Differential Long-Term Effects of Haloperidol and Risperidone on the Acquisition and Performance of Tasks of Spatial Working and Short-Term Memory and Sustained Attention in Rats

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ABSTRACT

A common feature of the neuropsychiatric disorders for which antipsychotic drugs are prescribed is cognitive dysfunction, yet the effects of long-term antipsychotic treatment on cognition are largely unknown. In the current study, we evaluated the effects of long-term oral treatment with the first-generation antipsychotic haloperidol (1.0 and 2.0 mg/kg daily) and the second-generation antipsychotic risperidone (1.25 and 2.5 mg/kg daily) on the acquisition and performance of two radial-arm maze (RAM) tasks and a five-choice serial reaction-time task (5C-SRTT) in rats during days 15–60 and 84–320 days of treatment, respectively. In the RAM, neither antipsychotic significantly affected the acquisition or performance of a spatial win shift or a delayed non-match-to-position task. Conversely, in the rats administered 5C-SRTT, haloperidol was associated with profound deficits in performance, and the subjects were not able to

progress through all stages of task acquisition. Depending on the dose, risperidone was associated with a greater number of trials to meet specific performance criteria during task acquisition compared with vehicle-treated controls; however, most subjects were eventually able to achieve all levels of task acquisition. Both haloperidol and risperidone also increased the number of perseverative and time-out responses during certain stages of task acquisition, and the response and reward latencies were slightly higher than controls during several stages of the study. These results in rats suggest that while long-term treatment with haloperidol or risperidone may not significantly affect spatial working or short-term memory, both antipsychotics can (depending on dose) impair sustained attention, decrease psychomotor speed, increase compulsive-type behaviors, and impair cognitive flexibility.

Introduction

The pharmaceuticals known as the antipsychotics rank among the most frequently prescribed medications in the United States, and they are now used to treat pediatric patients (e.g., for pervasive developmental disorder, oppositional behavior, irritability, and aggressive behaviors), young and mature adults (e.g., for schizophrenia, bipolar disease), and elderly patients (e.g., for the behavioral and psychological symptoms of dementia). Such widespread prescribing is beginning to cause controversy given the paucity of controlled clinical trial data on antipsychotics given long-term, especially in young and elderly populations (see reviews, Huybrechts et al., 2012; Seida et al., 2012).

Another controversy relates to the selection of particular antipsychotics when their use is warranted. It had been widely held (since their advent in the 1980s) that the class of antipsychotics known as the “atypicals” or “second-generation”

antipsychotics (SGAs) was preferred over the older, “typical” or “first-generation” antipsychotics (FGAs), primarily because of their lower incidence of extrapyramidal side effects. SGAs were also preferred for treatment of schizophrenia because of early reports of superior effects on negative symptoms, prevention of relapse, and increased functional capacity (see review, Miyamoto et al., 2005). The preference for SGAs over FGAs has been questioned more recently, however, because of the emergence of serious long-term side effects of SGAs (e.g., abnormal weight gain, diabetes mellitus, hyperlipidemias), cost concerns, and the results of large clinical trials, including the Clinical Antipsychotic Trials in Interventions Effectiveness (CATIE) (Lieberman et al., 2005) and the Cost Utility of the Latest APDs in Schizophrenia Study (CUtLASS) (Jones et al., 2006), which suggested that FGAs and SGAs were essentially similar when overall efficacy or tolerability were compared.

A common feature of many of the conditions for which antipsychotics are prescribed is cognitive dysfunction, yet the effects of long-term antipsychotic treatment on cognition are unclear. Most of the available clinical data regarding antipsychotics and cognition were obtained from studies of adult patients with schizophrenia. As in the case of efficacy (i.e., for

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ABBREVIATIONS: ANOVA, analysis of variance; CPT, continuous performance test; 5C-SRTT, five-choice serial reaction-time task; DNMT, delayed nonmatch to position; FGA, first-generation antipsychotic; RAM, radial-arm maze; SD, stimulus duration; SGA, second-generation antipsychotic.

positive and negative symptoms of schizophrenia) and tolerability comparisons, as described already, early reports suggesting that SGAs improved cognition in schizophrenia (and were superior to FGAs in this regard) have not been confirmed in more recent studies where randomized double-blind treatment conditions were maintained, acceptable dosing comparisons between SGAs and FGAs were made, and potential practice effects in the cognitive tasks were considered (see Goldberg et al., 2010; Hill et al., 2010). Furthermore, in the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer’s Disease study (CATIE-AD), SGAs (compared with placebo) were associated with greater rates of decline in cognitive function (Vigen et al., 2011).

