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## Long-term impacts of adolescent risperidone treatment on behavioral responsiveness to olanzapine and clozapine in adulthood

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### Abstract

This preclinical study investigated how a short-term risperidone treatment in adolescence impacts antipsychotic response to olanzapine and clozapine in adulthood. Antipsychotic effect was indexed by a drug's suppressive effect on avoidance responding in a rat conditioned avoidance response (CAR) model. Male adolescent Sprague-Dawley rats were first treated with risperidone (1.0 mg/kg, sc) or sterile water and tested in the CAR model for 5 consecutive days from postnatal days P 40 to 44. After they became adults (~P 80–84), they were switched to olanzapine (0.5 mg/kg, sc), clozapine (5.0 mg/kg, sc) or vehicle treatment and tested for avoidance for additional 5 days. During the adolescent period, repeated risperidone treatment produced a persistent inhibition of avoidance response. Throughout the 5 days of adulthood drug testing, rats previously treated with risperidone in adolescence made significantly fewer avoidance responses than the vehicle ones when they all were switched to olanzapine, indicating a risperidone-induced enhancement of behavioral sensitivity to olanzapine. In contrast, when switched to clozapine, rats previously treated with risperidone made significantly more avoidance responses than the vehicle rats, indicating a risperidone-induced decrease of behavioral sensitivity to clozapine. Performance in the prepulse inhibition of acoustic startle response in adulthood was not altered by adolescent risperidone treatment. Collectively, adolescent risperidone exposure induced a long-term change in behavioral sensitivity to other atypical antipsychotic drugs, with the specific direction of change (i.e. increase or decrease) dependent on the drug. These long-lasting changes are likely mediated by drug-induced neuroplastic changes and may also have significant clinical implications for antipsychotic treatment of chronic patients with an early onset of psychotic symptoms.

### Keywords

Risperidone; Olanzapine; Clozapine; Conditioned avoidance response; Adolescence; Sensitization

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## 1. INTRODUCTION

Adolescence (human: 10–19 years old; rats: 35–60 days old) (Andersen et al., 2000) is a period in which the brain and various psychological functions undergo dramatic transitions. It is also the time when symptoms of a variety of severe mental disorders often manifest. Accumulating evidence indicates that adolescents may have enhanced sensitivity to psychotropic drugs (Findling et al., 2010, Kumra et al., 2008, Sikich et al., 2008), and pharmacological interventions during this period alter brain structure and function in ways that are detectable at multiple levels (Singh and Chang, 2012). Such alterations are often long-lasting and could alter the trajectory of the brain and behavioral development of pediatric patients, which in turn may change their later response to drug treatment as adults. As pediatric treatment is administered at a critical period of rapid brain and behavioral development, there is a crucial need to evaluate the possible long-term impacts of antipsychotic medications in adolescence on psychological functions and drug response, and to identify the neurobiological mechanisms.

In recent years, we have focused our attention on the issue of how early antipsychotic exposure in adolescence modifies later behavioral responsiveness to antipsychotic re-exposure in adulthood (Qiao et al., 2013). We have used the conditioned avoidance response (CAR) model, a validated animal test of antipsychotic activity (Wadenberg and Hicks, 1999), to examine this issue. The general approach follows our previous adult CAR work which involves two phases of drug effect assessment: an induction phase and an expression phase (Feng et al., 2013, Li et al., 2012b, Li et al., 2010, Mead and Li, 2010, Swalve and Li, 2012, Zhang and Li, 2012). In the induction phase, rats are repeatedly treated with an antipsychotic drug or vehicle for a certain number of days (e.g. 5 or 7 days), and the drug's suppressive effect on avoidance response is recorded daily. In the expression phase, all rats are given a challenge dose of the drug and tested for avoidance response. This paradigm allows us to reveal that antipsychotic efficacy (as indexed by a drug's suppressive effect on avoidance response) can be increased or decreased with only 5 days of repeated drug treatment in adolescence. Specifically, we found that adolescent olanzapine treatment makes animals more sensitive to olanzapine re-exposure when they become adults (termed olanzapine sensitization), whereas clozapine treatment in adolescence makes animals less sensitive to clozapine re-exposure in adulthood (termed clozapine tolerance) (Qiao, Li, 2013). These findings have been validated in the PCP-induced hyperlocomotion model (Shu et al., accepted) – another behavioral test of antipsychotic activity (Millan et al., 1999, Sun et al., 2009).

In our adult rat studies, we have also found a cross-sensitization between haloperidol and olanzapine (Li et al., 2007, Mead and Li, 2010). Specifically, rats that had been treated with haloperidol showed enhanced sensitivity to the avoidance disruptive effect of olanzapine, and vice versa. A cross-sensitization was also found from risperidone to olanzapine, as rats previously treated with risperidone (1.0 mg/kg) showed stronger reactivity to the avoidance-disruptive effect of olanzapine (Zhang et al., 2011). Recently, we further demonstrated a cross-sensitization from aripiprazole to olanzapine (Qin et al., 2013). These findings, together with many from drug discrimination studies (Porter and Prus, 2009), suggest that there is a common mechanism underlying sensitization effects induced by various antipsychotics despite their different chemical structures and receptor binding profiles.

If cross-sensitization is a general principle associated with antipsychotic sensitization, one would expect to ascertain it in adult rats that have experienced an antipsychotic drug earlier when they were still adolescents. The present study reports our investigation of the possible cross-sensitization from risperidone to olanzapine and clozapine in the CAR model from adolescence to adulthood. Risperidone is an antipsychotic agent with a benzisoxazole

chemical structure that has potent dopamine D<sub>2</sub>, serotonin 5-HT<sub>2A</sub>, and  $\alpha_1$  receptor antagonism (Miyamoto et al., 2005). It is a Food and Drug Administration (FDA)-approved antipsychotic drug for pediatric use and has been one of the most prescribed antipsychotic agents for children and adolescents (Patel et al., 2005). Thus, the present study not only is important for the purpose of examining the general principles of antipsychotic sensitization and cross-sensitization, but also has significant clinical implications, as drug switching is quite common in people with schizophrenia during the course of optimizing therapeutic regimens for individual patients (Rosenheck et al., 2009). In addition, the design of this study also allowed us to assess whether adolescent risperidone treatment would cause a long-lasting impairment on instrumental learning in a modified avoidance conditioning task in adulthood or an attention deficit in a prepulse inhibition test (Swerdlow et al., 2000).

## 2. MATERIALS AND METHODS

### 2.1. Animals

Male Sprague-Dawley adolescent rats from Charles River Inc. (Portage, MI) (postnatal days, P 22–26, average age was assumed at P 24, 51–75 g on delivery date) were used. After arrival, they were housed two per cage, in 48.3 cm × 26.7 cm × 20.3 cm transparent polycarbonate cages under 12-h light/dark conditions (light on between 6:30 am and 6:30 pm). Room temperature was maintained at 22±1°C with a relative humidity of 45–60%. Food and water was available *ad libitum*. Animals were allowed 5 days of habituation to the animal facility before being used in the experiments. All procedures were approved by the Institutional Animal Care and Use Committee at the University of Nebraska-Lincoln.

