), respectively, whereas the mean number of ELP-C and ELP-U of the vehicle group that underwent regular extinction was 36.1 (SE=5.4) and 5.8 (SE=2.0), respectively. If, in discrete-trial procedures, rate of responding is reflected in the number of responses, then diazepam effects at low doses may be seen as decreasing the lowest and highest rates of responding, while leaving the intermediate rates unaffected. Benzodiazepines have been previously reported, however, to decrease high rates of responding and increase low rates of responding (Kelleher and Morse 1968). Thus, even if we take into account the different distribution of ELP-C and ELP-U in the two procedures, it seems that rate dependency cannot account for the differential effects of diazepam in the two procedures.

Drugs' effects on compulsive lever-pressing The finding that ELP-U in post-training signal attenuation and ELP-U in regular extinction are affected differently by the four classes of drugs suggests that signal-attenuation-induced ELP-U are both quantitatively and qualitatively different from ELP-U in regular extinction. Moreover, the finding that only the two SSRIs 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 the measure of compulsive responding in the signal attenuation model and lends the signal attenuation model predictive validity.

It could be argued, however, that this conclusion is unwarranted because we have used acute drug administration, whereas SRIs require several weeks of treatment to produce beneficial effects in humans. There is currently a disagreement on the importance of demonstrating similarity in treatment regimen (acute vs chronic) in an animal model and the modeled disease. Bourin et al. (2001) stated that a demonstration of a "therapeutic" effect in a model after acute treatment undermines the model's predictive validity. Matthysse (1986) included a demonstration that the pharmacological effect grows stronger with time among the requirements for establishing pharmacological isomorphism. Willner (1991) argued that the demonstration of drug effects in a model after a period of chronic administration is important for establishing its face validity, but is not relevant to the model's predictive validity and therefore to its ability to serve as a screening test for treatments for the modeled disease. Similarly, Geyer and Markou (2002) concluded that a demonstration of therapeutic effects following acute administration does not undermine the screening abilities of a specific paradigm, although it may detract from the validity of the model. Furthermore, Matthysse (1986) and Geyer and Markou (2002) pointed out to some difficulties with the notion of delayed drug effects in psychiatric disorders,

such as the fact that in most animal studies acute effects are obtained with much higher doses than would be tolerated by humans and the possibility that drugs may also have acute effects in humans, but that this effect may be hard to detect statistically (for a recent criticism of the notion of delayed-onset action, see Agid et al. 2003). These difficulties may also be relevant to OCD, especially because to prevent side effects, SSRI treatment is typically started with low doses which are gradually increased, and the difference between the initial dose and the therapeutic dose may be very large (e.g., 50 vs 200–300 mg/day, respectively, for fluvoxamine, Masand and Gupta 1999). With regard to the signal attenuation model, it may thus be argued that the extant results with acute drug administration support its predictive validity and therefore its ability to serve as a screening test for anticompulsive drugs. Clearly, a demonstration that therapeutic effects in the model are obtained following chronic administration of SSRIs at doses that do not produce a significant acute effect is needed before the model can be used to address temporal patterns characteristic of OCD pharmacology. It should be noted however that in its present form, the post-training signal attenuation procedure is not well suited for chronic drug administration studies because repeated drug administration may affect behavior in the early stages of the procedure (e.g., lever-press training, signal attenuation).

Blockade of D1 receptors: a potential treatment of OCD?

When studying the effects of dopaminergic manipulations on compulsive lever-pressing (Joel et al. 2001; Joel and Doljansky 2003), we found that administration of the D1 antagonist SCH 23390 (0.005, 0.01, and 0.03 mg/kg, administered i.p. 60 min before the test) prior to an extinction session of lever-press responding that was preceded by signal attenuation decreased the number of ELP-U without affecting the number of ELP-C. When administered prior to an extinction session not preceded by signal attenuation, SCH 23390 (0.01 mg/kg) had no effect on either measure (Joel and Doljansky 2003).