When interpreting the available clinical data on the effects of antipsychotics on cognition, one major limitation has been the relatively short duration of most of the studies. Antipsychotics are often prescribed for decades to patients with neuropsychiatric disorders, yet the clinical trial evaluations of these drugs rarely exceed several months to 1 or 2 years (presumably because of the costs and challenges associated with monitoring neuropsychiatric patients for extended periods). Accordingly, multiyear, prospective clinical studies designed specifically to identify antipsychotics that have optimal effects on cognition have not been conducted. Relevant animal studies may, therefore, be especially important in this context since they are more practical for long-term, prospective treatment evaluations. To date, only a small number of animal studies have been conducted in which the long-term effects of antipsychotic treatment on cognition have been evaluated, however. These studies include experiments in which 75 days of treatment with clozapine, haloperidol, and risperidone in drinking water impaired acquisition of an eight-arm radial maze in both young and aging rats, whereas olanzapine had no effect (Rosengarten and Quartermain, 2002). In another rat study, 28 days of treatment with risperidone or haloperidol delivered with osmotic minipumps impaired working memory in a cross-maze task (Karl et al., 2006). In a rat study in which olanzapine was administered subcutaneously for 21 days, water-maze (spatial learning) impairments were observed (Didriksen et al., 2006). In previous rat studies in our laboratory, in which longer periods of treatment were evaluated (i.e., 90–180 days in drinking water), water-maze spatial-learning deficits were associated with haloperidol, chlorpromazine, risperidone, olanzapine, and ziprasidone (see reviews, Terry and Mahadik, 2007; Terry et al., 2006, 2007a,b, 2008). The purpose of the study described here was to compare the effects of long-term treatment with the FGA haloperidol and the SGA risperidone on both the acquisition and performance of tasks designed to assess spatial working or short-term memory and sustained attention in rats.

Materials and Methods

Animal Care

All procedures used during this study were reviewed and approved by the Institutional Animal Care and Use Committee and are consistent with the *International Guidelines of the Association for Assessment and Accreditation of Laboratory Animal Care*. Measures were taken to minimize pain or discomfort in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory*

Animals (NIH Publication no. 80-23), revised in 1996. Significant efforts were also made to minimize the total number of animals used while maintaining statistically valid group numbers. Male albino Wistar rats (Harlan Sprague-Dawley, Inc., Indianapolis, IN), approximately 2 months old, were housed singly in a temperature-controlled room (25°C) and maintained on a reversed 12-hour light/dark cycle with free access to water. Food (Teklad Rodent Diet 8604 pellets; Harlan) was restricted to maintain a target weight of approximately 325 g. All animals were handled daily for several minutes for 4 days before the initiation of behavioral testing.

Drug Administration

Oral antipsychotic dosing was based on previous rodent studies in our laboratory in which time-dependent behavioral and neurochemical effects were detected and plasma drug levels were achieved that approximated those often associated with antipsychotic effects in humans (see Terry et al., 2007b, 2010). Furthermore, for both haloperidol and risperidone, the doses selected (see subsequent discussion) would be expected to achieve comparable (and therapeutically) relevant dopamine D2 receptor occupancy values in vivo (i.e., in the range 65–80%; see Kapur et al., 2003) based on the work of (Barth et al., 2006). Thus, rats were treated with 1.0 or 2.0 mg/kg daily of haloperidol (4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one; Sigma-Aldrich, St. Louis, MO) or 1.25 or 2.5 mg/kg daily of risperidone (4-[2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-1-piperidyl]ethyl]-3-methyl-2,6-diazabicyclo[4.4.0]deca-1,3-dien-5-one; Pfizer, Inc., New York, NY) orally for a period of 320 days ($n = 8$ –10 per treatment group). The antipsychotics were dissolved in 0.1 M acetic acid and subsequently diluted (1:100) with distilled, deionized water for daily drug administration in drinking water. Drug dosing was based on the average daily fluid consumption and the weight of the animals.

Behavioral Testing

Study subjects were transferred (in their home cages) to the behavioral testing rooms each morning approximately 30 minutes before the beginning of experiments.

Radial-Arm Maze Procedures. Beginning on day 15 of antipsychotic treatment, radial-arm maze testing (as we have described previously; see Terry et al., 2008) began using two Med Associates (MED-RAM-1R; St. Louis, MO) computer-automated, eight-arm radial mazes consisting of a central octagonal hub (arena) with automatic guillotine doors connected to aluminum arms (8.9 cm wide) radiating distally (45.7 cm long). Infrared photo-beam sensors are positioned at the entrance to each runway, and a food-pellet receptacle and head-entry detector were positioned at the end of each runway. The mazes were positioned approximately 90 cm above the floor in a testing room with a number of extra-maze cues (composed of large geometrical shapes).

Habituation phase. Test subjects were given two 15-minute free exploration (habituation) sessions before the Monday in which the win-shift portion of testing was conducted. This was done so that the animals became acquainted with the radial-arm maze apparatus, as well as the handling procedures associated with it. Reinforcement food pellets (45 mg; Dustless Precision Pellets; Bioserve, Frenchtown, NJ) were scattered randomly around the entire maze area during this session.

Acquisition (win-shift training). After the habituation phase, subjects were trained in a win-shift procedure. A trial began when the experimenter placed the test subject into the central octagonal arena. After a 60-second delay, all guillotine doors were raised, allowing access to all eight arms. When the animal broke a photo beam in the pellet receptacle at the end of each runway, a reward pellet was delivered once. When the rat moved back into the central arena, all doors closed for 5 seconds and then reopened. All reentries into an arm that had previously delivered a reward were scored as working memory errors. All animals were trained in win-shift (maze eight) for a minimum of

10 days. At the end of 10 days, animals advanced to the delayed nonmatch-to-position version (see "Delayed nonmatch to position" in the paragraph below) if the criterion was met. Criterion of win-shift was completion of the task within the time limit (15 minutes) on 4 consecutive days with two or fewer errors.

