Running Head: Prevalence of Motor and Cognitive Deficits

MOTORIC AND COGNITIVE EFFECTS OF RISPERIDONE AND HALOPERIDOL IN AN ANIMAL MODEL OF SCHIZOPHRENIA

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Abstract

Motor disturbances (also known as extrapyramidal side effects) and cognitive deficits are common side effects of antipsychotic drug therapies. Research has suggested that the prevalence rate of motor side effects is greater in typical antipsychotic drug therapies than in atypical antipsychotic drug therapies. The aims of the present study are to evaluate the ketamine-model of schizophrenia and determine whether the difference in the prevalence of motor side effects between typical and atypical antipsychotic drugs is due to the drug type itself or the typical dosage levels of these drugs. Forty, healthy, male Long-Evans hooded rats, *Rattus norvegicus*, served as the subjects for this study. The rats were approximately 120 days old. In order to observe motor disturbances and cognitive deficits, the rats were divided into four treatment groups: the *control* group, the *ketamine* group, the *ketamine/haloperidol* group, and the *ketamine/risperidone* group. The rats were put through an Alternative Task (t-maze), an Open-Field Activity Task, and a Swim Test. Significant differences in motor and cognitive abilities among the four treatment groups for each task were indicated by Kruskal-Wallis tests and differentiated by Mann-Whitney U post-hoc tests. Results indicate that the ketamine-model of schizophrenia is valid. A higher prevalence of motor side effects was indicated in the rats treated with the typical antipsychotic drug.

Introduction

Schizophrenia is a devastating mental disorder that affects approximately one percent of the world's population. The disease is characterized by both positive and negative symptoms. The positive symptoms of schizophrenia are often externally expressed and include hallucinations, delusions, and disorganized thought and speech patterns. In contrast to the visibility of the positive symptoms, negative symptoms are more obscure largely due to the fact that healthy individuals experience a continuum of the same experiences. The negative symptoms include feelings and behaviors such as apathy, isolation, and emotional withdrawal (Julien, 2005). While many other mental disorders can be treated successfully with a variety of different treatment methods, drug therapy is almost always necessary to treat schizophrenia. Treatments focus on the remission of both the positive and negative symptoms of the disorder. Fortunately, the positive symptoms respond to antipsychotic drug therapies. The control of the negative symptoms, however, has proven to be much more difficult.

Unfortunately, drug therapy is not always successful at ameliorating the positive *or* negative symptoms for a number of reasons. The fact that many antipsychotic drugs cause serious side effects is one such reason. Motor side effects (also known as extrapyramidal side effects), cognitive deficits, and emotional disturbances are classes of side effects that can influence individuals with schizophrenia to cease their drug regimens (Houltram & Scanlan, 2004). Once treatment ends, a reemergence of both the positive and negative symptoms is typically inevitable.

Most clinicians agree that drug therapy is necessary for the control of schizophrenic symptoms. The combinations of drugs to utilize in such therapies, however, are often sources of controversy. Antipsychotic drugs are categorized into two major categories: typical, or first generation, antipsychotic drugs and atypical, or second generation, antipsychotic drugs. The typical antipsychotic drugs were first developed in the 1950's. The first antipsychotic drug, chlorpromazine, was classified as a phenothiazine. Phenothiazines exert their antipsychotic effects by blocking dopamine-2 (D-2) receptors (Julien, 2005). Increased activity in the dopamine system of the brain is thought to be one of the causes of schizophrenia. The serious side effects associated with chlorpromazine, and other drugs in this class, prompted research and the development of novel antipsychotic drugs that continues today. Haloperidol, which is not classified as a phenothiazine, is another common typical antipsychotic drug developed due to the side-effects of chlorpromzine (Julien, 2005). Haloperidol became the drug-of-choice for treating schizophrenia throughout the 1970's and 1980's, but its side effects profile turned out to be similar to the phenothiazines. Similar to chlorpromazine and haloperidol, all other typical antipsychotic drugs exert their antipsychotic effects by blocking D_2receptors (Julien, 2005). The use of haloperidol, as well as the use of the other typical antipsychotic drugs, has been associated with the development of serious cognitive deficits such as lack of concentration and disorganized thought patterns as well as the serious motor disturbances known as extrapyramidal side effects (EPS).