If indeed a decrease in ELP-U in the post-training signal attenuation procedure but not in a regular extinction procedure is indicative of an anticompulsive effect, the pattern of results obtained with SCH 23390 suggests that a new approach to the treatment of OCD may be the blockade of D1 receptors. Interestingly, on the basis of a theoretical model of the pathophysiology of OCD, Saxena et al. (1998) have suggested that selective D1 blockade should reduce OCD symptoms. A potential hazard in using D1 blockers to alleviate compulsions, however, is that chronic administration of such drugs leads to increased density of D1 receptors in the striatum (Creese and Chen 1985; Giorgi et al. 1993; Hess et al. 1986, 1988; Lappalainen et al. 1992; Memo et al. 1987; O'Boyle et al. 1993; Porceddu et al. 1985), and therefore, discontinuation of pharmacotherapy may lead to worsening of symptoms. Indeed, repeated administration of SCH 23390 in rats led to an increase in compulsive behavior following the termination of drug administration (Joel et al. 2001). Such a risk may be prevented by using D1 agonists, rather than antagonists, for the treatment of OCD (for a detailed discussion of the rational for this suggestion, see Joel and Doljansky 2003).

Neural substrates of compulsive lever-pressing

Functional imaging data from patients with idiopathic OCD and evidence from patients with acquired OCD implicate most consistently the orbitofrontal cortex in the pathophysiology of this disorder (e.g., Baxter et al. 1987, 1988; Benkelfat et al. 1990; Berthier et al. 1996; Breiter and Rauch 1996; Breiter et al. 1996; Cottraux et al. 1996; Hugo et al. 1999; Insel 1992; McGuire et al. 1994; Rauch et al. 1994; Saxena et al. 1999; Stein et al. 1999; Swedo et al. 1992; for review, see Saxena et al. 1998). Although there are significant differences in the details and in the complexity of the organization of the cortex of rats and primates, hodological, electrophysiological, and behavioral data suggest that the rat orbital cortex may be analog to the primate orbitofrontal cortex (for recent reviews, see Groenewegen and Uylings 2000; Ongur and Price 2000; Schoenbaum and Setlow 2001; Uylings et al. 2003). In a series of studies, we have found that bilateral excitotoxic lesions of the rat orbital cortex result in an increase in the

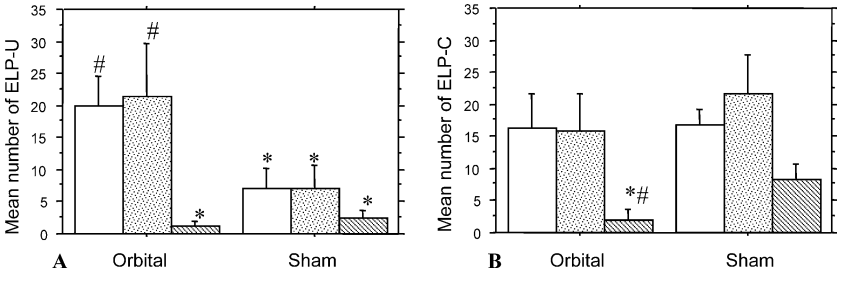

Fig. 6 The effects of 1 and 3 mg/kg paroxetine on the behavior of orbital-lesioned and sham-operated rats in post-training signal attenuation. Mean and standard error of the mean number of ELP-U (**a**) and ELP-C (**b**) in sham-operated rats and in orbital-lesioned rats treated with either vehicle (*white*), 1 mg/kg (*dotted*), or 3 mg/kg (*striated*) paroxetine (Reprinted from Joel et al. 2005a, with permission from Elsevier). *Significantly different from the orbital-vehicle group ($p<0.05$). #Significantly different from the sham-vehicle group ($p<0.05$)

