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ROLE OF THE ORBITAL CORTEX AND OF THE SEROTONERGIC SYSTEM IN A RAT MODEL OF OBSESSIVE COMPULSIVE DISORDER

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Abstract—The serotonergic system and the orbitofrontal cortex have been consistently implicated in the pathophysiology of obsessive compulsive disorder. Yet, the relations between these two systems and the ways they interact in producing obsessions and compulsions are poorly understood. The present study tested the hypothesis that pathology of the orbitofrontal cortex leads to a dysregulation of the serotonergic system which is manifested in compulsive behavior, using a new rat model of this disorder. In the model, 'compulsive' behavior is induced by attenuating a signal indicating that a lever-press response was effective in producing food. We found that lesion to the rat orbital cortex led to a selective increase in compulsive lever-pressing that was prevented by the serotonin re-uptake inhibitor, paroxetine, and was paralleled by an increase in the density of the striatal serotonin transporter, assessed using high affinity [^{3}H]imipramine binding. These results suggest that the serotonergic system is involved in orbital lesion-induced compulsivity, and provide a possible account for the observed association between obsessions and compulsions and dysfunction of the orbitofrontal cortex and of the serotonergic system in obsessive compulsive disorder.

Key words: post-training signal attenuation, 'compulsive' lever-pressing, extinction, orbitofrontal cortex, obsessive compulsive disorder (OCD), serotonin transporter.

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

The finding that serotonin reuptake inhibitors (SRIs) are effective in alleviating obsessions and compulsions in patients (Zohar and Insel, 1987; Zohar et al., 1992), has directed much attention to the involvement of the serotonergic system in the pathophysiology of OCD (for review see Sasson and Zohar, 1996; Stein, 2000). In parallel, the results of neuroimaging studies in patients with idiopathic and acquired OCD have increasingly pointed to a dysfunction of the orbitofrontal cortex (OFC, 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). At present, there is no evidence linking these pharmacological and neuroimaging lines of evidence.

The aim of the present study was to test one plausible hypothesis for the observed association between OCD and a dysfunction of the OFC and of the serotonergic system, namely, that OFC pathology leads to a dysregulation of the serotonergic system which is manifested in compulsive behavior, using a new rat model of OCD, the signal attenuation model (Joel and Avisar, 2001; Joel et al., 2004).

In the model, the attenuation of an external feedback for lever-press responding leads, in a subsequent extinction test, to excessive lever-pressing that is not accompanied by an attempt to collect a reward. This behavior, which we have named 'compulsive' lever-pressing because it may be analogous to the excessive and unreasonable behavior seen in OCD, is abolished by the SRIs, fluoxetine, paroxetine and fluvoxamine, but not by the anxiolytic drug, diazepam, or the tricyclic antidepressant, desipramine (Joel and Avisar, 2001; Joel et al., 2004), in accordance with the differential efficacy of these drugs in alleviating obsessions and compulsions in OCD patients (e.g. Dolberg et al., 1996; Piccinelli et al., 1995; Zohar et al., 1992).

The present study tested whether lesion to the rat orbital cortex would increase compulsive lever-pressing. Whether this increase would be reversed by an SRI; and whether the lesion would lead to alterations of the serotonergic system. Although there are significant differences in the details and in the complexity of the organization of the rat and primate cortex, hodological, electrophysiological and behavioral data suggest that the rat orbital cortex may be analog to the primate OFC (Groenewegen and Uylings, 2000; Kolb, 1990; Krettek and Price, 1977; Ongur and Price, 2000; Schoenbaum and Setlow, 2001; Uylings and van Eden, 1990). We expected that rats sustaining an excitotoxic lesion to the orbital cortex would exhibit an increased number of compulsive lever-presses in the post-training signal attenuation procedure (experiment 1). However, since the effects of signal attenuation on rats' lever-press responding are assessed under extinction condi-

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Abbreviations: ANOVA, analysis of variance; A-P, anterior to bregma; D-V, ventral from dura; ELP, extra lever-presses; ELP-C, extra lever-presses in completed trials; ELP-U, extra lever-presses in uncompleted trials; M-L, lateral to the midline; OCD, obsessive compulsive disorder; OFC, orbitofrontal cortex; SRI, serotonin reuptake inhibitor.

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tions, the orbital lesion may affect other behaviors typical to extinction (e.g. extinction burst). In order to better differentiate between the effects of the lesion on the behavioral response to signal attenuation and on extinction per se, orbital-lesioned and sham-operated rats were tested in an extinction session that was not preceded by signal attenuation (experiment 2; 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"). Following the demonstration that the effects of the orbital lesion are specific to the post-training signal attenuation procedure, we tested the effects of two doses of the SRI paroxetine on orbital-lesioned and sham-operated rats undergoing this procedure (experiment 3). Finally, the binding characteristics of the presynaptic serotonin transporter in the frontal cortex, striatum and hypothalamus of orbital and sham rats were assessed.

EXPERIMENTAL PROCEDURES

Subjects

Male Wistar rats (Tel-Aviv University, Sackler Faculty of Medicine, Israel) were housed under reversed cycle lighting and maintained on a 22 h food restriction schedule (see below) with freely available water. They were weighed twice a week to ensure that their body weight was not reduced below 90%. All experimental protocols were carried out according to the guidelines of the Institutional Animal Care and Use Committee of Tel Aviv University, which follow the guidelines laid down by the National Institute of Health in the United States, regarding the care and use of animals for experimental procedures. Care was taken to minimize the number of rats used and their suffering (see below).

Surgery

Rats received 3 mg/kg diazepam, and 20 min later were anesthetized with i.p. injection of Avertine (10 ml/kg). They were placed in a stereotaxic frame and an incision was made into the scalp to expose the skull. The vertical coordinates of bregma and lambda were measured in order to align them in same (level head) plane. Thirty-one gauge cannulae were vertically lowered into the brain through holes drilled in the skull. Bilateral infusions of 0.3 μl *N*-methyl-D-aspartate (NMDA) (Sigma Chemicals, Rehovot, Israel; diluted with phosphate buffer to a final pH of 7.4 and a concentration of 0.12 M) were delivered at a constant rate over 3 min at the following coordinates (Paxinos and Watson, 1998): 3.7 mm anterior to bregma, 2.4 mm lateral to the midline, and 3.3 mm ventral to dura. The cannulae were left in place for an additional 3 min, to reduce upward diffusion of the solution. *Sham operation:* Rats underwent the same surgical procedure as orbital rats but 0.3 μl of vehicle was infused instead of NMDA. Sterispon was used to cover the holes in the bone, the scalp incision was sutured by Michel clips, and rats were monitored on a daily basis. Behavioral experiments began at least 2 weeks after recovery from operation.