Delayed nonmatch to position. Testing began with an information (forced four) session in which four of the eight arms were blocked. This session ended when all four arms were visited or when the trial timed out (15 minutes). The animal remained in the testing room for the delay period. In the "free eight" (retention) test session, all eight arms were accessible; however, food reinforcement occurred only at the ends of the arms not visited in the previous information session. The test session continued until all four of the previously blocked arms were visited or until 15 minutes elapsed. The number of arm entries was recorded, along with two types of errors: reference-memory and working-memory errors. After the second (test) session in each trial block, the animal was returned to its home cage in the housing facility until the next day's information session. Animals were trained for a minimum of 10 days at a 15-minute delay between the forced four and the free eight sessions. When a criterion of 4 consecutive days with one error or no errors during the free eight sessions, animals advanced to longer delays of 1, 3, and 6 hours. Each longer delay (along with additional 15-minute delay sessions) was randomly presented twice.

Five-Choice Serial Reaction-Time Task. Training and testing in five-choice serial reaction-time task (5C-SRTT) was initiated on day 84 of antipsychotic treatment and conducted using six ventilated, sound-attenuated operant chambers (Med Associates) as we have described previously (Terry et al., 2012). Each operant chamber consisted of nine nose pokes or apertures, four of which were closed off with metal inserts, leaving every other nose poke available (2.5 cm wide, 4 cm deep). The apertures were arranged on a curved panel 2 cm above the floor of the chamber and were equipped with a photocell beam to detect nose pokes. There was a lamp (2.8 W) on the rear wall of each aperture that could be illuminated randomly and for varying durations. Food pellets (45 mg of Dustless Precision Pellets; Bio-Serv) were delivered automatically to a magazine on the opposite wall to the nose pokes. A light inside the food magazine was also turned on to indicate that a pellet (45 mg of chow pellet; Bio-Serv) had been dispensed. The food magazine was equidistant from all nose-poke apertures. There was a house light that remained on for the entire session unless an error or omission occurred; the light was located toward the roof of the operant chamber above the magazine. The apparatus was controlled using MedPC software (Med Associates).

Training and testing procedures. During each session, the rat was trained to push the food magazine to initiate a trial. Five seconds later, one of the five nose-poke apertures was lit for a specified stimulus length (e.g., 1 second). The rat was then trained to quickly respond with a nose poke in the hole in which the stimuli was just presented (correct response). The stimuli were presented across the five possible nose-poke apertures in a pseudorandom order. Each correct response was rewarded with a food pellet, and each failure to respond (omissions, longer than 5 or 10 seconds post stimuli presentation, depending on the stimulus duration) or incorrect response (response in aperture that was not lit by light stimulus) was punished with a 10-second time-out with no access to a food pellet.

The following parameters were measured to assess performance: % correct = [no. correct/(no. correct + no. incorrect)] $\times$ 100; % omissions = [no. omissions/(no. trials completed)] $\times$ 100; no. of premature responses (impulsivity) = the no. of responses made after a trial began but before onset of the light stimulus (i.e., during the 5-second intertrial interval); the number of perseverative responses (compulsivity) = the number of nose pokes made after the correct response was made (i.e., in same aperture) but before collecting the reward. The number of timeout responses = the number of nose pokes made in any aperture during a timeout period; latency to correct = time elapsed (in seconds) from the onset of the light stimulus to making the correct

nose-poke response; latency to incorrect = time elapsed (in seconds) from the onset of the light stimulus to making the incorrect nose-poke response; latency to reward = time elapsed (in seconds) from making a correct nose-poke response to retrieving the food reward from the magazine.

Animals ($n = 8$ –10 per treatment/vehicle group) moved through a series of five criterion points to complete the task. Subjects were exposed to 100 trials each day 5 days/week with a session length limited to 30 minutes. The criterion points consisted of 10-second stimulus length and 10-second response time; 5-second stimulus time/5-second response time; 2.5-second stimulus/5-second response time; 1-second stimulus/5-second response time; and 0.5-second stimulus/5-second response time. Criterion was defined as 5 consecutive days at 90% or greater correct responses for the first three stimulus durations but was decreased to 75% or greater for the last two stimulus durations. Animals were allowed a maximum of 150 days to reach and complete the final criterion phase. If an animal tested for 80 days at any one phase without progressing, it was discontinued from the task and the number of sessions to criterion was recorded as 80.

Statistical Analyses

Statistical analysis was performed using Sigma Plot 11.2 (Systat Software, Inc, San Jose, CA) and SAS 9.3 (SAS Institute Inc. Cary, NC), and statistical significance was assessed using an α level of 0.05. For all two-factor comparisons (i.e., treatment, test session) in the RAM and 5C-SRTT studies, a mixed-model analysis of variance (ANOVA, with repeated measures) was used followed by the Student-Newman-Keuls method for post hoc analysis. For the various stages of task acquisition in the 5C-SRTT, χ^2 or Fisher's exact tests (if the assumptions to the χ^2 test were violated) were used to examine differences between treatment groups within stimulus duration of the proportion of subjects meeting criteria. To compare each treatment with vehicle, χ^2 or Fisher's exact tests were used, and a Bonferroni adjustment to the overall α level was used to control for the number of comparisons within the stimulus level. To examine differences in the number of days (sessions) to meet criteria by treatment group and stimulus duration, a repeated-measures mixed model was used and included the main effects of treatment group, stimulus duration, and the two-factor interaction between treatment group and stimulus duration. Post hoc pairwise comparisons were performed using a Bonferroni adjustment to the overall α level for the number of comparisons made.

