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ORIGINAL INVESTIGATION

The role of NMDA receptors in the signal attenuation rat model of obsessive–compulsive disorder

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Abstract
Rationale In recent years, an increasing body of evidence points to the involvement of the glutamatergic system and specifically the glutamatergic ionotropic N-methyl-D-aspartate (NMDA) receptor in the pathophysiology of obsessive–compulsive disorder (OCD).
Objectives To test the role of NMDA receptors in compulsive behavior using the signal attenuation rat model of OCD. In this model, 'compulsive' behavior is induced by attenuating a signal indicating that a lever-press response was effective in producing food.
Methods The NMDA antagonist, MK 801 (0.025–0.100 mg/kg) and the partial NMDA agonist, D-cycloserine (3–100 mg/kg) were administered to rats just before assessing their lever-press responding following signal attenuation (Experiments 1 and 2, respectively). Because the effects of signal attenuation are assessed under extinction conditions, drug doses that were effective in Experiments 1 and 2 were also tested in an extinction session of lever-press responding that was not preceded by signal attenuation (Experiment 3).
Results Systemic administration of D-cycloserine (15 mg/kg) selectively decreased compulsive lever pressing, whereas systemic administration of MK 801 did not affect compulsive lever-pressing but dramatically increased resistance to extinction.
Conclusions Activation of NMDA receptors may have an anti-compulsive effect in OCD patients.

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Introduction

Obsessive–compulsive disorder (OCD) is a psychiatric disorder with a lifetime prevalence of 1–3% (Sasson et al. 1997), characterized by recurrent, intrusive, and unwanted thoughts (obsessions) and/or repetitive ritualistic behaviors (compulsions) (American Psychiatric Association 1994). Although the etiology of OCD is unknown, the prevailing view is that its pathophysiology involves a dysfunction of the serotonergic and/or dopaminergic systems (for recent reviews see Aouizerate et al. 2005; Denys et al. 2004).

In recent years, an increasing body of evidence points also to the involvement of the glutamatergic system in OCD (for review, see Pittenger et al. 2006). Specifically, elevated glutamate levels were found in the cerebrospinal fluid of drug-naïve OCD patients (Chakrabarty et al. 2005); symptom severity was found to correlate with the level of several glutamatergic metabolites (measured using magnetic resonance spectroscopy) in various brain regions implicated in OCD, including the caudate nucleus, the orbitofrontal cortex, and the cingulate cortex (Starck et al. 2008); and riluzole, a glutamatergic antagonist, was found to improve symptoms of both adult and pediatric OCD patients that were non-responsive to serotonin reuptake inhibitors (Coric et al. 2005; Grant et al. 2007). Several lines of evidence specifically implicate the glutamatergic ionotropic N-methyl-D-aspartate (NMDA) receptor in the pathophysiology of OCD. Thus, Arnold et al. (2004) found that certain polymorphisms in the NMDA receptor gene were associated with susceptibility to OCD; D-

cycloserine (DCS), a partial NMDA agonist, successfully augmented cognitive behavior therapy in OCD patients (Kushner et al. 2007; Wilhelm et al. 2008); and memantine, a non-competitive NMDA antagonist, was shown to improve OC symptoms in treatment-resistant OCD patients when given as an augmentation therapy to serotonin reuptake inhibitors (Aboujaoude et al. 2009).

Studies employing animal models of OCD also implicate the glutamatergic system in this disorder. Thus, various glutamatergic antagonists were found to reduce compulsive behavior in the marble burying test (Egashira et al. 2008); transgenic mice with increased glutamate input to the striatum exhibit an OC spectrum-like phenotype (Nordstrom and Burton 2002), and an NMDA antagonist increased compulsive-like behaviors in this model (McGrath et al. 2000).

The aim of the present study was to test the role of NMDA receptors in compulsive behavior using the signal attenuation rat model of OCD (for a recent review of the model, see Joel 2006b). This model was 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 1987, 1991; Reed 1977; Szechtman and Woody 2004; for review see Otto 1992). In the model, attenuation of a signal indicating that a lever-press response was effective in producing food 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 selective serotonin reuptake inhibitors fluoxetine, paroxetine, and fluvoxamine, but not by the anxiolytic drug, diazepam, the antipsychotic, haloperidol, or the tricyclic antidepressant, desipramine (Joel and Avisar 2001; Joel and Doljansky 2003; 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). In addition, manipulations of the rat orbital cortex affect compulsive lever pressing (Joel et al. 2005a, b; Joel and Klavir 2006), in line with the fact that functional imaging findings in OCD patients consistently implicate the orbitofrontal cortex in this disorder (for a recent review see Friedlander and Desrocher 2006). Finally, dopaminergic and serotonergic manipulations have been shown to affect compulsive lever pressing (Flaisher-Grinberg et al. 2008; Joel et al. 2001, 2004; Joel and Doljansky 2003), in line with clinical evidence implicating these systems in OCD (for review, see Goodman et al. 1990; McDougle et al. 1993; Stein 2002).