Apparatus and behavioral procedure

The apparatus and behavioral procedure have been described in detail elsewhere (Joel and Doljansky, 2003). Behavioral testing was conducted in four operant chambers (Campden Instruments, Loughborough, UK), housed in sound-attenuated boxes and equipped with a 3 W house light, a Sonalert module (Model SC 628) that could produce a 80 dB, 2.8 kHz tone, and two retractable levers on either side of a food magazine (fitted with a 3 W magazine light), into which 45 mg Noyes precision food pellets (Noyes, Sandown Chemical Limited, Hampton, UK) could be delivered. Access to the food magazine was through a hinged panel, the opening of which activated a micro-switch. Equipment programming and data recording were computer controlled.

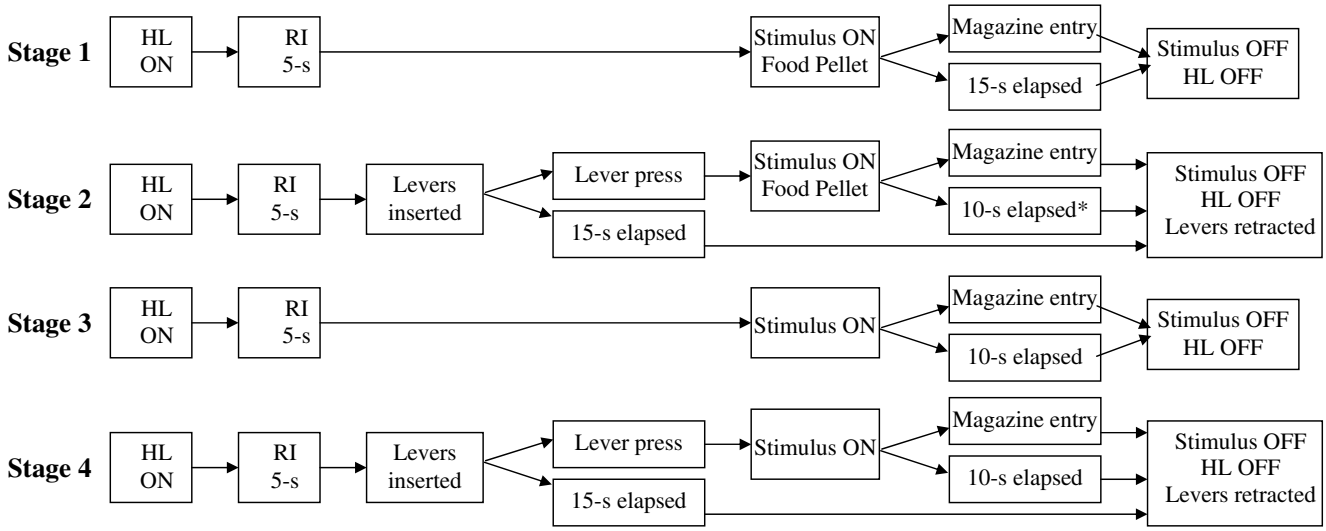
Prior to the beginning of the experiment, rats were handled for about 2 min daily for 5 days. A 22-h food restriction schedule began simultaneously with handling and continued throughout behavioral testing. Food was provided in the home cage between 14:00 and 16:00 h, at least half an hour after the end of the session. On the last 2 days, after handling, 20–30 food pellets used as reinforcement for operant training were introduced into the home cages on a tray. The tray was removed from the cage after each rat was observed to consume at least two pellets.

Post-training signal attenuation. The post-training signal attenuation procedure included four stages.

Stage 1: magazine training. On days 1–3, rats were trained to collect food pellets from the food magazine in the operant chamber, with the levers retracted. On each trial, a single food pellet was dropped into the food magazine, simultaneous with the onset of a compound stimulus consisting of the magazine light and the tone. The compound stimulus was turned off after the rat's head entered the food magazine or after 15 s had elapsed, and a 30-s intertrial interval began (for more details see Fig. 1). On each day, each rat was trained until it completed 30 trials in which it inserted its head into the food magazine during stimulus presentation (collected trials), or until a total of 40 trials was reached. The number of collected trials and the total number of trials were recorded.

Stage 2: lever-press training. On days 4–7 (4–6 in experiment 3), rats were trained to lever-press in a discrete-trial procedure. On each trial, both levers were inserted into the chamber. Responding on one of the levers (reinforced lever) resulted in the delivery of a single food pellet into the magazine, accompanied by the presentation of the compound stimulus. The levers were retracted and the compound stimulus was turned off, after the rat's head entered the food magazine or after 15 s from the rat's first lever-press had elapsed (see Diagram 1). Further lever-presses on the reinforced lever as well as responding on the other lever (nonreinforced lever) had no programmed consequences. The lever designated as reinforced lever was counterbalanced over subjects and remained the same for each rat over the entire experimental procedure. Each trial was followed by a 30-s intertrial interval. On day 4, each rat was trained until it completed 24 trials, that is, pressed the lever and inserted its head into the food magazine during stimulus presentation, or for a total of 60 trials. Rats that failed to attain at least 20 completed trials were returned to the test chamber at the end of the day for an additional session. Those that did not attain at least 20 completed trials in the second session were excluded from the experiment. On days 5–7 (5–6 in experiment 3), all rats were trained as on day 4, except that the compound stimulus was turned off after 10 s instead of after 15 s and training ended when the rat had attained 40 completed trials or for a total of 60 trials.

In order to assess acquisition of the lever-press response, the number of trials on which the rat did not press the reinforced lever (unpressed trials) and the number of trials on which the rat pressed the reinforced lever without inserting its head into the food magazine (uncompleted trials) were recorded in addition to the number of completed trials (see Diagram 1). In order 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) were recorded. The latter measure was further subdivided into ELP in uncompleted trials (that is, ELP not



HL- houselight

RI – random interval

* On the first day of lever-press training (Day 4) this time limit was 15-s

Fig. 1.

followed by insertion of the head into the food magazine; ELP-U), and ELP in completed trials (ELP-C).

