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# The Effects of Temporary Inactivation of the Orbital Cortex in the Signal Attenuation Rat Model of Obsessive Compulsive Disorder

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Rats undergoing extinction of lever pressing after an external feedback for this behavior was attenuated by extinguishing its Pavlovian association with the reward (*signal attenuation*) exhibit compulsive lever pressing. The present study tested the effects of temporary inactivation of the orbital cortex in rats undergoing extinction of lever pressing that was or was not preceded by signal attenuation (post-training signal attenuation and regular extinction, respectively). Orbital inactivation led to a nonspecific decrease in lever pressing in rats undergoing post-training signal attenuation and to the emergence of compulsive-like behavior in rats undergoing regular extinction. These results suggest that orbital inactivation and extinguishing a Pavlovian stimulus-reinforcer contingency have a similar effect on lever pressing and are in line with previous findings implicating the orbital cortex in mediating the effects of previously acquired stimulus-reinforcer associations on operant behavior.

*Keywords:* compulsive lever pressing, muscimol, operant behavior, Pavlovian stimulus-reinforcer association



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. 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; Joel & Avisar, 2001; Joel, Ben-Amir, Doljansky, & Flaisher, 2004; for a recent review see Joel, in press).

We have recently found that compulsive lever pressing is increased following lesions to the rat orbital cortex (Joel, Doljansky, Roz, & Rehavi, 2005; Joel, Doljansky, & Schiller, 2005). In line with current views that emphasize the involvement of the orbital cortex in suppressing behavior in the context of changed task contingencies (e.g., Dias, Robbins, & Roberts, 1996, 1997; Gallagher, McMahan, & Schoenbaum, 1999; Nobre, Coull, Frith, & Mesulam, 1999; Rolls, 2000; Schoenbaum, Chiba, & Gallagher, 1999, 2000; Zald & Kim, 2001), we suggested that the orbital cortex is crucial for suppressing lever pressing on the basis of the information that the stimulus no longer signals food, which was acquired at the signal-attenuation stage.

The aim of the present study was to test this hypothesis by assessing the effects of inactivation of the orbital cortex (by intracerebral infusion of the $GABA_A$ agonist muscimol) only at the stage in which compulsive lever pressing is exhibited, namely the extinction test. To better differentiate between the effects of orbital inactivation on the behavioral response to signal attenuation and on extinction per se (i.e., the encounter of nonreward in the test), we included orbital-inactivated and sham groups that underwent either PTSA or a control procedure that did not include signal attenuation (the latter procedure is referred to as *regular extinction* [RE]).

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## Method

### Subjects

Forty-four male Wistar rats (Harlan, Jerusalem, Israel), approximately 3 months old, were housed individually under reversed cycle lighting (lights on: 1900–0700). A 22-hr food restriction schedule with freely available water was started at the beginning of the experiment. All experimental protocols conformed to the guidelines of the Institutional Animal Care and Use Committee of Tel-Aviv University, Israel.

### Apparatus and Behavioral Procedure

Behavioral testing was conducted in operant chambers described in Joel, Doljansky, Roz, and Rehavi (2005). The chambers were equipped with a 3-W house light; a Sonalert module (Model SC 628; Mallory Sonalert, Indianapolis, IN) that could produce an 80-dB, 2.8-kHz tone; and two retractable levers on either side of a food magazine (fitted with a 3-W magazine light), into which 45-mg Noyes precision food pellets (Noyes, Sandown Chemical, Hampton, England) could be delivered. Access to the food magazine was through a hinged panel, the opening of which activated a microswitch. Equipment programming and data recording were computer controlled.

Prior to the beginning of training, rats were handled for about 2 min daily for 5 days. On the last 3 days after handling, rats were acquainted to the food pellets that would later serve as reinforcement for operant training.

### PTSA

The PTSA procedure included four stages. Surgery for cannula implantation was conducted within the second stage.

### *Presurgery Training*

*Stage 1: Magazine training.* Rats were trained to collect food pellets from the food magazine. On each trial, a single food pellet was dropped into the food magazine simultaneous with the onset of the magazine light and tone (the stimulus). The 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. Rats were given three sessions, each lasting until a rat completed 30 collected trials (magazine entry during stimulus presentation) or a total of 40 trials.

*Stage 2: Lever-press training.* On the following day, rats received a session of pretraining using a free-operant schedule. The houselight was on, and the two levers were present in the operant box throughout the entire session. Responding on one of the levers (reinforced lever, RL) resulted in the delivery of a food pellet, accompanied by the presentation of the stimulus. 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 (i.e., pressed the lever and inserted its head into the food magazine during stimulus presentation). Next, rats received two sessions (one session per day) of lever-press training 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 food pellet into the magazine, accompanied by the presentation of the stimulus. The levers were retracted and 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 (10 s on the second lever-press training session and on subsequent sessions). Further lever presses on the RL as well as responding on the other lever (nonreinforced lever, NRL) had no programmed consequences but were recorded. Each trial was followed by a 30-s intertrial interval. Each rat was trained until it completed 40 trials or a total of 60 trials.

In addition to the number of completed trials, 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. As in previous studies, the measures of prime interest were the number of lever presses on the RL after the first response (extra lever presses, ELP) in uncompleted trials (that is, ELP not followed by magazine entry; ELP-U) and ELP in completed trials (that is, ELP followed by magazine entry, ELP-C).