### 2.2. Drugs

Risperidone (RIS), olanzapine (OLZ), and clozapine (CLZ) (gifts from the NIMH drug supply program) were dissolved in distilled sterile water with 0.5–1.0% glacial acetic acid. They were administrated subcutaneously (sc) at 1.0 ml/kg. We tested RIS at 1.0 mg/kg during the adolescent period because our preliminary study shows that this dose of RIS induces a long-term sensitization effect that persists into adulthood (unpublished observation). Also in adult rats, RIS at 1.0 mg/kg disrupts avoidance response and other fear responses (Sun et al., 2010, Zhang, Fang, 2011), and gives rise to a clinically comparable level of striatal D2 occupancy (65–80%) (Kapur et al., 2003). OLZ at 0.5 mg/kg and CLZ at 5.0 mg/kg are commonly used challenge doses in the study of antipsychotic sensitization and tolerance (Feng, Sui, 2013, Li, Sun, 2012b, Qiao, Li, 2013, Swalve and Li, 2012, Zhang and Li, 2012).

### 2.3. Two-way avoidance conditioning apparatus

Eight identical two-way shuttle boxes custom designed and manufactured by Med Associates (St. Albans, VT) were used. Each box was housed in a ventilated, sound-insulated isolation cubicle (96.52 cm W × 35.56 cm D × 63.5 cm H). Each box was 64 cm long, 30 cm high (from grid floor), and 24 cm wide, and was divided into two equal-sized compartments by a partition with an arch style doorway (15 cm high × 9 cm wide at base). A barrier (4 cm high) was placed between the two compartments, so the rats had to jump from one compartment to the other. The grid floor consisted of 40 stainless-steel rods with a diameter of 0.48 cm, spaced 1.6 cm apart center to center, through which a scrambled footshock (unconditioned stimulus US, 0.8 mA, maximum duration: 5 s) was delivered by a constant current shock generator (Model ENV-410B) and scrambler (Model ENV-412). The rat's location and crossings between compartments were monitored by a set of 16 photobeams (ENV-256-8P) affixed at the bottom of the box (3.5 cm above the grid floor). The conditioned stimuli (either a 76 dB white noise CS1 or an 85 dB 2800 Hz pure tone CS2) were produced by a speaker mounted on the ceiling of the cubicle, centered above the

shuttle box. Illumination was provided by two houselights mounted at the top of each compartment. Background noise (approximately 74 dB) was provided by a ventilation fan affixed at the top corner of each isolation cubicle. All training and testing procedures were controlled by Med Associates programs running on a computer.

#### 2.4. Prepulse inhibition of acoustic startle reflex apparatus

The prepulse inhibition (PPI) test was performed using six Startle Monitor Systems (Kinder Scientific, Julian, CA). Each system, controlled by a PC, was housed in a compact sound attenuation cabinet (36 cm wide × 28 cm deep × 50 cm high). A speaker (diameter: 11 cm) mounted on the cabinet's ceiling was used to generate acoustic stimuli (70 dB–120 dB). The startle response was measured by a piezoelectric sensing platform on the floor, which was calibrated daily. During testing, a rat remained in a rectangular box made of transparent Plexiglas (19 cm wide × 9.8 cm deep × 14.6 cm high) with an adjustable ceiling positioned atop the box, providing only limited restraint while prohibiting ambulation.

#### 2.5. Experimental procedure

This experiment consisted of the following four stages: *repeated risperidone testing in adolescence; avoidance retraining/testing in adulthood; drug switching to olanzapine or clozapine in adulthood; and PPI assessment*. Figure 1 details the timeline of events and group information.

**2.5.1. Repeated risperidone testing in adolescence**—Forty-eight adolescent rats (~P 31) were first habituated to the CAR boxes for 2 days (20 min/day) and then trained for conditioned avoidance responding for 7 consecutive sessions (1 session/day). Each session consisted of 30 trials. Every trial started by presenting a white noise (CS) for 10 s, followed by a continuous scrambled foot shock (0.8 mA, US, maximum duration = 5 s) on the grid floor. An avoidance response was recorded if a rat moved from one compartment into the other within the 10 s of CS presentation. An escape response was recorded if the rat made a crossing only after receiving the footshock. If the rat did not respond during the entire 5 s presentation of the shock, the trial was terminated and the intertrial intervals started (30 – 60 s). The total number of avoidance responses (as an index of antipsychotic activity) and intertrial crossings (as a measure of general motor function/sedation) were recorded for each session.

At the end of the training session (~P 40), rats were first matched on avoidance performance on the last training day (i.e. predrug) and then randomly assigned to one of two groups: vehicle (sterile water, n = 24) and risperidone 1.0 mg/kg (RIS 1.0, n = 24). In the next 5 consecutive days, rats were tested under drug or vehicle daily in the CS-only (no shock, 30 trials/session) condition. During each test, rats were first injected with RIS (1.0 mg/kg, sc) or sterile water. One hour later, they were placed in the CAR boxes and tested. Number of avoidance and intertrial crossings in each session were recorded.

**2.5.2. Avoidance retraining/testing in adulthood**—After the adolescent RIS tests, the rats remained in their home cages until ~P 68 when they were returned to the CAR boxes for one habituation session, followed by 7 days of avoidance retraining/testing in a modified CAR procedure. This procedure has been used before (Chen et al., 2011, Li et al., 2009b, Li, Sun, 2012b, Zhang, Fang, 2011) and was used in the present study to assess whether early adolescent RIS treatment might have altered animals' learning and memory ability. Each session consisted of 30 trials. Ten trials used a 10 s 76 dB white noise as the CS (CS1) with its termination immediately followed by a shock (0.8 mA, maximum duration: 5 seconds) if the rats did not make an avoidance response. The remaining 20 trials (CS2 trials) used a pure tone (10s, 2800 kHz, 85 dB) as the CS (CS2). In 15 CS2 trials, the CS2 was followed by the

shock if the rat failed to respond to the CS2; whereas, in the remaining 5 trials no shock was used. The 10 CS1 trials were randomly intermixed with the 20 CS2 trials. Rats were trained in this procedure to re-acquire CS1 avoidance and acquire a new CS2 avoidance. Two days after the last CS1-CS2 training session, all rats were trained again for 3 days using the same procedure as used in the adolescent period (white noise as the only CS) to ensure that their avoidance responding was at a high level before switching to OLZ and CLZ challenge tests.

**2.5.3. Switching to olanzapine or clozapine in adulthood**—At the end of the 3<sup>rd</sup> retraining session (~P 79), rats in each group (VEH and RIS 1.0) were randomly subdivided into 3 subgroups based on their matched avoidance performance. The original VEH group was subdivided into: vehicle-vehicle (sterile water, VEH-VEH, n = 8), vehicle-olanzapine 0.5 mg/kg (VEH-OLZ 0.5, n = 8) and vehicle-clozapine 5.0 mg/kg (VEH-CLZ 5.0, n = 8). For the RIS 1.0 group, the 3 subgroups were: risperidone 1.0 mg/kg-vehicle (RIS 1.0-VEH, n = 8), risperidone 1.0 mg/kg-olanzapine 0.5 mg/kg (RIS 1.0-OLZ 0.5, n = 8) and risperidone 1.0 mg/kg-clozapine 5.0 mg/kg (RIS 1.0-CLZ 5.0, n = 8). Rats in different subgroups were tested under OLZ 0.5 mg/kg, CLZ 5.0 mg/kg or 1% acidic sterile water daily for 5 consecutive days. The CS-only (no shock, 30 trials/daily session) test session was initiated 1 h after drug injection. At the end of each test session, rats were taken out of the CAR apparatus and immediately injected with 5'-Bromo-2-deoxyuridine (BrdU) 50 mg/kg (2.5 ml/kg, sc) as a part of a pilot study to examine the drug-stimulated neurogenesis. Avoidance performance and intertrial crossings were recorded. BrdU at this dose did not affect avoidance behavior (our unpublished observation).