number of signal-attenuation-induced ELP-U (Joel et al. 2005a,b; Fig. 6a), while having no effect on the number of ELP-U in regular extinction (Joel et al. 2005a). The orbital-lesion-induced effect on ELP-U seems to be quite selective because although orbital-lesioned rats were found to exhibit a higher number of ELP-C compared to sham rats in one experiment (Joel et al. 2005a), such an increase was not exhibited by vehicle-treated orbital-lesioned rats undergoing post-training signal attenuation (Joel et al. 2005a,b; Fig. 6b) nor by orbital-lesioned rats undergoing regular extinction (Joel et al. 2005a). Orbital-lesioned rats were also not different from their controls in the number of ELP-C during lever-press training (Joel et al. 2005a,b) nor in the number of lever-presses on the nonreinforced lever in the lever-press training and test stages (Joel et al. 2005a,b). Taken together, these results suggest that lesions to the rat orbital cortex lead to a selective increase in compulsive lever-pressing that cannot be attributed to a general lesion-induced failure of response inhibition (e.g., Brutkowski 1964; Kolb et al. 1974; Konorski 1972).

The increase in compulsive lever-pressing following orbital lesion was prevented by the SSRI paroxetine (Fig. 6a) and was paralleled by an increase in the density of the striatal serotonin transporter, suggesting that orbital-lesion-induced compulsivity is mediated by alterations of the serotonergic system, possibly of the striatal serotonergic system (Joel et al. 2005a). These findings are of particular importance given that the orbitofrontal cortex and the striatum function abnormally in OCD and that drugs that block the serotonin transporter act in OCD patients to reduce symptoms as well as to reduce the increased metabolism of the orbitofrontal cortex and the striatum (Baxter et al. 1992; Benkelfat et al. 1990; Cottraux et al. 1996; McGuire et al. 1994; Rauch et al. 1994; Saxena et al. 1999; Swedo et al. 1992). Although the extrapolation from an animal model to the clinical condition is problematic, these findings raise the possibility that in some OCD patients a primary orbitofrontal dysfunction leads to striatal serotonergic malfunction and to compulsive behavior, and that antiobsessional/anticompulsive drugs act by normalizing the dysfunctional striatal serotonergic system (for a comprehensive discussion, see Joel et al. 2005a). Interestingly, several imaging studies have reported that patients with lower pretreatment orbitofrontal cortex metabolism responded better to SRI treatment (Brody et al. 1998; Rauch et al. 2002; Saxena et al. 1999; Swedo et al. 1989), and there is some evidence that orbitofrontal cortex volume is reduced in OCD patients (Choi et al. 2004; Pujol et al. 2004; Szeszko et al. 1999).

We have also studied the effects of lesions to the basolateral nucleus of the amygdala (BLA) and to the medial prefrontal cortex, which are anatomically connected and functionally related to the orbital cortex. Lesions to the basolateral amygdala or to the medial prefrontal cortex did not have any effect on compulsive lever-pressing (Joel et al. 2005b). Given that the rat medial prefrontal cortex may correspond to regions in the dorsal and lateral subdivisions of the primate prefrontal cortex (for recent reviews, see Groenewegen and Uylings 2000; Kesner 2000; Ongur and Price 2000; Uylings et al. 2003), the finding that compulsive lever-pressing is enhanced following lesions to the orbital cortex, but not to the medial prefrontal cortex or to the basolateral amygdala, is consistent with functional imaging findings in OCD patients which consistently implicate the orbitofrontal cortex in this disorder (see above), but rarely report evidence for an involvement of the dorsal and lateral prefrontal cortex (but see Kwon et al. 2003) or of the amygdala (but see Breiter et al. 1996; Horwitz et al. 1991; Szeszko et al. 1999).

In summary, the finding that orbital lesions affect ELP-U in post-training signal attenuation but not in regular extinction provides further support to our suggestion that these two types of lever-presses are qualitatively different. Moreover, the finding that lesions to the orbital cortex, but not to the medial prefrontal cortex or to the basolateral amygdala, selectively increase signal-attenuation-induced ELP-U supports our hypothesis that ELP-U may provide the measure of compulsive responding in the signal attenuation model.

What is the mechanism by which signal attenuation induces compulsive lever-pressing?