Results

Long-Term Treatment with Haloperidol or Risperidone Does Not Alter Radial Arm Maze Acquisition or Performance

Win-Shift Acquisition. Figure 1A illustrates the effects of risperidone and haloperidol on the acquisition of a win-shift task in a computer-automated, eight-arm radial-arm maze. There was no main effect of treatment on the number of errors committed ($P = 0.29$), nor was there a significant treatment by session interaction ($P = 0.35$). There was a significant effect of the day of testing ($F_{10,692} = 35.16$, $P < 0.001$), indicating that the test subjects in all treatment groups improved as they completed more test sessions. There were also no significant treatment-related differences in the number of sessions required to reach criterion ($P = 0.72$) (see Fig. 1A, inset).

Delayed Nonmatch-to-Position. The results of the delayed nonmatch to position (DNMTP, also referred to as a delayed spatial win-shift task) (see Taylor et al., 2003) training at 15-minute delays are presented in Fig. 1B. There

Fig. 1. Antipsychotic effects on radial-arm maze performance conducted during days 15–60 of treatment. (A) Win-shift acquisition over 10 consecutive days of testing as assessed by the number of errors per session (mean $\pm$ S.E.M.). Inset: Win-shift acquisition as assessed by the number of trials to reach a predetermined criterion (mean $\pm$ S.E.M.), defined as four consecutive sessions with two or fewer total errors. (B) Acquisition of a DNMTT task at 15-minute delays as assessed by the number of trials to criterion (mean $\pm$ S.E.M.), defined as one error or none for four consecutive sessions during the free eight sessions. (C) Delay dependent performance of the DNMTT task as assessed by the number errors per session (mean $\pm$ S.E.M.).

were no significant treatment-related differences in the number of sessions to reach criterion ($P = 0.80$). Likewise, there were no significant differences in the number of errors committed (i.e., combination of working and reference memory errors, $P = 0.50$, see below), nor was there a significant treatment by day interaction on errors made across groups ($P = 0.26$, data not shown). With the introduction of longer delays (Fig. 1C), the number of errors increased in all treatment groups ($F_{3,224} = 32.53$; $P < 0.001$); however, there were no significant treatment-related differences ($P = 0.18$), nor was there a significant treatment by delay interaction ($P = 0.63$). It should be noted that in this portion of the study, the clear majority of the errors made were reference memory errors (entries into unbaited arms that were active during the previous information session). Working memory (reentries into an arm that had previously delivered a reward during the retention session) and reference memory errors were analyzed separately as well as combined (total errors as illustrated in the figures). The same results (no significant treatment related differences) were observed.

Long-Term Treatment with Haloperidol or Risperidone Is Associated with Alterations in the Acquisition and Performance of a 5C-SRTT

Achievement of Training Criteria. The effects of long-term treatment with haloperidol and risperidone on the proportion of subjects meeting the predefined performance criteria (see *Materials and Methods*) and the number of test sessions required to meet criteria at each stimulus duration in a 5C-SRTT are illustrated in Table 1, which indicates a lower proportion of animals reaching criteria compared with vehicle-treated controls within stimulus duration (descriptive statistics by treatment group and stimulus duration, $P < 0.0125$, Bonferroni adjusted post hoc α level). For the number of sessions required to reach criterion, a repeated-measures,

mixed-model indicated a highly significant main effect of treatment ($F_{4,13} = 16.57$, $P < 0.0001$), a significant effect of the stimulus duration ($F_{4,9} = 6.53$, $P = 0.01$), with a non-significant treatment $\times$ stimulus duration interaction ($F_{12,9} = 1.21$, $P = 0.40$). Post hoc analysis indicated that within the 10-second stimulus duration, both haloperidol treatment groups required a greater mean number of days (sessions) to achieve criteria ($P = 0.002$ and $P < 0.0001$ for haloperidol 1.0 and 2.0, respectively). At the 5-second stimulus duration, both doses of haloperidol and the higher dose of risperidone were associated with a greater mean number of days to achieve criteria ($P = 0.0001$, $P < 0.0001$, and $P = 0.003$ for 1.0 and 2.0 mg/kg daily of haloperidol; 2.5 mg/kg daily of risperidone, respectively).

For each of the 5C-SRTT performance measures described below, the results of the first 10 individual days of training are provided (to illustrate the initial acquisition of the task), followed by the mean of the first 5 days of testing at each of the lower stimulus durations (SDs).

