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Increased impulsivity and disrupted attention induced by repeated phencyclidine are not attenuated by chronic quetiapine treatment

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ABSTRACT

Atypical antipsychotic medications differ in how effectively they attenuate cognitive and other deficits in schizophrenia. The present study aimed to explore whether quetiapine, an atypical antipsychotic medication, would reverse disruptions of performance in the 5-choice serial reaction time task (5-CSRTT), a test of attention and impulsivity, induced by repeated administration of the psychotomimetic phencyclidine (PCP). In confirmation of previous findings, repeated PCP administration (2 mg/kg, s.c., 30 min before behavioral testing, for 2 consecutive days, followed by a 2-week PCP-free period and then 5 consecutive days of PCP treatment) increased premature responding (impulsivity), decreased accuracy (attention), and increased response latencies (processing speed) and timeout responding (impulsivity/cognitive inflexibility). Chronic quetiapine (5 or 10 mg/kg/day, s.c.) did not attenuate these PCP-induced disruptions in performance, while at the highest dose used, quetiapine disrupted 5-CSRTT performance in the absence of PCP treatment and tended to exacerbate the PCP-induced increase in premature responding. Considering that clozapine, another atypical antipsychotic, was shown previously to reverse PCP-induced deficits in the same task [Amitai N, Semenova S, Markou A. Cognitive-disruptive effects of the psychotomimetic phencyclidine and attenuation by atypical antipsychotic medications in rats. Psychopharmacology (Berl) 2007;193:521–37], the present findings demonstrate differences between clozapine and quetiapine in their effectiveness on schizophrenia-like cognitive deficits and impulsivity that may be attributable to their different receptor affinity profiles.

1. Introduction

Schizophrenia is a devastating mental disorder that affects 1% of the population (Regier et al., 1993). The symptoms of schizophrenia include impulsivity and severe cognitive deficits that affect a wide range of cognitive modalities. Increased impulsivity in schizophrenia patients is reflected in disinhibition of inappropriate responding in cognitive tests, such as increased errors of commission in Go/No Go tasks (Kiehl et al., 2000; Weisbrod et al., 2000; Wykes et al., 2000; Badcock et al., 2002; Chan et al., 2006). Among cognitive deficits, attentional impairments are prominent (Nuechterlein and Dawson, 1984; Laurent et al., 1999). Additional aspects of cognition that are characteristically disrupted in schizophrenia patients include speed of processing (Nelson et al., 1990), cognitive flexibility (Goldberg et al., 1988; Morice, 1990), and memory (Tamlyn et al., 1992; Kuperberg and Heckers, 2000). Cognitive dysfunction in schizophrenia is highly correlated with functional impairment and is a major predictor of long-term disability (McGurk and Meltzer, 2000; Sharma and Antonova, 2003; Green et al., 2004). Typical neuroleptic medications do not ameliorate cognitive schizophrenia deficits, and in some cases have been found to worsen them (Bilder et al., 1992; Mortimer, 1997). Some studies have found enhancement of cognition in schizophrenia with the newer atypical antipsychotics (Meltzer and McGurk, 1999; Bilder et al., 2002; Bender et al., 2005), but improvement remains only partial and falls well short of restoring normal functioning (Sharma and Antonova, 2003; Keefe et al., 2004).

Interestingly, various atypical antipsychotic medications differ in their effects on impulsivity and cognition in schizophrenia. Specifically, differential effects on different cognitive modalities have been observed. For example, clozapine has been reported to improve attentional function but to have less or no effect on working memory (Sharma and Mockler, 1998; Meltzer and McGurk, 1999). The clinical record is still incomplete and confusing, however. For example, some studies indicate effectiveness of quetiapine at improving attention, but not cognitive flexibility (Velligan et al., 2002), while other studies have found enhancement of cognitive flexibility with quetiapine (Kivircik Akdede et al., 2005; Kopala et al., 2006). Similarly, some studies report amelioration of impulsivity in schizophrenia with clozapine (Spivak et al., 1997; Dursun et al., 2000), while other studies find clozapine to be ineffective (Strous et al., 2006). Olanzapine, but not risperidone, may also improve impulsivity in schizophrenia

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(Strous et al., 2006). Quetiapine has been found to beneficially affect impulsivity in borderline personality disorder, antisocial personality disorder, and bipolar disorder with co-occurring disruptive behavior disorders (Barzman et al., 2006; Hilger et al., 2003; Walker et al., 2003; Villeneuve and Lemelin, 2005), but little is known about its effects on impulsivity in schizophrenia.

Given the limitations and unavoidable confounds of clinical studies in humans, translational animal models of schizophrenia-like cognitive deficits may offer a more controllable means of exploring the differential effects of different atypical antipsychotic medications on cognition. Because the differences in effectiveness are likely related to the different receptor profiles of these medications, such studies are apt to generate new insight into the roles of various receptors and neurotransmitter systems in impulsivity and cognitive dysfunction in schizophrenia and its possible amelioration. This information then could guide the development of novel, more effective treatments for these schizophrenia symptoms.

In previous studies, we established a model of cognitive deficits and increased impulsivity in schizophrenia using repeated administration of phencyclidine (PCP) as the inducing condition that disrupts performance in the 5-choice serial reaction time test (5-CSRTT) as the dependent variable (Amitai et al., 2007). PCP is a dissociative anesthetic that acts as a noncompetitive antagonist at *N*-methyl-D-aspartate (NMDA) glutamate receptors. PCP intoxication produces a psychosis-like state in healthy humans that comprises both positive and negative symptoms of schizophrenia (Luby et al., 1959; Bakker and Amini, 1961; Allen and Young, 1978; Castellani et al., 1982; Javitt, 1987; Steinpreis, 1996). As a result, the effects of PCP on various behaviors have found wide recognition as models of different aspects of schizophrenia (Javitt, 1987; Sams-Dodd, 1996; Steinpreis, 1996; Jentsch and Roth, 1999). Most relevant to the topic of the present study is the fact that PCP exposure disrupts cognition in both humans (Rosenbaum et al., 1959; Yesavage and Freeman, 1979; Pearlson, 1981; Pradhan, 1984) and animals (Handelmann et al., 1987; Stefani and Moghaddam, 2005; Rodefer et al., 2005, 2008; Idris et al., 2003, 2005; Abdul-Monim et al., 2003, 2006, 2007; Depoortère et al., 2007; Didriksen et al., 2007) and increases impulsive responding in experimental animal models (Balster and Baird, 1979; Sanger and Jackson, 1989; Compton et al., 2001; Jentsch and Anzivino, 2004; Amitai et al., 2007), indicating the usefulness of PCP in inducing impulsivity and cognitive dysfunction with relevance to schizophrenia.