Experiments 1 and 2 tested the effects of several doses of MK 801 and of DCS, respectively, in the signal attenuation model. MK 801 is a non-competitive NMDA receptor antagonist, which acts primarily as an open-channel blocker and reduces neurotransmission at NMDA receptors (Moghaddam and Adams 1998). DCS is a ligand of the NMDA receptor-associated glycine B recognition site (Monahan et al. 1989), which displays about 40–86% of the efficacy of glycine (Hood et al. 1989; Priestley and Kemp 1994). DCS has been shown to have glycine agonistic effects at low doses (below 20 mg/kg) and antagonistic effects at higher ones (Emmett et al. 1991; Peterson and Schwade 1993). Therefore the present study included DCS doses from both low and high ranges. Because the effects of signal attenuation are assessed under extinction conditions, in order to test whether drug effects were specific to the behavioral response to signal attenuation, Experiment 3 tested drug doses that were effective in the post-training signal attenuation procedure in an extinction session of lever-press responding 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").

Methods

Subjects

Male Sprague–Dawley rats (Tel Aviv University, Israel), approximately 3–4 months old, were housed four to a cage under a reversed 12-h light–dark cycle (lights on 1900–0700) and maintained on a 22-h food restriction schedule (food was provided in the home cage at least half an hour after the end of behavioral training), with water freely available. Rats were weighed twice a week to ensure that their body weight was not reduced to below 90%. All experimental protocols were carried out according to the guidelines of the Institutional Animal Care and Use Committee of Tel Aviv University.

Apparatus and behavioral procedure

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

ing were computer controlled using the Animal Behavior Environment Test (ABET) system software (Lafayette Instrument Company, Lafayette, Indiana, USA).

Prior to the beginning of the experiment, rats were handled for about 2 min daily for 5 days. On the last 3 days after handling, ~20 food pellets used as reinforcement for operant training were introduced into the home cages.

Post-training signal attenuation The post-training signal attenuation procedure included four stages. The organization of a trial of each of these stages is presented in Fig. 1.

Stage 1: *Magazine training*. On Days 1–3, rats were trained to collect food pellets from the food magazine in the operant chamber, with the levers retracted. On each day, each rat was trained until it attained 30 collected trials (that is, trials on which the rat inserted its head into the food magazine during stimulus presentation), 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 Day 4, rats received a session of pre-training using a free-operant schedule. Throughout this session, the houselight was on, and one lever was present in the operant box. Responding on this lever (reinforced lever, RL) resulted in the delivery of a single food pellet into the magazine, accompanied by the presentation of the compound stimulus (magazine light and tone). The stimulus was turned off after the rat's head entered the food magazine or after 15 s from the rat's first lever-press had elapsed. The lever designated as RL was counterbalanced over subjects and remained the same for each rat over the entire experimental procedure. Each rat was trained until it completed 30 trials, that is, pressed the lever and inserted its head into the food magazine during stimulus presentation. Rats that failed to attain 30 completed trials within 30 min, were returned to the test chamber at the end of the day for an additional session. On Days 5–7, rats were trained to lever press in a discrete trial procedure (Fig. 1). Each rat was trained until it completed 40 trials, that is, pressed the lever and inserted its head into the food magazine during stimulus presentation, or for a total of 60 trials. In order to assess acquisition of the lever-press response, the number of trials on which the rat did not press the RL (unpressed trials) and the number of trials on which the rat pressed the RL without inserting its head into the food magazine (uncompleted trials) were recorded in addition to the number of completed trials. In order to assess rats' tendency for excessive lever pressing, the number of lever presses on the NRL and the number of lever-presses on the RL after the first response (extra lever presses, ELP) were recorded. The latter measure was further subdivided into ELP in uncompleted trials (that is, ELP not followed by insertion of the head into the food magazine; ELP-U), and ELP in completed trials (ELP-C). In addition, the number of nose pokes were recorded. Rats were randomly allocated to the different drug groups at the end of this stage. Analysis of the number of ELP-C was carried to make sure that there are no significant differences between the groups on this behavioral measure.

Stage 3: *Signal attenuation*. On Days 8–10, with the levers retracted, rats were exposed to the presentation of the compound stimulus as on Days 1–3, but no food was delivered to the food magazine (Fig. 1). Rats received 30 such trials on each day, and the number of collected trials was recorded. Rats that had more than 13 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 Day 11, rats were trained as in the lever-press training stage, except that no food was delivered to the food magazine, that is, pressing the lever resulted in the presentation of the compound stimulus only (Fig. 1). The session lasted for 50 trials. The behavioral measures recorded were the same as in the lever-press training stage. Compulsive lever pressing is operationally defined as the number of ELP-U in the test stage of the post-training signal attenuation procedure.

Regular extinction Rats were run exactly as in the post-training signal attenuation procedure, with the exception that they did not undergo the signal attenuation stage. On these days, rats were brought to the laboratory and left in their home cages for a period equivalent to the average duration of the signal attenuation stage.

Drugs

MK 801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5,10-imine maleate] (Sigma, Rehovot, Israel) and DCS (Sigma, Rehovot, Israel) was dissolved in saline to doses of 0.025, 0.050, 0.075, and 0.100 mg/kg or 3, 15, 30, and 100 mg/kg, respectively, and administered i.p. in a