Accuracy (Percent Correct). The effects of long-term treatment with haloperidol and risperidone on accuracy across the various stimulus durations are illustrated in Fig. 2 (top row, left column) and Fig. 3 (top row). Although performance in the subjects treated with the higher dose of haloperidol (2.0 mg/kg per day) was slightly inferior to that of control subjects at the 10-second stimulus duration, the percentage of correct nose pokes increased progressively in all treatment groups over the course of the first 10 sessions of training. As indicated in Table 1, however, the number of test sessions required to reach criteria (five consecutive sessions at 90% correct or higher) was clearly greater in both haloperidol treatment groups compared with vehicle controls, and (in fact) only two of the eight subjects administered the 2.0 mg/kg daily dose actually met the criteria. Therefore, rats administered the higher dose of haloperidol were not able to progress past this stimulus duration. At the 5.0-second stimulus duration, the following observations were made:

TABLE 1

Five-choice serial reaction time task (5C-SRTT) acquisition data

Treatment Group	N	Stimulus Duration				
		10.0 s	5.0 s	2.5 s	1.0 s	0.5 s
Proportion of Test Subjects Meeting Criteria						
Vehicle	10	1.00	1.00	1.00	1.00	0.60
Haloperidol 1.0 mg/kg/day	9	0.89	0.33*	0.22*	0.11*	na
Haloperidol 2.0 mg/kg/day	8	0.25*	0.00*	Na	na	na
Risperidone 1.25 mg/kg/day	8	1.00	0.88	0.75	0.75	0.50
Risperidone 2.5 mg/kg/day	8	1.00	0.75	0.75	0.75	0.38
No. of Test Sessions Required to Reach Criteria, Mean (S.D.)						
Vehicle	10	13.10 (3.70)	7.20 (1.87)	11.60 (8.02)	10.80 (11.48)	40.60 (28.73)
Haloperidol 1.0 mg/kg/day	9	39.11 (23.87)**	60.00 (28.49)***	30.67 (43.14)	45.50 (48.79)	na
Haloperidol 2.0 mg/kg/day	8	64.50 (28.72)***	80.00 (0.00)***	Na	na	na
Risperidone 1.25 mg/kg/day	8	14.25 (5.34)	32.88 (29.19)	32.14 (26.60)	8.50 (4.28)	26.67 (11.72)
Risperidone 2.5 mg/kg/day	8	15.75 (9.15)	49.00 (29.66)**	27.67 (11.20)	15.67 (6.65)	41.33 (27.29)

na, not applicable since test subjects at this antipsychotic dose did not advance from the previous stimulus duration; s, second.

* $P < 0.0125$; ** $P < 0.01$; *** $P < 0.001$, significantly different from vehicle-treated control performance.

Accuracy was impaired in all the remaining antipsychotic treatment groups during the first five test sessions, and the number of trials required to achieve criteria (five consecutive sessions at 90% correct or higher) was significantly higher in all treatment groups compared with controls) except those administered 1.25 mg/kg of risperidone daily. Accuracy was also slightly (but significantly) impaired in subjects administered the higher (2.0 mg/kg) daily dose of risperidone at the 2.5- and 1.0-second stimulus durations. Note: Haloperidol (2.0 mg/kg daily) is not illustrated at the 5-second stimulus duration since the subjects did not progress to this level. Likewise, most subjects administered the 1.0 mg/kg daily dose of haloperidol did not progress past the 5-second stimulus

duration, and thus this dose is not depicted in the figures where shorter stimulus durations are presented.

Premature Responses. The effects of long-term treatment with haloperidol and risperidone on the number of premature responses across the various stimulus durations are illustrated in Fig. 2 (middle row, left column) and Fig. 3 (middle row). There were no statistically significant differences in premature responses noted across the treatment groups.

Perseverative Responses. Antipsychotic effects on the number of perseverative responses across the various stimulus durations are illustrated in Fig. 2 (middle row, center column) and Fig. 3 (bottom row). As illustrated, during the

Fig. 2. Antipsychotic effects on the initial acquisition of a five-choice serial reaction-time task conducted during days 84–320 of treatment. Rats were treated with vehicle (VEH), haloperidol (HAL), or risperidone (RISP) in their drinking water (doses listed are in milligrams per kilogram per 24 hours) and then trained to meet specific performance criteria (explained in the text). The individual graphs show the first 10 sessions of training at the 10-second stimulus duration (SD). Each symbol represents the mean $\pm$ S.E.M. for each test group. The following performance measures are illustrated: accuracy (% Correct), percentage of omissions (% Omissions), premature responses (Prem Resp), perseverative responses (Persev Resp), time-out responses (Timeout Resp), response latencies associated with correct choices (Latency-C), incorrect choices (Latency-I), and with nose pokes into the food hopper to obtain rewards (Latency-RW). Abbreviated antipsychotics with a dose and an asterisk (e.g., HAL 2.0*) indicate a significant difference ($P < 0.05$) between the antipsychotic dose represented and the vehicle-associated performance level (main effect across sessions). The statistical test used was repeated-measures ANOVA.