The 5-CSRTT was developed originally as a test of attentional performance (for review, Robbins, 2002). In addition, this task allows assessment of disinhibition of inappropriate responding and has become recognized as a means to gauge impulsivity (Puumala et al., 1996; Puumala and Sirviö, 1998; Evenden, 1999; Talpos et al., 2006). Furthermore, the 5-CSRTT provides measures of processing speed and cognitive flexibility (Robbins, 2002). Repeated administration of PCP increases impulsivity and disrupts cognitive performance in the 5-CSRTT. The profile of deficits induced by PCP in the 5-CSRTT includes a profound increase in impulsive-type responding in PCP-treated animals. Repeated PCP administration also disrupts attentional performance in the task and decreases processing speed and cognitive flexibility (Amitai et al., 2007). Chronic clozapine treatment has been shown to significantly attenuate the increased impulsivity induced by repeated PCP. Moreover, it partially ameliorates the PCP-induced attentional disruption, but does not alter the effects of repeated PCP on processing speed and cognitive flexibility (Amitai et al., 2007).

In the present study, we investigated how chronic treatment with another atypical antipsychotic, quetiapine, affects the increased impulsivity and cognitive performance impairments induced in the 5-CSRTT by repeated PCP administration. Repeated injections of PCP were used because previous studies showed that a single injection of PCP produced a general, nonspecific response suppression that partially or completely occluded specific cognitive and other deficits with relevance to schizophrenia. For example, premature responses tended to be decreased after a single injection of PCP (as did all types of responding), whereas repeated administration of PCP led to a profound increase in premature responses, revealing the increased impulsivity induced by PCP (Amitai et al., 2007). While several studies have explored cognitive function after subchronic PCP administration followed by a significant washout period, when animals are no longer under the direct influence of PCP (Jentsch et al., 1997; Jentsch and Taylor, 2001; Rodefer et al., 2005, 2008; Abdul-Monim et al., 2006, 2007), it should be noted that the schizophrenia-like state evoked by PCP in humans is present during PCP intoxication, not during PCP withdrawal or during prolonged post-PCP abstinence (Pradhan, 1984). Therefore, we assessed impulsivity and cognitive performance during acute PCP re-challenges after repeated PCP exposures. A dose of 2 mg/kg was chosen because the higher PCP doses commonly used in subchronic studies that test behavior during the drug-free state (Jentsch et al., 1997; Jentsch and Taylor, 2001; Rodefer et al., 2005, 2008) profoundly disrupt 5-CSRTT responding and overall behavior during acute PCP intoxication.

Previous investigations in our laboratory have shown that acute quetiapine, given at a range from 2.5 to 7.5 mg/kg, did not affect performance of the 5-CSRTT under baseline conditions (i.e., in the absence of PCP administration), with the exception of a slight decrease in percent correct responses at the highest dose. Attentional accuracy and impulsive responding were not altered by any dose of quetiapine used (Amitai et al., 2007). While both clozapine and quetiapine are atypical antipsychotic medications commonly used to treat schizophrenia (McEvoy et al., 1999), quetiapine's receptor profile differs from that of clozapine in several ways (see Table 1). Quetiapine exhibits a smaller ratio of serotonin 5-HT_{2A} receptor antagonism to dopamine D_2 receptor antagonism than clozapine, and also lacks the significant antagonism of serotonin 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors expressed by clozapine (Bymaster et al., 1996; Schmidt et al., 2001). Thus, if the effects of chronic quetiapine on a model of schizophrenia-like impulsivity and cognitive deficits differ from those of clozapine, these disparities may provide clues to the importance of actions at different receptors in the effectiveness of atypical antipsychotics in decreasing impulsivity and improving cognition in schizophrenia.

2. Materials and methods

2.1. Subjects

Forty-one male Wistar rats (Charles River Laboratories, Wilmington, MA) were housed two per cage on a 12 h:12 h reversed light–dark cycle (lights off at 6:00 am). All behavioral testing was conducted during the animals' dark cycle. Rats were allowed to reach a body weight of at least 275 g before being restricted to 20 g of food per day (in addition to the food pellets earned during testing) and initiation of behavioral training. Water was available *ad libitum* at all times except during testing. Animals were treated in accordance with the guidelines of the American Association for the Accreditation of Laboratory Animal Care and the National Research Council's *Guide for Care and Use of Laboratory Animals.* All experiments were approved by the

Table 1
Receptor affinities of quetiapine and clozapine.

Receptor	Quetiapine	Clozapine
D_2	180 nM	130 nM
5-HT_{2A}	220 nM	8.9 nM
5-HT_{2A}:D_2 affinity ratio	0.82	14.6
5-HT_{2C}	1400 nM	17 nM
5-HT_6	4100 nM	11 nM
5-HT_7	1800 nM	66 nM
Histamine H_1	8.7 nM	1.8 nM

Data are presented as K_i values and based on Schmidt et al. (2001).

University of California, San Diego, Institutional Animal Care and Use Committee.

2.2. Drugs

D-phencyclidine hydrochloride (PCP) was obtained from the National Institute on Drug Abuse (Bethesda, MD, USA). Quetiapine was provided as a generous gift by AstraZeneca Pharmaceuticals (Newark, DE, USA). PCP was dissolved in 0.9% saline solution and administered by subcutaneous (s.c.) injection in a volume of 2 ml/kg. Quetiapine was dissolved in HCl 0.133 N and diluted with saline (approximately half of the volume) according to the rat's body weight. Matched vehicle consisted of saline containing the same amounts of HCl 0.133 N. Quetiapine was administered via s.c. osmotic minipumps.

2.3. Apparatus

Training and testing were conducted in operant testing chambers enclosed in sound-attenuating chambers (Med Associates, St. Albans, VT, USA). Each testing chamber contained a curved rear wall with nine contiguous apertures. Metal inserts covered every alternate hole, leaving open holes 1, 3, 5, 7, and 9. A photocell beam located at the entrance of each aperture detected nosepoke responses, and a 3 W stimulus light was located at the rear of each aperture. Food pellets could be delivered automatically into a magazine located in the opposite wall via a food dispenser; a photocell beam detected head entries into the magazine. A computer running MedPC software (Med Associates, St. Albans, VT, USA) controlled the apparatus.

