



Effects of antipsychotic drugs on MK-801-induced attentional and motivational deficits in rats

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ABSTRACT

Background: Attentional deficits that accompany schizophrenia are not effectively treated by available antipsychotic medications. Disruption of NMDA receptor function is often used to model aspects of this disorder in rodents. We used the 5-choice serial reaction time task (5CSRTT) to characterize attentional deficits caused by acute administration or withdrawal from chronic administration of the NMDA receptor antagonist MK-801, and determine if they are ameliorated by haloperidol or clozapine.

Methods: Acute studies involved tests in the presence of MK-801: rats were administered haloperidol (0.008–0.125 mg/kg, SC) or clozapine (0.16–2.5 mg/kg, SC) in combination with MK-801 (0.25 mg/kg, IP) prior to daily test sessions. Chronic studies involved tests in the absence of MK-801: following daily tests, rats were administered MK-801 (0.5 mg/kg, IP) and tested 24 h later in the absence or presence of haloperidol or clozapine.

Results: Acute MK-801 disrupted performance: it decreased accuracy while increasing omissions, premature responses, and magazine entries. Haloperidol reduced disruptive effects associated with increased activation, whereas it exacerbated other deficits. Clozapine dose-dependently attenuated several of the MK-801-induced performance deficits. Withdrawal from chronic MK-801 progressively increased omissions and response latencies and decreased premature responding, suggesting an amotivational state. Neither haloperidol nor clozapine ameliorated these performance deficits.

Discussion: Acute administration and withdrawal from chronic MK-801 administration produced distinct behavioral profiles in the 5CSRTT. Acute MK-801 impaired attention and impulse control whereas chronic MK-801 withdrawal caused signs consistent with amotivation. Haloperidol and clozapine were more effective at attenuating deficits caused by acute MK-801 administration.

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1. Introduction

Schizophrenia affects 1% of the population worldwide and is characterized by positive symptoms (hallucinations, delusions, thought disorder), negative symptoms (amotivation, flattened affect) and cognitive symptoms (impaired attention, working memory and executive functioning) (<http://www.nimh.nih.gov/publicat/schizop.cfm>). Attentional deficits precede the illness onset, are stable across phases of illness, and are present in non-schizophrenic first-degree relatives of people with schizophrenia (Cornblatt and Malhotra, 2001; Chen and Faraone, 2000). Furthermore, cognitive deficits predict patient difficulties in maintaining employment, living independently and having meaningful social interactions (Green et al.,

2004). Effective treatment of such deficits could have a profound impact on the lives of people with schizophrenia.

Early experiments addressing the effects of antipsychotic medications on cognition suggested that atypical (second generation) antipsychotics were more beneficial than classical (first generation) antipsychotics (Keefe et al., 1999). These early experiments can be difficult to interpret because they often involved small sample sizes, lack of comparator groups, high doses of classical antipsychotics, and adjunctive therapy with anticholinergic drugs (Keefe et al., 2007). Recent meta-analyses suggest that classical antipsychotics may have pro-cognitive effects comparable to atypical antipsychotics (Mishara and Goldberg, 2004; Keefe et al., 2007). However, repeated cognitive assessments themselves can lead to measurable cognitive improvements, an effect that may explain the apparent pro-cognitive effects of antipsychotic treatment (Goldberg et al., 2007). Studies using animals may help resolve discrepancies in the clinical literature regarding the relative pro-cognitive efficacy of antipsychotics.

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The present studies were designed to examine if a classical (haloperidol) or an atypical (clozapine) antipsychotic drug would have pro-cognitive effects as measured in the 5-choice serial reaction time task (5CSRTT). The 5CSRTT is a rodent task of attention analogous to the continuous performance task used to study attention in humans (Robbins, 2002). Because our initial studies indicated that neither haloperidol nor clozapine had pro-cognitive effects when administered alone, we then examined if they would attenuate cognitive deficits observed following acute administration of the *N*-methyl-D-aspartate (NMDA) receptor antagonist MK-801. Acute NMDA receptor antagonism models aspects of schizophrenia-causing both psychotic symptoms and cognitive deficits (e.g., impairments in attention and working memory) in healthy volunteers and people with schizophrenia (Lahti et al., 2001; Coyle and Tsai, 2004; Jentsch and Roth, 1999). Consistent with previous reports, MK-801 administration impaired attention (Paine et al., 2007), but these effects were not substantially attenuated by either acute haloperidol or acute clozapine administration. Because acute MK-801 administration causes non-specific behavioral changes that may interfere with the ability to detect pro-cognitive effects of antipsychotic treatments (Jentsch and Roth, 1999), we also tested whether acute antipsychotic treatment could alleviate the deficits observed during withdrawal from chronic MK-801 administration. Withdrawal from chronic NMDA receptor antagonism impairs cognitive function in rodents (Dunn and Killcross, 2006; Madillo et al., 2003; O'Donnell et al., 2003; Jentsch et al., 1997a; Rujescu et al., 2006; Shroeder et al., 2000; Hashimoto et al., 2005) and causes pathological changes reminiscent of schizophrenia (Jentsch et al., 1997a; Tsukada et al., 2005; Pratt et al., 2008; Behrens et al., 2007; Lewis and Gonzalez-Burgos, 2006).

2. Methods

2.1. Rats

Twenty-eight male Sprague–Dawley rats (Charles River Laboratories, Raleigh, NC) weighing 250–300 g at the start of the experiment were housed in pairs on a 12-h/12-h light–dark cycle (lights on at 0700 h). Rats were given 1 week to acclimate to the housing conditions with free access to food (Purina Rat Chow) and water. Twenty-four hours prior to the onset of training and throughout training, rats were food restricted to 85% of their free-feeding weights. Rats had free access to water while in the home cage. Experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Academy Press, 1996) and McLean Hospital policies.

2.2. Behavioral apparatus

Testing was conducted in 5CSRTT operant chambers that were contained in sound-attenuating ventilated cubicles (Med-Associates, St. Albans, VT). Five equally spaced $2.5 \times 2.5 \times 2.2$ cm apertures were set into a curved aluminum wall; each aperture was fitted with a yellow LED stimulus light (6.4 mm in diameter) and an infrared detector (1.0 cm from the front of the aperture). The opposite wall was fitted with a food magazine connected to a 45-mg pellet dispenser; an infrared detector located horizontally across the magazine allowed for the detection of nose pokes into the magazine. The top of the magazine was fitted with a light (1.0 cm in diameter). The house light was located on the ceiling directly above the magazine. The sidewalls and ceiling were made of clear polycarbonate and the floor was a stainless steel grid.

2.3. The 5-choice serial reaction time task (5CSRTT)

We trained the rats as described previously (Paine et al., 2007). Sessions started with the delivery of 1 food pellet (45-mg, Bio-Serv, Frenchtown, NJ); the first trial commenced upon retrieval. A nose poke into the magazine initiated a 5-s inter-trial interval (ITI) and illumination of a house light. At the end of the ITI, a 1.0-s light stimulus was presented at the rear of one of the five stimulus locations (apertures). Rats had up to 5 s (limited hold) to make a response. A response in the illuminated aperture (correct response) triggered delivery of 1 food pellet and illumination of the magazine light, which remained illuminated for 5 s following pellet delivery. Nose pokes in the remaining apertures during the limited hold were considered incorrect responses and triggered a 5-s time-out during which the house light was extinguished. Similarly, failure to respond during the limited hold (i.e., an omission)

triggered a 5-s time-out. The subsequent trial was initiated at the end of the time-out period. Responses occurring prior to stimulus presentation (i.e., during the ITI) were considered premature responses and also triggered a 5-s time-out; the same trial was re-started at the end of the time-out period. Responses occurring during the time-out period had no programmed consequences. Each session ended after 90 trials or 30 min. Performance measures of interest were % accuracy ((correct responses/[correct + incorrect responses])*100), % omissions ([omissions/trials completed]*100), premature responses, magazine entries, correct response latency (the time from the stimulus onset to a correct response) and reward latency (the time from a correct response to the collection of the food). Testing began when accuracy was greater than 60% and omissions were fewer than 20% for 3 consecutive days.