The above findings suggest that signal attenuation prior to an extinction test may lead to the emergence of compulsive behavior. In the following, we analyze the post-training signal attenuation procedure in terms of the processes that may be involved at each stage and use current knowledge of the neural substrates of these processes in an attempt to identify the mechanism that may underlie the induction of compulsive lever-presses.

The post-training signal attenuation procedure includes an early stage (i.e., magazine training) of classical conditioning between a neutral stimulus and a primary reinforcer (i.e., food). Stimuli that have been paired with a primary reinforcer can influence behavior in diverse ways. Such stimuli can elicit responses, can act as discriminative stimuli for responding, and can serve as conditioned reinforcers (e.g., Mackintosh 1974; Robbins 1978). The latter refers to the ability of a stimulus to serve as a reinforcer for the acquisition of a new response and to maintain responding in extinction (Mackintosh 1974). These abilities may depend on the "motivational" properties of the stimulus, i.e., its conditioned *value*, acquired through the pairing of the stimulus with a primary reinforcer, and/or on the "informational" properties of the stimulus, i.e., its ability to "highlight that a response has registered, in much the same sense as response feedback is commonly used" (Williams 1994, p. 458) and the ability to "signal that a reinforcer is about to occur, thus serving to bridge the gap between the response and the subsequent reinforcer" (Williams 1994, p. 458).

The different modes by which a stimulus can influence behavior are subserved by the different associations that may be formed during pavlovian conditioning (for recent reviews, see Cardinal et al. 2002; Dickinson and Balleine 2002). Thus, the pairing of a conditioned stimulus (CS)

with an unconditioned stimulus (US) may lead to the formation of a direct link between the CS and the response elicited by the US. As a result, the CS comes to elicit conditioned responses; the CS may be associated with the affect elicited by the US. Through this association, the stimulus acquires conditioned value; the CS may become associated with the specific sensory properties of the US. This latter association may serve the informational properties of a conditioned stimulus described above.

In the second stage of the post-training signal attenuation procedure, the lever-press training stage, the conditioned stimulus accompanies reward delivery following a lever-press on the reinforced lever. The different associations acquired at the magazine training stage are expected to remain intact because the CS–US contingency is preserved. [It may be noted, however, that the acquisition of the lever-press response at this stage most likely does not depend on the presentation of the stimulus because conditioned reinforcers are reported not to have a significant contribution to learning when the response is also followed by a primary reinforcer (Mackintosh 1974).]

In the subsequent signal attenuation stage, the classical contingency between the stimulus and food is extinguished. This procedure is expected to alter the different properties/associations of the stimulus, including its conditioned reinforcement properties (Mackintosh 1974). At the last stage, the extinction test, a lever-press is followed only by the now-extinguished conditioned stimulus.

The differences between responding in extinction with an intact conditioned stimulus and with an extinguished conditioned stimulus are clearly seen when comparing the behavior of rats undergoing the regular extinction and the post-training signal attenuation procedures. Rats that underwent signal attenuation prior to the test stop lever-pressing much earlier in the session compared to rats undergoing regular extinction, as is clearly seen in the higher number of unpressed trials they exhibit from the early stages of the test (Fig. 7). Thus, the suppressive effects of encountering nonreward are evident earlier in rats responding with an extinguished conditioned stimulus. In addition, although the total number of excessive lever-presses (ELP-C + ELP-U), which may reflect the frustration effects of encountering nonreward, is typically similar in the post-training signal attenuation and regular extinction procedures, the finding that the anxiolytic diazepam is much less effective in reducing excessive lever-presses in the post-training signal attenuation procedure suggests that frustration may not play a critical role in inducing excessive lever-pressing in this procedure. Finally, as detailed above, the ELP-C–ELP-U distribution is different in the two procedures.