### *Postsurgery Training*

Following the two sessions of lever-press training, rats underwent surgery for cannula implantation (see below). Following at least 7 recovery days with ad lib food and water, rats were returned to the 22-hr food restriction schedule, and 3 days later behavioral training continued. Rats were given two additional sessions of lever-press training, identical to the sessions given presurgery.

*Stage 3: Signal attenuation.* On the following 3 days, with the levers retracted, rats were exposed to the presentation of the stimulus as in the magazine training sessions, but no food was delivered to the food magazine. Rats received 30 such trials on each day. The number of collected trials was recorded. Rats that had more than 12 collected trials on the last day of signal attenuation were returned to the test chamber at the end of the day for an additional session.

*Stage 4: Test.* On the following day, rats were trained as in the lever-press training sessions, except that no food was delivered to the food magazine (i.e., pressing the lever resulted in the presentation of the stimulus only). The session lasted for 50 trials. The behavioral measures recorded were the same as in the lever-press training stage. We defined compulsive lever pressing as the number of ELP-U in the test stage of the PTSA procedure.

*RE.* Rats were run exactly as in the PTSA procedure, with the exception that they did not undergo the signal-attenuation stage. On the corresponding 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.

### *Surgery*

Rats received 3-mg diazepam and were anaesthetized 20 min later with an intraperitoneal injection of Avertin (10 ml/kg). Bilateral 26-gauge, stainless-steel guide cannulas (Bilaney, Düsseldorf, Germany), were implanted at the following coordinates (Paxinos & Watson, 1998): 3.7-mm anterior to bregma, 2.4-mm lateral to the midline, and 3.3-mm ventral to dura. Removable stylets were placed in the guide cannulas and held in place with a screw-on dust cap. The sham-operation rats underwent the same surgical procedure, except that the guide cannulas were removed 1 min after their insertion.

*Microinjection.* Fifty minutes before the test, intracerebral microinjections were made bilaterally using a dual-syringe infusion pump (CMA/100 microinjection pump; Medecin AB, Solona, Sweden). Rats were lightly anaesthetized with Halothane, the stylets were removed, and the injection needles (30 gauge) were inserted into the guide cannulas to protrude 1 mm below their tips. Crystallized muscimol (0.3 μl of muscimol dissolved in phosphate-buffered saline to a concentration of 0.5 μg/μl; Enco Diagnostics, Petach-Tiqva, Israel) was slowly delivered at a constant rate over 30 s. One min following the injection, the needles were slowly removed and replaced by the stylet. Sham rats were anaesthetized with Halothane for an equivalent period of time.

The volume and concentration of muscimol injection were selected on the basis of a study by Edeline, Hars, Hennevin, and Cotillon (2002), which combined electrophysiology and autoradiography to estimate muscimol's diffusion distance and duration of effectiveness, as well as previous behavioral studies that used muscimol for inactivation (Coutureau & Killcross, 2003; Izaki, Maruki, Hori, & Nomura, 2001; Samson & Chappell, 2001).

*Histology.* One to three weeks after the completion of behavioral testing, all rats implanted with cannulas and 3 sham rats were overdosed with Avertin (30 ml/kg, ip) and perfused intracardially with phosphate-buffered saline followed by 10% (vol/vol) buffered formalin. The brains were removed and placed in 10% (vol/vol) buffered formalin for at least 24 hr, followed by 20% (wt/vol) sucrose solution. The brains were sectioned in the coronal plane at 50-μm thickness and stained with Thionin Blue.

## Results

### *Anatomical*

Figure 1A presents a photomicrograph of a coronal section taken from a representative orbital-inactivated (left) and sham (right) rat. The only visible damage in orbital-inactivated and sham-operated rats was the cannula tracks toward the target areas. Figure 1B presents a schematic reconstruction of cannula placement in the orbital cortex. In most rats, cannula tips were located within the lateral and dorsolateral orbital cortex. Two rats in whom the tip of one cannula was located in the olfactory bulb were excluded from statistical analysis.

### *Behavioral*

Four rats died during or soon after surgery. Two implanted rats were excluded from the analysis because of misplaced cannula. Two rats that underwent RE (one implanted and one sham) were excluded from the analysis because their performance on one of the behavioral measures in the test was more than four standard deviations higher than their group mean. Thus, the final analysis