2.4. Experiment 1. Effects of acute antipsychotic administration on performance

Upon reaching criterion performance, rats were tested following administration of haloperidol ($n = 8$, 0.0–0.25 mg/kg) or clozapine ($n = 6$, 0.0–2.50 mg/kg). Drugs were administered subcutaneously (SC) 60 min prior to testing. Doses of haloperidol and clozapine were administered in an ascending order with the exception that vehicle was administered last. To avoid potential carry-over effects rats were given a minimum of two drug-free days between drug tests and had to perform at criterion on the session preceding drug testing.

2.5. Experiment 2. Effects of acute MK-801 administration on performance

Rats from Experiment 1 were re-stabilized for at least 5 days and then tested following administration of either haloperidol or clozapine in combination with acute MK-801. The rats were grouped according to their previous history (e.g., rats that previously received haloperidol continued to receive haloperidol). One rat from the haloperidol group was excluded from the remainder of the experiment because his performance failed to re-stabilize. In addition, new (drug naïve) rats were added to each condition (4/group); pre-testing baseline data from these animals did not differ from those that had been tested in Experiment 1. Haloperidol ($n = 11$, 0.0–0.063 mg/kg, SC) and clozapine ($n = 10$, 0.0–1.25 mg/kg, SC) were administered 60 min prior to testing. MK-801 (0.25 mg/kg, IP) was administered 30 min prior to testing; this dose impairs attention (% accuracy) in the 5CSRTT (Paine et al., 2007). To avoid potential order effects of repeated MK-801 administration, doses of haloperidol and clozapine were administered in a pseudo-random order (each dose was given only once). As above, rats were allowed a minimum of two drug-free days before drug tests and had to perform at criterion on the session preceding drug testing.

2.6. Experiment 3. Effects of chronic MK-801 exposure on performance

Rats were re-stabilized for at least 5 days and then the effects of a regimen of repeated MK-801 administration on performance in the 5CSRTT was assessed. As in Experiment 2, the rats were grouped according to their previous history. For 12 consecutive days, rats were administered MK-801 (0.5 mg/kg, IP) ~30 min after their daily test sessions such that rats were tested in the absence of MK-801. This dose of MK-801 was administered because it is known to cause schizophrenia-like pathologies in rats (Kondziella et al., 2006; Hashimoto et al., 2007). On days 6, 8, 10 and 12 rats were pretreated with haloperidol ($n = 11$, 0.0–0.016 mg/kg, SC) or clozapine ($n = 11$; 0.0–0.32 mg/kg, SC) 60 min prior to test sessions. One rat from the clozapine group was excluded from this portion of the experiment because his performance failed to re-stabilize. Two rats in the clozapine group were drug naïve prior to chronic MK-801 administration; data from these animals did not differ from those that had been tested in the earlier experiments. Doses of haloperidol and clozapine were administered in a pseudo-random order.

2.7. Drugs

Drugs were purchased from Sigma (St. Louis, MO). (+)-MK-801 hydrogen maleate was dissolved in saline. Haloperidol was dissolved in 75% dimethyl sulfoxide (DMSO). Clozapine was dissolved in a minimum amount of 0.1 N HCl, adjusted to pH 6.0 with 0.1 N NaOH, and then diluted with saline. Drugs were administered in a volume of 1.0 ml/kg.

2.8. Statistics

To ensure that there were no carry-over drug effects or any systematic effects of repeated testing, performance on baseline sessions in Experiments 1 and 2 was subjected to repeated measures analyses of variance. Baseline sessions for each drug test session consisted of the training session on the day preceding that test session.

Data from the drug testing sessions were also analyzed using a repeated measures ANOVA with dose (Experiment 1), drug treatment (Experiments 2 and 3) or day (Experiment 3) as the within subjects factor. For Experiment 3, baseline values were calculated by averaging the 3 days preceding drug treatment. All significant main effects were examined further using Fisher's protected *t*-tests.

3. Results

3.1. Experiment 1. Effects of acute antipsychotic administration on performance

3.1.1. Haloperidol

The 0.25 mg/kg dose of haloperidol was excluded from statistical analyses because it profoundly disrupted performance (>99% omissions). With one exception (omissions), baseline (drug-free) performance was stable across sessions [all $F(5, 35) = 2.21$, $P > 0.08$, Table 1]. Omissions differed across baseline sessions [$F(5, 35) = 2.57$, $P < 0.05$]: omissions were increased on baseline session 3 compared to baseline session 1 ($P < 0.05$, Fisher's protected t -tests). The lack of a linear trend for an increase in omissions suggests that there were no systematic effects of repeated testing or carry-over drug effects.

Repeated measures ANOVAs indicated that acute haloperidol administration (Table 2) affected accuracy [$F(5, 35) = 5.99$, $P = 0.01$], omissions [$F(5, 35) = 141.37$, $P < 0.01$], premature responses [$F(5, 35) = 6.29$, $P = 0.01$], magazine entries [$F(5, 35) = 16.97$, $P < 0.01$], correct response latencies [$F(5, 35) = 9.22$, $P < 0.01$], and reward retrieval latencies [$F(5, 35) = 18.65$, $P < 0.01$]. Post hoc analyses (Fisher's protected t -tests) revealed that acute haloperidol administration reduced accuracy (0.125 mg/kg, $P < 0.01$), premature responses (0.016–0.125 mg/kg, P 's < 0.05 –0.01), and magazine entries (0.032–0.125 mg/kg, P 's < 0.05 –0.01). In contrast, haloperidol increased omissions (0.063–0.125 mg/kg, P 's < 0.01), correct response latencies (0.063–0.125 mg/kg, P 's < 0.05 –0.01), and reward retrieval latencies (0.063 mg/kg, $P < 0.01$).

3.1.2. Clozapine

Baseline (drug-free) performance was unaltered across sessions [all $F(6, 30) < 1.90$, $P > 0.11$, Table 1] indicating that there were no systematic changes in performance over time nor any carry-over drug effects resulting from repeated clozapine administration.

Acute clozapine administration (Table 2) affected accuracy [$F(6, 30) = 5.05$, $P < 0.01$], omissions [$F(6, 30) = 21.05$, $P < 0.01$], premature responses [$F(6, 30) = 4.74$, $P < 0.01$], correct response latencies [$F(6, 30) = 42.47$, $P < 0.01$], and reward retrieval latencies [$F(6, 30) = 8.63$, $P < 0.01$]. Post hoc analyses revealed that clozapine decreased accuracy (2.5 mg/kg, $P < 0.01$) but increased omissions (2.5 mg/kg, $P < 0.01$), premature responses (0.16 mg/kg, $P < 0.05$),

correct response latencies (1.25–2.5 mg/kg, P 's < 0.01), and reward retrieval latencies (2.5 mg/kg, $P < 0.01$).

3.2. Experiment 2. Effects of acute MK-801 administration on performance

3.2.1. Haloperidol

Baseline (drug-free) performance was not altered across sessions [all $F(5, 50) < 1.86$, $P > 0.12$, Table 3] indicating that there were no long-term (>72 h) effects of acute drug administration.