Fig. 3. Antipsychotic effects on the acquisition of a five-choice serial reaction-time task conducted during days 84–320 of treatment as stimulus durations (SDs) decreased. Rats were treated with vehicle (VEH), haloperidol (HAL), or risperidone (RISP) in their drinking water (doses listed are milligrams per kilogram per 24 hours) and then trained to meet specific performance criteria (explained in the text). The individual histograms show the mean $\pm$ S.E.M. of the first five sessions of training at each SD that followed the initial (10-second SD) training sessions (i.e., 5 seconds down to 0.5 seconds; see top of figure). The following performance measures are illustrated: accuracy (% Correct), premature responses (Prem Resp), and perseverative responses. * $P < 0.05$ indicates a significant difference between the antipsychotic dose represented and the vehicle-associated performance level (main effect across sessions). The statistical test used was repeated measures AVOVA. Note: For the haloperidol treatment groups, only the 1.0 mg/kg dose is shown for the 5-second stimulus duration since the remaining subjects failed to meet the training criteria (see *Materials and Methods*) at 5 seconds or shorter SDs and, therefore, did not progress past this level.

first 10 sessions of training, both doses of haloperidol were associated with a significantly greater number of perseverative responses compared with vehicle controls. This effect of haloperidol was also present at the 5-second stimulus duration with the 1.0 mg/kg daily dose. Risperidone (either the 2.5 or both the 2.5 and 1.25 mg/kg daily doses) was also associated with a greater number of perseverative responses at the 5.0-, 2.5-, and 1.0-second stimulus durations.

Time-Out Responses. The effects of the antipsychotics on the number of time-out responses across the various stimulus durations are illustrated in Fig. 2 (middle row, right column) and Fig. 4 (top row). At the beginning of 5C-SRTT training (at the 10-second stimulus duration), the number of timeout responses began relatively high (40–60), was not statistically different between the treatment groups, and progressively decreased over the course of the first 10 sessions. At the 5-second stimulus duration, the number of time-out responses was higher (compared with vehicle controls) in the subjects administered 1.0 mg/kg daily dose of haloperidol, as well as those administered 1.25 or 2.5 mg/kg risperidone daily. In addition, both doses of risperidone were associated with increases in time-out responses at the 1.0-second stimulus

duration; the 2.5 mg/kg daily dose of risperidone was also associated with increases in time-out responses at the 0.5-second stimulus duration.

Response Latencies. The response latencies associated with correct and incorrect responses and with collecting food rewards across the various stimulus durations are illustrated in Fig. 2 (bottom row) and Table 2. At the beginning of 5C-SRTT training (at the 10-second stimulus duration), the latencies (for both correct and incorrect responses) began around 3.5–5.0 seconds and progressively decreased over the course of the first 10 sessions. For correct choices, response latencies were slightly elevated in all antipsychotic groups (compared with vehicle controls) at the 10.0-, 5.0-, and 2.5-second stimulus durations. At the lower (i.e., 1.0 and 0.5 seconds) stimulus durations, where only risperidone-treated subjects remained, no significant differences from control were noted. For incorrect choices, only the 2.0 mg/kg daily dose of haloperidol (at the 10-second stimulus duration) was associated with higher response latencies. At the beginning of 5C-SRTT training (at the 10-second stimulus duration), the reward latencies began around 6.0–10.0 seconds and progressively decreased over the course of the first 10 sessions.

Fig. 4. Antipsychotic effects on the acquisition of a five-choice serial reaction-time task conducted during days 84–320 of treatment as stimulus durations (SDs) decreased. Rats were treated with vehicle (VEH), haloperidol (HAL), or risperidone (RISP) in their drinking water (doses listed are milligrams per kilogram per 24 hours) and then trained to meet specific performance criteria (explained in the text). The individual histograms show the mean $\pm$ S.E.M. of the first five sessions of training at each SD that followed the initial (10-second SD) training sessions (i.e., 5 seconds down to 0.5 seconds; see top of figure). The following performance measures are illustrated: time-out responses (Timeout Resp), percentage of omissions (% Omissions). * $P < 0.05$ indicates a significant difference between the antipsychotic dose represented and the vehicle-associated performance level (main effect across sessions). The statistical test used was repeated-measures ANOVA. Note: For the haloperidol treatment groups, only the 1.0 mg/kg dose is shown for the 5-second stimulus duration since the remaining subjects failed to meet the training criteria (see *Materials and Methods*) at the 5-second or shorter SDs and, therefore, did not progress past this level.

As illustrated, both doses of haloperidol and the higher dose of risperidone were associated with slightly higher latencies to collect food rewards (compared with vehicle controls) at all stimulus durations for which treatment effects were compared.

Omissions. The percents of omissions across the various stimulus durations are illustrated in Fig. 2 (top row, center column) and Fig. 4 (bottom row). At the beginning of 5C-SRTT training (at the 10-second stimulus duration),

omissions in all treatment groups were relatively high (~60) but progressively decreased over the course of the first 10 sessions. Statistical comparisons indicated the following: omissions were higher (compared with control) in subjects administered 2.0 mg/kg haloperidol daily at the 10-second stimulus duration, 2.0 mg/kg haloperidol daily, both doses of risperidone at the 5.0-second stimulus duration, and both doses of risperidone at the 2.5-second stimulus duration.

TABLE 2

Effects of haloperidol and risperidone on response latencies at different stimulus durations in the five-choice serial reaction-time task

Data are presented as mean $\pm$ S.E.M.