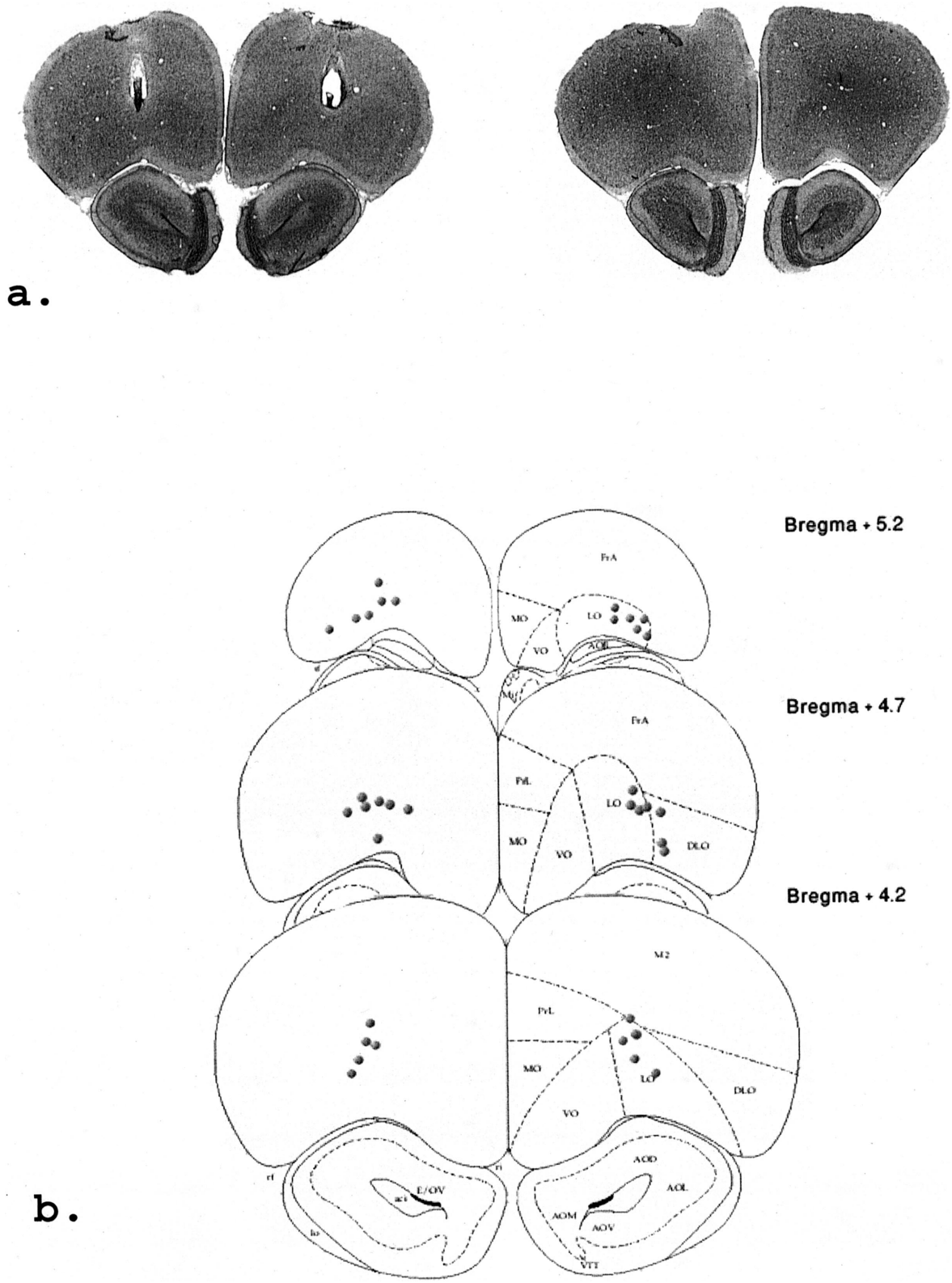


*Figure 1.* a: A photomicrograph of a coronal section taken through the orbital cortex in a representative orbital-inactivated (left) and sham (right) rat. b: A reconstruction of cannula placement in orbital-inactivated rats. Coordinates of the coronal sections are indicated with reference to bregma and are reprinted from *The Rat Brain in Stereotaxic Coordinates*, 4th ed., G. Paxinos and C. Watson, pp. 1–3, Copyright 1998, with permission from Elsevier.

included 8, 8, 10, and 10 rats in the RE–sham, RE–orbital, PTSA–sham, and PTSA–orbital groups.

### *Lever-Press Training*

All rats readily acquired lever pressing. On the last day of lever-press training, all rats achieved 40 completed trials, typically with no unpressed trials (6 sham and 3 implanted rats had between one to five unpressed trials) and with no uncompleted trials and therefore with no ELP-U. From the 2nd day of lever-press training, rats rarely pressed the NRL. The two groups that were implanted with cannulas tended to exhibit a higher number of ELP-C compared with the sham groups (see Figure 2a). An Inactivation (orbital inactivation, sham) × Procedure (PTSA, RE) analysis of variance (ANOVA) yielded an almost significant effect of inactivation, $F(1, 32) = 3.09$, $p = .089$. The effect of procedure and the Inactivation × Procedure interaction were not significant ($F$s < 1).

### *Signal Attenuation*

At the signal-attenuation stage, there were no differences between the sham and implanted groups in the extinction of the compound stimulus (as reflected in the number of collected trials) in either the rate of extinction or in the performance level at the end of this stage (see Figure 2b). An Inactivation × Sessions ANOVA yielded only a significant effect of sessions, $F(2, 36) = 102.14$, $p < .0001$. The effect of inactivation and the Inactivation × Session interaction were not significant ($F$s < 1).