Stage 3: signal attenuation. On the next 3 days, with the levers retracted, rats were exposed to the presentation of the compound stimulus as on days 1–3, but no food was delivered to the food magazine (see Diagram 1). Rats received 30 such trials on each day, and the number of collected trials was recorded.

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

Regular extinction. Rats were run exactly as in the post-training signal attenuation procedure, with the exception that they did not undergo the signal attenuation stage. On 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.

Table 1. Number (mean±S.E.) of collected trials during the signal attenuation stage of orbital-lesioned and sham-operated rats (experiments 1 and 3)

	Day 1	Day 2	Day 3
Experiment 1			
Sham	20.3 (2.19)	5.3 (0.99)	4.7 (1.08)
Lesion	21.4 (1.43)	8.2 (1.22)	5.3 (0.58)
Experiment 3			
Sham	24.5 (1.00)	10.8 (1.06)	3.2 (0.65)
Lesion	25.8 (0.80)	9.5 (1.12)	2.6 (0.45)

Drugs

Paroxetine (Unipharm, Ramat Gan, Israel), dissolved in distilled water, was administered intraperitoneally in a volume of 1 ml/kg, at a dose of 1 or 3 mg/kg (calculated as the weight of the salt), 30 min before the beginning of the test stage. The dose of 3 mg/kg was chosen because we have previously found it to be the lowest paroxetine dose effective in alleviating compulsive lever-pressing in intact rats (Joel et al., 2004). The dose of 1 mg/kg (which is not effective in intact rats) was used in order to test whether orbital rats are more responsive than sham rats to the ameliorating effect of paroxetine. No-drug controls received an equivalent volume of distilled water.

Statistical analysis

Data from the magazine training, lever-press training and signal attenuation stages were analyzed using analysis of variance (ANOVA) with a main factor of group (sham, lesion) and a repeated measurements factor of days. Data from the test stage were analyzed using ANOVAs with a main factor of group (sham, lesion) and, when relevant, an additional main factor of drug or a repeated measurements factor of 10-trial blocks.

Histology and [^{3}H]imipramine binding

Three to 5 weeks after the completion of behavioral testing, orbital and sham rats from the different experiments were randomly assigned to undergo histology or [^{3}H]imipramine binding. For histology, orbital and sham rats (nine and four from experiment 1; seven and two from experiment 2; six and three from experiment 3) were overdosed with sodium pentobarbital (60 mg/kg, i.p.) and perfused intracardially with a solution of 0.9% NaCl (Fluka, Buchs, Switzerland) at room temperature for 2 min (flow rate 35 ml/min), followed by 10% buffered formalin for 15 min. The brains were removed from their skulls and placed in 10% buffered formalin for at least 3 days. The brains were sectioned in the coronal plane using freezing microtome at 50 μm thickness and stained with Cresyl Violet. The atlas of Paxinos and Watson (1998) was used to verify the placement and the extent of the lesions.

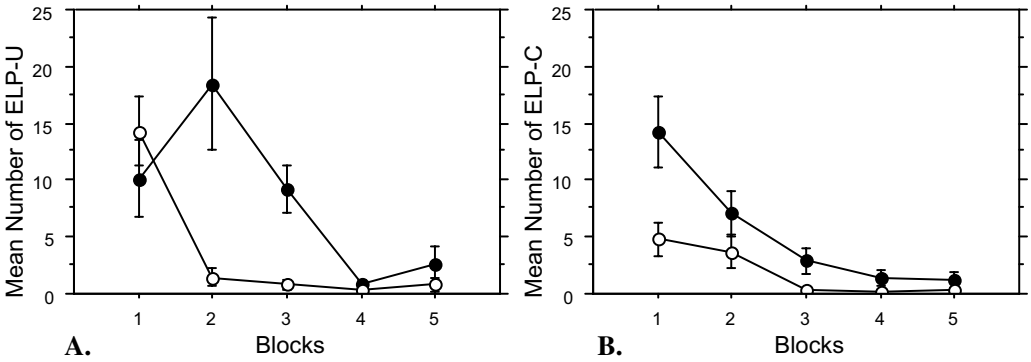


Fig. 2. Effects of orbital lesion on post-training signal attenuation. Mean and standard error of the mean number of excessive lever-presses that (A) were not accompanied by insertion of the head into the food magazine (ELP-U), and (B) were accompanied by insertion of the head into the food magazine (ELP-C), in sham-operated (open circles) and in orbital-lesioned (black circles) rats undergoing post-training signal attenuation (experiment 1).

For [^{3}H]imipramine binding, orbital and sham rats were decapitated, and the brain regions of interest were dissected immediately on ice. In the first assessment, the frontal cortex, hypothalamus and striatum of nine orbital and nine sham rats (six and six from experiment 1; three and three from experiment 2) were obtained. Because this assessment revealed a significant difference between the two groups in the binding characteristics of imipramine in the striatum only, we obtained the striatum of additional 10 orbital and nine sham rats. These rats had previously undergone post-training signal attenuation, receiving either vehicle, 3 or 7 mg/kg paroxetine at the test stage (the behavioral results will be published elsewhere), similarly to rats in experiment 3 of the present study. Tissue was homogenized with a polytron tissue disrupter (setting 7, 20 s) in 50 volumes of 50 mM Tris hydrochloride buffer containing 120 mM NaCl and 5 mM KCl at a pH of 7.4. The homogenate was centrifuged three times (and resuspended twice in equal volume of buffer) for 10 min at 30,000×*g*. The resulting pellet was reconstituted to give a tissue concentration of approximately 30 mg original wet weight per ml buffer. For imipramine binding in the striatum, the striata of two rats were combined. The incubation mixture contained 200 μl of striatal or cortical membranes, 100 μl [^{3}H]imipramine (0.5–16 nM; specific activity 40 Ci/mmol; New England Nuclear, Boston, MA, USA) and 50 μl of buffer. Following 60 min incubation at 0 °C, the incubate was quickly diluted in 4 ml of ice-cold buffer and filtered under vacuum through glass-fiber filters. The filters were washed three times with 4 ml ice-cold buffer and counted in a scintillation cocktail (Opti-flour; Packard) in a liquid scintillation counter (Tri-carb 2100 TR). Non-specific binding was measured in the presence of 1 μM clomipramine. Scatchard plots were constructed and both maximal binding of [^{3}H]imipramine (Bmax) and its affinity to its binding site (Kd) were determined by linear regression analysis. The binding to hypothalamic membranes was measured using only two concentrations of [^{3}H]imipramine (3.2 nM and 12.0 nM) because of a limited amount of tissue (the data of one orbital rat for the two concentrations and the data for one sham rat for one concentration were lost). [^{3}H]imipramine was chosen to label the serotonin transporter because this ligand has been used extensively in our previous studies (Attali et al., 1997; Cohen et al., 1990; Eyal et al., 1996; Rehavi et al., 1980, 1988; Weizman et al., 1994, 1996) and we have a reliable database concerning its binding parameters in rats.