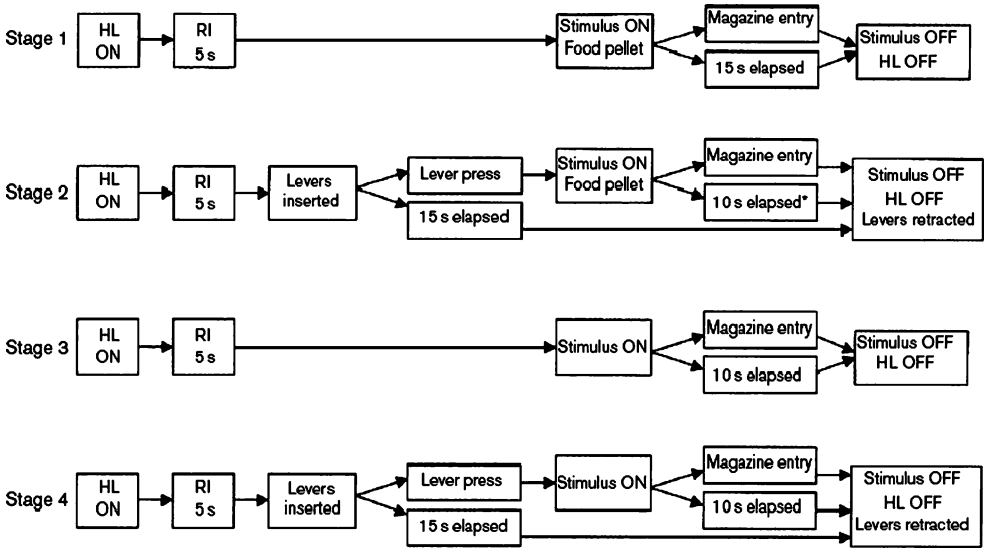

Fig. 1 A schematic diagram of the organization of a trial in each of the different training stages of the post-training signal attenuation procedure. HL, houselight; RI, random interval; * on the first day of lever-press training (Day 5) this time limit was 15 s

volume of 1 ml/kg, 30 min before the beginning of the test stage. The doses of MK 801 were selected on the basis of previous studies which showed that similar doses of MK 801 were effective in altering behavior (Gaisler-Salomon and Weiner 2003; van der Meulen et al. 2003) including lever-press responding (Shannon and Love 2004) without completely abolishing it. The doses of DCS were chosen on the basis of previous behavioral studies (Dall'Olio and Gandolfi 1993; Dall'Olio et al. 1994; Depoortere et al. 1999).

Statistical analysis

Rats' performance on the test stage was analyzed using analysis of variance (ANOVA) with a main factor of Dose (Experiments 1 and 2; Drug, Experiment 3) performed on the number of ELP-C and ELP-U as well as on the number of completed, uncompleted, and unpressed trials and the number of nose pokes and presses on the non-reinforced lever. Significant dose effects were followed by post hoc least significant difference (LSD) comparisons comparing each of the drug-treated groups with the vehicle group. For all comparisons, significance was assumed at $p<0.05$. For experiments ran in several replications (Experiments 1 and 2 were run in two partially overlapping replications), data of the overlapping groups were analyzed using ANOVAs with replication and dose as main factors. Because in these experiments, the effect of replication and the replication×dose interaction in the different analyses were non-significant; data from different replications were combined.

Although drugs were administered only prior to the test stage, rats' performance on the lever-press training and signal attenuation stages was also analyzed, to ensure that differences in performance at the test stage were not a result of an earlier difference. For the former, the number of ELP-C and unpressed trials on the last day of lever-press training were analyzed (as all rats had 40 completed trials and almost no uncompleted trials, the variability of all other variables was too low to enable statistical analysis). Performance on the signal attenuation stage was analyzed using a mixed ANOVA performed on the number of completed trials on the three sessions of the signal attenuation stage.

Results

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

Experiment 1: the effects of the NMDA antagonist MK 801 in the post-training signal attenuation procedure

There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown, all p's>0.62). Figure 2a and b presents the mean number of ELP-C and ELP-U, respectively, at the test stage of the PTSA procedure of rats treated with vehicle or 0.025, 0.050, 0.075, or 0.100 mg/kg MK 801. As can be seen, MK 801 dramatically increased the number of ELP-C exerting an inverse U-like effect, with 0.050 mg/kg increasing the number of ELP-C more than four-folds (one-way ANOVA yielded a significant main effect of dose, $F(4,72)=12.483$, $p<0.0001$; a further analysis revealed that both the linear and the quadratic trend components of the ANOVA were significant, $F(1,72)=11.128$, $p<0.005$ and $F(1,72)=18.613$, $p<0.0001$, respectively. See Fig. 2a for the results of the post hoc comparisons). In contrast, MK 801 had no effect on the number of ELP-U ($F(4,72)=0.775$, $p>0.54$), except for the 0.075 mg/kg dose, which tended to increase this measure. It should be noted that the large standard error of the 0.075 mg/kg group reflects the bi-modal distribution of

Table 1 Summary of experiments

Exp	Drug	Procedure	Number of rats in experiment	Number of rats excluded	Dose (mg/kg)	Final *n* per group
1	MK 801	PTSA	80	3, statistical	Vehicle	23
					0.025	14
					0.05	18
					0.075	12
					0.1	10
2	DCS	PTSA	73	3, statistical	Vehicle	16
					3	14
					15	16
					30	16
					100	8
3	MK 801 & DCS	RE	46	5, statistical	Vehicle	10
					0.05 (MK 801)	9
					0.075 (MK 801)	10
					15 (DCS)	12

The table presents the number of rats allocated to each experiment, the number of rats excluded from each experiment, and the final number of rats in each group. PTSA—the post-training signal attenuation procedure; RE—the regular extinction procedure; Statistical: rats were excluded if their score on ELP-C and/or ELP-U was more than four standard deviations above their group mean.