### *Test*

Figures 2c and 2d present the mean number of ELP-C and ELP-U in the test of the RE and PTSA procedures of rats whose orbital cortices have been temporarily inactivated (orbital rats) and of sham-operated rats. As can be seen, orbital inactivation led to a reduction in the number of ELP-C compared with sham rats in both the PTSA and RE procedures (see Figure 2c). An Inactivation × Procedure ANOVA yielded significant effects of inactivation, $F(1, 32) = 18.35$, $p < .0005$, and procedure, $F(1, 32) = 9.57$, $p < .005$. In contrast, orbital inactivation led to opposite effects on ELP-U, decreasing the number of ELP-U in rats undergoing PTSA but increasing it in rats undergoing RE (see Figure 2d). An Inactivation × Procedure ANOVA yielded only a significant Inactivation × Procedure interaction, $F(1, 32) = 9.63$, $p < .005$.

A comparison of the number of ELP-C and ELP-U (see Figures 2c and 2d) in rats undergoing PTSA reveals that although the orbital group exhibited a much lower number of excessive lever presses compared with the sham group, in both groups the number of ELP-U was similar to or higher than the number of ELP-C. An Inactivation × Type of ELP ANOVA yielded a significant effect of inactivation, $F(1, 18) = 18.21$, $p < .0005$; the effect of type of ELP approached significance, $F(1, 18) = 2.97$, $p = .1$; and the Inactivation × Type of ELP interaction was not significant ($F < 1$).

Inspection of Figures 2c and 2d further reveals that whereas the performance of orbital rats undergoing RE was very different from that of their sham-operated controls, it was very similar to that of sham rats undergoing PTSA. Because Figures 2c and 2d present only the total number of ELP-C and ELP-U over the entire test session, we have also analyzed the number of ELP-C and ELP-U in each of five 10-trials test blocks to better evaluate this apparent similarity (see Figures 2e and 2f, respectively). As can be seen, the number of ELP-C and ELP-U was very similar in the RE–orbital and in the PTSA–sham groups in the five test blocks.

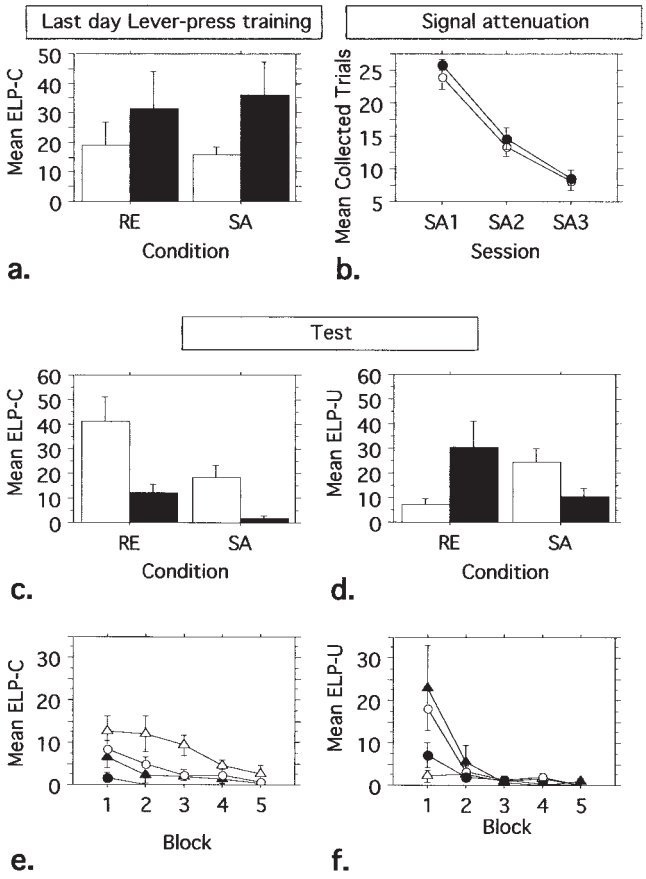


*Figure 2.* The mean and standard error of the mean number of (a) extra lever presses that were followed by an attempt to collect a reward (ELP-C) in the last lever-press training session of sham (empty bars) and implanted (filled bars) rats that will undergo the regular extinction (RE) or post-training signal-attenuation procedure (SA); (b) collected trials in the three sessions of signal attenuation of sham (empty circles) and implanted (filled circles) rats; (c) ELP-C in the test of sham (empty bars) and orbital-inactivated (filled bars) rats undergoing RE or SA; (d) extra lever presses that were not followed by an attempt to collect a reward (ELP-U) in the test of sham (empty bars) and orbital-inactivated (filled bars) rats undergoing RE or SA; (e) ELP-C in the five 10-trial blocks of the test of sham (empty symbols) and orbital-inactivated (filled symbols) rats undergoing RE (triangles) or SA (circles). Significant effects of inactivation, $F(1, 32) = 18.35$, $p < .0005$, procedure, $F(1, 32) = 9.57$, $p < .005$, repeated measurements factor of blocks, $F(4, 128) = 11.37$, $p < .0001$, and Inactivation × Blocks interaction, $F(4, 128) = 2.74$, $p < .05$; (f) ELP-U in the five 10-trial blocks of the test of sham (empty symbols) and orbital-inactivated (filled symbols) rats undergoing the RE (triangles) or SA (circles) procedure. Significant Inactivation × Procedure interaction, $F(1, 32) = 9.63$, $p < .005$, repeated measurements factor of blocks, $F(4, 128) = 14.55$, $p < .0001$, and Inactivation × Procedure × Blocks interaction, $F(4, 128) = 6.48$, $p < .0001$ (f).