RESULTS

Behavioral

Experiment 1: the effects of orbital lesion on post-training signal attenuation. Twenty-eight rats were randomly assigned to two groups (orbital lesion, $n=16$, and sham operation, $n=12$). Four rats needed another lever-press training session on day 4. Three (two sham, one orbital) rats did not attain the criterion of 20 completed trials in the second session and were excluded from the experiment. Thus, the final analysis included 10 and 15 rats in the sham and orbital groups, respectively. During lever-press training all rats achieved 40 completed trials with no uncompleted trials and therefore with no ELP-U, and with a similar number of unpressed trials. Importantly, there was no difference between the two groups on the number of ELP-C (main effect of group, $F<1$; group by day interaction, $F<1$). At the signal attenuation stage, there were no differences between the 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 (Table 1; main effect of group, $F(1,23)=1.17$, $P>0.29$; group by day interaction, $F<1$). From the second day of lever-press training rats rarely pressed the nonreinforced lever. In both groups there was no increase in lever-presses on the nonreinforced lever in the test stage.

In the test, orbital rats showed a profound increase in the number of ELP-U compared with sham-operated rats (Fig. 2a, main effect of group, $F(1,23)=5.13$, $P<0.05$). Orbital-lesioned rats also exhibited an increase in the number of ELP-C (Fig. 2b, main effect of group, $F(1,23)=5.37$, $P<0.05$), albeit the pattern of change in ELP-U and ELP-C over the five 10-trial test blocks in the two groups was markedly different. The number of ELP-C was higher in orbital compared with sham rats particularly on the first 10-trial block, and both groups had relatively low number of ELP-C from the second block onwards (group by blocks interaction, $F(4,92)=3.08$, $P<0.05$). In contrast, the number of ELP-U was similar in the orbital and control groups on the first test block, but whereas sham rats had almost no ELP-U from the second block onwards, orbital rats continued to exhibit a high number of ELP-U for additional two blocks (group by blocks interaction, $F(4,92)=4.08$, $P<0.01$).

Experiment 2: the effects of orbital lesion on regular extinction. Nineteen rats were randomly assigned to two groups (orbital lesion, $n=10$, and sham operation, $n=9$). Four rats needed another lever-press training session on

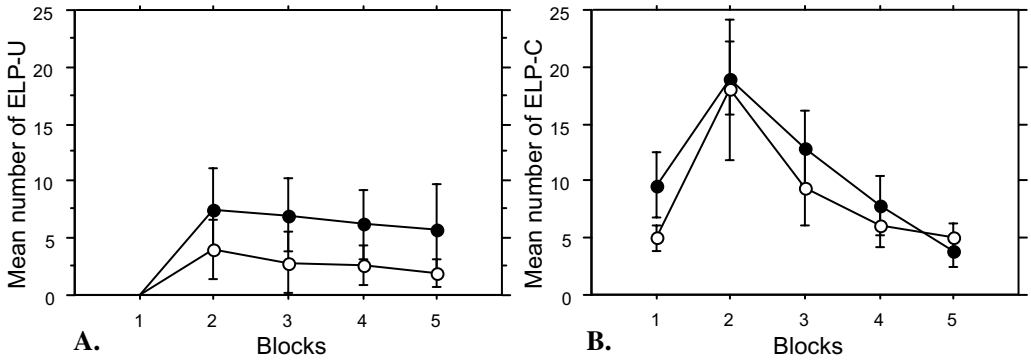


Fig. 3. Effects of orbital lesion on regular extinction. Mean and standard error of the mean number of (A) ELP-U and (B) ELP-C, in sham-operated (open circles) and in orbital-lesioned (black circles) rats undergoing regular extinction (experiment 2).

day 4. Two (sham) rats did not attain the criterion of 20 completed trials in the second session and were excluded from the experiment. Thus, the final analysis included seven and 10 rats in the sham and orbital groups, respectively. During lever-press training all rats achieved 40 completed trials with no uncompleted trials and therefore no ELP-U, and with a similar number of unpressed trials. There was no difference between the groups on the number of ELP-C ($F<1$). From the second day of lever-press training rats rarely pressed the nonreinforced lever. In both groups there was no increase in lever-presses on the nonreinforced lever in the test stage.

In the test, there were no differences between the two groups in the number of ELP-U (Fig. 3a, main effect of group, $F(1,15)=2.23$, $P>0.15$, group by blocks interaction, $F<1$) and in the number of ELP-C (Fig. 3b, main effect of group, $F<1$, group by blocks interaction, $F<1$).

Experiment 3: the effects of 1 and 3 mg/kg paroxetine on the behavior of orbital-lesioned and sham-operated rats in post-training signal attenuation. Thirty-six rats were randomly assigned to six groups, in a two (sham, lesion) by three (0, 1, 3 mg/kg paroxetine) factorial design. Eight rats needed another lever-press training session on day 4. One orbital rat did not attain the criterion of 20 completed trials in the second session and was excluded from the experiment. Thus, the final analysis included six rats in each group, except for the orbital-3 mg/kg paroxetine which included five rats. During lever-press training all rats achieved 40 completed trials with no uncompleted trials and therefore no ELP-U, and with a similar number of unpressed trials. There was no difference between the groups on the number of ELP-C ($F<1$). At the signal attenuation stage, there was no difference between the 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 (Table 1; main effect of group, $F<1$; group by day interaction, $F<1$). From the second day of lever-press training rats rarely pressed the nonreinforced lever. There was no increase in lever-presses on the nonreinforced lever in the test stage in any of the groups.