**2.5.4. PPI assessment**—Two PPI tests were conducted, one during the late adolescent period (~P 45, 1 day after the 5 drug test days) and one during the early adulthood period (~P 67, 2 days before the adulthood CAR training procedure). The PPI test procedure was adapted from Culm and Hammer (2004) and has been successfully used in the study of the PPI disruptive effect of PCP antipsychotic drugs' reversal of this disruption (Li et al., 2011a, Li et al., 2011b). Each session lasted approximately 18 minutes and began with a 5 minute period of 70 dB background noise (which continued throughout the duration of the session) followed by four different trial types: PULSE ALONE trials and three types of PREPULSE + PULSE trials, which consisted of a 20 ms 73, 76, or 82 dB prepulse (3, 6, and 12 dB above background) followed 100 ms later by a 120 dB pulse (40 ms in duration). Each session was divided into 4 blocks. Blocks 1 and 4 were identical, each consisting of 4 PULSE ALONE trials. Blocks 2 and 3 were also identical and each consisted of 8 PULSE ALONE trials and 5 of each PREPULSE + PULSE trial type. A total of 54 trials were presented during each test session. Trials within each block were presented in a pseudorandom order and were separated by a variable intertrial interval averaging 15 s (ranging from 9–21 s). Startle magnitude was defined as the maximum force (measured in Newtons) applied by the rat to the startle apparatus recorded over a period of 100 ms beginning at the onset of the pulse stimulus. Between each stimulus trial, 100 ms of activity was recorded when no stimulus was present. These trials were called NOSTIM trials and were not included in the calculation of intertrial intervals. Responses recorded during NOSTIM trials are considered a measure of gross motor activity within the PPI boxes. Startle responses from testing blocks 2 and 3 were used to calculate percent prepulse inhibition (%PPI) for each acoustic prepulse trial type:

$$\%PPI = 100 - \left[ \left( \frac{\text{average startle response to PREPULSE+PULSE trials}}{\text{average startle response to PULSE ALONE trials}} \right) \times 100 \right]$$



## 2.6. Statistical Analysis

Avoidance response data were expressed as mean avoidance percent + SEM [number of avoidance responses divided by the total number of trials: either 30, or 10 (CS1 avoidance) or 20 (CS2 avoidance)] and analyzed using a factorial repeated measures analysis of variance (ANOVA) with a between-subjects factors of group or prior adolescence drug treatment (i.e. risperidone vs. vehicle) and a within-subjects factor of test day or CS type (CS1 vs. CS2 avoidance). Differences between groups on specific test days were analyzed using independent-samples t test. Percent PPI data were presented separately for three prepulse intensities (e.g. 73, 76 and 82 dB) and were analyzed using repeated measures ANOVAs with drug treatment group as a between-subjects factor and prepulse level as a within-subjects factor. For all analyses,  $p < 0.05$  was considered statistically significant and all data were analyzed using SPSS version 19.

## 3. RESULTS

### 3.1. Repeated risperidone treatment suppressed avoidance response and intertrial crossing in adolescent rats

**Avoidance response**—Fig. 2A shows the mean avoidance percent on the last training (predrug) day and 5 drug test days. There was no group difference on the last training day. Throughout the drug test days, RIS treatment disrupted avoidance response persistently. Repeated measures ANOVA revealed a main effect of *group*,  $F(1, 46) = 275.042$ ,  $p < 0.001$ , *day*,  $F(4, 184) = 5.050$ ,  $p = 0.001$ , but no significant *group*  $\times$  *day* interaction. Independent-samples t test revealed that the RIS 1.0 group had significantly lower avoidance than the VEH group on each of the 5 drug days, all  $ps < 0.001$ .

**Intertrial crossing**—During the drug test days, RIS 1.0 group had fewer intertrial crossings in comparison to the VEH group, consistent with its motor side effect (Fig. 2B). Repeated measures ANOVA revealed a main effect of *group*,  $F(1, 46) = 178.860$ ,  $p < 0.001$ , *day*,  $F(4, 184) = 5.081$ ,  $p = 0.001$ , but no significant *group*  $\times$  *day* interaction. Independent-samples t test revealed that the RIS 1.0 group made significantly fewer intertrial crossings than the VEH group on each of the 5 drug days, all  $ps < 0.001$ .

### 3.2. Prior adolescence risperidone treatment did not impair the acquisition of CS2 avoidance and re-acquisition of CS1 avoidance

Throughout the 7 avoidance training sessions to the two CS trials, the CS1 avoidance percent was higher than that to the CS2 (Fig. 3), consistent with our previous findings (Chen, Wang, 2011, Li, He, 2009b, Li, Sun, 2012b, Zhang, Fang, 2011). The three-way repeated ANOVA revealed a main effect of *session*,  $F(6, 276) = 13.531$ ,  $p < 0.001$ , and a main effect of *CS type*,  $F(1, 46) = 137.114$ ,  $p < 0.001$ . However, the main effect of group was not significant, neither were its interactions with *session* and *CS type*, all  $ps > 0.327$ , suggesting that prior RIS treatment did not cause a significant impairment of the acquisition of a new avoidance response (i.e. CS2 avoidance) and expression of a learned one (i.e. CS1 avoidance).

### 3.3. Risperidone treatment in adolescence enhanced behavioral sensitivity to olanzapine, but decreased sensitivity to clozapine in adulthood

**Avoidance response on the 1<sup>st</sup> switching test day**—Fig. 4A shows the mean avoidance percent on the predrug day and the first drug switching challenge test day under VEH, OLZ 0.5 mg/kg or CLZ 5.0 mg/kg (~P 80). Before the challenge test, there was no significant group difference. Also, the prior RIS group and VEH group were not different under the vehicle test condition,  $t_{14} = 0.149$ ,  $p = 0.884$ . However, when switched to OLZ 0.5

mg/kg test, the prior RIS group had significantly lower avoidance than the prior VEH group,  $t_{14} = 4.327$ ,  $p = 0.001$ . In contrast, when switched to CLZ 5.0 mg/kg test, the prior RIS group had significantly higher avoidance than the prior VEH group,  $t_{14} = -2.714$ ,  $p = 0.017$ . These data indicate that adolescent RIS treatment enhanced behavioral sensitivity to OLZ, but decreased sensitivity to CLZ in adulthood.