2.4. 5-choice serial reaction time task procedure

Rats were trained on the 5-CSRTT using a procedure based on the one established by Carli et al. (1983). Following the training methodology described in detail in Amitai et al. (2007), animals were trained to initiate each trial by a head entry into the food magazine, which started a 5 s intertrial interval, followed by presentation of a 1 s light stimulus in one of the response apertures at a pseudorandom location. A nosepoke in this aperture within a 5 s limited hold period (correct response) resulted in the delivery of a food pellet into the magazine. Nosepokes in a wrong aperture (incorrect responses) or failures to respond within the limited hold period (omissions) were punished by a 5 s timeout, marked by extinction of the house light and no delivery of food reward. Nosepokes in any aperture made before presentation of the target stimulus (premature responses) or further responses into the apertures after the performance of a correct response, but before reward retrieval from the magazine/initiation of a new trial (perseverative responses), likewise resulted in a timeout and no food reward. Nosepokes during the timeout period (timeout responses) reset the timeout period. An initial noncontingent food pellet was delivered into the magazine at the start of each session to facilitate initiation of the first trial. Each session lasted 30 min or until 100 trials had been completed, whichever occurred first. Rats were trained until they had achieved criterion performance (>70% accuracy and <20 omissions) and stable baselines (<10% variation in accuracy over 5 consecutive days). On average, 40 sessions were required for rats to attain criterion performance. New cohorts of rats were trained for each experiment. The following measures were recorded to assess task performance:

Accuracy: the number of correct responses divided by the sum of correct and incorrect responses: [# correct responses/(# correct responses + # incorrect responses)] × 100. Accuracy was only computed if correct + incorrect responses totaled 10 or more.

Percent correct responses: (total # correct responses / total # of trials) × 100.

Percent incorrect responses: (total # incorrect responses / total # of trials) × 100.

Percent omissions: (total # omissions / total # of trials) × 100.

Premature responses: total # of responses performed during the intertrial interval, before presentation of the light stimulus.

Timeout responses: total # of responses performed during a timeout period.

Latency to correct response: time from the onset of the light stimulus to the performance of a correct nosepoke response.

Latency to incorrect response: time from the onset of the light stimulus to the performance of a correct nosepoke response. This latency measure was assessed in all experiments but is not reported here because it exhibited essentially the same drug effects as latency to correct response.

Latency to reward retrieval: time from the performance of a correct response to the retrieval of the food reward from the magazine.

Perseverative responses: nosepoke responses performed after a correct response but before collection of the reward. These responses were assessed in all experiments but are not reported here because they did not show any systematic changes in any of the experiments.

Total trials: total # of trials initiated during the session.

2.5. Osmotic minipump implantation and removal

Rats were anesthetized with a 1–3% isoflurane/oxygen vapor mixture, and an osmotic minipump (Alzet model 2ML1 7 day pump or model 2ML2 14 day pump, Alza Corporation, Palo Alto, CA, USA) was inserted subcutaneously on the back of the animal parallel to the spine, with the flow moderator directed posteriorly. The wound was stapled, and an antibacterial ointment was applied to the incision area. In Experiment 1, on day 7, the first minipump was removed, and a second minipump was inserted contralateral to the first minipump under anesthesia. On day 14, the second minipump (Experiment 1) or first minipump (Experiment 2) was removed. For pump removal, an incision was made under anesthesia, the pump was removed, the wound was closed with surgical staples, and an antibacterial ointment was applied.

2.6. Experimental design

2.6.1. Experiment 1: Effects of 10 mg/kg/day quetiapine and repeated PCP on 5-CSRTT performance

After establishment of stable performance in the 5-CSRTT (<10% variation in accuracy over 5 consecutive days), rats received two initial s.c. injections of 2 mg/kg PCP, 24 h apart. The rats then were assigned to two groups that did not differ in accuracy, correct responses, incorrect responses, and premature responses both under baseline conditions and during this initial PCP exposure. This group-matching procedure was necessitated by the considerable variability in responsiveness to performance disruption with PCP, which cannot be predicted from an animal's baseline performance. Balancing the groups based on both their performance in the absence of PCP and during PCP exposure ensured that differential responsiveness to PCP would not confound the results after antipsychotic treatment. One group ($n = 10$) was prepared with two consecutive 7-day osmotic minipumps delivering 10 mg/kg/day quetiapine (salt); the other group ($n = 10$) received pumps containing vehicle. This dose of quetiapine was chosen based on our previous observation that 5 mg/kg was the highest acute bolus dose that did not induce disruption in 5-CSRTT performance by itself (Amitai et al., 2007) and on previous experience in converting acute bolus doses of atypical antipsychotics to chronic daily doses infused continuously. Our previous data with clozapine indicated that a cumulative daily dose approximately twice as large as the highest acute bolus dose that does not induce disruption in 5-CSRTT performance was successful in attenuating repeated PCP effects

without affecting 5-CSRTT performance by itself (Amitai et al., 2007). The limited solubility of quetiapine at the concentration required to deliver 10 mg/kg/day in the maximal volume that could be contained in the minipumps prevented the use of a single 14-day osmotic minipump. After three initial days of quetiapine/vehicle exposure, all rats received five consecutive daily saline injections s.c. 30 min before 5-CSRTT testing, followed by five consecutive daily injections with 2 mg/kg PCP, s.c., 30 min before 5-CSRTT testing. Overall, this design allowed for the comparison of the effects of quetiapine versus vehicle (between-subjects factor) as well as the effects of PCP versus those of saline (within-subjects factor), with all factorial combinations (vehicle/saline, vehicle/PCP, quetiapine/saline, quetiapine/PCP) explored. The mixed within/between-subjects design was necessitated by the long training times required by the task, and the large numbers of animals needed in each group to reduce the considerable variation in the behavioral effects of PCP that is commonly observed. Previous studies in our laboratory using repeated saline injections have demonstrated that the repeated injection procedure alone does not induce changes in any of the task parameters (Amitai et al., 2007).

Pumps were removed on the 14th day of quetiapine/vehicle exposure, and rats were tested daily in the 5-CSRTT for 10 additional days to assess the return of performance to baseline levels (see Fig. 1 for a diagram of the experimental design). This design examining the potential of an atypical antipsychotic medication to prevent PCP effects parallels the prevention of recurrence of a psychotic episode in schizophrenia by antipsychotic treatment. PCP was administered at a concentration of 2 ml/kg because irritation at the injection site has been observed with repeated PCP injections at 1 ml/kg, even when varying the injection site.