The effects of haloperidol pretreatment on behavioral deficits produced by acute MK-801 are illustrated in Fig. 1. Drug treatment affected accuracy [$F(5, 50) = 3.96$, $P < 0.01$, Fig. 1a], omissions [$F(5, 50) = 9.90$, $P < 0.01$, Fig. 1b], premature responses [$F(5, 50) = 5.20$, $P < 0.01$, Fig. 1c], magazine entries [$F(5, 50) = 2.98$, $P < 0.05$, Fig. 1d], correct response latency [$F(5, 50) = 3.13$, $P < 0.05$, Fig. 1e], and reward retrieval latencies [$F(5, 50) = 6.48$, $P < 0.01$, Fig. 1f]. Post hoc analyses revealed that MK-801 alone reduced accuracy and increased omissions, premature responses and magazine entries (P 's < 0.05 –0.01). A dose of haloperidol that affected performance when administered alone (0.063 mg/kg) reduced the MK-801-induced increase in premature responses ($P < 0.05$) and magazine entries ($P < 0.01$). High doses of haloperidol also potentiated the increase in omissions caused by acute MK-801 administration (0.032–0.063 mg/kg, P 's < 0.05 –0.01). Although MK-801 alone did not affect either correct response latencies or reward retrieval latencies, MK-801 in combination with haloperidol increased both correct response latencies (0.016 and 0.063 mg/kg, P 's < 0.05) and reward retrieval latencies (0.032–0.063 mg/kg, P 's < 0.05 –0.01) compared to vehicle.

3.2.2. Clozapine

Baseline (drug-free) performance was not altered across sessions [all $F(4, 45) < 1.58$, $P > 0.18$, Table 3] indicating that there were no long-term (>72 h) effects of acute drug administration.

The effects of clozapine pretreatment on behavioral deficits produced by acute MK-801 administration are shown in Fig. 2. Drug treatment affected accuracy [$F(5, 45) = 4.15$, $P < 0.01$, Fig. 2a], omissions [$F(5, 45) = 5.20$, $P < 0.01$, Fig. 2b], premature responses, [$F(5, 45) = 8.58$, $P < 0.01$, Fig. 2c], magazine entries [$F(5, 45) = 7.96$, $P < 0.01$, Fig. 2d], correct response latencies [$F(5, 45) = 3.23$, $P < 0.05$, Fig. 2e], and reward retrieval latencies [$F(5, 45) = 3.37$, $P = 0.01$, Fig. 2f]. Post hoc analyses revealed that MK-801 alone

Table 1
Baseline performance on 5CSRTT during acute antipsychotic administration.

	% Accuracy	% Omissions	Premature responses	Magazine entries	Correct response latency (s)	Reward retrieval latency (s)
<i>Haloperidol</i>						
1	67.79 ± 3.41	4.58 ± 1.79	35.63 ± 8.90	220.75 ± 41.34	0.89 ± 0.08	1.70 ± 0.12
2	69.75 ± 2.88	8.20 ± 1.13	22.25 ± 5.62	181.13 ± 29.45	0.86 ± 0.06	1.65 ± 0.10
3	72.41 ± 2.46	10.56 ± 2.09*	22.88 ± 3.92	183.50 ± 24.60	0.88 ± 0.06	1.60 ± 0.09
4	73.02 ± 2.98	5.55 ± 1.74	20.38 ± 4.70	169.25 ± 26.16	0.93 ± 0.08	1.59 ± 0.08
5	71.69 ± 2.82	7.92 ± 2.16	22.63 ± 4.72	173.88 ± 31.56	0.96 ± 0.06	1.71 ± 0.11
6	69.56 ± 2.93	5.83 ± 1.58	24.50 ± 7.34	188.63 ± 32.14	1.01 ± 0.06	1.69 ± 0.12
<i>Clozapine</i>						
1	74.70 ± 2.43	8.89 ± 2.24	27.83 ± 6.05	209.83 ± 15.36	0.79 ± 0.03	1.58 ± 0.06
2	70.88 ± 2.55	6.85 ± 1.85	36.17 ± 8.97	244.67 ± 30.47	0.86 ± 0.06	1.47 ± 0.07
3	70.75 ± 2.30	9.81 ± 2.37	30.83 ± 8.36	219.50 ± 20.41	0.84 ± 0.05	1.51 ± 0.07
4	71.29 ± 1.03	6.67 ± 2.30	27.50 ± 6.53	195.83 ± 11.82	0.83 ± 0.06	1.48 ± 0.09
5	70.79 ± 3.41	6.85 ± 1.56	23.17 ± 4.59	194.17 ± 9.39	0.84 ± 0.05	1.54 ± 0.11
6	74.57 ± 2.80	7.59 ± 1.80	21.67 ± 8.04	204.17 ± 8.25	0.79 ± 0.05	1.55 ± 0.09
7	73.59 ± 1.53	6.29 ± 1.10	37.67 ± 8.78	244.50 ± 17.72	0.81 ± 0.05	1.51 ± 0.10

Note: Rats were administered haloperidol or clozapine with a minimum of two drug-free days between drug doses. Baseline sessions (days 1–7) consisted of the training session on the day prior to drug testing. Because drug doses were administered in an ascending order these data indicate that performance was stable across time. And, with one exception, these data indicate that there were no long-term (>72 h) carry-over effects of acute antipsychotic administration on 5CSRTT performance. Significantly different from haloperidol day 1, * $P < 0.05$ Fisher's protected t -tests.

Table 2

Effects of acute antipsychotic administration on performance in the 5-choice serial reaction time task.

	% Accuracy	% Omissions	Premature responses	Magazine entries	Correct response latency (s)	Reward retrieval latency (s)
<i>Haloperidol</i>						
0.0	66.78 ± 3.77	7.22 ± 2.53	23.50 ± 5.01	184.25 ± 26.27	0.94 ± 0.05	1.68 ± 0.21
0.008	71.08 ± 2.79	3.05 ± 0.88	27.88 ± 7.04	192.13 ± 22.92	0.86 ± 0.06	1.58 ± 0.09
0.016	72.58 ± 3.13	7.36 ± 2.27	12.75 ± 2.53*	155.00 ± 16.94	0.94 ± 0.05	1.61 ± 0.10
0.032	71.99 ± 2.31	9.03 ± 3.67	10.88 ± 1.42*	133.50 ± 11.66*	1.21 ± 0.04	1.71 ± 0.09
0.063	63.41 ± 3.68	58.33 ± 6.46**	11.63 ± 2.25*	76.13 ± 9.88**	1.26 ± 0.07*	1.91 ± 0.13
0.125	41.64 ± 9.13**	90.28 ± 3.40**	3.88 ± 0.95**	38.63 ± 10.38**	1.64 ± 0.19**	2.69 ± 0.24**
<i>Clozapine</i>						
0.0	71.07 ± 2.22	4.44 ± 1.65	29.33 ± 2.26	231.50 ± 17.25	0.81 ± 0.05	1.60 ± 0.14
0.08	74.08 ± 2.54	6.85 ± 1.61	29.67 ± 5.54	223.33 ± 26.58	0.78 ± 0.06	1.45 ± 0.04
0.16	70.44 ± 2.43	5.23 ± 2.05	48.50 ± 12.81*	258.67 ± 34.00	0.78 ± 0.05	1.43 ± 0.05
0.32	73.71 ± 3.18	3.52 ± 1.45	34.83 ± 6.16	226.83 ± 21.75	0.81 ± 0.03	1.48 ± 0.06
0.63	69.44 ± 1.71	4.07 ± 2.34	21.17 ± 3.64	221.50 ± 13.60	0.90 ± 0.05	1.60 ± 0.08
1.25	67.93 ± 2.60	12.41 ± 2.70	14.00 ± 4.48	314.33 ± 57.28	1.11 ± 0.04**	1.72 ± 0.10
2.5	57.64 ± 2.39**	47.78 ± 7.40**	14.17 ± 2.36	262.00 ± 25.98	1.50 ± 0.07**	1.92 ± 0.09**

Note: Haloperidol and clozapine were administered (SC) 60 min prior to testing. Significantly different from vehicle (0.0 mg/kg), * $P < 0.05$, ** $P < 0.01$ Fisher's protected t -tests.

decreased accuracy and increased omissions, premature responses, magazine entries, and correct response latencies (P 's < 0.05 – 0.01). Clozapine administration attenuated the MK-801-induced decrease in accuracy (0.16 mg/kg, $P < 0.05$) and the MK-801-induced increase in omissions (0.16–0.32 mg/kg, P 's < 0.05 – 0.01), premature responses (1.25 mg/kg, $P < 0.01$), magazine entries (0.16 mg/kg, 0.063–1.25 mg/kg, P 's < 0.05 – 0.01), and correct response latencies (0.16 mg/kg, $P < 0.05$).