**Intertrial crossing on P 80**—Fig. 4B shows the number of intertrial crossing on the predrug day and the first challenge test day under VEH, OLZ 0.5 mg/kg or CLZ 5.0 mg/kg (~P 80). Before the challenge test, there were no significant group differences. The group difference between the prior RIS group and VEH group under the vehicle test condition was also not significant,  $t_{14} = 0.568$ ,  $p = 0.579$ . When switched to OLZ 0.5 mg/kg test, the prior RIS group had significantly fewer intertrial crossings than the prior VEH group,  $t_{14} = 2.960$ ,  $p = 0.010$ . In contrast, when switched to CLZ 5.0 mg/kg test, the prior RIS group had significantly more intertrial crossings than the prior VEH group,  $t_{14} = -2.785$ ,  $p = 0.015$ .

**Avoidance response throughout the 5 drug switching test days**—During the repeated drug switching test period, the differential impact of adolescent RIS exposure on the avoidance disruptive effect of adulthood OLZ and CLZ treatment persisted (Fig. 5A, 5B, 5C). One rat from the RIS 1.0-CLZ 5.0 subgroup died on day 3 of testing unexpectedly, so the subsequent repeated ANOVA was conducted without its data. As can be seen in Figure 5A, under the vehicle treatment, there was no significant group difference between the prior RIS group and VEH group. Repeated measures ANOVA found no main effect of *group*, *day*, nor *group*  $\times$  *day* interaction, all  $ps > 0.280$ . Under the OLZ 0.5 mg/kg test condition, the prior vehicle group showed a progressive across-session decline in avoidance responding, while the prior RIS group maintained a consistently lower level of avoidance (Fig. 5B). Repeated measures ANOVA revealed a main effect of *adolescent treatment*,  $F(1, 14) = 17.136$ ,  $p = 0.001$ , *day*,  $F(4, 56) = 7.640$ ,  $p < 0.001$ , and a significant *adolescent treatment*  $\times$  *day* interaction,  $F(4, 56) = 4.470$ ,  $p = 0.003$ . Further tests found that the RIS 1.0-OLZ 0.5 subgroup had significantly lower avoidance than the VEH-OLZ 0.5 subgroup on all 5 test days, all  $ps < 0.024$ . Under the CLZ 5.0 mg/kg test condition, the prior RIS group had significantly higher avoidance than the prior VEH group (Fig. 5C). Repeated measures ANOVA revealed a main effect of *adolescent treatment*,  $F(1, 13) = 5.029$ ,  $p = 0.043$ , *day*,  $F(4, 52) = 4.559$ ,  $p = 0.003$ , but no significant *adolescent treatment*  $\times$  *day* interaction. Independent-samples t test found significant differences between the two subgroups on the 1<sup>st</sup> and 3<sup>rd</sup> test days, all  $ps < 0.018$ .

**Intertrial crossing throughout the 5 drug switching test days**—The differential impact of adolescent RIS exposure on behavioral sensitivity to adulthood OLZ and CLZ treatment also manifested in the intertrial crossing (Fig. 5D, 5E, 5F). Under the OLZ 0.5 mg/kg test condition, the prior RIS group had significantly lower numbers of crossings than the prior VEH group. Repeated measures ANOVA revealed a main effect of *adolescent treatment*,  $F(1, 14) = 10.564$ ,  $p = 0.006$ , *day*,  $F(4, 56) = 4.135$ ,  $p = 0.005$ , but no significant *adolescent treatment*  $\times$  *day* interaction. Independent-samples t test found significant group differences on all 5 test days, all  $ps < 0.044$ .

Under the CLZ 5.0 mg/kg test condition, the prior RIS group had significantly higher number of crossings than the prior VEH group. Repeated measures ANOVA revealed a main effect of *adolescent treatment*,  $F(1, 13) = 5.496$ ,  $p = 0.036$ , *day*,  $F(4, 52) = 3.514$ ,  $p = 0.013$ , but no significant *adolescent treatment*  $\times$  *day* interaction. Independent-samples t test found significant group differences on the 1<sup>st</sup>, 2<sup>nd</sup> and 4<sup>th</sup> test days, all  $ps < 0.047$ .



### 3.4. Performance in the prepulse inhibition of acoustic startle in adulthood was not altered by adolescent risperidone treatment

Analysis of PPI data from the 1<sup>st</sup> test day (~P 45) revealed a main effect of *group*,  $F(1, 46) = 4.645$ ,  $p = 0.036$ , *prepulse level*,  $F(2, 92) = 130.994$ ,  $p < 0.001$ , but no *group*  $\times$  *prepulse* interaction,  $F(2, 92) = 0.336$ ,  $p = 0.715$ . Inspection of the data shows that RIS rats had significantly higher PPIs than the vehicle rats (data not shown). Analysis of PPI data from the 2<sup>nd</sup> test day (~P 67) found a significant main effect of *prepulse level*,  $F(2, 92) = 131.875$ ,  $p < 0.001$ , but no *group* effect,  $F(1, 46) = 0.562$ ,  $p = 0.457$ , nor the *group*  $\times$  *prepulse level* interactions,  $F(2, 92) = 0.618$ ,  $p = 0.541$ . These findings suggest that adolescence RIS treatment enhanced the sensorimotor gating ability in the short-term but this effect was transient and did not last into adulthood.

## 4. DISCUSSION

The main finding of the present study was that adolescent RIS treatment as short as 5 days caused a long-term alteration of behavioral sensitivity to other antipsychotic drugs in adulthood (> 30-day interval). Specifically, we showed that RIS exposure from postnatal days 40 to 44 increased behavioral sensitivity to OLZ as indexed by its effects on avoidance responding and intertrial crossing, but decreased it to CLZ. This change of behavioral sensitivity to an antipsychotic drug was revealed only under the drug treatment condition (i.e. switched to OLZ or CLZ), but not under the non-drug (vehicle) condition, indicating that the change is essentially the consequence of drug-induced behavioral and brain changes. Additionally, RIS transiently increased PPI performance in adolescence, but this effect did not persist into adulthood. Adolescent RIS treatment also did not cause a long-term change in the learning and memory abilities of rats in the CAR model, as supported by the finding that rats previously treated with RIS acquired a new instrumental response (active avoidance to CS2) at the same rate as those previously treated with water. Thus, the present study not only reinforces the notion that antipsychotic drug experience in an early developmental period can alter drug sensitivity in the long run (Piontkewitz et al., 2011, Qiao, Li, 2013), but also suggests that such a change is a general effect (not a drug-specific effect), transferable from one drug to another within the same drug category (Li, Fletcher, 2007).

The present study extended our previous adult work on cross-sensitization by showing that it also happens across different developmental periods against the process of brain maturation. Because RIS is similar to OLZ in giving rise to a sensitization effect in multiple animal models of antipsychotic activity upon repeated drug administration in adolescent and adult animals (Li, Fletcher, 2007, Li, He, 2011a, Li, He, 2009b, Mead and Li, 2010, Shu et al., 2013), it is easily understood that the RIS-induced increase in behavioral sensitivity to OLZ reflects a cross-sensitization effect from RIS to OLZ, consistent with our previous finding in adult rats (Zhang, Fang, 2011). The RIS-induced decreased sensitivity to CLZ was somewhat an unexpected finding, as repeated CLZ treatment often causes a tolerance effect (Feng et al., 2012, Li, Fletcher, 2007, Li et al., 2012a, Li, Sun, 2010, Qiao, Li, 2013), an opposite behavioral response pattern to that of RIS. In the CAR model, this tolerance effect reflects the finding that prior CLZ treatment causes a decrease in its ability to suppress avoidance responding in a challenge test. In this regard, the decreased behavioral sensitivity to CLZ by adolescent RIS treatment could be characterized as an enhancement of CLZ tolerance. This conceptualization would provide a unitary explanation of RIS impact on adulthood OLZ and CLZ responses by stating that adolescent RIS treatment enhances OLZ sensitization, as well as CLZ tolerance.