As previously mentioned, the serious side effects associated with the typical antipsychotic drugs prompted an increase in pharmacological research that resulted in the production of the other typical antipsychotic drugs and eventually in the development of the atypical antipsychotic drugs. The first atypical antipsychotic drug introduced in the United States was Clozapine in 1991 (Julien, 2005). Other atypical antipsychotic drugs include quetiapine, olazapine, and risperidone (McElwain, unpublished thesis). In contrast to the typical antipsychotic drugs, atypical antipsychotic drugs are thought to exert their antipsychotic effects in a number of different ways. Risperidone, one of the most commonly prescribed atypical antispychotics, is a D_2 and 5-HT_2 inhibitor (Julien, 2005). Research suggests that atypical antipsychotic drugs are effective in reducing the negative symptoms of schizophrenia as well as the positive symptoms (Julien, 2005). A second significant characteristic of atypical antipsychotic drugs is the lack of extrapyramidal side effects associated with their use.

The high prevalence of extrapyramidal side effects associated with typical antipsychotic drug regimens is one factor in the diminishing popularity of the typical antipsychotic drugs and the increased popularity of the atypical antipsychotic drugs in the treatment of schizophrenia. The low prevalence of extrapyramidal side effects among atypical antipsychotic drugs is certainly a vital characteristic of this class of drug. There may be, however, extraneous variables that account for the different prevalence of EPS between the typical and atypical antipsychotic drugs. For instance, it is not clear how dosage rates of each class of antipsychotic drug influence the prevalence rates of EPS. At clinically equivalent dosages, or the doses that are typically prescribed for each type of drug, is the emergence of EPS significantly greater for the typical antipsychotic drugs? Are the differences seen between the two classes truly due to the drug type (typical vs. atypical) or to the typical prescribed doses of the drugs? These are important questions that could have a tremendous impact on the way schizophrenia is treated in the future. The present study will attempt to determine if there is a significant difference in EPS between haloperidol, a typical antipsychotic drug that exerts its clinical effects through the blockage of D_2 receptors, and risperidone, an atypical antipsychotic drug that inhibits both D_2 receptors and 5-HT_2 receptors (Julien, 2005).

Ketamine, an antagonist at the glutamate NMDA receptor is commonly used as a veterinary anesthetic. At sub-anesthetic doses, it has also been shown to produce the typical and atypical symptoms of schizophrenia in humans via the NMDA or serotonergic pathway and has therefore been used to create both human and animal models of psychosis (Keilhoff, et al., 2004). Both the human model of ketamine-induced psychosis and the rat model of ketamine-induced psychosis show both positive-like symptoms such as disorganized behavioral patterns and negative-like symptoms such as apathy and social withdrawal that are typical in individuals with schizophrenia (Keilhoff, et al., 2004). In addition to the observable behavioral changes evident in rats treated with ketamine (face validity), construct validity has been illustrated by increased D_2 binding in the hippocampus and characteristic changes in both serotonergic and dopaminergic pathways (Keilhoff, et al., 2004). The fact that changes are observed in both the serotonergic and dopaminergic pathways supports the validity of the ketamine-model of schizophrenia, because similar changes can be observed in both the serotonergic and dopaminergic pathways of schizophrenic humans. While face validity and construct validity appear to be evident, it must be taken into consideration that it is not possible to conclusively determine if ketamine treated rats experience the positive symptoms of schizophrenia because rats cannot verbally communicate. This, however, is a limitation of animal research in general. By utilizing the rat model of ketamine-induced psychosis, it is possible to examine the clinical effects of antipsychotic drugs on individuals with schizophrenia without the use of human participants. The present study utilized the rat-model of ketamine-induced psychosis to compare the prevalence of extrapyramidal side effects, cognitive deficits, and emotional disturbances between the typical antipsychotic drug, haloperidol, and the atypical antipsychotic drug, risperidone.

Method

Subjects

Forty, healthy, male Long-Evans hooded rats, *Rattus norvegicus*, served as the subjects for this study. All rats were approximately 120 days old, weighed between 336 and 504 grams and were derived from the Western Illinois University animal colony. Due to the fact that rats are nocturnal, they were housed under reverse light cycle conditions (12 h dark/12 h light) so that all testing could take place during the animals' active period. Rats were housed in the animal colony in the basement of Waggoner Hall. The animals had free access to food and water at all times. Animal treatment was in accordance with the ethical standards of the American Psychological Association and Western Illinois University's Institutional Animal Care and Use Committee.