Table 1 presents the mean number of completed, uncompleted, and unpressed trials in the test of the RE and PTSA procedures of

Table 1
*Means (SD) of Completed, Uncompleted, and Unpressed Trials and of Lever Presses on the Nonreinforced Lever (NRL) on the Test*

| | Completed trials | Uncompleted trials | Unpressed trials | Lever presses on NRL |
|---|---|---|---|---|
| Group | | | | |
| SA–sham | 9.50 (4.72) | 4.30 (2.16) | 36.20 (3.77) | 10.90 (10.58) |
| SA–inactivation | 1.00 (1.63) | 3.40 (2.68) | 45.60 (3.87) | 3.80 (3.74) |
| RE–sham | 32.88 (6.53) | 1.25 (0.71) | 15.88 (6.66) | 2.25 (3.01) |
| RE–inactivation | 6.00 (4.72) | 4.88 (2.64) | 39.13 (3.40) | 10.38 (8.54) |
| Procedure × Inactivation ANOVA | | | | |
| Procedure | $F(1, 32) = 95.80$, $p < .0001$ | $F(1, 32) = 1.10$, $p = .30$ | $F(1, 32) = 78.10$, $p < .0001$ | $F(1, 32) = 0.18$, $p = .67$ |
| Inactivation | $F(1, 32) = 149.00$, $p < .0001$ | $F(1, 32) = 3.30$, $p = .078$ | $F(1, 32) = 116.00$, $p < .0001$ | $F(1, 32) = 0.04$, $p = .84$ |
| Procedure × Inactivation | $F(1, 32) = 40.20$, $p < .0001$ | $F(1, 32) = 9.17$, $p < .005$ | $F(1, 32) = 20.90$, $p < .0001$ | $F(1, 32) = 9.66$, $p < .005$ |

*Note.* SA = signal-attenuation procedure; RE = regular extinction procedure; ANOVA = analysis of variance.



orbital and sham rats. As can be seen, orbital inactivation prior to the test decreased the number of completed trials and increased the number of unpressed trials compared with sham rats in both the PTSA and RE procedures, suggesting facilitated extinction of the lever-press response. The effects of orbital inactivation on the number of uncompleted trials were different in the two procedures, with orbital inactivation increasing the number of uncompleted trials in rats undergoing RE but having no effect on the number of uncompleted trials in rats undergoing PTSA.

Table 1 also presents the number of lever presses on the NRL in the test. As can be seen, orbital inactivation increased this behavior in rats undergoing RE but decreased it in rats undergoing PTSA. These effects are very similar to the effects of orbital inactivation on ELP-U.

## Discussion

Inactivation of the orbital cortex prior to an extinction test of lever-press responding led to a lower number of ELP-C in both the PTSA and RE procedures. In contrast, orbital inactivation led to opposite effects on the number of ELP-U, decreasing it in rats undergoing PTSA but increasing it in rats undergoing RE. Interestingly, orbital inactivation exerted a very similar effect on the number of lever presses on the NRL. Although the significance of this latter finding is not clear because none of the pharmacological and lesion manipulations we have tested thus far have led to an increase in lever presses on the NRL, a careful inspection of this behavior reveals several similarities to ELP-U. Specifically, both lever presses on the NRL and ELP-U are either not followed by magazine entry at all or the magazine entry occurs after a long delay (on most trials this delay is longer than 3 s; in contrast, ELP-Cs are always followed by magazine entry at short delays; Joel, in press). This dissociation between lever presses and magazine entry may suggest that both NRL presses and ELP-U are not goal directed and, in this sense, are inappropriate. This similarity may account for the similar effects orbital inactivation exerts on these two types of lever presses. There are, however, two important differences between these two types of lever presses. First, ELP-U constitutes lever presses on the RL, which had been an element of a goal-directed behavioral sequence, whereas lever presses on the NRL were never part of a goal-directed behavioral sequence. Second, whereas ELP-U are performed, by definition, while the stimulus is already on, almost all lever presses on the NRL (97%; there were no significant differences between the groups) were performed in the absence of the stimulus. Therefore, ELP-U, but not lever presses on the NRL, may reflect a failure to inhibit a response in a learned behavioral sequence so that the next response in the sequence can be performed (for further discussion, see Joel, in press). Such an inhibitory deficit has been related to compulsive behaviors (Chudasama et al., 2003; Robbins, 2002), and there are lesion and pharmacological data that support the relevance of ELP-U to compulsive behaviors (for review, see Joel, in press).

In the PTSA procedure, inactivation of the orbital cortex prior to the test stage resulted in a decrease in the number of ELP-C and ELP-U without affecting the ELP-C–ELP-U distribution (i.e., the number of ELP-U was similar to or higher than the number of ELP-C). This pattern is typically seen in an extinction test preceded by signal attenuation (e.g., Joel et al., 2004), and is markedly different from that seen in RE, in which the number of ELP-C is much higher than the number of ELP-U (present study, Joel et al., 2004). Thus, although orbital inactivation decreased the overall level of lever-press responding in PTSA, it seems to have spared the effects of signal attenuation on the ELP-C–ELP-U distribution.