ELP-U in this group, with eight rats performing less than 60 ELP-U, and four rats performing more than 120 ELP-U (the distribution of ELP-C was not bi-modal for this or the other MK 801 groups). Table 2 presents the mean (SE) number of completed, uncompleted, and unpressed trials as well as the mean (SE) number of lever presses on the non-reinforced lever (NRL) and of nose pokes during the test in the five groups. MK 801 increased the number of completed trials and decreased the number of unpressed trials in a U-like manner, with 0.050 mg/kg having the strongest effect. In contrast, MK 801 did not significantly affect the number of uncompleted trials. In contrast to the strong effect of MK 801 on the number of ELP-C, this drug did not significantly affect the number of presses on the NRL (although the lowest dose tended to increase this behavior). Similarly, the effect of MK 801 on the number of nose pokes was not significant (see Table 2 for the full results of the statistical analyses).

Because MK 801 affected both the number of ELP-C and the number of completed trials, we also analyzed the number of ELP-C per completed trial and the number of ELP-U per uncompleted trial (Fig. 2c–d). This analysis revealed that MK 801 had no significant effect on the number of ELP-C per completed trial ($F(4,72)=1.474$, $p=0.219$), but at a dose of 0.050 mg/kg significantly increased the number of ELP-U per uncompleted trial ($F(4,72)=2.99$, $p<0.025$, see Fig. 2d for the results of the post hoc comparisons).

Experiment 2: the effects of the NMDA agonist DCS in the post-training signal attenuation procedure

There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown, all p's>0.18). Figure 3a and b presents the mean number of ELP-C and ELP-U, respectively, at the test stage of the PTSA procedure of rats treated with vehicle or 3, 15, 30, or 100 mg/kg DCS. DCS had no effect on the number of ELP-C, $F(4,65)=1.96$, $p>0.11$. However, at 15 mg/kg, DCS significantly decreased the number of ELP-U, $F(4,65)=3.18$, $p<0.02$ (see Fig. 3b for the results of the post hoc comparisons). Table 2 presents the mean (SE) number of completed, uncompleted, and unpressed trials as well as the mean (SE) number of lever presses on the non-reinforced lever (NRL) and of nose pokes during the test in the five groups. At doses of 3, 30, and 100 mg/kg, DCS had no effect on these measures (except 3 mg/kg DCS, which tended to increase the number of nose pokes). In contrast, 15 mg/kg DCS significantly decreased the number of uncompleted trials and increased the number of unpressed trials without affecting the number of completed trials, or the number of nose pokes and of lever presses on the NRL (see Table 2 for the full results of the statistical analyses).

Because DCS decreased both the number of ELP-U and the number of uncompleted trials, we also analyzed the number of ELP-C per completed trial and the number of ELP-U per uncompleted trial (Fig. 3c–d). This analysis revealed that DCS had no significant effect on the two measures (ELP-C per completed trial, $F(4,65)=1.174$, $p=0.331$; ELP-U per uncompleted trial, $F(4,65)=1.00$, $p=0.414$).

Experiment 3: the effects of MK 801 and DCS in the regular extinction procedure

All of the doses of MK 801 tested in the PTSA procedure increased the number of ELP-C without affecting the number of ELP-U, except 0.075 mg/kg that tended to increase the

Table 2 Performance in the test

Experiment & Group	Completed	Uncompleted	Unpressed	NRL	NP
Exp. 1 MK-801(mg/kg) in post-training signal attenuation					
0	10(0.88)	9.52(0.63)	30.43(1.08)	14.43(2.73)	79.87(13.97)
0.025	14.64(2.2)	11(1.47)	24.14(2.98)	24.36(6.38)	108.64(15.99)
0.050	30.72(2.16)	6.83(1.19)	12.39(1.96)	11.44(3.13)	121(23.12)
0.075	16.33(3.17)	10.58(2.5)	23.08(4.49)	10.83(3.31)	94.42(20.8)
0.1	20.8(5.1)	8.7(2)	20.5(3.59)	17.1(5.16)	107.6(28.08)
F, *p*	$F(4,72)=13.47$, $p<0.0001$	$F(4,72)=1.41$, $p=0.24$	$F(4,72)=8.4$, $p<0.0001$	$F(4,72)=1.7$, $p=0.16$	$F(4,72)=0.79$, $p=0.53$
Exp. 2 DCS(mg/kg) in post-training signal attenuation					
0	8(0.99)	9.56(0.95)	32.44(1.28)	15.56(3.53)	50.69(8.95)
3	11.21(2.54)	8(0.93)	30.79(2.51)	15(4.19)	84(13.37)
15	7.56(0.85)	4.75(0.7)	37.56(1.18)	12.37(2.11)	52.19(8.04)
30	10.37(1.12)	9.06(0.86)	30.44(1.8)	13.87(2.39)	77.25(9.2)
100	9.87(1.26)	9.75(1.7)	30(1.96)	12.25(2.55)	69.5(21.88)
F, *p*	$F(4,65)=1.22$, $p=0.31$	$F(4,65)=4.9$, $p<0.005$	$F(4,65)=3.22$, $p<0.05$	$F(4,65)=0.22$, $p=0.92$	$F(4,65)=1.91$, $p=0.12$
Exp. 3 MK-801 & DCS(mg/kg) in regular extinction					
0	32.09(1.73)	2.9(0.79)	15(1.61)	9.36(1.73)	162.27(20.03)
MK-801 (0.05)	41.11(2.54)	2.11(0.73)	6.67(2.63)	12.67(3.58)	283.44(46.28)
MK-801 (0.075)	45.3(1.97)	1.4(0.67)	3.2(1.36)	21.3(11.87)	431.9(84.74)
DCS (15)	29.08(2.03)	4.08(1.09)	16.83(1.9)	6.5(2.13)	164.75(18.41)
F, *p*	$F(3,38)=3.13$, $p<0.0001$	$F(3,38)=1.76$, $p=0.16$	$F(3,38)=12.07$, $p<0.0001$	$F(3,38)=1.14$, $p=0.34$	$F(3,38)=7.3$, $p<0.005$