Apparatus

Alternation Task

A raised white wooden t-maze was utilized for the Alternation Task. The Alternation Task was used in order to test the subjects' spatial discrimination skills and short-term memory abilities (Berachchea et al., 2002). Deficits in spatial discrimination skills correspond to the cognitive deficits typical of schizophrenia. This maze consisted of a vertical runway (63.50 cm x 19.05 cm x 8.89 cm) connected perpendicularly to a horizontal runway (130.81 cm x 19.05 cm x 8.389 cm) in order to provide for a t-shaped enclosure. A removable wooden gate was constructed at the starting portion of the vertical section of the maze so that the experimenter could control the start of each trial. An erasable pencil line was drawn approximately five centimeters from the end of each arm of the maze in order to operationally define a *selection*. The rat was judged to have made a selection of an arm when his entire body crossed the line.

Open-Field Activity Task

A large (121.92 cm x 121.92 cm) wooden grid box was employed for the Open-Field Activity Task. The box was enclosed on all four sides with the floor being demarcated into grids consisting of sixteen (24.13 cm x 24.13 cm) squares. The sixteen squares were divided using colored electrical tape to construct an *outside* grid and an *inside* grid. The wooden grid box was partitioned into an *outside* and an *inside* grid in order to differentiate between crossings adjacent to the edges of the box from crossings in the central portion of the grid box. The Open-Field Activity task allowed the researcher to test for observable motor disturbances, hyperactivity, and anxiety. Any observable motor disturbances were measured by comparing the differences in grooming behaviors, total crossings, and the ratio between total and inside crossings among the treatment groups. The activity levels of the rats could easily be compared among the four treatment groups simply by counting the number of crossings, either *outside* crossings or *inside* crossings, each rat completed. Any noticeable motor disturbances could indicate the occurrence of EPS. By examining the total number of crossings performed in each of the four treatment groups, trends could be deciphered. Rats prefer dimly lit and enclosed spaces, and therefore normal rats tend to remain close to the edges of the grid box. An elevated number of *inside* (central) crossings could indicate cognitive or emotional disturbances, both of which are typical in schizophrenia.

Swim Test

An oblong (172.72 cm x 58.42 cm x 60.96 cm) metal water tank (i.e., horse feeding trough) was utilized for the timed Swim Test. A raised horizontal metal platform was placed toward the distal end of the tank. The tank was filled with opaque water prior to testing. Because rats find water to be aversive, they will reliably attempt to escape from the water-filled tank. This fact alone provides the justification for using this task. After being placed into water, normal rats will swim quickly to the platform, climb onto the platform, and dry themselves. Normal rats are typically able to swim to the platform with little difficulty. Therefore, any prolonged swim times or prolonged attempts to climb onto the platform could indicate perceptual, motoric, or mood disturbances. All the previously mentioned constructs are either common symptoms of schizophrenia or common side effects of antipsychotic drugs.

Procedure

All tasks were performed in a dimly-lit laboratory in the presence of a white-noise machine in order to reduce the stress placed upon the rats. Each rat had been handled by the researcher for a period of at least ten minutes before the study began in order to acclimate the rats to the researcher. Prior to initializing the study, the 40 rats were divided into four treatment groups of 10. The first group was designated as the *control* group and was assigned to receive saline injections at a volume of 20 ml/kg of body weight only. The second group of ten rats was designated as the *ketamine* group and was assigned to receive one saline injection (20 ml/kg of body weight) and one ketamine injection (20 ml/kg of body weight) each. The third treatment group was designated as the *ketamine/haloperidol* group and received one injection of haloperidol (a *typical* antipsychotic drug) at a volume of 0.5 ml/kg of body weight and one injection of ketamine at a volume of 20 ml/kg of body weight. The fourth treatment group was designated as the *ketamine/risperidone* group and received one injection of risperidone (an *atypical* antipsychotic drug) at a volume of 1.0 ml/kg of body weight and one injection of ketamine (20 ml/kg of body weight).

All 40 rats were tested over a period of four days: 9 rats on day one, 11 rats on day two, 9 rats on day three, and 11 rats on day four. Each day the rats were tested in alternating order (*control group, ketamine group, ketamine/haloperidol, ketamine/risperidone*) in order to account for any extraneous time variables. Each rat was weighed prior to their first injection in order to monitor the rats' health throughout the testing period and to determine the correct drug doses.