In contrast, in rats undergoing RE, orbital inactivation did not affect the general level of lever pressing, but led to the emergence of a signal attenuation-like ELP-C–ELP-U distribution (i.e., the number of ELP-U was higher than the number of ELP-C in orbital-inactivated rats undergoing RE and was very similar to the number of ELP-C and of ELP-U in sham rats undergoing PTSA). This similarity suggests that orbital inactivation in rats undergoing RE has the same effect as undergoing signal attenuation prior to extinction. Because signal attenuation constitutes extinction of the Pavlovian stimulus-food contingency, the present results suggest that orbital inactivation and extinguishing a Pavlovian stimulus-reinforcer contingency have a similar effect on lever pressing (please note that this suggestion does not imply that orbital inactivation interferes with the acquisition of stimulus-reinforcer associations).

This suggestion may also account for decreased lever-press responding seen here in orbital rats undergoing extinction follow-

ing signal attenuation. Thus, compared with sham rats, orbital inactivation may be expected to lead to a further decrease in the control of the Pavlovian stimulus–food association on lever pressing in the test. Because one of the properties of Pavlovian stimuli is their ability to maintain operant responding in extinction (a property typically referred to as conditioned reinforcement; Mackintosh, 1974), this reduction is expected to lead to a faster extinction of the lever-press response.

The possibility that orbital inactivation weakens the effects of stimulus-reinforcer associations on lever-press responding is in line with previous findings suggesting that the orbital cortex plays a critical role in mediating the effects of stimulus-reinforcer associations on operant behavior. Thus, Fuchs, Evans, Parker, and See (2004) reported that inactivation of the lateral orbital cortex (the same region as the one inactivated in the present study) blocked conditioned cue-induced reinstatement of lever pressing for cocaine. Cue-induced reinstatement is thought to rely on the learning of stimulus-reinforcer associations during self-administration training as well as the recall and use of this information during reinstatement testing, and its disruption by orbital inactivation was taken to suggest that the functional integrity of the orbital cortex is necessary for the storage, retrieval, or use of stimulus–reward associations of cocaine-conditioned stimuli or the use of this information to guide cocaine-seeking behavior (Fuchs et al., 2004). Additional supportive evidence comes from a recent demonstration that post-training orbital lesions impair outcome-specific Pavlovian-instrumental transfer (Ostlund & Balleine, 2005)—one form of modulation of operant behavior by conditioned (Pavlovian) stimuli, which is thought to depend on the association between the conditioned stimulus and the specific sensory properties of the reinforcer (Cardinal, Parkinson, Hall, & Everitt, 2002).

There are two important points to note in this context. First, the orbital cortex seems to play a critical role in guiding operant behavior according to stimulus-reinforcer associations only if these associations were acquired with an intact orbital cortex (as in post-training orbital lesion or inactivation). Thus, orbital lesions had no effect on cue-induced reinstatement (Fuchs et al., 2004) and on performance in RE (Joel, Doljansky, Roz, & Rehavi, 2005) when the lesions were made prior to training (i.e., pretraining lesions). Rather, following pretraining orbital lesions, subjects seem to have difficulty in guiding behavior in the context of changed task contingencies (e.g., Chudasama & Robbins, 2003; Dias et al., 1996, 1997; Gallagher et al., 1999; Nobre et al., 1999; Rolls, 2000; Schoenbaum et al., 1999, 2000).[1] The different effects of pretraining and post-training orbital manipulations are also evident in the PTSA procedure, as orbital inactivation results in a nonselective decrease in lever pressing, whereas pretraining orbital lesions result in a selective increase in compulsive lever pressing (Joel, Doljansky, Roz, & Rehavi, 2005; Joel, Doljansky, & Schiller, 2005).

Second, the conclusion that the orbital cortex mediates the effects of a previously acquired Pavlovian stimulus-reinforcement association on behavior seems to hold only in situations in which the Pavlovian association is modulating operant behavior (as in the present study, in cue-induced reinstatement, and in Pavlovian-instrumental transfer), but not when the behavior in question is directly controlled by the Pavlovian association, as in conditioned approach to Pavlovian stimuli (for a detailed exposition of this distinction, see Cardinal et al., 2002; Mackintosh, 1983). In the latter case, post-training orbital manipulations either do not alter the preoperatively trained behavior (e.g., Chudasama and Robbins [2003] found that orbital lesions did not alter a preoperatively trained conditioned approach to a Pavlovian stimulus), or, when task contingencies change, orbital dysfunction seems to impair subjects' ability to suppress the preoperatively trained behavior—the same effect that is found with pretraining orbital lesions. For example, the finding that posttraining orbital lesions abolish the effects of outcome devaluation was obtained in a Pavlovian version of this task, in which the required response was approaching the food magazine (Pickens, Saddoris, Gallagher, & Holland, 2005). Similarly, the finding that orbital inactivation disrupts odor reversal learning was obtained using a discrimination procedure that requires approach to the correct stimulus (Kim & Ragozzino, 2005)—a discrimination that can be solved on the basis of Pavlovian conditioning of approach without the intervention of operant processes (Mackintosh, 1983).