Some structural and functional receptor studies on antipsychotic sensitization and tolerance suggest this unitary effect of adolescent RIS on OLZ and CLZ is possible, likely acting through dopamine D<sub>2</sub> receptor mechanisms. First, repeated administration of all three

atypical antipsychotic drugs, RIS, CLZ and OLZ dose-dependently increases D<sub>2</sub> receptor in critical brain regions implicated in the action of antipsychotic drugs (medial prefrontal cortex, caudate-putamen, nucleus accumbens) in both adolescent rats and adult rats (Moran-Gates et al., 2006). Because D<sub>2</sub> receptors in these limbic regions undergo a natural pruning process throughout the development, and stress or drug exposure in adolescence are capable of altering this process (Burke et al., 2011, Teicher et al., 1995, Vuillermot et al., 2010), it is conceivable that antipsychotic treatment in adolescence may impair this process and cause a less of D<sub>2</sub> receptor decline. These changes could potentially last from adolescence to adulthood. Second, pretreatment of quinpirole (a selective dopamine D<sub>2/3</sub> receptor agonist) can attenuate OLZ sensitization, but enhance CLZ tolerance as measured in the CAR model in adult rats (Li, Sun, 2010). The opposing effect of quinpirole on OLZ sensitization and CLZ tolerance is especially interesting as it is in agreement with the opposing impact of adolescent RIS treatment on these phenomena as shown in the present study, and also supports the idea that both OLZ sensitization and CLZ tolerance are likely mediated by their actions on the D<sub>2/3</sub> receptor system. Third, in our unpublished studies, we demonstrated that repeated administration of RIS and CLZ in adult rats for 5 days caused an increased level of locomotor activity in response to quinpirole challenge. Quinpirole-induced hyperlocomotion is a sensitive behavioral assay of D<sub>2</sub>-mediated neurotransmission (Koller et al., 1987, Prosser et al., 1989). This finding strongly suggests that repeated treatment of RIS and CLZ might cause a functional upregulation of dopamine D<sub>2</sub> receptors due to their common antagonist action against this receptor. Based on these findings, we propose the following explanation for the enhancement effect of adolescent RIS treatment on adulthood OLZ sensitization and CLZ tolerance: (1) the neural networks (e.g. medial prefrontal cortex, caudate-putamen, nucleus accumbens) undergo neuroplastic changes initiated by repeated RIS exposure during adolescence, including the possible upregulation of D<sub>2</sub> receptor due to the impairment effect of RIS on the pruning process; (2) in adulthood, the drug-altered networks are being reactivated by other antipsychotic drugs with similar molecular targets (e.g. D<sub>2</sub>). As a result, drug-treated animals may show an increased (in the case of OLZ) or decreased (in the case of CLZ) response to a drug when they become adults. Therefore, the long-lasting change of D<sub>2</sub> receptors instigated during adolescence might have manifested at the behavioral level as a sensitization effect in OLZ and RIS, but as a tolerance effect in CLZ in adulthood. The reason that avoidance response can capture antipsychotic response and antipsychotic sensitization or tolerance is because the major components of the network (e.g. medial prefrontal cortex, caudate-putamen, nucleus accumbens) upon which antipsychotic act are the same as those that mediate conditioned avoidance response (Koob et al., 1984, Wadenberg et al., 1990, White and Rebec, 1993). Because all 3 atypical drugs are also potent 5-HT<sub>2A/2C</sub> receptor antagonists (Meltzer et al., 2003, Meltzer et al., 1989), and repeated treatment of these drugs also cause persistent long-term changes in these receptors in adolescent rats (Choi et al., 2010), we cannot rule out the contribution of 5-HT<sub>2A/2C</sub> receptors in the mediation of the enhancement effect of adolescent RIS effect on adulthood OLZ sensitization and CLZ tolerance. One important future task is to determine the relevant forms of neuroplasticity initiated by drug actions on these receptors in adolescence that persist into adulthood and their clinical implications.

In our previous studies, we have suggested that a drug-state dependent “memory-like” mechanism allows animal to “remember” their past drug experience (Li, Fletcher, 2007, Li et al., 2009a, Mead and Li, 2010). This mechanism is likely driven by the interoceptive state caused by the antipsychotics (Overton, 1979, Schechter and Cook, 1975). This behavioral explanation could also be used to explain the enhancement effect of adolescent RIS effect on adulthood OLZ sensitization and CLZ tolerance. It is likely that all 3 antipsychotics share a common “antipsychotic” interoceptive drug state that allows one drug to alter the sensitivity to another.

In the present study, we found that RIS transiently increased PPI performance in adolescence, but this effect did not persist into adulthood, an interesting finding that deserves further investigation to determine its validity, as no such an effect was found with OLZ treatment (Llorente-Berzal et al., 2012). Also, the lack of impairment effect of adolescent RIS treatment on learning (e.g. acquisition of a new avoidance response to CS2) and memory (e.g. re-acquisition of CS1 avoidance) is consistent with other reports in the literature indicating a lack of any apparent long-term detrimental effects of adolescent antipsychotic treatment (Addy and Levin, 2002, Meyer et al., 2010, Piontkewitz, Arad, 2011).

In the clinical treatment of schizophrenia, drug switching is a quite common practice (Essock et al., 2006). Many reasons prompt for the implementation of this practice, including inadequate efficacy, partial compliance or noncompliance with medication, and the presence of adverse events such as movement disorders, weight gain, somnolence, endocrine side effects, and metabolic dysfunction (Rosenheck, Davis, 2009). Several documented problems might occur on switching, such as rebound worsening of psychotic symptoms, added side effects, or side effects specific to the new drug, or differences in efficacy between the drugs (Davis and Leucht, 2008). Overall, it appears that switching to a new medication does not yield much advantage over staying on the previous medication and switching to a new medication may actually increase drug discontinuation (Gardos, 1974, Rosenheck, Davis, 2009). One interesting exception is CLZ, as switching to CLZ is more likely to lead to successful antipsychotic medication switch. In addition, patients receiving CLZ are found to be less likely to discontinue treatment for reasons of inefficacy (McEvoy et al., 2006). Our finding that adolescent RIS treatment altered behavioral sensitivity to OLZ and CLZ differentially in rats has important clinical implications. It suggests that the past history of a patient's experience with a given drug may impact his/her later response to a new drug. Thus, clinicians working with adult patients who have been treated with one drug (e.g. RIS) but wish to switch to another drug (e.g. OLZ or CLZ) may need to consider possible changes in antipsychotic efficacy and monitor patients' symptom response to the new drug during this switching process.

## 5. Conclusions

This study shows positive behavioral interactions between adolescent risperidone exposure and the treatment of two other antipsychotic drugs in adulthood. Furthermore, the directions of the interactions are different for switching to olanzapine and clozapine. This study provided new information for drug switching in patients who need a cross development clinical therapy. Future studies need to pay more attention to the molecular mechanisms underlying the interactions.