The table presents the mean (SE) number of completed, uncompleted and unpressed trials as well as the mean (SE) number of lever-presses on the non-reinforced lever (NRL) and of nose pokes (NP) during the test

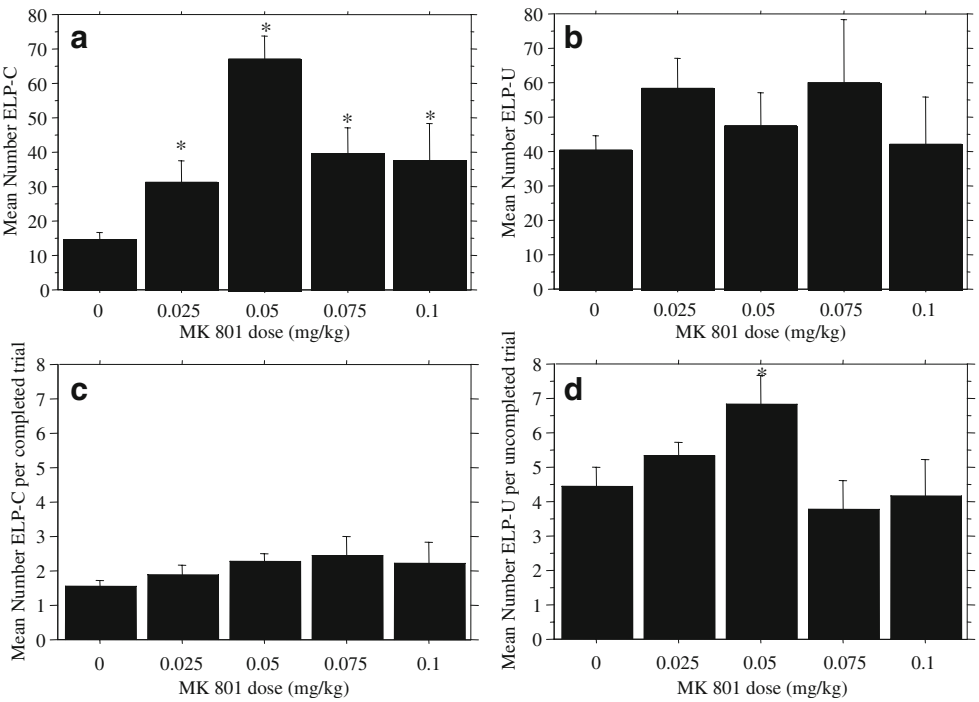

Fig. 2 Mean and standard error of **a** the number of extra lever presses that were followed by magazine entry (ELP-C), **b** the number of extra lever presses that were not followed by magazine entry (ELP-U), **c** the number of ELP-C per completed trial, and **d** the number of ELP-U per uncompleted trial of rats treated with vehicle or 0.025, 0.050, 0.075, or 0.100 mg/kg MK 801 on the test day of the post-training signal attenuation procedure (Experiment 1). * Significantly different from the vehicle group ($p<0.05$)