We have previously suggested that the extinction of the contingency between the stimulus and food in the signal-attenuation stage alters the ability of the stimulus to provide feedback that the response was effective in producing food, and that this alteration may simulate a deficient response feedback hypothesized to underlie obsessions and compulsions in OCD patients (e.g., Baxter, 1999; Pitman, 1991; Pitman, Green, Jenike, & Mesulam, 1987; Reed, 1977; Szechtman & Woody, 2004; for review, see Otto, 1992). This hypothesis receives indirect support from the present finding that signal attenuation and orbital inactivation have a similar effect on rats' behavior in the test, because orbital inactivation has been shown to disrupt the association between a conditioned stimulus and the specific sensory properties of the reinforcer (Ostlund & Balleine, 2005), an association that may subserve the informational properties of the conditioned stimulus, that is, 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).

On the basis of our previous observation that orbital lesions increase signal-attenuation-induced compulsivity, we have suggested that the orbital cortex may be involved in suppressing compulsive behaviors triggered elsewhere (Joel, Doljansky, Roz, & Rehavi, 2005). The present results raise an additional mechanism by which the orbital cortex may be involved in OCD, namely, that dysfunctioning orbital cortex may induce

[1] It should be pointed out that the orbital cortex seems to play a role in behavioral flexibility when there is a change at the level of stimulus-reinforcement associations (e.g., as in reversal of a discrimination), whereas other regions of the prefrontal cortex are involved in switching of general rules, strategies, or attentional sets (e.g., as in extradimensional shift; Birrell & Brown, 2000; Brown & Bowman, 2002; Dias et al., 1996, 1997; Joel, Weiner, & Feldon, 1997; Kesner, 2000; McAlonan & Brown, 2003; Ragozzino, Detrick, & Kesner 1999; Ragozzino, Wilcox, Raso, & Kesner, 1999).

compulsive behaviors by attenuating signals of task completion—signals that have been established by association with primary reinforcers during the acquisition of normal goal-directed behaviors.

## References


Baxter, L. R. (1999). Functional imaging of brain systems mediating obsessive–compulsive disorder. In C. E. Nestler & W. Bunney (Eds.), *Neurobiology of mental illness* (pp. 534–547). New York: Oxford University Press.

Birrell, J. M., & Brown, V. J. (2000). Medial frontal cortex mediates perceptual attentional set shifting in the rat. *Journal of Neuroscience, 20,* 4320–4324.

Brown, V. J., & Bowman, E. M. (2002). Rodent models of prefrontal cortical function. *Trends in Neurosciences, 25,* 340–343.

Cardinal, R. N., Parkinson, J. A., Hall, J., & Everitt, B. J. (2002). Emotion and motivation: The role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience and Biobehavioral Reviews, 26,* 321–352.

Chudasama, Y., Passetti, F., Rhodes, S. E., Lopian, D., Desai, A., & Robbins, T. W. (2003). Dissociable aspects of performance on the 5-choice serial reaction time task following lesions of the dorsal anterior cingulate, infralimbic and orbitofrontal cortex in the rat: Differential effects on selectivity, impulsivity and compulsivity. *Behavioural Brain Research, 146,* 105–119.

Chudasama, Y., & Robbins, T. W. (2003). Dissociable contributions of the orbitofrontal and infralimbic cortex to Pavlovian autoshaping and discrimination reversal learning: Further evidence for the functional heterogeneity of the rodent frontal cortex. *Journal of Neuroscience, 23,* 8771–8780.

Coutureau, E., & Killcross, S. (2003). Inactivation of the infralimbic prefrontal cortex reinstates goal-directed responding in overtrained rats. *Behavioural Brain Research, 146,* 167–174.

Dias, R., Robbins, T. W., & Roberts, A. C. (1996, March 7). Dissociation in prefrontal cortex of affective and attentional shifts. *Nature, 380,* 69–72.

Dias, R., Robbins, T. W., & Roberts, A. C. (1997). Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin Card Sort Test: Restriction to novel situations and independence from "on-line" processing. *Journal of Neuroscience, 17,* 9285–9297.

Edeline, J. M., Hars, B., Hennevin, E., & Cotillon, N. (2002). Muscimol diffusion after intracerebral microinjections: A reevaluation based on electrophysiological and autoradiographic quantifications. *Neurobiology of Learning and Memory, 78,* 100–124.

Fuchs, R. A., Evans, K. A., Parker, M. P., & See, R. E. (2004). Differential involvement of orbitofrontal cortex subregions in conditioned cue-induced and cocaine-primed reinstatement of cocaine seeking in rats. *Journal of Neuroscience, 24,* 6600–6610.

Gallagher, M., McMahan, R. W., & Schoenbaum, G. (1999). Orbitofrontal cortex and representation of incentive value in associative learning. *Journal of Neuroscience, 19,* 6610–6614.

Izaki, Y., Maruki, K., Hori, K., & Nomura, M. (2001). Effects of rat medial prefrontal cortex temporal inactivation on a delayed alternation task. *Neuroscience Letters, 315,* 129–132.

Joel, D. (in press). The signal attenuation rat model of obsessive–compulsive disorder: A review. *Psychopharmacology*.

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

Joel, D., Ben-Amir, E., Doljansky, J., & Flaisher, S. (2004). "Compulsive" lever pressing in rats is attenuated by the serotonin re-uptake inhibitors paroxetine and fluvoxamine but not by the tricyclic antidepressant desipramine or the anxiolytic diazepam. *Behavioural Pharmacology, 15,* 241–252.

Joel, D., Doljansky, J., Roz, N., & Rehavi, M. (2005). Role of the orbital cortex and the serotonergic system in a rat model of obsessive–compulsive disorder. *Neuroscience, 130,* 25–36.