2.6.2. Experiment 2: Effects of 5 mg/kg/day quetiapine and repeated PCP on 5-CSRTT performance

Because disruptive effects of quetiapine were observed at the 10 mg/kg/day dose, the experiment was repeated with a new cohort of rats that received a single 14-day osmotic minipump delivering either 5 mg/kg/day quetiapine ($n=11$) or vehicle ($n=10$).

2.7. Data analyses

Data were analyzed using two-way mixed-design analysis of variance (ANOVA). To assess the effects of chronic quetiapine by itself, average values from the 5 days preceding any drug treatment ("baseline days") were compared with average values obtained during the 9 days of PCP-free pump treatment. Pump Content (quetiapine/vehicle) was the between-subjects factor, and Presence of Pump (before pump implantation/during pump exposure) was the within-subjects factor. To assess the effects of chronic quetiapine on performance disruption induced by repeated PCP administration, average values from the 5 days of saline injection during pump treatment were compared with average values from the 5 days of PCP administration during pump treatment. Pump Content (quetiapine/vehicle) was the between-subjects factor, and Drug Challenge (PCP/saline) was the within-subjects factor. Where statistically significant effects were found in the ANOVAs, *post hoc* comparisons among means were conducted using Bonferroni tests. The level of significance was set at 0.05. Data were analyzed using the GraphPad Prism statistical package (GraphPad, San Diego, CA, USA).

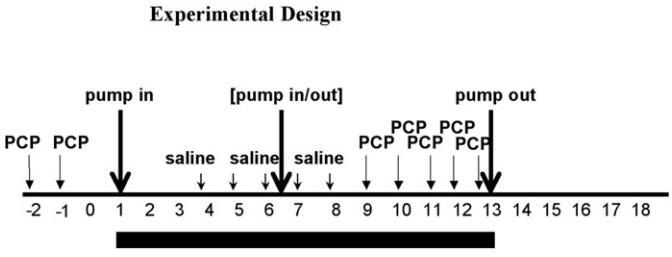

Fig. 1. Diagram of experimental design.

3. Results

3.1. Effects of chronic quetiapine on 5-CSRTT under baseline conditions (i.e., in the absence of PCP treatment; see Table 2 for summary of results and comparison with the effects of chronic clozapine)

In Experiment 1, premature responses were unaltered by pump treatment (Fig. 2a). However, ANOVA revealed a significant main effect of Presence of Pump on accuracy [$F(1,18)=8.77$, $p<0.01$; Fig. 2b], reflecting a decrease in accuracy after pump implantation. A significant main effect of Presence of Pump on percent correct responses [$F(1,18)=16.18$, $p<0.001$] and a significant Presence of Pump × Pump Content interaction [$F(1,18)=5.05$, $p<0.05$] indicated that percent correct responses was reduced in rats exposed to 10 mg/kg/day quetiapine (Fig. 2c). A significant Presence of Pump × Pump Content interaction was also found for percent incorrect responses [$F(1,18)=6.13$, $p<0.05$], reflecting higher levels of incorrect responding in rats treated with 10 mg/kg/day quetiapine (data not shown) than in the vehicle-treated control group. Percent omissions was significantly increased by Presence of Pump [$F(1,18)=7.08$, $p<0.05$; Fig. 2d], but no main effect of Pump Content or Presence of Pump × Pump Content interaction was observed. Quetiapine at 10 mg/kg/day also significantly increased latency to correct response, demonstrated by a significant main effect of Presence of Pump [$F(1,18)=50.32$, $p<0.0001$], a significant Presence of Pump × Pump Content interaction [$F(1,18)=7.30$, $p<0.05$], and a trend toward a main effect of Pump Content [$F(1,18)=3.15$, $p=0.09$; Fig. 2e]. When applying a mixed-design ANOVA to compare latency to correct response separately on each day of pump treatment, a significant effect of Pump Content was found [$F(1,126)=5.029$, $p<0.05$], further supporting the finding that this dose of quetiapine disrupted this measure. A main effect of Presence of Pump on reward latency [$F(1,18)=10.62$, $p<0.01$] and a significant Presence of Pump × Pump Content interaction [$F(1,18)=4.69$, $p<0.05$] appeared to be caused by a faster latency to reward retrieval during baseline in the group of rats later treated with 10 mg/kg/day quetiapine; this difference was lost during pump treatment (data not shown). No effects on timeout responses (Fig. 2f) and total trials (data not shown) were seen. Average trials completed per group were 100 ± 0.00 during baseline and 99.27 ± 0.26 during pump exposure for vehicle-treated rats, and 100 ± 0 during baseline and pump exposure for quetiapine-treated rats (Table 2).

None of the measures were affected by implantation of pumps delivering 5 mg/kg/day vehicle in Experiment 2 (Fig. 3), except for a main effect of Presence of Pump on percent omissions [$F(1,19)=6.15$, $p<0.05$], reflecting a slight increase in omissions after pump implantation (Fig. 3d). No main effect of Pump Content on percent omissions and no Presence of Pump × Pump Content interaction were found. Average trials completed per group were 99.75 ± 0.17 during baseline and 99.79 ± 0.22 during pump exposure for vehicle-treated rats, and 99.82 ± 0.19 during baseline and 99.88 ± 0.13 during pump exposure for quetiapine-treated rats.

3.2. Effects of chronic quetiapine and repeated PCP administration on 5-CSRTT performance (see Table 2 for summary of results and comparison with the effects of chronic clozapine)

In Experiment 1, a significant main effect of Drug Challenge indicated that repeated PCP increased premature responses [$F(1,18)=37.64$, $p<0.0001$; Fig. 2a]. While no main effect of quetiapine was observed, a strong trend toward a PCP × quetiapine interaction was found [$F(1,18)=4.192$, $p=0.056$], reflecting even higher levels of premature responding during some days of repeated PCP administration

Table 2
Summary of repeated PCP effects, chronic quetiapine effects under baseline conditions, chronic quetiapine effects on PCP-induced disruptions, and comparison with chronic clozapine effects.