Although extinction of the classical contingency between the stimulus and the primary reinforcer in the signal attenuation stage is expected to alter the different properties/associations of the stimulus, it is not clear alteration of which of these properties is responsible for the emergence of compulsive lever-pressing in the subsequent test stage. In the following, an attempt is made to shed light on this question by analyzing the effects of lesion manipulations

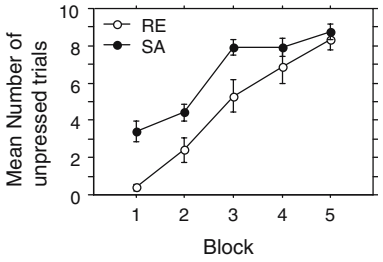

Fig. 7 The mean and standard error of the mean number of unpressed trials of intact rats undergoing the test of the post-training signal attenuation procedure (*SA*) or of the regular extinction procedure (*RE*). Mixed ANOVA with a main factor of procedure (SA, RE) and a repeated measurements factor of blocks yielded significant effects of procedure, $F(1,20)=13.47$, $p<0.005$, and blocks, $F(4,80)=61.13$, $p<0.0001$, and a nearly significant procedure × blocks interaction, $F(4,80)=2.26$, $p=0.07$

in the post-training signal attenuation procedure in light of current knowledge of the role of the lesioned neural systems in mediating specific properties of conditioned stimuli.

On the basis of the effects of orbital and BLA lesions in different behavioral procedures, it has been suggested that these two regions form a functional system that is required for a CS to retrieve the current motivational (affective) value of the US with which it is associated (Baxter et al. 2000; Cador et al. 1989; Cardinal et al. 2002; Cousens and Otto 2003; Everitt and Robbins 1992; Everitt et al. 1989; Gallagher and Schoenbaum 1999; Gallagher et al. 1999; Hatfield et al. 1996; Holland and Gallagher 1999; Parkinson et al. 2001; Pears et al. 2003; Rolls 1996, 1999, 2000a,b; Schoenbaum and Roesch 2005; Schoenbaum and Setlow 2001; Schoenbaum et al. 2002, 2003a; Setlow et al. 2002; Whitelaw et al. 1996). Electrophysiological (Rolls 1996; Schoenbaum et al. 1998, 1999, 2000, 2003b; Thorpe et al. 1983) and recent lesion studies (Cousens and Otto 2003; Izquierdo et al. 2004; Kim and Ragozzino 2005; Parkinson et al. 2001; Pears et al. 2003; Pickens et al. 2003, 2005; Setlow et al. 2002; Winstanley et al. 2004) have further suggested that the orbital cortex and BLA play distinct roles in mediating the effects of motivationally significant stimuli on behavior, with the BLA being primarily involved in the acquisition of the motivational significance of stimuli and the orbital cortex being particularly critical for flexible adjustment of responding when reinforcement contingencies change (Pickens et al. 2003; Rolls 1996, 1999, 2000a,b; Schoenbaum and Roesch 2005; Schoenbaum and Setlow 2001; Winstanley et al. 2004).

The finding that orbital-lesioned rats exhibited elevated levels of compulsive lever-pressing in a test preceded by signal attenuation (Joel et al. 2005a,b) suggests that in the intact brain, the orbital cortex is crucial for suppressing behavior on the basis of the information acquired at the signal attenuation stage (i.e., that the stimulus no longer signals food) and is in line with the functions ascribed to this brain region. The finding that BLA lesions did not affect responding following signal attenuation suggests that the behavioral changes induced by signal attenuation do not depend on the change in the conditioned value (motivational significance) of the stimulus in the signal

attenuation stage, but rather on a change in some other property of the stimulus.

We have recently obtained evidence suggesting indirectly that alteration of the association between the stimulus and the specific sensory properties of the US may be the critical factor in inducing compulsive lever-pressing. Specifically, we have found that inactivation of the orbital cortex in rats just prior to an extinction session in the regular extinction procedure induces the same ELP-C–ELP-U distribution that is seen in sham-operated rats undergoing the post-training signal attenuation procedure (Joel and Klavir, in press). These results suggest that orbital inactivation has the same effect on behavior as undergoing signal attenuation prior to the extinction test. A recent study by Ostlund and Balleine (2005) suggests that orbital inactivation may specifically disrupt the association between a CS and the specific sensory properties of the US. It may therefore be speculated that alteration of this association in the signal attenuation stage is the critical factor in inducing compulsive lever-pressing in the subsequent extinction test.