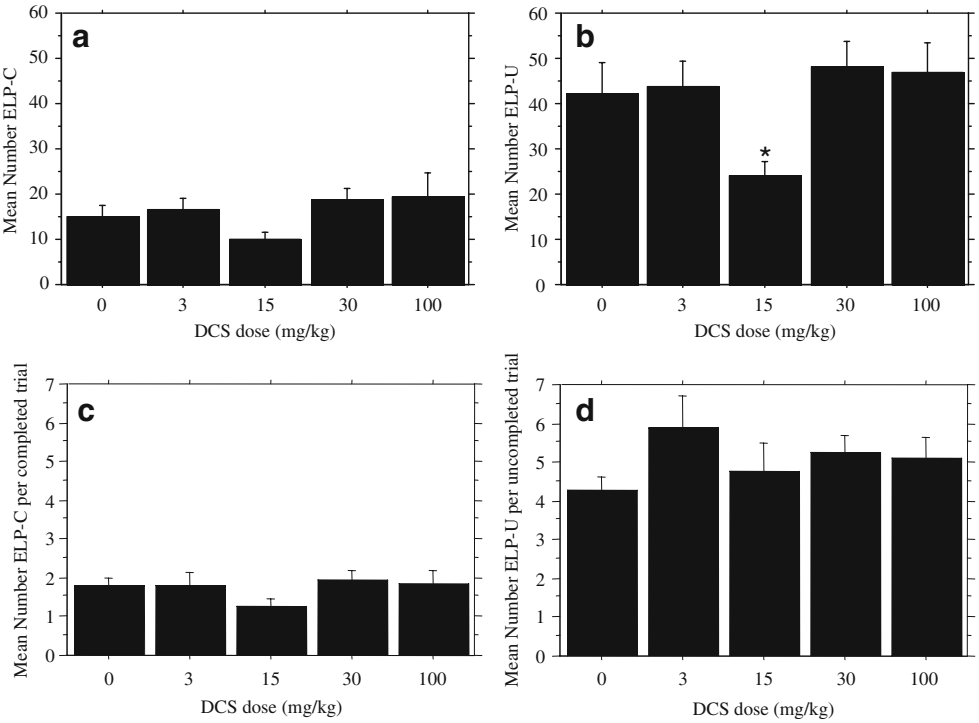

Fig. 3 Mean and standard error of **a** the number of extra lever presses that were followed by magazine entry (ELP-C), **b** the number of extra lever presses that were not followed by magazine entry (ELP-U), **c** the number of ELP-C per completed trial, and **d** the number of ELP-U per uncompleted trial of rats treated with vehicle or 3, 15, 30, or 100 mg/kg DCS on the test day of the post-training signal attenuation procedure (Experiment 2). * Significantly different from the vehicle group ($p<0.05$)

latter. We have therefore tested the effects of this dose as well as of 0.050 mg/kg (which had the strongest effect on ELP-C) in the regular extinction procedure. We have also tested the effects of 15 mg/kg DCS in the regular extinction procedure, as of the doses of DCS tested in the PTSA procedure, only 15 mg/kg was effective in reducing ELP-U.

There were no differences between the groups at the lever-press training and signal attenuation stages (data not shown, all p's>0.58). Figure 4a and b presents the mean number of ELP-C and ELP-U, respectively, at the test stage of the PTSA and regular extinction procedures of rats treated with vehicle, 0.050 mg/kg MK 801, 0.075 mg/kg

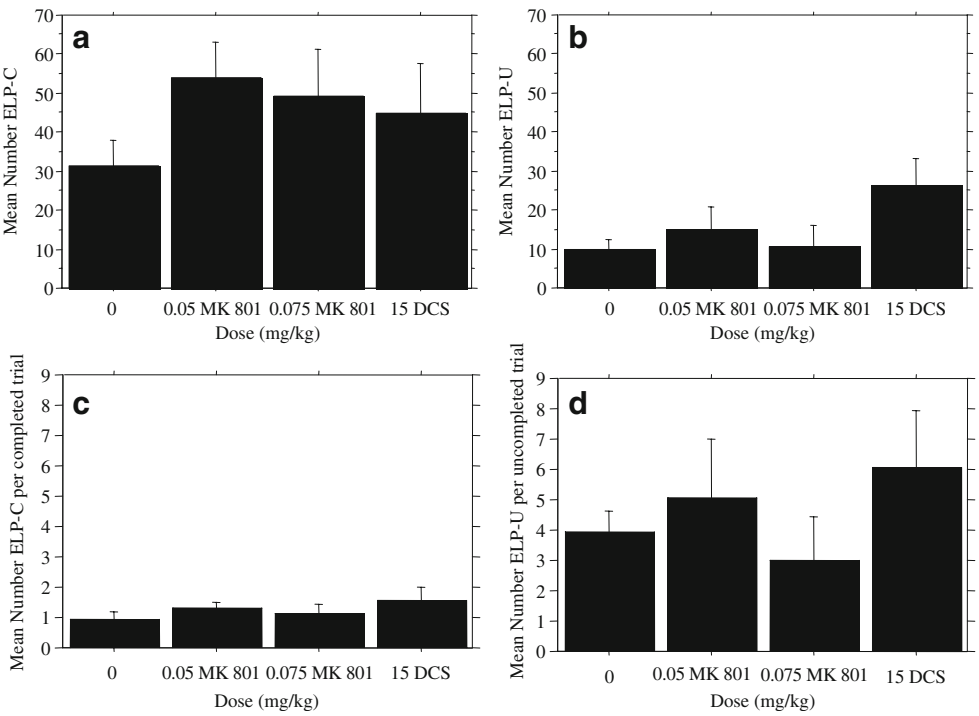

Fig. 4 Mean and standard error of **a** the number of extra lever presses that were followed by magazine entry (ELP-C), **b** the number of extra lever presses that were not followed by magazine entry (ELP-U), **c** the number of ELP-C per completed trial, and **d** the number of ELP-U per uncompleted trial of rats treated with vehicle or 0.050 or 0.075 mg/kg MK 801 or 15 mg/kg DCS on the test day of the regular extinction procedure (Experiment 3)

MK 801, or 15 mg/kg DCS. As can be seen, MK 801 and DCS slightly increased the number of ELP-C, but this effect was far from significance (main effect of drug: $F(3,37)=0.77$, $p>0.52$). DCS also tended to increase the number of ELP-U, whereas MK 801 did not significantly affect this behavior (main effect of drug: $F(3,37)=2.04$, $p=0.125$). Similar to its effects in PTSA, MK 801 increased the number of completed trials and decreased the number of unpressed trials without exerting a significant effect on the number of uncompleted trials (see Table 2 for the full results and the statistical analyses). Yet, MK 801's effects in regular extinction were much weaker compared to its effects in PTSA. MK 801 dose-dependently increased the number of nose pokes but had no effect on the number of lever presses on the NRL; the mean number of NRL in the 0.075 mg/kg group is biased by the performance of one rat that had 126 NRL, whereas all the other rats in this group had less than 26 NRL. The effects of 15 mg/kg DCS in regular extinction were different from its effects in PTSA. Specifically, DCS did not affect the number of completed and unpressed trials and tended to increase the number of uncompleted trials. DCS also did not significantly affect the number of nose pokes and of lever-presses on the NRL.