## Acknowledgments

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## Abbreviations

<b>BrdU</b>	5'-Bromo-2-deoxyuridine
<b>CAR</b>	conditioned avoidance response
<b>CLZ</b>	clozapine
<b>CLZ 5.0</b>	clozapine 5.0 mg/kg
<b>CS</b>	conditioned stimulus

<b>DA</b>	dopamine
<b>FDA</b>	Food and Drug Administration
<b>GABA</b>	gamma amino butyric acid
<b>OLZ</b>	olanzapine
<b>OLZ 0.5</b>	olanzapine 0.5 mg/kg
<b>P</b>	postnatal
<b>PCP</b>	phencyclidine
<b>PFC</b>	prefrontal cortex
<b>PPI</b>	prepulse inhibition
<b>sc</b>	subcutaneously
<b>RIS</b>	risperidone
<b>RIS 1.0</b>	risperidone 1.0 mg/kg
<b>VEH</b>	vehicle
<b>US</b>	unconditioned stimulus
<b>% PPI</b>	percent prepulse inhibition

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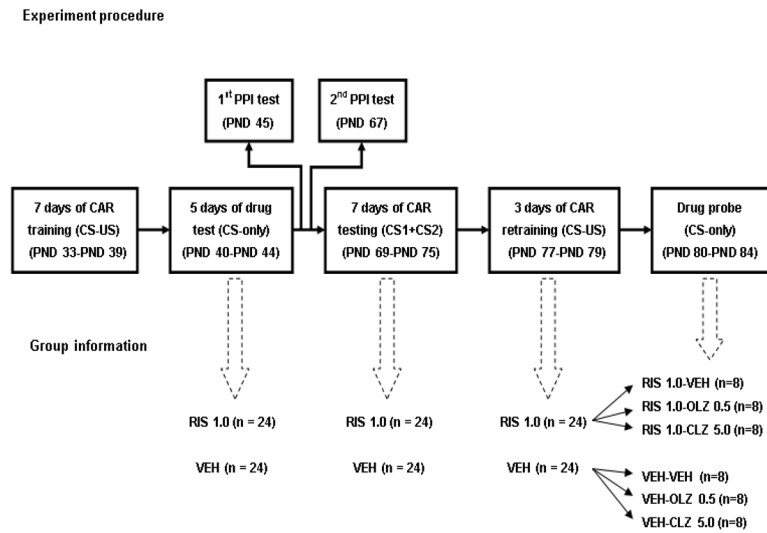
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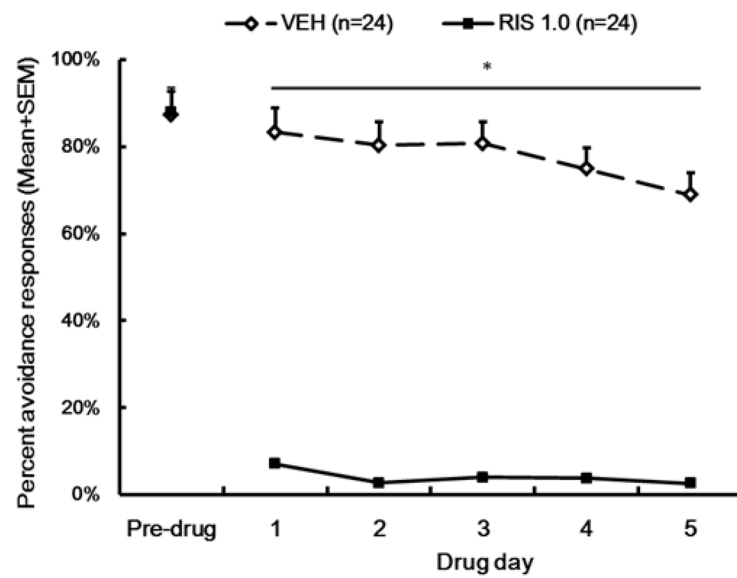
**Highlights**

- Adolescent risperidone exposure enhanced the avoidance disruption of olanzapine in adulthood.
- Adolescent risperidone exposure decreased the avoidance disruption of clozapine in adulthood.
- Performance in prepulse inhibition in adulthood was not altered by early risperidone treatment.
- Prior risperidone treatment did not affect avoidance learning in adulthood.