3.3. Experiment 3. Effects of exposure to chronic MK-801 treatment on performance

Comparison of the effects of withdrawal from chronic MK-801 on 5CSRTT performance in rats from the haloperidol and clozapine treatment groups revealed that these groups were not statistically different (not shown), thus analyses were conducted on the combined data set. Chronic MK-801 affected accuracy [$F(8, 184) = 3.37$, $P < 0.01$, Fig. 3a], omissions [$F(8, 184) = 14.28$, $P < 0.01$, Fig. 3b], premature responses [$F(8, 184) = 2.87$, $P = 0.01$, Fig. 3c], magazine entries [$F(8, 184) = 2.60$, $P < 0.01$, Fig. 3d], correct response latencies [$F(8, 184) = 7.59$, $P < 0.01$, Fig. 3e], and reward retrieval latencies [$F(8, 184) = 3.48$, $P < 0.01$, Fig. 3f]. The latency with which withdrawal from chronic MK-801 affected performance in the 5CSRTT differed across measures. Premature responses and

response latencies (both correct response and reward retrieval) were affected on test day 1 (i.e., the first day of withdrawal). There was a transient decrease in premature responses, which waned by test day 9. In contrast, response latencies were persistently increased throughout the drug administration regimen. Omissions, magazine entries and accuracy all required repeated administration of MK-801 before differences from baseline (e.g., omissions-day 4, magazine entries-day 5, accuracy-day 7) became persistently impaired (P 's < 0.05 – 0.01).

3.3.1. Chronic MK-801 + haloperidol

The effect of haloperidol on the behavioral deficits caused by withdrawal from chronic MK-801 administration is illustrated in Fig. 4. Drug treatment affected accuracy [$F(4, 40) = 2.57$, $P = 0.05$, Fig. 4a], omissions [$F(4, 40) = 9.99$, $P < 0.01$, Fig. 4b], magazine entries [$F(4, 40) = 4.65$, $P = 0.004$, Fig. 4d], correct response latencies [$F(4, 40) = 10.46$, $P < 0.01$, Fig. 4e], and reward retrieval latencies [$F(4, 40) = 5.38$, $P < 0.01$, Fig. 4f]. Withdrawal from chronic MK-801 increased omissions, correct response latencies and reward retrieval latencies while it decreased magazine entries (P 's < 0.01). Rather than attenuating the effects of withdrawal from chronic MK-801, haloperidol potentiated increases in correct response latency (0.008–0.016 mg/kg, P 's < 0.05 – 0.01) and resulted in the emergence of a decrease in accuracy (0.004–0.016 mg/kg, P 's < 0.05 – 0.01).

Table 3

Baseline performance during acute MK-801 + antipsychotic administration.

	% Accuracy	% Omissions	Premature responses	Magazine entries	Correct response latency (s)	Reward retrieval latency (s)
<i>Haloperidol</i>						
1	73.96 ± 3.10	6.36 ± 1.80	19.27 ± 4.06	210.36 ± 40.21	0.91 ± 0.04	1.62 ± 0.09
2	73.34 ± 2.34	6.36 ± 0.93	27.45 ± 7.51	224.18 ± 44.18	0.87 ± 0.06	1.61 ± 0.09
3	73.41 ± 2.45	7.45 ± 1.39	19.10 ± 8.30	226.90 ± 56.21	0.92 ± 0.05	1.61 ± 0.09
4	74.23 ± 2.66	7.27 ± 1.18	17.09 ± 4.58	194.27 ± 34.54	0.97 ± 0.05	1.71 ± 0.11
5	71.90 ± 2.63	7.27 ± 1.40	27.00 ± 5.62	200.64 ± 32.92	0.87 ± 0.05	1.70 ± 0.10
6	71.07 ± 2.64	8.72 ± 1.45	14.18 ± 2.39	188.09 ± 29.63	0.97 ± 0.05	1.68 ± 0.10
<i>Clozapine</i>						
1	77.63 ± 2.19	7.78 ± 1.85	20.50 ± 6.62	172.60 ± 14.51	0.82 ± 0.04	1.62 ± 0.09
2	74.55 ± 1.44	6.78 ± 2.01	19.30 ± 4.95	176.80 ± 8.94	0.82 ± 0.04	1.58 ± 0.07
3	76.11 ± 2.42	7.28 ± 1.39	16.11 ± 4.84	189.22 ± 16.30	0.87 ± 0.05	1.66 ± 0.06
4	74.22 ± 3.42	9.22 ± 1.97	17.60 ± 5.39	184.30 ± 16.27	0.87 ± 0.05	1.56 ± 0.06
5	73.13 ± 2.54	6.33 ± 0.91	19.60 ± 5.99	196.10 ± 21.64	0.86 ± 0.05	1.51 ± 0.08
6	74.57 ± 2.65	7.22 ± 1.25	20.70 ± 4.14	184.22 ± 10.39	0.83 ± 0.05	1.65 ± 0.10

Note: Rats were administered MK-801 (0.0 or 0.25 mg/kg) in combination with haloperidol (0.0–0.0125 mg/kg, SC) or clozapine (0.0–1.25 mg/kg) with a minimum of two drug-free days between drug doses. Baseline sessions (days 1–6) consisted of the training session on the day prior to drug testing. Because drug doses were administered in a pseudo-random order, these data indicate that there were no long-term (> 72 h) carry-over effects of drug administration on 5CSRTT performance or any systematic change in performance.