Each day of testing, the *control* group rats were first injected with saline at a volume of 20 ml/kg of body weight. Twenty five minutes after their first injections, the rats were given a second injection of saline in order to keep the routine of all treatment groups the same. Five minutes after their second injections of saline, the rats were tested on all three tasks. The *ketamine* group rats were first injected with saline at a volume of 20 ml/kg of body weight. Twenty-five minutes after their first injections of saline, they were given injections of ketamine at a volume of 20 ml/kg of body weight in order to induce schizophrenic-like symptoms. The volume of 20 ml/kg was selected after examining prior research and selecting a moderate dose. Five minutes after their second injections (first injection of ketamine), the rats underwent testing. The *ketamine/haloperidol* rats were first given injections of haloperidol at volume of 0.5 ml/kg of body weight. This volume was selected in the same manner as the level of ketamine. Twenty-five minutes after their first injections, they were injected with ketamine at a volume of 20 ml/kg of body weight in order to induce schizophrenic-like symptoms. Ketamine was injected after the haloperidol in order to allow for the haloperidol to circulate throughout the rats' bodies prior to the ketamine injection. Five minutes after being injected with the ketamine, the rats were tested on all three tasks. The *ketamine/risperidone* rats were first injected with risperidone at a volume of 1.0 ml/kg of body weight. This volume was selected as a moderate dose after researching prior work. Twenty-five minutes later, they received injections of ketamine at a volume of 20 ml/kg of body weight. The risperidone was injected twenty-five minutes after the ketamine injection in order to allow for the risperidone to circulate throughout the rats' bodies prior to the ketamine injection.

The first task each rat completed was the Alternation Task (t-maze) used to measure spatial discrimination skills and short-term memory. The rats underwent 10 trials of this test in order to elicit an appropriate amount of data for analysis. Using an even number of trials also made it possible for the rats to select each direction (right and left) an equal number of times. Each rat was placed in a gated compartment located at the front of the vertical section of the t-maze prior to testing. Once the rat was securely within the gated area, the gate was opened and timing began. Each rat was given 60 seconds to run down the vertical section of the t-maze and make a selection as to whether to turn right or left down the horizontal section of the maze. After the rats had turned right or left, their choice was recorded as *L* or *R* if they crossed over the pencil line. If the rats did not make a selection within 60 seconds, the trial was recorded as "60 seconds." After each rat had made his choice on a given trial, they were placed back in the gated section of the vertical portion of the maze to await their next trials. In between each trial, all visible signs of urine/feces were removed.

After completing the Alternation Task, the rats were put through an Open-Field Activity Task. As previously mentioned, the grid box had been partitioned into *outside* and *inside* squares in order to differentiate between border crossings and central crossings. The number of border crossings versus the number of central crossings can be compared to test for constructs such as motor disturbances and anxiety. To begin testing, each rat was placed in the middle of the open grid box. Each rat was allowed to explore the box for a period of five minutes. During this five minute period, the number of *outside* boxes the rats crossed and the number of *inside* boxes the rats crossed were recorded. The rat was considered to have crossed into an adjacent square once his front two paws were firmly planted in the adjacent square. The number of inside crossings and the number of outside crossings were recorded independently. In addition to the number of *outside* and *inside* crossings the rats made, the total number of crossings and the number of times each rat groomed himself was recorded.

After the rats completed the Open-Field Activity Task, they were put through a Swim Test. Each rat was placed in the proximal end of an oblong water tank filled with opaque water. The rats were first timed as to how long it took them to locate a platform raised slightly above the water and positioned at the distal end of the tank. The rats were considered to have located the platform once their tails touched any part of the platform. Rats were allowed five minutes to locate the platform. The amount of time taken to locate the platform was recorded. If they did not reach the platform within five minutes, they were removed from the tank and received a score of five minutes. No further testing was done on these animals. The rats that did successfully reach the platform were then timed as to how long it took them to physically climb onto the platform. Their entire body had to be on the platform for the trial to be scored as successful. After having located the platform, the rats were given a time period of one minute to climb onto the platform. If the rats could not climb onto the platform within one minute, they were given a score of one minute.

Results

Alternation Task

After all 40 rats had been run; it became obvious that the data collected from the Alternation Task was of no value. Each of the rats was put through ten trials of the Alternative Task. None of the 40 rats completed all ten trials. The vast majority of the rats did not even complete five out of the ten trials. This could have been due to experimenter error because previous researchers have used this test successfully. As opposed to previous research, the rats were not tested on the t-maze prior to testing and did not receive rewards for their first correct response. Due to the lack of findings, the results from this task were discarded and not included in data analyses.