5-CSRTT measure	Repeated PCP	5 mg/kg/day quetiapine (baseline)	5 mg/kg/day quetiapine + PCP	10 mg/kg/day quetiapine (baseline)	10 mg/kg/day quetiapine + PCP	Clozapine (baseline)	Clozapine + PCP
Premature responses	↑	↔	No effect	↔	**Exacerbate**	↔	**Attenuate**
Accuracy	↓	↔	No effect	↓	No effect	↔	**Attenuate**
% correct responses	↓	↔	No effect	↓	No effect	↔	No effect
% omissions	↑	↔	No effect	↑	No effect	↔	No effect
Latency to correct response	↑	↔	No effect	↑	No effect	↔	No effect
Timeout responses	↑	↔	No effect	↔	No effect	↔	No effect

Clozapine data are based on Amitai et al. (2007).

in rats treated with 10 mg/kg/day quetiapine. Moreover, a strong trend toward a decrease in accuracy during repeated PCP administration was detected by ANOVA [$F(1,18) = 4.27$, $p = 0.053$; Fig. 2b]. Repeated PCP also decreased percent correct responses [$F(1,18) = 19.18$, $p < 0.001$; Fig. 2c] and total trials [$F(1,18) = 43.20$, $p < 0.0001$; data not shown], and increased percent omissions [$F(1,18) = 23.86$, $p < 0.001$; Fig. 2d], latency to correct response [$F(1,18) = 19.07$, $p < 0.001$; Fig. 2e], and timeout responses [$F(1,18) = 20.94$, $p < 0.001$; Fig. 2f]. On all of these measures, no main effect of quetiapine and no PCP×quetiapine interaction were found. No effects on percent incorrect responses or reward latency were observed (data not shown). Average trials completed per group were 99.6 ± 0.42 during saline administration and 79.32 ± 4.85

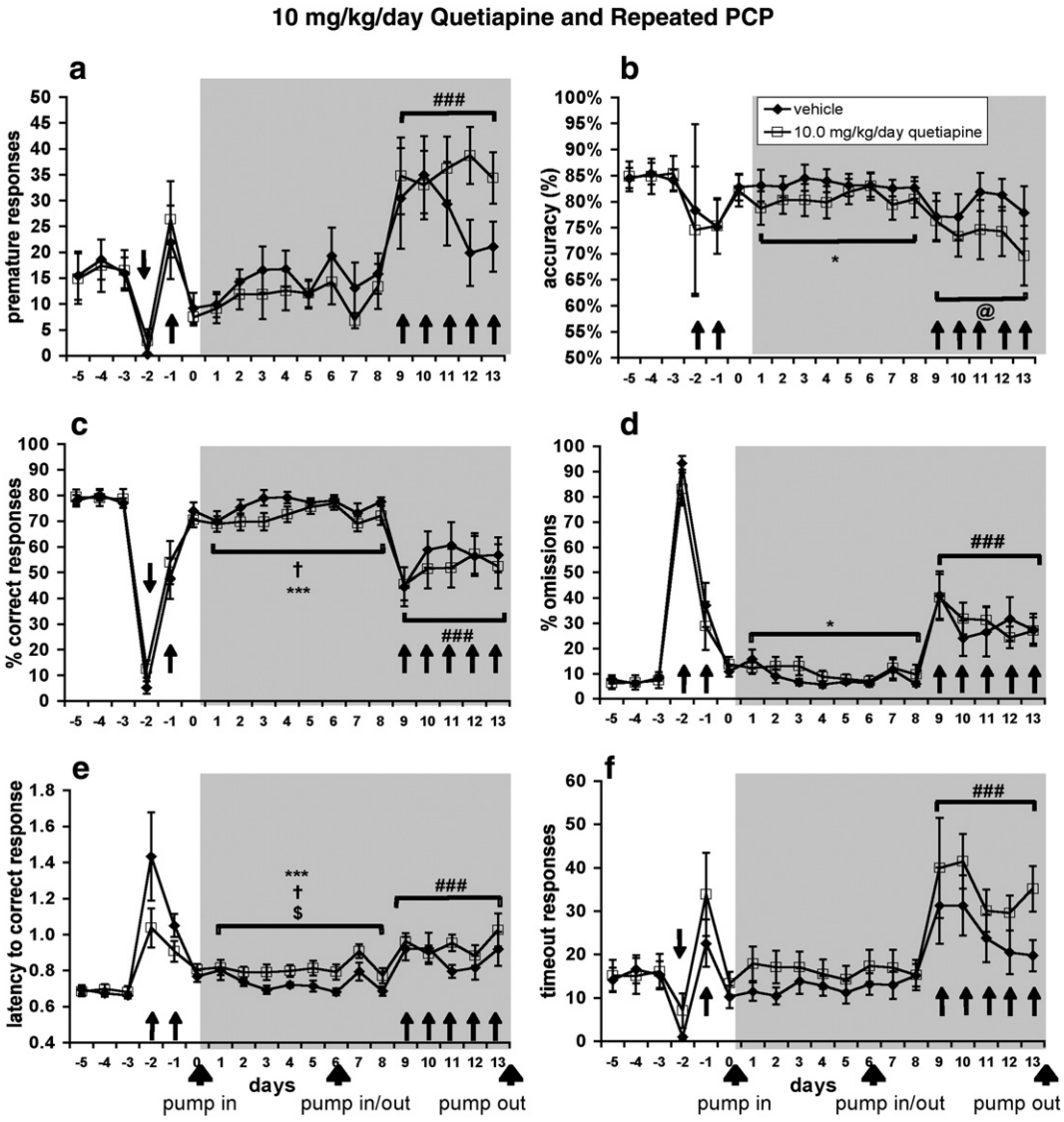

Fig. 2. Effects of 10 mg/kg/day quetiapine treatment on 5-CSRTT performance under baseline conditions and during repeated PCP administration ($n = 10$ per group). Premature responses (a), accuracy (b), percent correct responses (c), percent omissions (d), latency to correct response (e), and timeout responses (f) are shown as mean ± SEM. Asterisks indicate statistically significant differences compared with baseline performance (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). Dagger indicates a statistically significant Presence of Pump × Pump Content interaction ($^{\dagger}p < 0.05$). Dollar sign indicates a statistically significant difference from rats treated with vehicle-containing minipumps ($^{\$}p < 0.05$). Hash signs indicate a statistically significant difference compared with performance after saline injections ($^{\#\#\#}p < 0.001$). "At" sign indicates a trend toward a significant difference compared with performance after saline injections ($^{@}p < 0.06$). Shaded areas indicate the period of pump treatment. ↑ denotes a PCP injection.