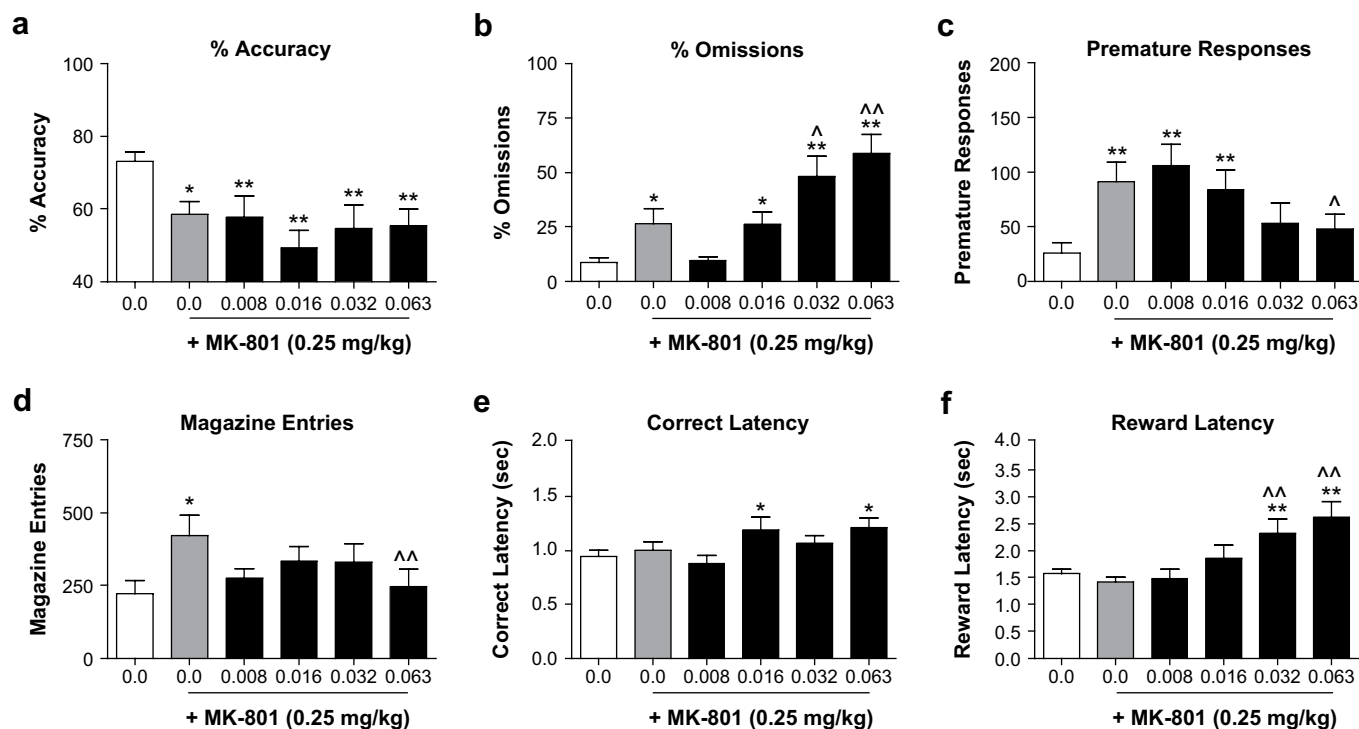


Fig. 1. Effect of haloperidol pretreatment on behavioral deficits induced by acute MK-801 administration. Haloperidol (0.0–0.063 mg/kg, SC) was administered 60 min prior to testing and MK-801 (0.25 mg/kg, IP) was administered 30 min prior to testing. MK-801 administration (grey bar) reduced accuracy (a), increased omissions (b), premature responses (c), and magazine entries (d), but did not affect correct response latencies (e) or reward retrieval latencies (f). Haloperidol significantly attenuated the MK-801-induced increase in premature responses and magazine entries, but it exaggerated the MK-801-induced increase in omissions and reward retrieval latencies. Significantly different from 0.0 mg/kg MK-801 + 0.0 mg/kg haloperidol, * $P < 0.05$, ** $P < 0.01$, Fisher's protected t -tests. Significantly different from MK-801 (0.25 mg/kg) + haloperidol (0.0 mg/kg), ^ $P < 0.05$, ^^ $P < 0.01$, Fisher's protected t -tests.

3.3.2. Chronic MK-801 + clozapine

The effect of clozapine on the behavioral deficits caused by withdrawal from chronic MK-801 administration is illustrated in Fig. 5. Drug treatment affected accuracy [$F(4, 40) = 3.23$, $P < 0.05$, Fig. 5a], omissions [$F(4, 40) = 11.66$, $P < 0.01$, Fig. 5b], correct response latencies [$F(4, 40) = 9.49$, $P < 0.01$, Fig. 5e], and reward retrieval latencies [$F(4, 40) = 6.05$, $P < 0.01$, Fig. 5f]. There was a trend for drug treatment to affect magazine entries [$F(4, 40) = 2.67$, $P = 0.07$, Fig. 5d]. Withdrawal from chronic MK-801 increased omissions, correct response latencies and, reward retrieval latencies while it decreased magazine entries (P 's < 0.01). Clozapine significantly attenuated the increase in reward retrieval latencies (0.08 mg/kg, $P < 0.05$). Like haloperidol, clozapine administration resulted in the emergence of accuracy deficits (0.08–0.32 mg/kg, P 's < 0.05 –0.01).

4. Discussion

Here we show that neither acute haloperidol nor acute clozapine is substantially pro-cognitive in the 5CSRTT. The pro-cognitive efficacy of each drug was evaluated under three conditions: alone, in combination with acute MK-801 administration, or in combination with withdrawal from chronic MK-801 administration. At high doses, both haloperidol and clozapine disrupted attention when administered alone. Haloperidol pretreatment reduced some of the disruptive effects of acute MK-801—primarily those associated with increased activation—whereas it exacerbated others. Clozapine pretreatment attenuated several acute MK-801-induced performance deficits (e.g., decreased accuracy and increased omission errors). Both haloperidol and clozapine had minimal effects on performance deficits associated with chronic MK-801

withdrawal. At least on the surface, these observations are consistent with the hypothesis that atypical antipsychotic medications have more beneficial effects on cognition than classical antipsychotic medications (Keefe et al., 1999). The modest effects of clozapine, however, underscore the need to develop more effective treatments for the attentional deficits in schizophrenia.

4.1. Effects of acute MK-801 and chronic MK-801 withdrawal on the 5CSRTT

Acute MK-801 and chronic MK-801 withdrawal produced distinct behavioral profiles in the 5CSRTT. Acute MK-801 administration decreased accuracy and increased omissions, premature responses, and magazine entries—a behavioral profile that likely reflects impaired attention and inhibitory control. In contrast, chronic MK-801 withdrawal decreased response rates (i.e., increased omissions and decreased premature responding), reduced food-seeking behavior (magazine entries) and slowed response and reward retrieval latencies. This pattern of behavior may reflect reduced motivation. Although accuracy was impaired during chronic MK-801 withdrawal, this effect was not apparent until after rats started receiving intermittent antipsychotic administration, suggesting that the decrease in accuracy was not a result of withdrawal from chronic MK-801 administration *per se* but due to carry-over effects of the antipsychotic treatment. Longer periods of MK-801 exposure without concurrent antipsychotic administration do not reduce accuracy (T.A. Paine and W.A. Carlezon, unpublished observations).

The failure to observe a 'pure' attentional deficit during chronic MK-801 withdrawal is surprising given that early withdrawal from chronic NDMA receptor antagonism causes a number of