Analysis of the effect of MK 801 and DCS on the number of ELP-C per completed trial and on the number of ELP-U per uncompleted trial (Fig. 4c–d) revealed that the two drugs did not exert a significant effect on the two measures (F's<1).

Discussion

The present study tested the role of NMDA receptors in compulsive behavior, as assessed in the signal attenuation rat model of OCD. The effects of MK 801 and DCS were assessed in rats undergoing an extinction test of lever-press responding that was preceded by signal attenuation (the PTSA procedure), and in rats undergoing a control procedure in which the extinction test was not preceded by signal attenuation (the 'regular extinction' procedure). This design enables the differentiation between the effects of signal attenuation and of extinction per se. Briefly, a drug's effect on compulsive responding is evidenced in a change in the number of excessive lever-presses that are not followed by magazine entry (ELP-U) in the PTSA procedure but not in the regular extinction procedure, whereas a drug's effect on extinction is manifested in a change in the number of excessive lever presses that are followed by magazine entry (ELP-C) in both the PTSA and regular extinction procedures (for a detailed discussion see Joel 2006b).

The main findings of the present study are that systemic administration of the NMDA agonist DCS decreased compulsive lever pressing, whereas systemic administration of the NMDA antagonist MK 801 dramatically increased resistance to extinction.

The effects of MK 801 in the PTSA and regular extinction procedures

Systemic administration of the NMDA antagonist MK 801 (0.025, 0.050, 0.075, and 0.100 mg/kg) prior to the test stage of the PTSA procedure resulted in a dramatic inverse U-like increase in the number of excessive lever presses that were followed by magazine entry (i.e., ELP-C). The increase in ELP-C was very specific, as MK 801 did not affect the number of excessive lever-presses that were not followed by magazine entry (i.e., ELP-U), the number of lever presses on the NRL and the number of nose pokes. When administered prior to the regular extinction procedure, MK 801 (0.050 and 0.075 mg/kg) exerted a similar, although weaker, effect on the number of ELP-C, completed trials and unpressed trials to the one observed in the PTSA procedure, and in addition increased the number of nose pokes. Taken together, these results suggest that MK 801 strongly affects extinction but has no effect on compulsive responding in the model.

It is noteworthy that MK 801 effects on the number of ELP-C per completed trial and on the number of ELP-U per uncompleted trial in the PTSA procedure were opposite to its effects on the total number of ELP-C and ELP-U. Specifically, MK 801 increased the total number of ELP-C but did not affect the number of ELP-C per completed trial, and increased the number of ELP-U per uncompleted trial but did not affect the total number of ELP-U. Although these results are intriguing, they are difficult to interpret because it is not clear what underlying processes the ratio measures are reflecting. Specifically, our previous work suggested that the total number of ELP-U is the measure of compulsive responding in the model because it shows the same pharmacological selectivity as OC symptoms (see Introduction). This is not the case for the two ratio measures, suggesting that these measures are not reflecting compulsive responding.

Our conclusion that MK 801 does not affect compulsive responding in the model is in line with a previous report that 0.03 and 0.10 mg/kg MK 801 did not affect marble burying (Egashira et al. 2008), another rodent model of OCD (for review see Joel 2006a). It should be noted that at a higher dose (0.30 mg/kg) MK 801 decreased the number of marbles buried, suggesting an anti-compulsive effect; yet the authors concluded that this inhibitory effect is most likely not specific (Egashira et al. 2008). The finding that MK 801 does not have an anti-compulsive effect contradicts, however, a previous report that in OCD patients memantine, another non-competitive open-channel NMDA

blocker, improves OC symptoms when given as an augmentation therapy to serotonin reuptake inhibitors (Aboujaoude et al. 2009). Yet, there are many reports that memantine differs from other non-competitive NMDA antagonists, including MK 801, in its behavioral effects, and several hypotheses have been raised regarding the mechanistic difference that may underlie the differences in the clinical effects (for review see Johnson and Kotermanski 2006; Lipton 2006).

Although MK 801 at similar doses to the ones tested here was previously found to increase the rate of lever pressing (Shannon and Love 2004), the present finding that MK 801 did not affect the number of ELP-U and of lever presses on the NRL does not support a non-specific disinhibitory effect of MK 801. Rather, the present results suggest that MK 801 increased resistance to extinction of the lever-press response, in terms of both the decrease in the number of unpressed trials and the increase in the number of completed trials and of ELP-C (but not of the number of ELP-C per completed trial), which we have previously suggested to be equivalent to Skinner's extinction burst (Joel 2006b). It is noteworthy that MK 801 also increased the number of nose pokes in rats undergoing regular extinction but not in rats undergoing PTSA. As nose poking was already extinguished by the time of the test in PTSA rats (as a result of the signal attenuation stage), the pattern of MK 801 effects on nose pokes in the two procedures is also consistent with the possibility that MK 801 impairs extinction. Interference with the extinction of nose poking, which was in effect in rats undergoing regular extinction but not PTSA, may also account for the smaller effect of MK 801 on ELP-C in the former procedure. This is because in regular extinction rats had two predominant behaviors, lever pressing and nose poking, so that rats may have stopped lever pressing in order to nose poke, whereas in PTSA there was no competing behavior to lever pressing. Only one study to date has tested the effects of MK 801 on the extinction of operant responding, and this study has found, in contrast to the present findings, that at 0.1 mg/kg, MK 801 enhanced the extinction of free-operant lever pressing for a food reward (Port and Seybold 1998). The reason for this inconsistency is not clear but may be attributed to differences between the task used in Port and Seybold's (1998) study and in the present study, including training in a free-operant schedule versus a discrete trial schedule, and differences in the role of nose poking in the behavioral sequence (it is not clear in Port and Seybold (1998) what response was needed in order to collect the food pellet).