In the test, the number of ELP-U was markedly increased in rats sustaining lesions to the orbital cortex, replicating the results of experiment 1 (Fig. 4a). Paroxetine at a dose of 3 mg/kg greatly reduced the number of ELP-U in orbital-lesioned rats, and a similar tendency was observed in sham-operated rats; 1 mg/kg paroxetine had no effect on the orbital and sham rats (main effect of lesion, $F(2,29)=5.74$, $P<0.025$, main effect of drug, $F(2,29)=4.80$, $P<0.025$. Post hoc comparisons using the error term

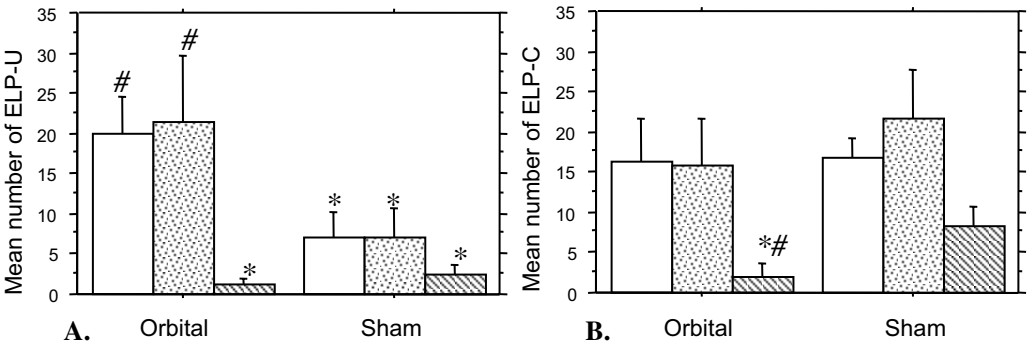


Fig. 4. The effects of 1 and 3 mg/kg paroxetine on the behavior of orbital-lesioned and sham-operated rats in post-training signal attenuation. Mean and standard error of the mean number of (A) ELP-U and (B) ELP-C, in sham-operated rats and in orbital-lesioned rats treated with either vehicle (white), 1 mg/kg (dotted) or 3 mg/kg (striated) paroxetine (experiment 3). * Significantly different from the orbital-vehicle group ($P<0.05$). # Significantly different from the sham-vehicle group ($P<0.05$).

derived from the ANOVA indicated that the orbital-vehicle and the orbital-1 mg/kg paroxetine groups had significantly more ELP-U than the sham-vehicle group, and that the orbital-3 mg/kg paroxetine and the sham-3 mg/kg paroxetine groups had significantly less ELP-U than the orbital-vehicle group, P's<0.05). The number of ELP-C was similar in orbital-lesioned and sham-operated rats treated with vehicle (Fig. 4b). One mg/kg paroxetine had no effect, whereas 3 mg/kg decreased the number of ELP-C in orbital rats and tended to decrease it in sham rats (main effect of drug, $F(2,29)=5.13$, $P<0.025$. Post hoc comparisons using the error term derived from the ANOVA indicated that the orbital-3 mg/kg paroxetine group had significantly less ELP-C than the orbital-vehicle and the sham-vehicle groups, P's<0.05).

Anatomical

The orbital lesions obtained in the different experiments were very similar. Neuronal loss and accumulation of glia cells were evident in the lateral and ventrolateral orbital cortices. In three rats (one in experiment 1, and two in experiment 2) signs of lesion were evident also in the agranular insular cortex, but these rats performed similarly to the other orbital-lesioned rats. In most animals, the lesion extended from 4.7–2.7 mm anterior to bregma (A-P), 0.9–3.6 mm lateral to the midline (M-L), and from 2.3–4.3 mm ventral from dura (D-V). Maximal damage was between 4.7 mm to 3.2 A-P, from 0.9 mm to 3.2 mm M-L, and from 2.9–4.2 mm D-V (Figs. 5 and 6).

Imipramine binding

The binding parameters of [^{3}H]imipramine to striatal and cortical membranes of drug-naive rats from experiments 1 and 2 are presented in Table 2. As can be seen, the number of [^{3}H]imipramine binding sites (Bmax), but not the dissociation constant (Kd), was significantly increased in the striatum, but not cortex, of orbital-lesioned rats compared with sham-operated rats. The results of [^{3}H]imipramine binding to hypothalamic membranes at two concentrations (3.2 nM and 12.0 nM; Table 3) revealed no differences between orbital and sham rats. The finding of increased Bmax but not Kd in the striatum of orbital rats was replicated in an additional series of brains obtained from orbital-lesioned and sham-operated rats that underwent the same behavioral procedure and a similar pharmacological treatment to that of rats in experiment 3 (Table 2). Because imipramine binds to both the serotonin and noradrenalin transporters, the lack of change in imipramine binding in the cortex and hypothalamus may be a result of opposite changes in the density and/or affinity of the serotonergic and noradrenergic transporters, rather than reflect an absence of effect of the lesion on these parameters. However, because the striatum is practically devoid of noradrenalin transporters (Tejani-Butt, 1992), the finding of an increased number of [^{3}H]imipramine binding sites in the striatum of orbital-lesioned rats reflects an increase in the density of the striatal serotonin transporter following the orbital lesion.

DISCUSSION

Rats sustaining lesions to the orbital cortex exhibited a profound increase in the number of excessive lever-presses that were *not* followed by magazine entry (i.e. ELP-U) in an extinction of lever-press responding that was preceded by signal attenuation (experiments 1 and 3). In contrast, when the extinction of the lever-press response was not preceded by a signal attenuation stage (i.e. regular extinction), the number of ELP-U exhibited by orbital-lesioned rats was similar to that exhibited by sham-operated rats (experiment 2). The effects of the orbital lesions on the number of excessive lever-presses that were followed by magazine entry (i.e. ELP-C) are less clear. Thus, orbital-lesioned rats exhibited a higher number of ELP-C compared with sham-operated rats in experiment 1. However, such an increase was not exhibited by vehicle-treated orbital-lesioned rats undergoing post-training signal attenuation (experiment 3, as well as unpublished observations), nor by orbital-lesioned rats undergoing regular extinction. Orbital-lesioned rats were also not different from their controls in the number of ELP-C during lever-press training (experiments 1–3; there were no ELP-U during this stage), nor in the number of lever-presses on the nonreinforced lever in the lever-press training and test stages. Taken together, the present 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).