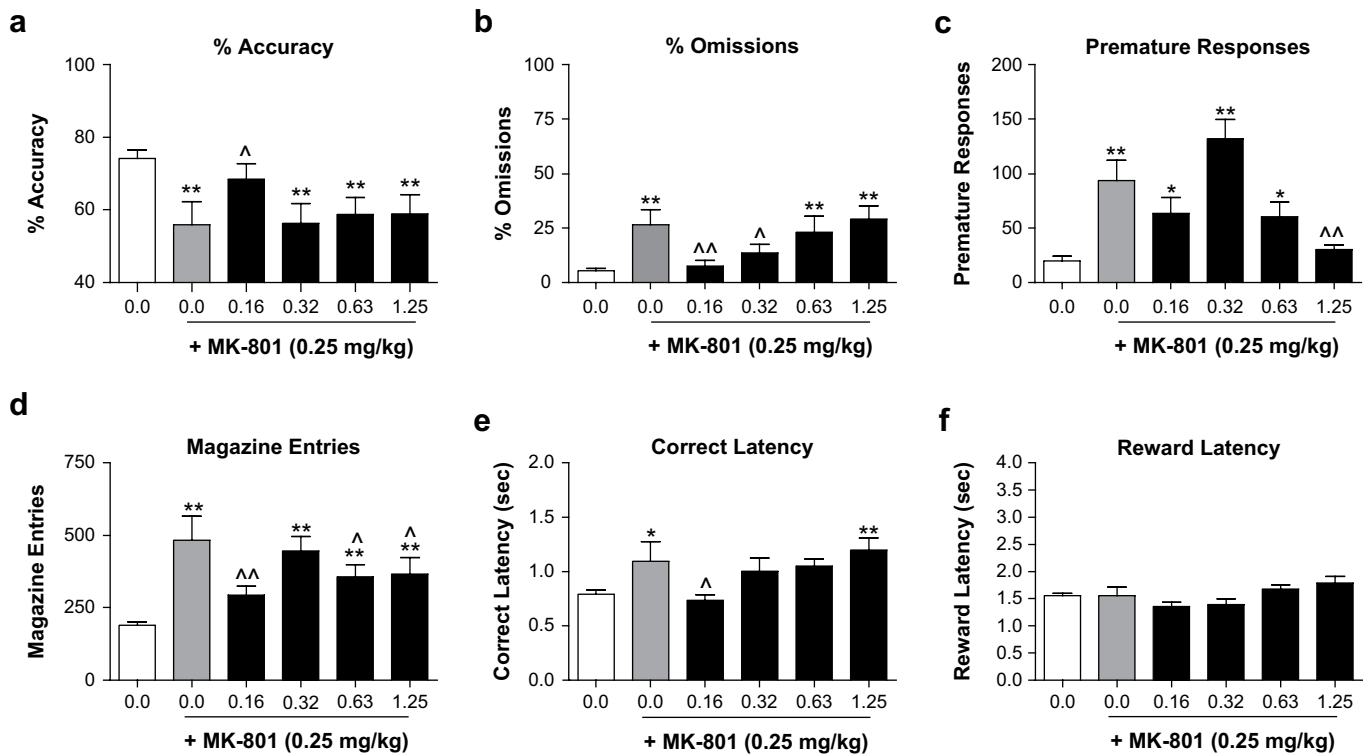


Fig. 2. Effect of clozapine pretreatment on behavioral deficits induced by acute MK-801 administration. Clozapine (0.0–1.25 mg/kg, SC) was administered 60 min prior to testing and MK-801 (0.25 mg/kg, IP) was administered 30 min prior to testing. MK-801 administration (grey bar) reduced accuracy (a), increased omissions (b), premature responses (c), magazine entries (d), and correct response latencies (e). Clozapine attenuated MK-801-induced behavioral deficits. Significantly different from 0.0 mg/kg MK-801 + 0.0 mg/kg clozapine, * $P < 0.05$, ** $P < 0.01$, Fisher's protected t -tests. Significantly different from MK-801 (0.25 mg/kg) + clozapine (0.0 mg/kg), ^ $P < 0.05$, ^^ $P < 0.01$ Fisher's protected t -tests.

physiological changes that mimic the pathophysiology of schizophrenia (Lewis and Gonzalez-Burgos, 2006). For example, the 67-kDa isoform of glutamic acid decarboxylase and parvalbumin are reduced after chronic exposure to NMDA receptor antagonists (Pratt et al., 2008; Behrens et al., 2007). Chronic NMDA receptor antagonist regimens also reduce dopamine utilization (Jentsch et al., 1997a) and extracellular glutamate concentration within the prefrontal cortex (PFC) (Tsukada et al., 2005). Importantly, withdrawal from chronic NMDA receptor antagonism also produces cognitive deficits in rodent models including deficits in conditional discrimination (Dunn and Killcross, 2006), spatial learning (Madillo et al., 2003; O'Donnell et al., 2003), working memory (Jentsch et al., 1997a; Tsukada et al., 2005), short-term memory (Rujescu et al., 2006; Schroeder et al., 2000), and novel-object recognition (Hashimoto et al., 2005).

Attentional deficits following chronic drug administration regimens, however, have not been observed. Although acute NMDA receptor antagonism causes schizophrenia-like attentional deficits in humans (Lahti et al., 2001; Coyle and Tsai, 2004; Jentsch and Roth, 1999), to the best of our knowledge persistent attentional deficits have not been described, even in chronic phencyclidine users (Prahdan, 1984; Cosgrove and Newell, 1991). In rodents, neither early withdrawal from chronic ketamine (Nelson et al., 2002) nor chronic amphetamine (Martinez and Sarter, 2008) affects attention in a signal detection task. Similarly, early withdrawal from PCP does not affect attention in the 5CSRTT (Amitai et al., 2007). Despite the failure to observe an attentional deficit here, we tested the ability of acute antipsychotic medications to remediate the behavioral deficits caused by early withdrawal from chronic MK-801 because these deficits recapitulate aspects of the negative symptomatology of schizophrenia, namely disruptions in motivation and decision making.

4.2. Effects of antipsychotic medications

When administered alone, neither haloperidol nor clozapine had pro-cognitive effects in the 5CSRTT. Instead, high doses of both haloperidol and clozapine disrupted all aspects of 5CSRTT performance. Similar detrimental effects of clozapine on attention have been reported previously (Martinez and Sarter, 2008; Amitai et al., 2007; Rezvani et al., 2008).

Acute haloperidol administration did not attenuate attentional deficits caused by acute MK-801 administration. High doses of haloperidol potentiated MK-801-induced increases in omissions and reward retrieval latencies but attenuated MK-801-induced increases in premature responses and magazine entries. These doses of haloperidol increased omissions and decreased premature responses and magazine entries on their own, complicating interpretation of our findings. These haloperidol effects may reflect a generalized motivational deficit or locomotor activity impairment that, coincidentally, cancels certain aspects of MK-801-induced hyperstimulation. Haloperidol reduces the impact of many types of rewards, including lateral hypothalamic brain stimulation (Benaliouad et al., 2007; Mobini et al., 2000) while producing profound motor impairments in laboratory animals and humans (O'Neill and Shaw, 1999; Correll et al., 2004). Conceivably, the ability of haloperidol to treat some symptoms of schizophrenia may occur by normalizing states of hyperstimulation that interfere with behavior. Neither high nor low doses of haloperidol attenuated the accuracy deficit caused by acute MK-801 administration, indicating that haloperidol did not have pro-cognitive effects in the 5CSRTT under these testing conditions.

Clozapine administration had dose-dependent effects on the behavior elicited by acute MK-801 administration. Low doses of clozapine attenuated the decrease in accuracy and the increase in