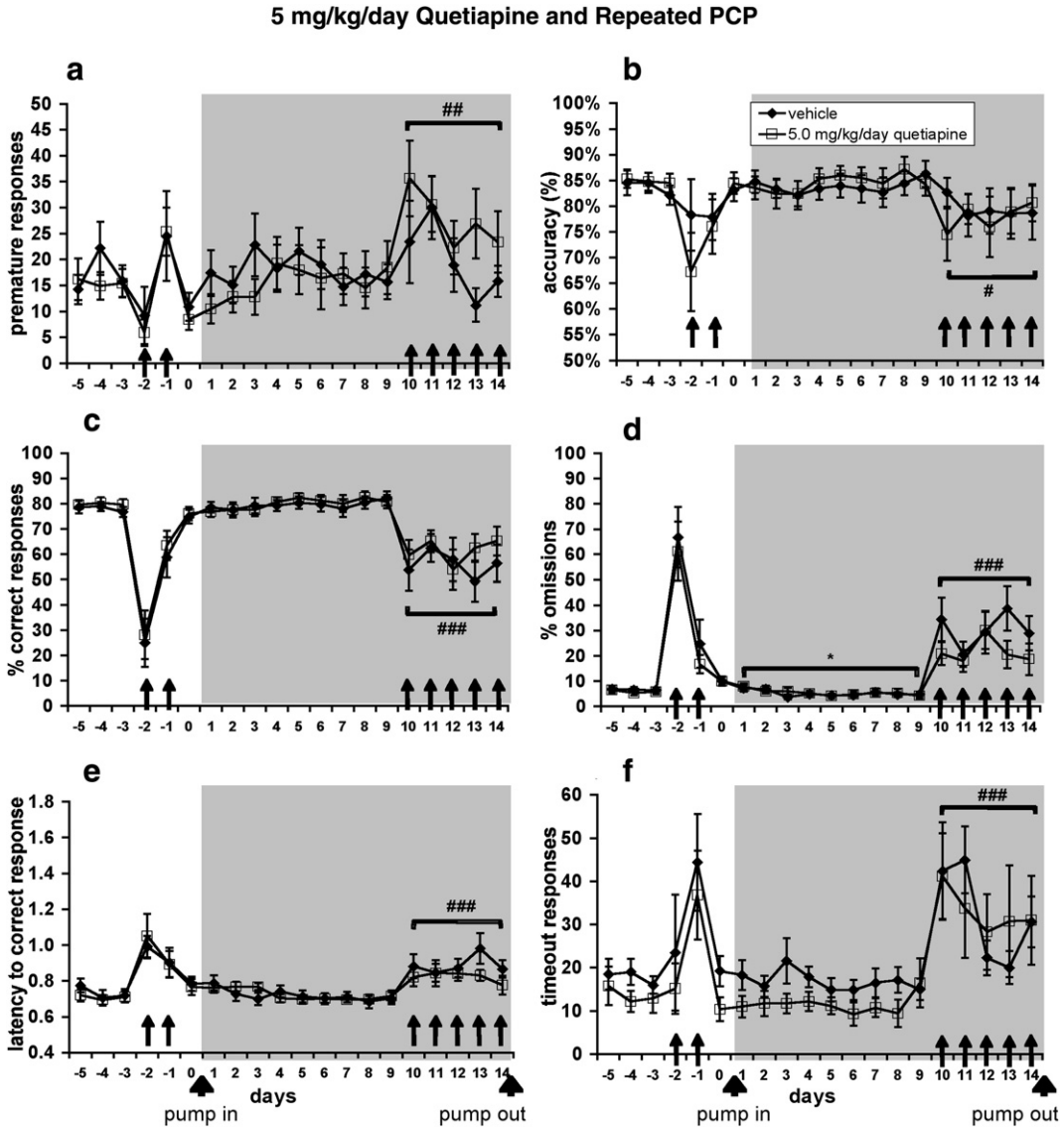

Fig. 3. Effects of 5 mg/kg/day quetiapine treatment on 5-CSRTT performance under baseline conditions and during repeated PCP administration ($n = 10$–11 per group). Premature responses (a), accuracy (b), percent correct responses (c), percent omissions (d), latency to correct response (e), and timeout responses (f) are shown as mean + SEM. Asterisks indicate statistically significant differences compared with baseline performance ($^{*}p<0.05$). Hash signs indicate a statistically significant difference compared with performance after saline injections ($^{\#\#}p<0.01$; $^{\#\#\#}p<0.001$). Shaded areas indicate the period of pump treatment. ↑ denotes a PCP injection.

during PCP administration for vehicle-treated rats, and 100 ± 0.00 during saline administration and 82.4 ± 3.92 during PCP administration for quetiapine-treated rats. The minimum # of trials completed by any rat at any point was 32.

A similar strong tendency toward increased premature responses was observed with repeated PCP administration in Experiment 2 [$F(1,19) = 4.071$, $p = 0.058$; Fig. 3a]. A mixed-design ANOVA analyzing average premature responding during saline administration versus each separate day of repeated PCP exposure revealed a significant main effect of PCP [$F(1.95) = 1.70$, $p<0.01$]. A strong trend toward reduced accuracy with repeated PCP administration was also found [$F(1,19) = 4.16$, $p = 0.056$; Fig. 3b]. Again, a mixed-design ANOVA analyzing accuracy during saline administration versus each separate day of repeated PCP exposure detected a significant main effect of PCP [$F(1,95) = 2.49$, $p<0.05$]. Furthermore, repeated PCP again decreased percent correct responses [$F(1,19) = 32.52$, $p<0.0001$; Fig. 3c] and total trials [$F(1,19) = 15.61$, $p<0.001$; data not shown], and increased percent omissions [$F(1,19) = 46.47$, $p<0.0001$; Fig. 3d], latency to correct response [$F(1,19) = 34.54$, $p<0.0001$; Fig. 3e], and timeout responses [$F(1,19) = 19.97$, $p<0.001$; Fig. 3f]. Repeated PCP did not affect reward latency or percent incorrect responses (data not shown). Treatment with 5 mg/kg/day quetiapine showed no main effect and no interaction with PCP on any measure. Average trials completed per group were 100 ± 0.00 during saline administration and 82.2 ± 5.76 during PCP administration for vehicle-treated rats, and 99.78 ± 0.23 during saline administration and 86.65 ± 5.83 during PCP administration for quetiapine-treated rats. The minimum # of trials completed by any rat at any point was 34.