Joel, D., Doljansky, J., & Schiller, D. (2005). "Compulsive" lever pressing in rats is enhanced following lesions to the orbital cortex, but not to the basolateral nucleus of the amygdala or to the dorsal medial prefrontal cortex. *European Journal of Neuroscience, 21,* 2252–2262.

Joel, D., Weiner, I., & Feldon, J. (1997). Electrolytic lesions of the medial prefrontal cortex in rats disrupt performance on an analog of the Wisconsin Card Sorting Test, but do not disrupt latent inhibition: Implications for animal models of schizophrenia. *Behavioural Brain Research, 85,* 187–201.

Kesner, P. (2000). Subregional analysis of mnemonic functions of the prefrontal cortex in the rat. *Psychobiology, 28,* 219–228.

Kim, J., & Ragozzino, M. E. (2005). The involvement of the orbitofrontal cortex in learning under changing task contingencies. *Neurobiology of Learning and Memory, 83,* 125–133.

Mackintosh, N. J. (1974). *The psychology of animal learning*. London: Academic Press.

Mackintosh, N. J. (1983). *Conditioning and associative learning*. Oxford, United Kingdom: Clarendon Press.

McAlonan, K., & Brown, V. J. (2003). Orbital prefrontal cortex mediates reversal learning and not attentional set shifting in the rat. *Behavioural Brain Research, 146,* 97–103.

Nobre, A. C., Coull, J. T., Frith, C. D., & Mesulam, M. M. (1999). Orbitofrontal cortex is activated during breaches of expectation in tasks of visual attention. *Nature Neuroscience, 2,* 11–12.

Ostlund, S. B., & Balleine, B. B. (2005). *Lesions of the orbitofrontal cortex disrupt Pavlovian, but not instrumental, outcome-encoding*. Poster session presented at the 35th annual meeting of the Society for Neuroscience, Washington, DC.

Otto, M. W. (1992). Normal and abnormal information processing: A neuropsychological perspective on obsessive–compulsive disorder. In M. A. Jenike (Ed.), *The psychiatric clinics of North America: Obsessional disorders* (Vol. 15, pp. 825–848). Chicago: W. B. Saunders.

Paxinos, G., & Watson, C. (1998). *The rat brain in stereotaxic coordinates*. (4th ed.). San Diego: Academic Press.

Pickens, C. L., Saddoris, M. P., Gallagher, M., & Holland, P. C. (2005). Orbitofrontal lesions impair use of cue-outcome associations in a devaluation task. *Behavioral Neuroscience, 119,* 317–322.

Pitman, R. (1991). Historical considerations. In J. Zohar, T. Insel, & S. Rasmussen (Eds.), *The psychobiology of obsessive–compulsive disorder* (pp. 1–12). New York: Springer Publishing Company.

Pitman, R. K., Green, R. C., Jenike, M. A., & Mesulam, M. M. (1987). Clinical comparison of Tourette's disorder and obsessive–compulsive disorder. *American Journal of Psychiatry, 144,* 1166–1171.

Ragozzino, M. E., Detrick, S., & Kesner, R. P. (1999). Involvement of the prelimbic–infralimbic areas of the rodent prefrontal cortex in behavioral flexibility for place and response learning. *Journal of Neuroscience, 19,* 4585–4594.

Ragozzino, M. E., Wilcox, C., Raso, M., & Kesner, R. P. (1999). Involvement of rodent prefrontal cortex subregions in strategy switching. *Behavioral Neuroscience, 113,* 32–41.

Reed, G. F. (1977). Obsessional personality disorder and remembering. *British Journal of Psychiatry, 130,* 177–183.

Robbins, T. W. (2002). The 5-choice serial reaction time task: Behavioural pharmacology and functional neurochemistry. *Psychopharmacology (Berlin), 163,* 362–380.

Rolls, E. T. (2000). The orbitofrontal cortex and reward. *Cerebral Cortex, 10,* 284–294.

Samson, H. H., & Chappell, A. (2001). Muscimol injected into the medial

prefrontal cortex of the rat alters ethanol self-administration. *Physiology & Behavior, 74,* 581–587.

Schoenbaum, G., Chiba, A. A., & Gallagher, M. (1999). Neural encoding in orbitofrontal cortex and basolateral amygdala during olfactory discrimination learning. *Journal of Neuroscience, 19,* 1876–1884.

Schoenbaum, G., Chiba, A. A., & Gallagher, M. (2000). Changes in functional connectivity in orbitofrontal cortex and basolateral amygdala during learning and reversal training. *Journal of Neuroscience, 20,* 5179–5189.

Szechtman, H., & Woody, E. (2004). Obsessive–compulsive disorder as a disturbance of security motivation. *Psychological Review, 111,* 111–127.

Williams, B. (1994). Conditioned reinforcement: Neglect or outmoded explanatory construct? *Psychonomic Bulletin & Review, 1,* 457–475.

Zald, D. H., & Kim, S. W. (2001). The orbitofrontal cortex. In S. P. Salloway, P. F. Malloy, & J. D. Duffy (Eds.), *The frontal lobes and neuropsychiatric illness* (pp. 33–69). Washington, DC: American Psychiatric Publishing.

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