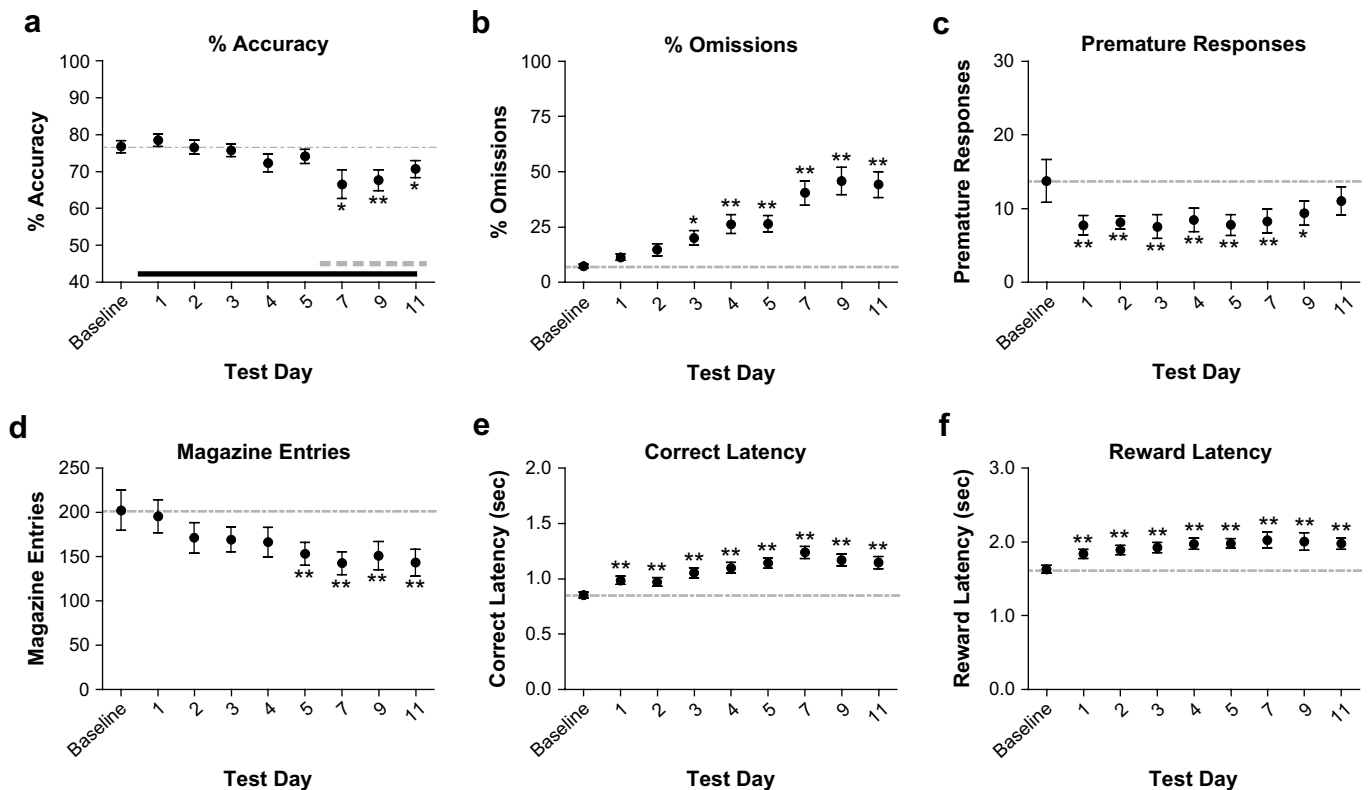


Fig. 3. Effects of chronic MK-801 withdrawal on 5CSRTT performance. Because data from the haloperidol and clozapine groups did not differ on days when antipsychotics were not administered, these data were pooled for statistical analyses. Beginning after baseline was established, MK-801 (0.5 mg/kg, IP) was administered 30 min after daily test sessions; tests were conducted 23.5 h later. Chronic MK-801 withdrawal decreased accuracy of responding (a), premature responses (c) and, magazine entries (d) while it increased omissions (b), correct response latencies (e), and reward retrieval latencies (f) relative to baseline. Solid black bar in (a) represents period of chronic MK-801 administration and the grey dashed bar (a) represents time period of acute intermittent antipsychotic treatment. Baseline scores were the average of the 3 test sessions preceding the initiation of MK-801 administration. Significantly different from baseline, * $P < 0.05$, ** $P < 0.01$, Fisher's protected t -tests.

both omissions and magazine entries caused by acute MK-801 administration. High doses of clozapine attenuated the increase in premature responding but did not affect other performance measures. Clozapine acts at multiple receptor targets (Nasrallah, 2008); dose-dependent improvements following clozapine administration may therefore reflect dose-dependent efficacies at different receptors. As one example, clozapine actions at 5-HT_{2A} receptors might account for its dose-dependent effects: the 5-HT_{2A} receptor antagonist M100907 improves impairments in impulse control (Higgins et al., 2003; Carli et al., 2006) and attention (Carli et al., 2006) caused by acute NMDA receptor antagonism. Consistent with our results, acute clozapine attenuates attentional and impulse control deficits caused by intra-PFC 3-(R)-2-carboxypiperazin-4-propyl-1-phosphonic acid (CPP) (Baviera et al., 2008) and attentional deficits caused by acute amphetamine in amphetamine-sensitized rats (Martinez and Sarter, 2008). In contrast, neither acute nor chronic clozapine administration reversed behavioral deficits in the 5CSRTT caused by acute PCP administration (Amitai et al., 2007). These discrepant findings may indicate that any pro-cognitive effects of clozapine are evident only under very specific testing conditions.

Neither haloperidol nor clozapine dramatically attenuated behavioral deficits observed during chronic MK-801 withdrawal. In fact, both drugs caused the emergence of accuracy deficits and haloperidol potentiated the increase in correct response latencies. Clozapine did have one therapeutic-like effect—attenuating the chronic MK-801 withdrawal-induced increase in reward retrieval latencies—raising the possibility that it might reduce amotivation associated with MK-801 withdrawal. The poor efficacy of

haloperidol to ameliorate deficits caused by withdrawal from NMDA receptor antagonists has been observed using conditional discrimination (Dunn and Killcross, 2006) and novel-object recognition tasks (Hashimoto et al., 2005). Clozapine has inconsistent effects on behavioral deficits observed during withdrawal from chronic NMDA receptor antagonism: acute clozapine administration does not attenuate deficits in novel-object recognition (Hashimoto et al., 2005), but attenuates deficits in conditional discrimination (Dunn and Killcross, 2006) observed during chronic PCP withdrawal. Acute clozapine administration consistently attenuates deficits caused by chronic PCP exposure following a “washout” period (Abdul-Monim et al., 2006; Grayson et al., 2007; Jentsch et al., 1997b; Jentsch and Roth, 1999). In these previous studies, high doses (e.g., >5.0 mg/kg) of clozapine are required to observe a therapeutic effect. Similar doses of clozapine were not tested here because they potentiated performance deficits in preliminary experiments and because only our low dose of clozapine (0.16 mg/kg) attenuated the effects of acute MK-801 administration.

It is unclear whether acute antipsychotic treatment is sufficient to remediate cognitive deficits in schizophrenics. In rats, sub-chronic but not acute clozapine attenuates deficits in novel-object recognition following chronic PCP treatment (Hashimoto et al., 2005). Chronic clozapine administration also blocks the development of attentional deficits caused by repeated PCP administration in the 5CSRTT (Amitai et al., 2007). In that previous experiment, clozapine was administered for eight days prior to the chronic PCP administration regimen and attention was measured during acute PCP intoxication. Future experiments are needed to determine