Treatment	Latency Type	Stimulus Duration			
		5.0 s	2.5 s	1.0 s	0.5 s
	Correct Response				
Vehicle		1.10 ± 0.06	0.98 ± 0.03	0.70 ± 0.02	0.68 ± 0.03
Risperidone 1.25 mg/kg		1.41 ± 0.07*	1.14 ± 0.04*	0.72 ± 0.05	0.77 ± 0.06
Risperidone 2.5 mg/kg		1.50 ± 0.04*	1.16 ± 0.04*	0.86 ± 0.07	0.76 ± 0.07
Haloperidol 1.0 mg/kg		1.48 ± 0.09*	na	na	na
	Incorrect Response				
Vehicle		0.71 ± 0.04	1.03 ± 0.16	2.19 ± 0.12	1.96 ± 0.09
Risperidone 1.25 mg/kg		1.00 ± 0.04	1.50 ± 0.27	2.43 ± 0.10	2.21 ± 0.10
Risperidone 2.5 mg/kg		0.90 ± 0.08	1.63 ± 0.26	2.37 ± 0.14	2.07 ± 0.18
Haloperidol 1.0 mg/kg		0.92 ± 0.07	na	na	na
	Reward				
Vehicle		1.23 ± 0.06	1.24 ± 0.08	1.22 ± 0.07	1.20 ± 0.09
Risperidone 1.25 mg/kg		1.45 ± 0.10	1.47 ± 0.16	1.28 ± 0.08	1.24 ± 0.08
Risperidone 2.5 mg/kg		1.92 ± 0.22*	2.21 ± 0.17	2.04 ± 0.22*	1.92 ± 0.27*
Haloperidol 1.0 mg/kg		2.98 ± 0.38*	na	na	na

na, not applicable (test subjects at this antipsychotic dose did not advance from the previous stimulus duration. S, second.

* $P < 0.05$; significant difference from vehicle-treated group.

Discussion

The results of this study can be summarized as follows: 1) in the RAM, neither antipsychotic agent significantly affected the acquisition or performance of a win-shift or DNMTT task; 2) in the 5C-SRTT, haloperidol was associated with profound deficits in performance, and none of the test subjects was able to progress through all stages of task acquisition; 3) risperidone was associated with a greater number of trials to meet specific performance criteria during task acquisition compared with controls, but most subjects were able to achieve all levels of task acquisition; and 4) both haloperidol and risperidone increased the number of perseverative and time-out responses during certain stages of task acquisition, and the response and reward latencies were slightly higher than for controls in several phases of the study.

The first observation (lack of antipsychotic effects in the RAM) was somewhat surprising, given the aforementioned study where 75 days of treatment with haloperidol and risperidone in drinking water impaired RAM acquisition in both young and aging rats (Rosengarten and Quartermain, 2002). In our study, the length of previous drug exposure was shorter (testing began after 15 days of treatment vs. 75 days), and there were some differences in the test apparatus between the studies that could have resulted in differences in task difficulty. For example, the arm widths and lengths were 12 and 60 cm, respectively, in the Rosengarten and Quartermain studies compared with 8.9 and 45.7 cm, respectively, in our study. Other possible sources of the disparate results could include differences in intramaze and extramaze cues and differences in the strain of rats tested (Fisher 344 in the Rosengarten and Quartermain study compared with Wistar rats in our study). It is important to note, however, that in a previous study in our laboratory using a 12-arm RAM with arms 10 cm wide and 70 cm long (with testing begun during washout after a 90-day drug exposure period in Wistar rats), neither haloperidol nor risperidone affected the number of working or reference memory errors compared with vehicle-treated controls (Terry et al., 2007a).

In the second phase of this study, we were interested in the effects of long-term antipsychotic treatment on the acquisition and performance of a task of sustained attention in rats. Among the variety of cognitive deficits reported in schizophrenia patients (who are often administered antipsychotics long-term), impairments in sustained attention, as assessed by the continuous performance test (CPT) (Beck et al., 1956), are a relatively consistent observation (Nuechterlein and Dawson, 1984; Cornblatt and Keilp, 1994) and often persist during both active psychotic episodes and periods of remission. Hence, we used the rodent 5C-SRTT (Robbins 2002), which is thought to model the human CPT. In the 5C-SRTT, attention and inhibitory response control (thought to be a form of executive functioning) is indexed by the accuracy measurement. Our first notable observation was that haloperidol markedly impaired performance of the 5C-SRTT so that subjects were not able to progress through many stages of task acquisition. Risperidone was also associated with a greater number of trials to meet specific (accuracy-related) performance criteria; however (as noted already), most subjects eventually achieved all levels of task acquisition, suggesting that risperidone may be superior to haloperidol in terms of sustained attention.

Another notable observation in the 5C-SRTT experiments was that both antipsychotics increased perseverative responses (i.e., a repeated nose poke into the same aperture after a correct response), as well as time-out responses (i.e., nose pokes made during the time-out interval, which occurred after an incorrect response or an omission) during certain stages of task acquisition. Perseverative responses in the 5C-SRTT are generally interpreted as a form of compulsive-like behavior. Time-out responses have been suggested to represent both a form of compulsive-like behavior and cognitive inflexibility (i.e., the inability to alter behavior in reaction to changing situational demands, in this case, disorganized responses that are not tied to the stimulus presentation; see Amitai and Markou, 2010). These observations in animals suggest that cognitive inflexibility, which is likely innate in many patients suffering from schizophrenia and other mental health disorders (see Amitai and Markou, 2010), could be exacerbated by long-term antipsychotic exposure.