Increased compulsivity of orbital-lesioned rats at the test stage was also not a result of lesion-induced alterations at the stages preceding the test. Thus, in the three experiments, there were no differences between the behavior of the orbital and sham groups in the magazine training, lever-press training and signal attenuation (experiment 1 and 3 only) stages. Of particular importance in the present context is the finding that orbital rats did not differ from their controls in the number of trials in which rats inserted their head into the food magazine during stimulus presentation (i.e. collected trials) during the signal attenuation stage. This finding indicates that orbital rats' increased compulsivity was not a result of an alteration in the extinction of the association between the stimulus and food.

The pattern of results obtained here in the post-training signal attenuation procedure is comparable to that obtained by Gallagher et al. (1999) in a post-training reinforcement devaluation procedure. These authors found increased magazine-approach responding in orbital-lesioned compared with control rats in an extinction test of the magazine-approach response, that was conducted following reinforcer devaluation. Similarly to the present results, there were no differences between orbital and control rats at the earlier stages of the task, namely, the acquisition of the magazine-approach response (procedurally equivalent to the lever-press response in the present procedure), and the acquisition of the aversion to the food (procedurally equivalent to the extinction of the stimulus-

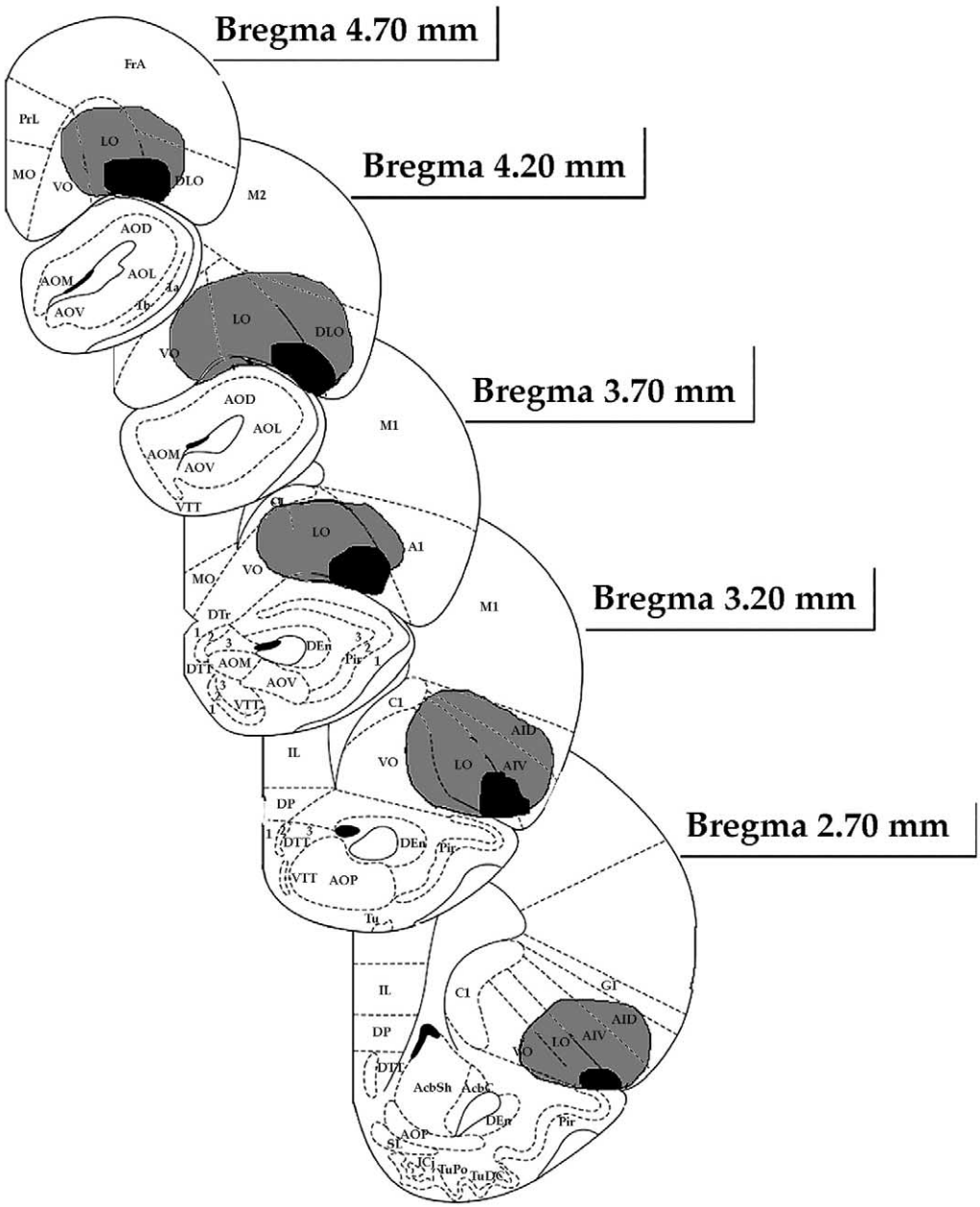


Fig. 5. Reconstruction of the orbital lesion. A series of coronal sections illustrating the orbital lesion in successive brain sections representing the minimal (black) and the maximal (gray) extent of the damage, in common for all rats in the group.

food association in the signal attenuation stage). Although there are important differences between the post-training signal attenuation procedure and post-training reinforcement devaluation procedures (for discussion see Joel and Avisar, 2001), the common feature that may make these two classes of procedures sensitive to orbital lesion is the need to use previously acquired information (extinction of stimulus-food association, conditioning of food aversion) to guide current behavior. This suggestion is consistent with current views of OFC function which emphasize its involvement in guiding behavior in the context of changed task contingencies (e.g. Dias et al., 1996, 1997; Gallagher et al., 1999; Nobre et al., 1999; Rolls, 2000; Schoenbaum et al., 1999, 2000). These views are based on behavioral findings that following damage to the OFC subjects are unable to withhold prepotent responses based on the original associations (Dias et al., 1996, 1997; Ferry et al., 2000; Gallagher et al., 1999; Jones and Mishkin, 1972; Rolls et al., 1994; Rolls, 2000; Zald and Kim, 2001), as well as on electrophysiological evidence that OFC neurons encode the motivational significance of stimuli and the expected outcome of responses, and change their responses rapidly when reinforcement contingencies change (Rolls, 2000; Schoenbaum and Eichenbaum, 1995; Schoenbaum et al., 1998; Tremblay and Schultz, 1999; Yonemori et al., 2000). It may therefore be speculated that