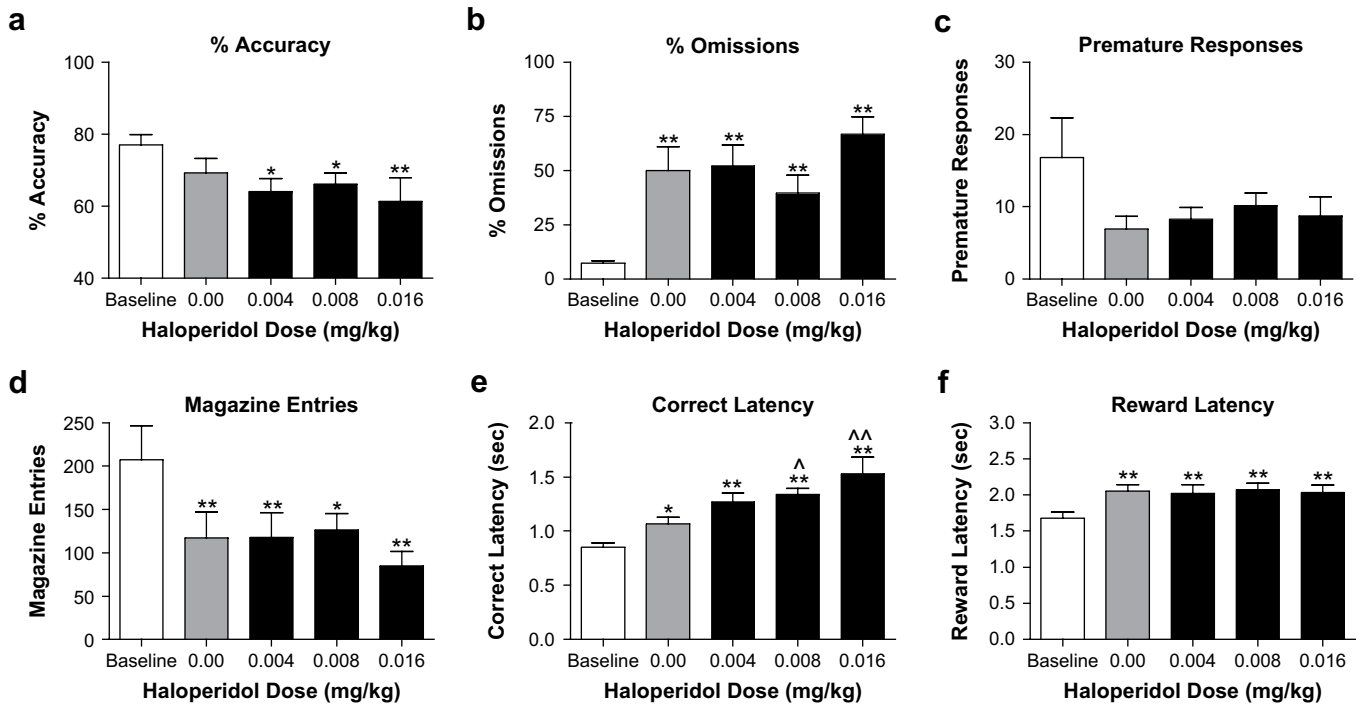


Fig. 4. Ability of haloperidol pretreatment to attenuate performance deficits caused by exposure to a regimen of chronic MK-801 administration. MK-801 (0.5 mg/kg, IP) was administered 30 min after daily training sessions; testing occurred 23.5 h later. On days 6, 8, 10 and 12 of MK-801 administration, haloperidol (0.0–0.016 mg/kg, SC) was administered 60 min prior to testing. Exposure to MK-801 administration alone (grey bar) did not affect accuracy (a), but it impaired accuracy in combination with haloperidol (0.004–0.016 mg/kg). Exposure to MK-801 increased omissions (c) and reward retrieval latencies (f), and decreased premature responses (c) and magazine entries (d). These effects were not altered by haloperidol (0.004–0.016 mg/kg). Exposure to MK-801 increased correct response latencies (e), and haloperidol (0.008–0.016 mg/kg) potentiated this effect. Significantly different from baseline, * $P < 0.05$, ** $P < 0.01$, Fisher's protected t -tests. Significantly different from chronic MK-801 + haloperidol (0.0 mg/kg), ^ $P < 0.01$, Fisher's protected t -tests.

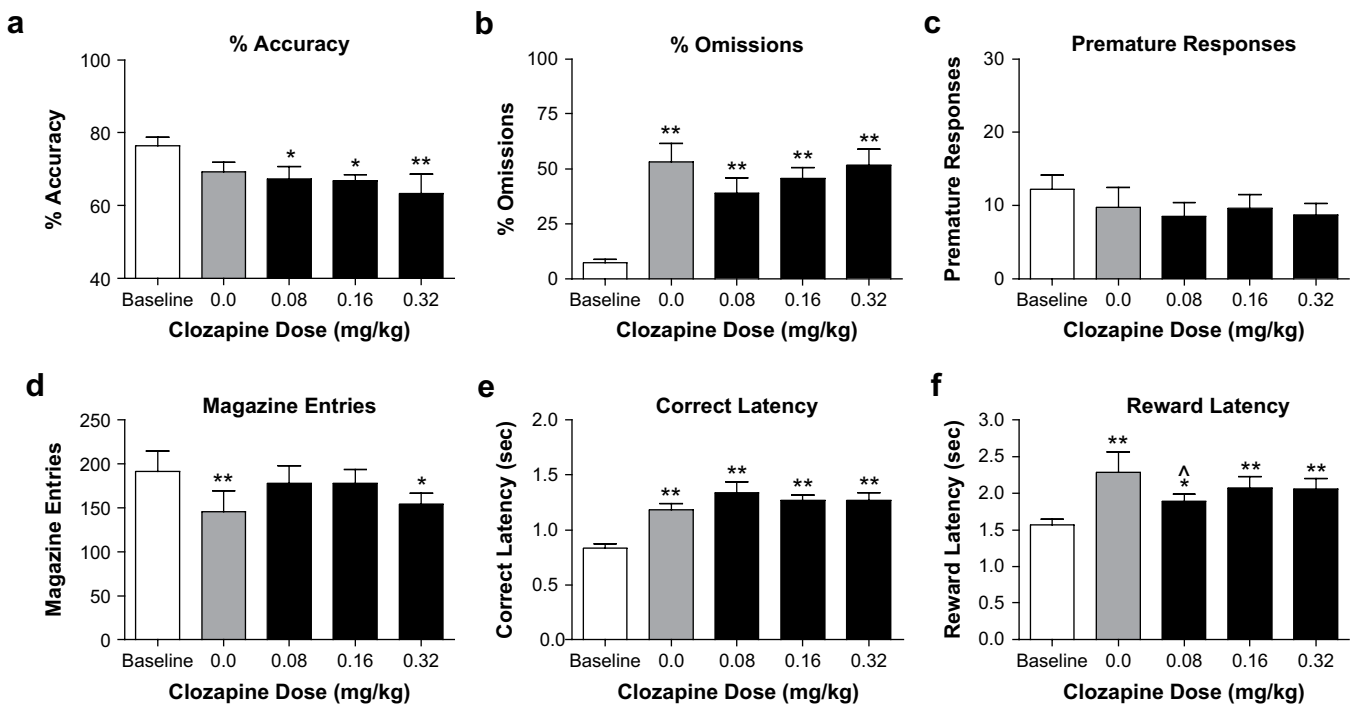


Fig. 5. Ability of clozapine pretreatment to attenuate performance deficits caused by exposure to a regimen of chronic MK-801 administration. MK-801 (0.5 mg/kg, IP) was administered 30 min after daily training sessions; testing occurred 23.5 h later. On days 6, 8, 10 and 12 of MK-801 administration, clozapine (0.08–0.63 mg/kg, SC) was administered 60 min prior to testing. Exposure to MK-801 administration alone (grey bar) did not affect accuracy (a), but it impaired accuracy in combination with clozapine (0.08–0.32 mg/kg). Exposure to MK-801 administration increased omissions (b) and correct response latencies (e), but decreased magazine entries (d). These effects were not altered by clozapine (0.08–0.32 mg/kg). Exposure to MK-801 did not affect premature responses (c), but it increased reward retrieval latencies, an effect attenuated by clozapine (0.08 mg/kg). Significantly different from baseline, * $P < 0.05$, ** $P < 0.01$, Fisher's protected t -tests.

whether chronic administration of clozapine would ameliorate deficits observed during chronic MK-801 withdrawal.

The ability of haloperidol and clozapine to treat cognitive symptoms of schizophrenia is controversial. While there are some reports that clozapine has more beneficial effects on cognition than haloperidol (Keefe et al., 1999), the findings are not consistent (Keefe et al., 2007; Mishara and Goldberg, 2004). Further, there is speculation that cognitive improvements following antipsychotic treatment may reflect 'practice effects' rather than clinically relevant symptom improvements (Goldberg et al., 2007). Our data indicate that, by the strictest definition, both haloperidol and clozapine can improve performance in the 5CSRTT under some testing conditions. The effects of haloperidol likely reflect sedation rather than improved cognition, and the effects of clozapine are modest at best. Since severe attentional deficits in schizophrenia are often associated with a poor prognosis (Green et al., 2004), our studies underscore the need to develop improved treatments.

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