It is of interest to note that MK 801-treated rats responded to the encounter of no reward in the extinction test, as evidenced in the emergence of repeated lever-presses (the extinction burst). Yet, these rats were unable to switch responding following the change in reward contingencies, that is, were unable to suppress the now non-rewarded lever-press (and nose poke) behavior. In line with our findings and interpretation are several reports that MK 801 and other non-competitive NMDA antagonists interfere with exerting inhibitory control over behavior (as for example in impulsive responding, Higgins et al. 2003; Stephens and Cole 1996; Welzl et al. 1991), and with switching behavior when reward contingencies change (which also requires the inhibition of the now non-rewarded behavior) (e.g., Gaisler-Salomon and Weiner 2003; Gaisler-Salomon et al. 2008; Shannon and Love 2004).

The effects of DCS in the PTSA and regular extinction procedures

Systemic administration of the NMDA partial agonist DCS (3, 15, 30, and 100 mg/kg) prior to the test stage of the PTSA procedure had almost no effect on rats' behavior, except for the 15 mg/kg dose, which significantly decreased the number of ELP-U and the number of uncompleted trials. The effects of 15 mg/kg DCS in regular extinction were opposite to those observed in PTSA, with DCS tending to increase the number of ELP-U and of uncompleted trials. Taken together, these results suggest that DCS exerts an anti-compulsive effect, albeit at a very narrow dose range, without affecting extinction per se.

It should be noted, however, that DCS did not significantly affect the number of ELP-U per uncompleted trial, suggesting that DCS' effect on the number of ELP-U was a result of its effect on the number of uncompleted trials. As detailed above, however, using pharmacological similarity as a criterion, the total number of ELP-U rather than the number of ELP-U per uncompleted trial is the measure of compulsive responding in the model.

There are many studies on the effects of DCS on extinction of Pavlovian responses, mainly following fear conditioning (for a recent review see Norberg et al. 2008), but only a few studies tested the effects of DCS on the extinction of operant responding. The present finding that DCS did not affect the extinction of lever pressing is in line with a previous report that DCS (5 mg/kg) did not affect the extinction of lever pressing for a water reward (Vengeliene et al. 2008). However, there are also contradictory findings. Thus, DCS (5 mg/kg) was found to facilitate extinction of lever pressing for alcohol reward (Vengeliene et al. 2008) and to retard extinction of free-operant lever pressing for a food reward (3 mg/kg; Port and Seybold 1998).

There are no previous studies on the effects of DCS on compulsive behavior in animal models. In humans, DCS was found to successfully augment cognitive behavior therapy in OCD patients (Kushner et al. 2007; Wilhelm et

al. 2008). Although the extrapolation from an animal model to the clinic should be made with great caution, the present findings suggest that DCS may also exert a direct anti-compulsive effect.

The role of NMDA receptors in compulsive behavior

The present study found that a low dose (15 mg/kg) of the NMDA partial agonist DCS exerts an anti-compulsive effect in the signal attenuation model of OCD, whereas a wide range of doses of the non-competitive NMDA antagonist MK 801 do not affect compulsive lever-pressing. Since DCS is less effective than glycine in inducing NMDA receptor activation, it may act as a net NMDA antagonist in the presence of physiological glycine levels. DCS's agonist effects would prevail at low doses, whereas its antagonist effects would prevail at high doses (Kanahara et al. 2008), leading to an extremely narrow therapeutic window (Cascella et al. 1994). It is therefore likely that the anti-compulsive effect exerted in the present study by 15 mg/kg DCS reflects DCS' agonistic action (Emmett et al. 1991; Peterson and Schwade 1993). It is noteworthy that higher doses of DCS, which most likely exert an antagonistic action, did not affect compulsive responding, similarly to the lack of effect of MK 801 on this behavior.

The finding that a low dose of DCS (15 mg/kg) and of MK 801 does not exert opposite effects on compulsive lever pressing, as may be expected from an agonist and an antagonist of the same receptor, is in line with previous findings. For example, both non-competitive NMDA antagonists and DCS were reported to worsen schizophrenia symptoms (Cascella et al. 1994; Lahti et al. 1995; Malhotra et al. 1997). In addition, DCS was found not to counteract the deleterious effects of MK 801 administration on pre-pulse inhibition (Kanahara et al. 2008) and on performance in the Morris water maze and the radial arm maze tasks (Pitkanen et al. 1995). One possible interpretation of the present findings is that under physiological conditions, activation of NMDA receptors does not play a role in the production of compulsive behavior; therefore, the blockade of these receptors does not affect compulsive behavior. Yet, pharmacological activation of these receptors does exert an anti-compulsive effect.

The experiments reported in the present study comply with the current laws of Israel.

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