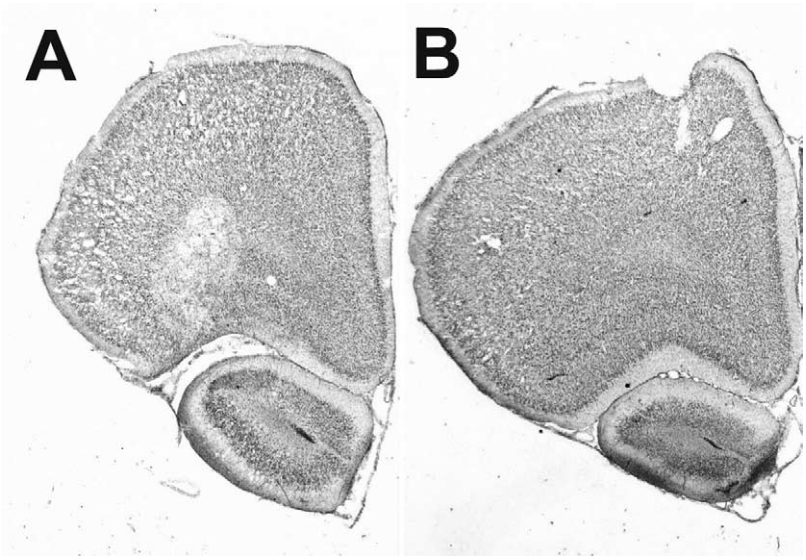


Fig. 6. A photomicrograph of (A) a representative orbital lesion, and (B) the orbital cortex of a sham-operated rat.

in the test stage of the post-training signal attenuation procedure, the orbital cortex provides the information (acquired at the signal attenuation stage) that the stimulus no longer signals food delivery, and this information serves to facilitate the suppression of compulsive lever-pressing induced by signal attenuation. Indeed, sham-operated rats were faster than orbital-lesioned rats to suppress compulsive lever-pressing at the test stage (sham rats exhibited compulsive lever-pressing for one 10-trial block compared with three blocks in the orbital group; see Fig. 2).

The increase in compulsive lever-pressing (i.e. signal attenuation-induced ELP-U) in orbital rats was abolished by the administration of 3 mg/kg paroxetine (experiment 3), and a similar, although not significant, effect was obtained in sham rats. (The lack of significant effect of paroxetine at 3 mg/kg in sham rats probably reflects a floor effect. Indeed, we have previously found a significant effect of paroxetine at this dose on compulsive lever-pressing in intact rats [Joel et al., 2004].) At 1 mg/kg, paroxetine had no effect on compulsive lever-pressing in either group. These findings are in line with the effects of paroxetine at these doses in intact rats (Joel et al., 2004), and suggest that orbital-lesioned rats are not more responsive than sham or intact rats to the effects of paroxetine. The finding that paroxetine reduced ELP-C in addition to ELP-U in both orbital and sham rats raises the possibility that this drug has a non-specific effect on lever-press responding. Although the present results cannot refute this possibility, results obtained in intact rats suggest that paroxetine's effects on ELP-C reflect its facilitating effect on extinction of lever-press responding. Thus, we have found that in intact rats undergoing regular extinction, paroxetine reduced the number of ELP-C while not affecting the number of ELP-U (Joel et al., 2004). An identical pattern of results (i.e. reduction of both ELP-C and ELP-U in rats undergoing post-training signal attenuation, but of only ELP-C in rats undergoing regular extinction) was also obtained with an additional SRI, fluvoxamine (Joel et al., 2004). Taken together, these results suggest that SRIs may exert a facilitating effect on extinction of lever-press responding, which is evident in both regular extinction and extinction following signal attenuation as a reduction in ELP-C, and in addition, reduce compulsive lever-pressing, that is, ELP-U induced by signal attenuation (Joel et al., 2004).

Although largely speculative at present, the finding that orbital lesion-induced ELP-U was alleviated following inhibition of serotonin reuptake suggests that the serotonergic system is involved in mediating orbital lesion-induced compulsivity. This possibility was supported by the results of [^{3}H]imipramine binding that revealed an increase in the density of the presynaptic serotonin transporter in the striatum of orbital-lesioned rats. Although further studies are needed to clarify the nature of the alteration(s) in the serotonergic system, the present finding is, to the best of

Table 2. The binding parameters (Bmax, in fmol/mg protein, and Kd, in nM, (mean±SE)) of [^{3}H]imipramine in orbital-lesioned and sham-operated rats

	Cortex (experiments 1–2)		Striatum (experiment 1–2)		Striatum (replication)	
	Bmax	Kd	Bmax	Kd	Bmax	Kd
Sham	634 (38)	4.10 (0.32)	515 (50)	4.00 (0.39)	520 (32)	3.81 (0.19)
Lesion	635 (31)	4.08 (0.27)	668 (40)	4.11 (0.40)	628 (31)	4.15 (0.28)
F	$F<1$	$F<1$	$F(1,8)=5.70$	$F<1$	$F(1,10)=5.81$	$F(1,10)=1.05$
P	$=0.99$	$=0.96$	<0.05	$=0.84$	<0.05	$=0.33$

Table 3. [^{3}H]imipramine binding (mean±S.E.) in the hypothalamus of orbital-lesioned and sham-operated rats (experiments 1–2)

	Ligand concentration, B (fmol/mg protein)	
	3.2 nM	12.0 nM
Sham	308 (16)	520 (18)
Lesion	320 (13)	553 (17)
F	$F(1,15)<0.36$	$F(1,14)<1.84$
P	$=0.56$	$=0.20$

our knowledge, the first to suggest that manipulation of the orbital cortex can affect the striatal serotonergic system. The latter is in line with the known anatomy of the serotonergic system, as the dorsal raphe nucleus, which provides serotonergic input to the striatum (Vertes, 1991), receives extensive projections from the orbital cortex (Peyron et al., 1998). Indeed, based on the latter, Peyron et al. (1998) suggested that the projections from the orbital cortex to the dorsal raphe may play a role in OCD. An alternative mechanism by which manipulations of the orbital cortex could influence striatal serotonin is via the direct glutamatergic projections from the orbital cortex to the striatum (Groenewegen et al., 1990; Uylings and van Eden, 1990), as glutamate has been shown to affect striatal serotonin release and turnover as well as mRNA expression of serotonin receptors (Abellan et al., 2000; Cartmell et al., 2000; Healy and Meador-Woodruff, 1999).