The modest increases in response latencies, reward latencies, and omissions in several portions of the study (i.e., observed in all antipsychotic-treated groups, depending on the dose and the phase of task acquisition) suggest that the drug effects on 5C-SRTT acquisition (which was based primarily on accuracy-related performance criteria) may have been due in part to alterations in signal detection, psychomotor speed, or more overt effects on motor function or reward motivation. To argue against the last possibility, it is important to note that omissions were relatively low (less than 15% for most phases of the study) and the reward latencies typically were well below 3 seconds for most phases of the study.

Our results with haloperidol in the 5C-SRTT are in general agreement with another study in rats in which the FGA was administered for 3 months (i.e., injected daily 45 minutes before behavioral testing) and found to disrupt sustained attention and to increase response latencies, as well as the number of omissions (Brockel and Fowler, 1995). Interestingly, in a task designed to maximize attention and minimize movement requirements, haloperidol (administered short-term) increased errors of omission and reaction time; however, the lack of a significant correlation between these two measures suggested that attentional accuracy may be independent of the motor-slowness effect (Skjoldager and Fowler, 1991). A more recent study found that both haloperidol and risperidone (administered short-term) impaired sustained attention in an operant visual-signal detection task and that both antipsychotics increased response latencies, whereas haloperidol (but not risperidone) increased the rate of response omissions (Rezvani and Levin, 2004).

The 5C-SRTT studies suggest that long-term exposure to either haloperidol or risperidone may lead to performance deficits of tasks that require sustained attention, especially those that require rapid response times and motor actions (i.e., deficits that could have important implications for a number of day-to-day activities in psychiatric patients). Notably, concerns have been raised about the higher rate of automobile accidents (and the potential involvement of antipsychotics) in psychiatric patients, who often demonstrate psychomotor impairment (see Brunner et al., 2004).

Collectively, the results of the animal experiments described here may be especially important given the limitations of the available clinical studies, which often were of

relatively short duration, conducted in small numbers of patients, and not placebo controlled (especially in schizophrenia), thus making it difficult to distinguish drug effects from disease symptoms. Moreover, the clinical studies have often yielded equivocal results. For example, one older study found that long-term haloperidol treatment impaired spatial working memory in schizophrenic smokers (Levin et al., 1996); however, the test subjects were deprived of cigarettes at the time of cognitive testing, introducing the potential confound of the withdrawal effects of nicotine. In a more recent study, risperidone was found to improve spatial working memory compared with haloperidol; however, this superiority was eliminated when the confounding effects of the anticholinergic benztropine (administered adjunctively with haloperidol) were considered (McGurk et al., 2004). Other studies in subjects with schizophrenia have documented both improvements (McGurk et al., 2005) and impairments (Reilly et al., 2006) in spatial working memory associated with long-term risperidone treatment. The clinical effects of antipsychotics on sustained attention also appear to be equivocal. For example, although both a 12-week (Liu et al., 2000) and 2-year (Green et al., 2002) comparison of haloperidol and risperidone on performance of a CPT found no significant drug-related effects, Chen et al. (2004) reported plasma concentration-dependent impairments in the CPT associated with risperidone and its active metabolite 9-hydroxy-risperidone after 1 year of exposure.

The current study has some limitations that should be discussed. As noted in *Materials and Methods*, the dosing approach in drinking water was based on previous studies in which plasma antipsychotic levels fit in the range associated with therapeutic responses in schizophrenia patients. However, only the 2.0 and 2.5 mg/kg doses of haloperidol and risperidone, respectively, were evaluated, and it is unclear whether the lower doses (1.0 and 1.25 mg/kg) behaviorally tested here would generate therapeutic plasma levels. Furthermore, the doses used in very young and elderly patients are generally lower than those used in adult schizophrenic patients, and therefore, it is unclear whether the behavioral effects described here would be relevant for these patient populations. Finally, this study was conducted in normal Wistar rats, so it is unclear whether similar antipsychotic effects would be observed in neuropsychiatric disease-related animal models. The differential sensitivity to the antipsychotics in the RAM versus the 5C-SRTT may be due at least in part to the longer exposure times in the 5C-SRTT. Although (as noted already herein) we evaluated antipsychotic exposure times up to 90 days in the RAM, we have not evaluated exposure times as long as those that were evaluated in the 5C-SRTT in this study (i.e., 84–320 days). An additional possibility for the differential drug sensitivity is the nature of the behavioral tasks (i.e., free exploration and foraging behaviors in the RAM versus nose-poke (operant-based) behaviors in 5C-SRTT, where the environment is more restrictive). It is thus interesting to speculate that the more natural (ethologically relevant) RAM may simply be less difficult to master and therefore less sensitive to drug impairment.

In conclusion, the results of this study in rats suggest that whereas long-term treatment with haloperidol or risperidone may not significantly affect spatial working or short-term memory, both antipsychotics can impair sustained attention (in a dose-dependent manner), decrease psychomotor speed,

increase compulsive-type behaviors, and impair cognitive flexibility. Given the widespread use of these agents across multiple neuropsychiatric disorders and patient populations, such long-term effects observed in animals should be considered.

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Authorship Contributions

Participated in research design: Hutchings, Terry.

Conducted experiments: Hutchings.

Performed data analysis: Hutchings, Waller, Terry.

Wrote or contributed to the writing of the manuscript: Hutchings, Waller, Terry.

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