As detailed above, the association between a CS and the specific sensory properties of the US may subserve the informational properties of conditioned stimuli. Thus, the degradation of this association in the signal attenuation stage may alter the ability of the stimulus to highlight that the response has registered or to signal that the response was effective in producing food. Although the possibility that alteration of this association is the critical factor in inducing compulsive lever-pressing is highly speculative, it is of interest given theories of OCD which postulate a deficient response feedback in the production of obsessions and compulsions (Baxter 1999; Gray 1982; Malloy 1987; Pitman 1991; Pitman et al. 1987; Reed 1977; Szechtman and Woody 2004; for review, see Otto 1992).

Summary

On the basis of the results reviewed, we suggest that signal attenuation may provide an animal model of 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, i.e., the behavior induced by signal attenuation (compulsive lever-pressing) and compulsions are both excessive and unreasonable; and predictive validity, i.e., selectivity for antiobsessional/anticompulsive drugs. (The application of the terms construct, face, and predictive validity to animal models of psychopathology is after McKinney 1988 and Willner 1991.)

We would like to note that the model is the inducing manipulation, namely, signal attenuation, which is hypothesized to simulate an abnormal psychological process that may underlie obsessions and compulsions in OCD patients. However, whereas OCD patients are assumed to suffer from this deficiency at all times, in the model, this state is induced by a behavioral manipulation and is temporary (i.e., compulsive lever-pressing is exhibited only for a short duration). In this sense, the effects of signal attenuation on the behavior of normal rats suggest that obsessions and compulsions in patients may be viewed as a normal reaction to an abnormal situation (i.e., a deficient response feedback). In the model, ELP-U are the behavioral measure of compulsive behavior (in contrast to other behaviors exhibited during the test of the post-training signal attenuation procedures, such as ELP-C). Importantly, it is the combination of ELP-U and the inducing mechanism (i.e., signal attenuation) that provides a measure of compulsive behavior, and not the behavior alone, as lever-presses not followed by magazine entry have been reported following additional behavioral manipulations (e.g., regular extinction, reinforcer devaluation without incentive learning), but only signal-attenuation-induced ELP-U have been shown to have pharmacological and neurobiological similarities to compulsive behaviors in OCD.

The signal attenuation model has strengths and weaknesses as an animal model of OCD. These are summarized below with regard to specific aims animal models may serve (for a comprehensive review of the strengths and weaknesses of other animal models of OCD, see Joel, in press). In the context of screening for anti-compulsive activity, the most critical features of a model are its predictive validity and its cost-effectiveness. The signal attenuation model has good predictive validity, as it can differentiate between the effects of SSRI's and of drugs not effective in the treatment of OCD. It requires, however, special equipment (operant boxes) and about 2 weeks of behavioral training. In addition, the post-training signal attenuation procedure is not well suited for chronic drug administration studies because repeated drug administration may affect behavior in the early stages of the procedure. An additional use of animal models is the elucidation of the neurobiological mechanisms of the modeled condition. In this context, similarity in the inducing mechanism seems to be the critical feature, although it cannot be evaluated directly, as the etiology of OCD is currently unknown. The signal attenuation model attempts to simulate a psychological process that is assumed to underlie compulsive behaviors. Although there are clear differences between a deficient internal response feedback mechanism and an attenuated external feedback, the finding that compulsive behavior in the model has similarities to compulsive behaviors in patients in terms of response to treatment and neural systems involved suggests that this model may be useful in the study of the neurobiological mechanisms of compulsive behaviors. As detailed above, this model has already yielded findings which may shed light on the observed association between a dysfunction of the orbitofrontal cortex and of the serotonergic system in OCD.

In summary, although the signal attenuation model does not provide an ideal animal model of OCD, it is currently one of the most validated animal models of OCD. It is now crucial that this model is tested by other groups. It is hoped that future studies using this model will help the elucidation of the pathological mechanisms underlying OCD as well as

the development of new treatment approaches to this disorder.

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