We have previously suggested that the extinction of the classical contingency between the light+tone stimulus and food in the signal attenuation stage, alters the ability of the stimulus to signal that the response was effective in producing food, and that this leads, in the subsequent test stage, to repeated emission of the lever-press response (Joel and Avisar, 2001; Joel and Doljansky, 2003). We have further speculated that signal attenuation may simulate a deficient response feedback or a deficient signaling that the conditions have changed following the organism's response, which have been hypothesized to underlie obsessions and compulsions in patients (e.g. Baxter, 1999; Gray, 1982; Malloy, 1987; Pitman, 1987, 1991; Reed, 1977; Szechtman and Woody, 2004, for review see Otto, 1992). The possibility that ELP-U induced by signal attenuation may provide an animal model of compulsive behavior in OCD, is further supported by 1. a similar pharmacological profile (i.e. alleviation by SRIs but not by anxiolytic, antipsychotic and classical tricyclic antidepressant drugs); 2. some evidence for common neural substrates (i.e. involvement of the serotonergic and dopaminergic systems); and 3. face similarity, that is, both ELP-U and compulsions are excessive and inappropriate (Joel and Avisar, 2001; Joel and Doljansky, 2003; Joel et al., 2001, 2004).

Given that in humans, lesion to the OFC may result in compulsive behavior which is similar to that of idiopathic OCD (Berthier et al., 1996; Hugo et al., 1999), the present demonstration that compulsive lever-pressing is selectively enhanced following lesion to the orbital cortex supports our hypothesis that this behavioral pattern may serve to model compulsive behavior in OCD. This hypothesis is further supported by the demonstration that orbital lesion-induced compulsivity is prevented by a serotonin reuptake inhibitor. It should be noted, however, that the present study has used acute drug administration, whereas SRIs require several weeks of treatment to produce beneficial effects in humans. As pointed out by Willner (1991), the demonstration of drug effects in the model after a period of chronic administration is important for establishing its face validity, but differences in treatment regimen (acute versus chronic) between the animal model and the modeled disease do not undermine the model's predictive validity.

The findings suggesting that orbital lesion-induced compulsivity in rats is mediated by alterations of the serotonergic system, possibly of the striatal serotonergic system, are of particular interest in view of the evidence implicating the striatum and the serotonergic system, in addition to the OFC, in the pathophysiology of OCD. Numerous functional imaging studies have found increased metabolism in the OFC and the striatum in OCD patients at rest and during symptom provocation, and "normalized" metabolism in these regions following a successful treatment with an SRI (e.g. 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). Several studies have also reported that patients with lower pretreatment OFC metabolism responded better to SRI treatment (Brody et al., 1998; Rauch et al., 2002; Saxena et al., 1999; Swedo et al., 1989, but see Hoehn-Saric et al., 2001). On the basis of Blier and colleagues' findings of increased serotonergic neurotransmission in the orbital cortex of intact rats and guinea-pigs after a prolonged SRI treatment (Blier and de Montigny, 1998; El Mansari et al., 1995), these imaging findings have been typically taken to suggest that SRIs might have their beneficial anti-compulsive effect in OCD patients by enhancing serotonergic transmission within the OFC (e.g. Rauch et al., 2002; Saxena et al., 1999). Although the extrapolation from an animal model to the clinical condition is problematic, the present finding that orbital lesion-induced compulsivity is paralleled by an increase in the striatal serotonin transporter and is attenuated by the SRI paroxetine raises an additional possibility, namely, that in some subsets of OCD patients a primary OFC dysfunction leads to striatal serotonergic changes and to compulsive behavior, and that anti-obsessional/anti-compulsive drugs act, in these patients, by normalizing the dysfunctional striatal serotonergic system.

It should be noted that these two possibilities are not mutually exclusive, as it is very likely that there are several subtypes of OCD which differ in the underlying pathophysiology. With respect to the involvement of the OFC, several authors have hypothesized that in some patients this cortical region may be the site of primary pathology whereas in other patients it may be merely reacting to pathology elsewhere, probably at the striatal level (e.g. Hendler et al., 2003; Hugo et al., 1999; Insel, 1992). This hypothesis is in line with current views of OCD as a disorder of basal ganglia-thalamocortical circuits (e.g. Graybiel and Rauch,

2000; Modell et al., 1989; Rapoport and Wise, 1988; Saxena et al., 1998; Stahl, 1988). A central postulate of models of basal ganglia-thalamocortical circuitry is that damage to different stations within these circuits can result in a similar behavioral alteration, and by corollary, that behavioral abnormalities resulting from damage to a specific station of a basal ganglia–thalamocortical circuit can be counteracted by manipulation at different stations of the circuit (e.g. Parkinsonism can be ameliorated by lesions to specific regions within the globus pallidus, the subthalamic nucleus and the thalamus; for a recent review see Benabid, 2003). It is therefore likely that drugs as well as other therapeutic manipulations can act at different stations of the circuits to alleviate OCD symptoms in different subtypes of the disorder, depending on the site of the primary pathology. Interestingly, there is some indication that response to different types of treatment is associated with different patterns of pre-treatment regional brain metabolism. Thus, whereas there is an inverse correlation between OFC pre-treatment metabolism and response to SRIs treatment (Brody et al., 1998; Rauch et al., 2002; Saxena et al., 1999; Swedo et al., 1989), Brody et al. (1998) reported also a positive correlation between OFC pre-treatment metabolism and response to cognitive-behavioral treatment.

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