Open-Field Activity Task

Grooming Behavior

For the Open-Field Activity Task, three different dependent variables were analyzed: the total number of crossings, the ratio of inside crossings to total crossings per rat, and the number of grooming behaviors per rat. Due to the fact that the variances between groups were non-homogenous, non-parametric tests were utilized to analyze the data from for all three dependent variables. A Kruskal-Wallis test indicated a significant difference (See Figure 1.A) among the four treatment groups for the total number of grooming behaviors per treatment group, H = 14.46 (3, N = 40), p = 0.002. After finding this significant Kruskal-Wallis test statistic, Mann-Whitney U tests were run to compare the grooming behavior ranks amongst the *control* group (N = 10), the *ketamine* group (N = 10), the *ketamine/haloperidol* group (N = 10), and the *ketamine/risperidone* group (N =1 0). Significant differences were found between the *control* group and the *ketamine* group, U = 23.00, p = .016, indicating that rats treated with ketamine showed significantly higher levels of anxiety than the control rats. Significant results were indicated between the *control* group and the *ketamine/haloperidol* group, U = 20.00, p = 0.005 indicating that the *ketamine/haloperidol* rats showed significantly more grooming than the *control* group. Finally, significant results were also found between the *control* group and *ketamine/risperidone* group, U = 23.00, p = 0.016, indicating that the *ketamine/risperidone* group also showed significantly more grooming behaviors than the *control* group rats. None of the remaining comparisons were significant (*ketamine* vs *ketamine/haloperidol, ketamine* vs *ketamine/risperidone,* and *ketamine/haloperidol* vs *ketamine/risperidone.*) These results suggest that exposure to any of the three drug regimens (*ketamine, ketamine/haloperidol, ketamine/risperidone*) increased grooming behavior, a measure that is likely indicative of increased anxiety among these drug-exposed rats.

Total Crossings

Analysis of the total crossing test variable using a Kruskal-Wallis test indicated a significant difference (See Figure 2.A) among the four treatment groups, H = 16.26 (3, N = 40), p = 0.001. Mann-Whitney U tests were run post-hoc in order to identify the specific significant differences among the *control* (N =1 0), *ketamine* (N = 10), *ketamine/haloperidol* (N = 10), and *ketamine/risperidone* groups (N = 10). Significant results were found between the *control* group and the *ketamine* group, U = 11.0, p = 0.003], indicating a significantly higher level of locomotor activity in the rats treated with ketamine. No significant difference was found between the *control* group and the *ketamine/haloperidol* group, U = 30.5, p = 0.140 or between the *control* group and the *ketamine/risperidone* group, U = 50.0, p = 1.00 Significant results were found between the *ketamine* group and the *ketamine//haloperidol* group, U = 7.5, p = 0.001, indicating a significantly lower level of locomotor activity in the *ketamine/haloperidol* group. Significant results were found between the *ketamine* group and the *ketamine/risperidone* group, U = 9.0, p = 0.002 indicating a significantly lower level of locomotor activity in the rats treated with risperidone. No difference was indicated between the *ketamine/haloperidol* group and the *ketamine/risperidone* group, U = 33.00, p = 0.198. Thus, although ketamine increased locomotor activity (compared to controls), this effect was reversed by exposing rats to either of the two antispsychotic drugs.

Inside/Total Ratio

Analysis of the *Inside/Total* crossings using a Kruskal-Wallis test indicated a significant difference (See Figure 3.A) among the four treatment groups, H = 8.81 (3, N = 40), p = 0.032. Mann-Whitney U tests were run post-hoc in order to identify the specific significant differences amongst the *control* group (N = 10), the *ketamine* group (N = 10), the *ketamine/haloperidol* group (N = 10), and the *ketamine/risperidone* group (N = 10). No significant differences were observed between the *control* group and the *ketamine* group U = 37.0, p = 0.33, between the *control* group and the *ketamine/haloperidol* group U = 21.0, p = 0.28, between the *control* group and the *ketamine/risperidone* group U = 44.0, p = 0.650, or between the *ketamine* group and the *ketamine/risperidone* group U = 46.0, p = 0.762. Significant results were found between the *ketamine* and the *ketamine/haloperidol* groups, U = 16.0, p = 0.01, indicating an increased ratio of inside-to-outside crossings (i.e., increased anxiety) in rats treated with haloperidol compared to rats treated only with ketamine. The *ketamine/haloperidol group* also had a higher ratio than and the *ketamine/risperidone* group U = 21.5, p = 0.031, indicating lower anxiety levels in the rats treated with haloperidol.