4. Discussion

The results indicated robust schizophrenia-like impulsivity and cognitive disruptions induced by repeated PCP administration but no attenuation of these deficits by chronic quetiapine treatment. As in previous studies (Amitai et al., 2007), repeated PCP exposure led to significant impairment of 5-CSRTT performance. The deficit profile included increased impulsivity, revealed by an increase in premature responses (Figs. 2a, 3a). Repeated PCP administration also disrupted attention, indicated by a decrease in accuracy (Figs. 2b, 3b) and percent correct responses (Figs. 2c, 3c) and an increase in percent

omissions (Figs. 2d, 3d). Repeated PCP also slowed processing speed, denoted by an increase in latency to correct response (Figs. 2e, 3e). The fact that latency to reward retrieval remained unaffected by repeated PCP administration confirms that the increased latency to correct response is not caused by an overall locomotor impairment, and likely reflects a decrease in cognitive processing speed. Finally, the number of timeout responses was increased by repeated PCP administration (Figs. 2f, 3f). Timeout responses have not been as thoroughly studied to date as other 5-CSRTT measures, and no consensus has yet emerged regarding which behavioral construct they may model. Because timeout responses involve the continuation of a behavioral response past the point when the response is no longer rewarded, they can be considered to be an expression of compulsivity, a type of cognitive inflexibility. Moreover, timeout responses constitute the failure of inhibition of an inappropriate response, and may therefore be another reflection of impulsivity. Overall, the profile of disruptions produced by PCP in our study corresponds to the cognitive deficits present in schizophrenia, which are characterized by increased impulsivity, impaired attention, slowed processing speed, and cognitive inflexibility (Nuechterlein and Dawson, 1984; Goldberg et al., 1988; Morice, 1990; Nelson et al., 1990; Laurent et al., 1999; Kiehl et al., 2000; Weisbrod et al., 2000; Wykes et al., 2000; Badcock et al., 2002; Chan et al., 2006).

Chronic treatment with quetiapine at two different doses did not attenuate any of the PCP-induced cognitive disruptions. This lack of efficacy of quetiapine is unlikely to be due to the use of insufficiently high doses of quetiapine. The higher of the two doses of quetiapine actually led to disruption of 5-CSRTT performance by itself, and also tended to further elevate premature responding in the presence of repeated PCP administration (Fig. 2).

These findings contrast with the results of an earlier study that showed that chronic treatment with a different atypical antipsychotic, clozapine, ameliorated 5-CSRTT deficits induced by repeated PCP administration (Amitai et al., 2007). Specifically, clozapine significantly attenuated the profound increase in premature responding seen during repeated PCP exposure, indicating a beneficial effect on PCP-induced impulsivity. Furthermore, chronic clozapine partially attenuated the decrease in accuracy during PCP exposure, suggesting an improvement of PCP-induced attentional impairment. These differences in the effects of clozapine and quetiapine demonstrate that atypical antipsychotics differ in their effectiveness against schizophrenia-like cognitive deficits. Such differences are also suggested by the results of a number of clinical trials (see Introduction).

The differences in effectiveness between quetiapine and clozapine on the 5-CSRTT performance disruptions induced by repeated PCP are likely due to somewhat dissimilar receptor profiles of the two medications (see Table 1 for a summary of receptor affinities). Quetiapine and clozapine share actions at a number of receptors. Both compounds are antagonists at dopamine D_2 receptors (Bymaster et al., 1996; Schmidt et al., 2001). Quetiapine and clozapine also both dissociate rapidly from D_2 receptors, setting them apart from typical antipsychotic medications, as well as from certain atypical antipsychotics, such as risperidone (Seeman and Tallerico, 1999). In addition, both compounds have strong affinity for histamine H_1 receptors, where they act as antagonists (Schotte et al., 1996; Schmidt et al., 2001). Antagonism of D_2 receptors, rapid dissociation from D_2 receptors, and histamine antagonism have all been implicated in the antipsychotic activity and overall behavioral profiles of atypical antipsychotics (Kapur et al., 2000; Kapur and Seeman, 2001; Akhtar et al., 2006; Pani et al., 2007). However, as these receptor actions, as well as others (e.g. antagonism of muscarinic and noradrenergic receptors) are shared by both clozapine and quetiapine, they are unlikely to underlie the differences in their effectiveness on cognitive deficits in the present study, as well as in clinical applications.

Much interest has focused on the actions of atypical antipsychotics at serotonin receptors. The serotonergic actions of atypical antipsychotics have been proposed to be central to their "atypical" profile and their beneficial effects on a range of schizophrenia symptoms, including negative and cognitive symptoms (Meltzer et al., 2003). In this context, it is notable that serotonin neurotransmission has been suggested to play a critical role in impulsivity and in the 5-CSRTT measure of impulsivity, premature responding (Harrison et al., 1997; Winstanley et al., 2003), and that the beneficial actions of clozapine on 5-CSRTT deficits induced by repeated PCP were particularly pronounced for the case of premature responding (Amitai et al., 2007). Particular emphasis has been placed on the serotonin 5-HT_{2A} receptor. Selective 5-HT_{2A} antagonists have been found to decrease premature responses in the 5-CSRTT both under baseline conditions or when premature responding had been increased by the NMDA antagonist dizocilpine or by lengthening the intertrial interval (Higgins et al., 2003; Fletcher et al., 2007). While both quetiapine and clozapine are 5-HT_{2A} antagonists (Bymaster et al., 1996; Schmidt et al., 2001), the ratio of 5-HT_{2A} antagonism to D2 antagonism is significantly smaller with quetiapine than with clozapine. While clozapine binds to 5-HT_{2A} receptors ($K_i = 8.9$ nM) with over 10-fold greater affinity than to D2 receptors ($K_i = 130$ nM), the affinity of quetiapine for 5-HT_{2A} receptors ($K_i = 220$ nM) is slightly less than that of its affinity for D2 receptors ($K_i = 180$ nM) (Schmidt et al., 2001). Clozapine increases dopamine release in the prefrontal cortex (PFC) (Moghaddam and Bunney, 1990), an effect that can be reproduced by concomitant administration of a 5-HT_{2A} antagonist and a D_2 antagonist (Ichikawa et al., 2001; Liegeois et al., 2002). Quetiapine, in contrast, does not elevate prefrontal dopamine levels (Volonté et al., 1997). Studies suggest that cognitive impairment in schizophrenia is associated with hypofunction of the PFC (Weinberger et al., 1986, Goldberg et al., 1988; Andreasen et al., 1992) and that this "hypofrontality" may include reduced dopaminergic activity in the PFC (Weinberger et al., 1988; Davis et al., 1991; Goldman-Rakic et al., 2004). Decreased dopamine neurotransmission in the PFC can disrupt cognition (Brozoski et al., 1979; Sawaguchi and Goldman-Rakic, 1991; Castner et al., 2004; Goldman-Rakic et al., 2004). A high ratio of 5-HT_{2A} antagonism to D_2 antagonism may therefore allow clozapine to overcome a hypodopaminergic state in schizophrenia patients by elevating prefrontal dopamine levels, and thus improving cognitive schizophrenia symptoms. This high 5-HT_{2A}/D_2 antagonism ratio may also explain why clozapine succeeded in attenuating deficits in response inhibition/impulsivity and attention induced by repeated PCP treatment, while quetiapine did not. Studies examining how 5-CSRTT performance disruption induced by repeated PCP is affected by atypical antipsychotics with a high ratio of 5-HT_{2A} antagonism to D_2 antagonism that lack some of the other antagonist properties of clozapine (e.g. at 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors; see below) may further clarify the importance of these receptor mechanisms.