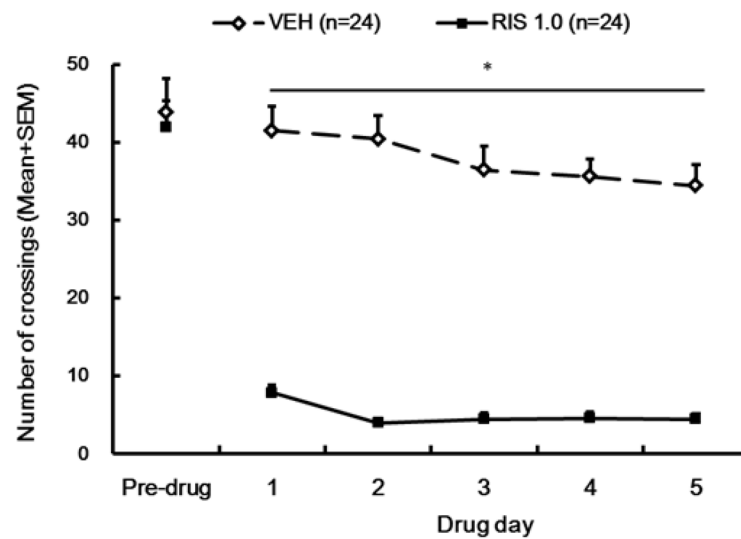


**Figure 1.**  
Schematic representation of experimental design and procedure.

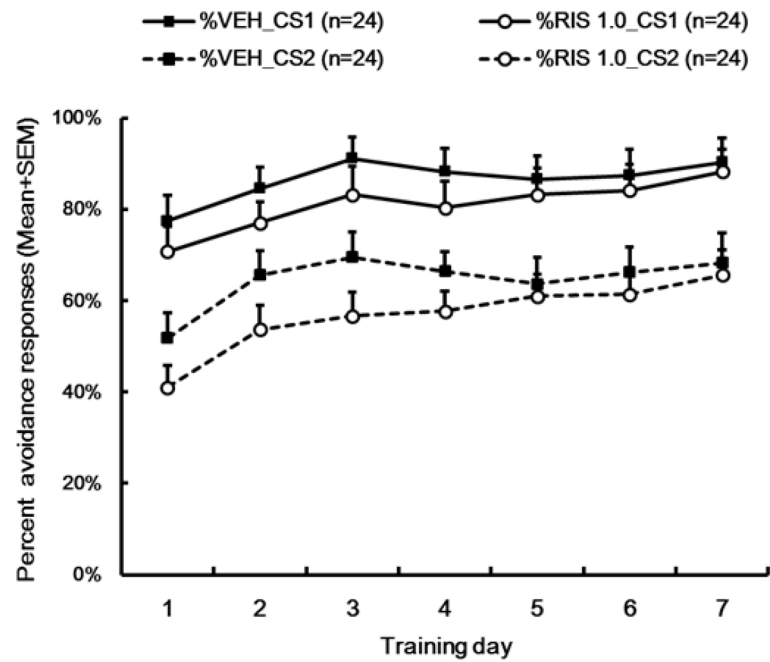
Figure 2 A



B

**Figure 2.**

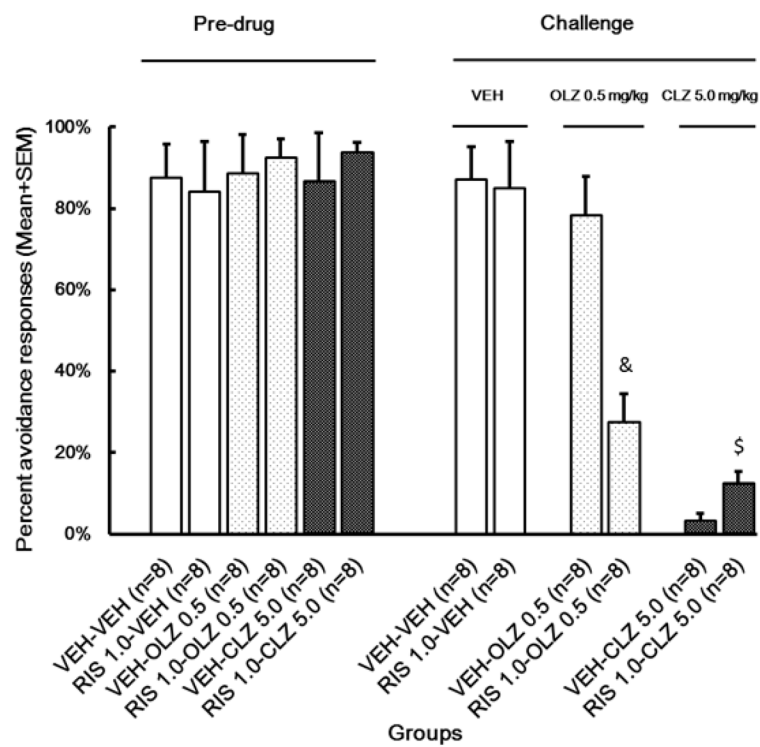
Effects of repeated risperidone treatment (1.0 mg/kg, sc) on the mean avoidance percent (A) and intertrial crossings (B) in adolescence. Data on the last training (predrug) day and throughout the 5 drug test days are expressed as mean + SEM. \*  $p < 0.05$  relative to the VEH group.



**Figure 3.**

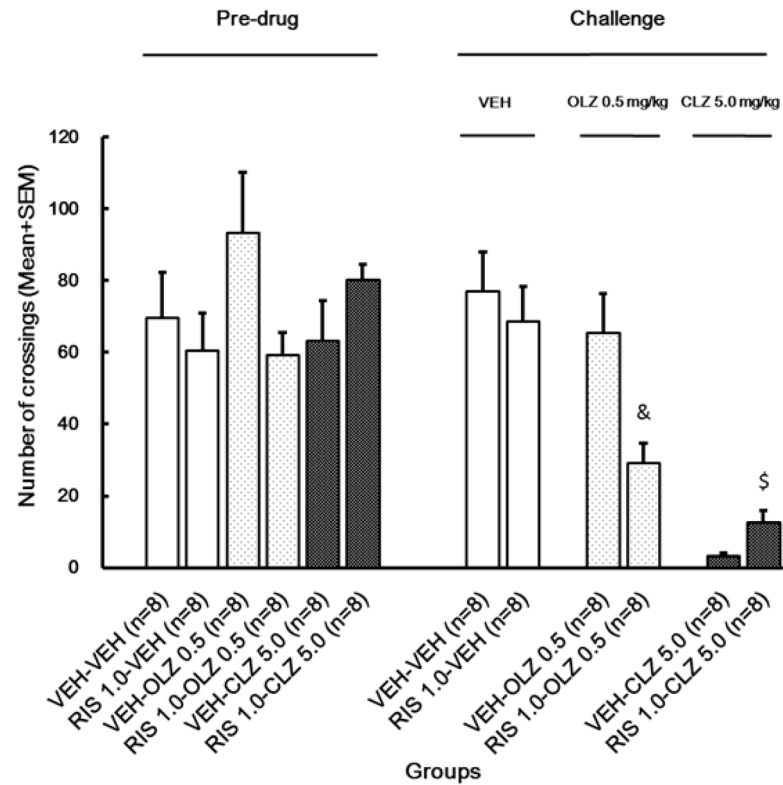
Avoidance percent to CS1 and CS2 (mean + SEM) throughout the 7 days of avoidance retraining/testing in adulthood in rats previously treated with risperidone (1.0 mg/kg) or sterile water in adolescence. CS2 avoidance was lower than CS1 avoidance but the group difference was not significant.

A



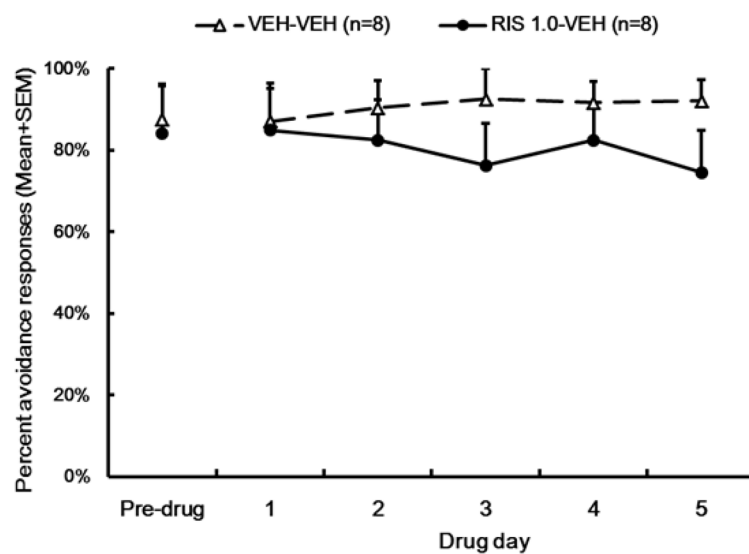


B

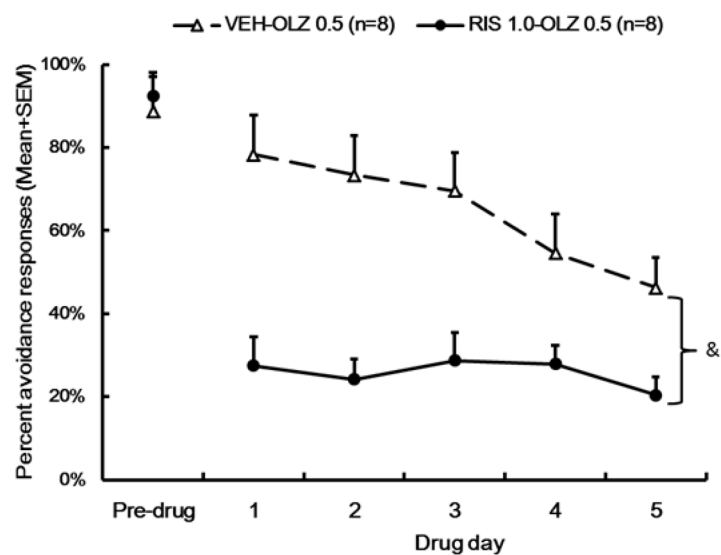
**Figure 4.**

Mean avoidance percent (A) and number of intertrial crossings (B) made by the rats from the VEH-VEH, RIS 1.0-VEH, VEH-OLZ 0.5, RIS 1.0-OLZ 0.5, VEH-CLZ 5.0 and RIS 1.0-CLZ 5.0 groups on the last retraining (predrug) day and on the first olanzapine or clozapine challenge test. &  $p < 0.05$  relative to the VEH-OLZ 0.5 ; \$  $p < 0.05$  relative to the VEH-CLZ 5.0 group.