Clozapine also strongly antagonizes 5-HT_{2C} receptors ($K_i = 17$ nM), while quetiapine has no strong affinity for this receptor ($K_i = 1400$ nM) (Schmidt et al., 2001), suggesting that quetiapine may have been less effective at attenuating PCP-induced cognitive deficits due to a lack of action on the 5-HT2C receptor. However, selective 5-HT_{2C} antagonists did not ameliorate dizocilpine-induced increases in 5-CSRTT premature responding, and increased premature responses by themselves (Higgins et al., 2003; Fletcher et al., 2007). This pattern of results suggests that clozapine's 5-HT_{2C} receptor antagonist properties may not underlie its beneficial effects on impulsive responding.

An additional serotonin receptor that has recently garnered attention is the 5-HT_6 receptor. Clozapine exhibits significant 5-HT_6 receptor antagonism, while quetiapine does not interact significantly with this receptor. Some studies have found altered 5-HT_6 mRNA expression in schizophrenia patients (East et al., 2002), and a 5-HT_6 polymorphism has been reported to be a risk factor for schizophrenia (Tsai et al., 1999; but see Shinkai et al., 1999; Ohmori et al., 2001) and to affect the therapeutic response to clozapine treatment (Yu et al., 1999; Huezo-Diaz et al., 2001). Selective 5-HT_6 receptor antagonists

have been found to improve performance in a range of cognitive tasks in adult (Rogers and Hagan, 2001; Woolley et al., 2001; Hatcher et al., 2005; Hirst et al., 2003; King et al., 2004; but see Lindner et al., 2003) and aged rats (Foley et al., 2004; Kwon et al., 2004; Hirst et al., 2006), and attenuate memory impairment induced by anticholinergic drugs (Meneses, 2001; Szczepanski et al., 2002; Hirst et al., 2003, 2006; Woolley et al., 2003). In contrast, selective 5-HT_6 receptor antagonists were ineffective at reversing disruptions of prepulse inhibition, latent inhibition, social interaction, or memory induced by NMDA receptor antagonists (Leng et al., 2003; Pouzet et al., 2002a; Woolley et al., 2004). However, a PCP-induced deficit in set-shifting was successfully reversed by a selective 5-HT_6 receptor antagonist (Rodefer et al., 2008). Disruption of some cognitive modalities by NMDA receptor antagonists may therefore depend more on 5-HT_6 receptor mechanisms than other cognitive modalities. 5-HT_6 receptor antagonism may be another mechanism underlying the different patterns of results observed with quetiapine and clozapine. Future studies exploring the effect of selective 5-HT_6 receptor antagonists on 5-CSRTT performance, both under baseline conditions and after disruption by repeated PCP administration, would be of interest.

Finally, clozapine, but not quetiapine, exerts significant antagonism at the 5-HT_7 receptor (Schmidt et al., 2001), another receptor for which altered mRNA expression levels have been reported in schizophrenia patients (East et al., 2002). Selective 5-HT_7 receptor antagonists attenuated PCP-induced disruption of prepulse inhibition in rats, although disruption of social interaction induced by PCP was unaffected (Pouzet et al., 2002b). Moreover, while PCP-induced disruption of prepulse inhibition in mice is unaltered by selective 5-HT_7 receptor antagonists, mice lacking the 5-HT_7 receptor exhibit reduced disruption of prepulse inhibition in response to PCP (Semenova et al., 2008). Actions at the 5-HT_7 receptor may therefore also mediate the different effects of quetiapine and clozapine on impulsivity and cognitive disruption after repeated PCP administration, as well as their different profiles in treating schizophrenia symptoms.

Although quetiapine did not improve the PCP-induced cognitive deficits observed in the 5-CSRTT, this medication may prove to be effective in models of deficits in other cognitive modalities or behavioral aspects known to be disrupted in schizophrenia, such as various forms of memory impairment. One study found improvement of PCP-induced deficits in spatial reference memory with subchronic quetiapine treatment (He et al., 2006). Investigations of pre-attentional sensory gating also found attenuation of PCP-induced disruption of prepulse inhibition by acute quetiapine administration (Swerdlow et al., 1996; Martinez et al., 2002). Future studies exploring the effects of quetiapine treatment on PCP-induced disruptions of tasks assessing other aspects of memory, such as working memory, or other cognitive modalities such as set-shifting, would be of considerable interest. Attenuation of deficits in these cognitive modalities may not depend as heavily on the receptor actions that are specific to clozapine, and may involve neurotransmitter systems successfully targeted by quetiapine. Moreover, investigation of other atypical antipsychotics with subtly different receptor profiles, such as olanzapine or ziprasidone, or new antipsychotics hypothesized to act predominantly through partial D_2 agonism, such as aripiprazole, may yield further insights into the role of different receptor actions in impulsivity and cognitive deficits characterizing schizophrenia, as well as how these deficits may be ameliorated.

In summary, the present results indicated that chronic quetiapine treatment does not reduce PCP-induced disruption of 5-CSRTT performance. As this model is sensitive to attenuation with chronic clozapine treatment, these findings demonstrate a difference between two atypical antipsychotic medications in their effectiveness at treating schizophrenia-like cognitive deficits. These results emphasize the importance of examining and comparing the effects of different existing antipsychotics on various cognitive measures, and of carefully assessing the full cognitive profile of putative novel antipsychotic medications.

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