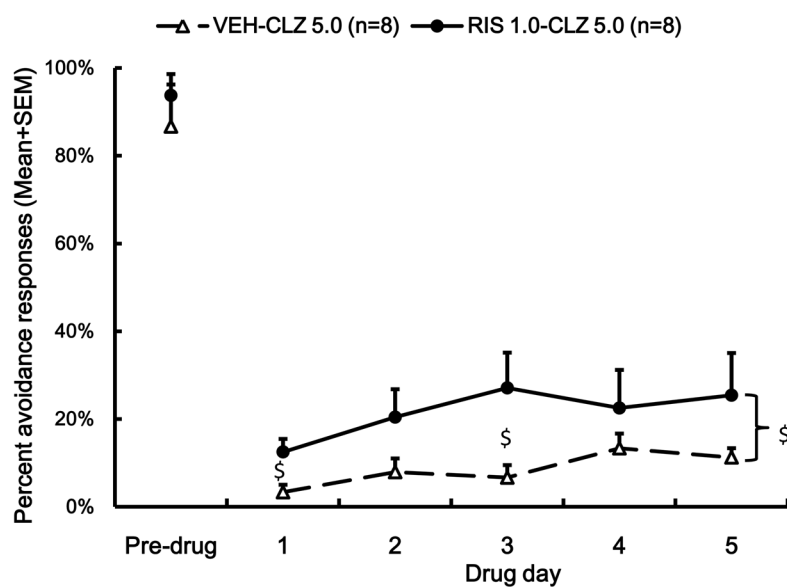
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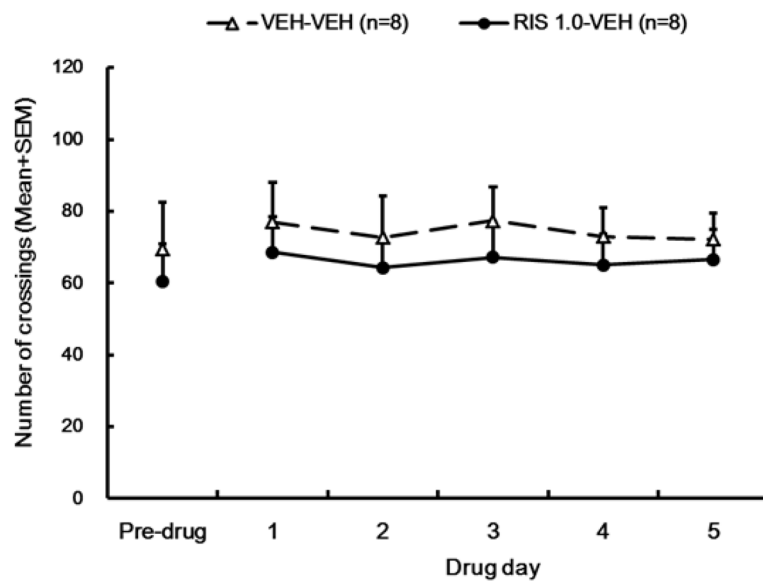
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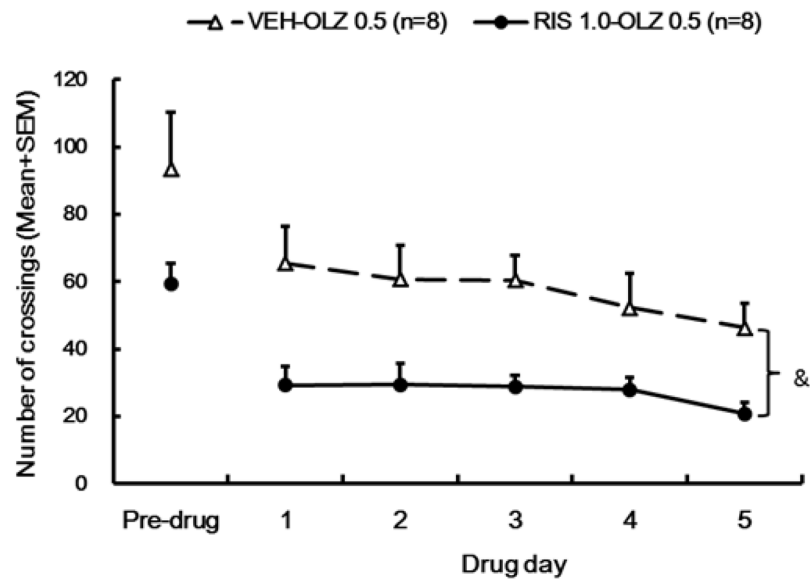
C



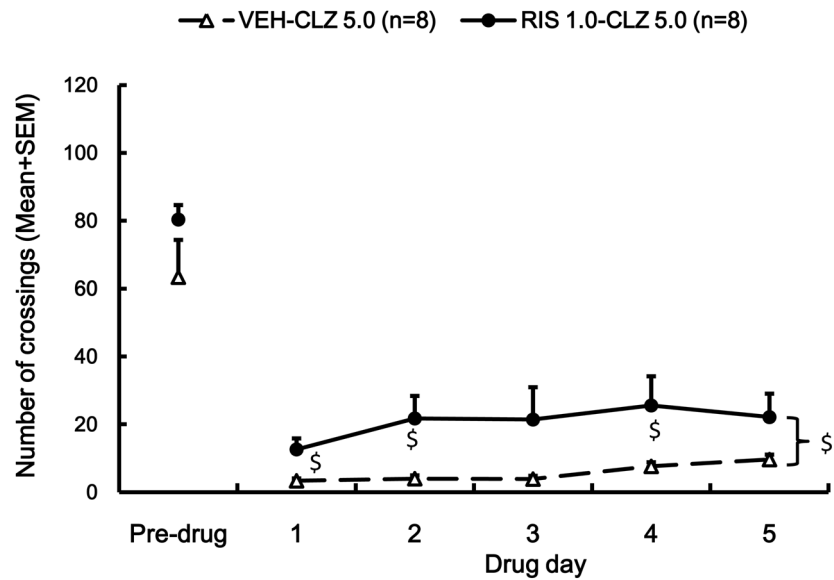
D



E



F

**Figure 5.**

Effects of repeated vehicle, olanzapine or clozapine treatment (0.5 or 1.0 mg/kg, sc) on the avoidance percent (A, B, C) and intertrial crossings (D, E, F) from ~ P80–84. Data on the last training (predrug) day and throughout the five drug test days are expressed as mean + SEM. &  $p < 0.05$  relative to the VEH-OLZ 0.5; \$  $p < 0.05$  relative to the VEH-CLZ 5.0 group.