Swim Test

Reach Time

The swim test was used to measure drug effects on locomotor activity and perceptual processes. Two dependent variables were analyzed: latency to reach the raised platform and the time it took the rats to climb onto the platform. Non-parametric statistics were used instead of an ANOVA to account for violations of the homogeneity of variance assumption. A Kruskal-Wallis test indicated a significant difference (See

Figure 4.A) among the four treatment groups in the time it took to reach the platform, H = 11.954, (3, N = 40), p = 0.008. Mann-Whitney U tests were conducted post-hoc to compare group differences. The *control* group and the *ketamine* group did not differ significantly, U = 45.0, p = 0.704. Significant results were found between the *control* group and the *ketamine/haloperidol* group, U = 6.0, p = 0.0, indicating that the haloperidol did have a significant detrimental effect on locating the platform. No significant results were found between the *control* group and the *ketamine/risperidone* group, U = 26.0, p = 0.068. Significant results were found between the *ketamine* and *ketamine/haloperidol* groups, U = 23.0, p = 0.017, once again indicating that haloperidol impaired animals' abilities to locate the platform. No significant results were found between the *ketamine* and *ketamine/risperidone* groups, U = 39.0, p = 0.383. No significant results were found between the *haloperidol* and *risperidone* groups, U = 30.5, p = 0.069.

Platform Climb

A Kruskal-Wallis test on the latency to climb onto the platform indicated significant differences (See Figure 5.A) among the four treatment groups, H = 13.328 (3, n = 40), p = 0.004. Mann-Whitney U tests were conducted to locate the differences among the *control* group (N = 10), the *ketamine* group (N = 10), the *ketamine/haloperidol* group (N = 10), and the *ketamine/risperidone* group (N = 10). Significant results were found between the *control* and *ketamine* groups, U = 20.5, p = 0.019, indicating that ketamine does induce significant locomotor effects. Significant results were found between the *control* and *ketamine/haloperidol* groups, U = 11.0, p = 0.001, indicating that haloperidol exerts significant locomotor side effects. A significant difference was indicated between the *control* and *ketamine/risperidone* groups, U = 19.0, p = 0.014. This phenomenon could be due to the motor effects exerted by ketamine, which apparently were not alleviated by treatment with either antipsychotic drug. It may also indicate that risperidone causes significant motor side effects. No significant differences were found between the *ketamine* and *ketamine/haloperidol* groups, U = 40.0, p = 0.279, the *ketamine* and *ketamine/risperidione* groups, U = 50.0, p = 1.0, and the *ketamine/haloperidol* and the *ketamine/risperidone* groups, U = 40.5, p = 0.304. The fact that the previous three tests did not indicate significant differences in motor effects could indicate that the ketamine, and not the antipsychotic drugs, were causing the observed motor effects.

Discussion

An analysis of the Open Field Activity Task results yielded some interesting findings. When analyzing the grooming behavior results from the Open Field Activity Task, significant differences were found between the *control* group and the other three treatment groups. No significant differences were found between the *ketamine* and *ketamine/haloperidol* groups, the *ketamine* and *ketamine/risperidone* groups, or the *ketamine/haloperidol* and *ketamine/risperidone* groups. These facts provide support for the ketamine-model of schizophrenia because they indicate significant differences in anxiety-like behavior between the *control* group and the groups treated with ketamine. Differences in anxiety levels are also noticeable between the *control* groups and the groups treated with antipsychotic drugs. The fact that no significant anxiety-like behavioral differences were found between the *ketamine* group and the groups treated with the antipsychotic drugs supports the idea that the observed significant differences in anxiety-like behavior were due to the ketamine rather than the antipsychotic drugs.

Findings from the total crossings test also provide support for the ketamine-model of schizophrenia. While significant differences were found between the *control* group and the *ketamine* group, no significant differences were found between the *control* group and the groups treated with the antipsychotic drugs. The large significant difference between the *control* group and the *ketamine* group supports the idea that ketamine can induce the motor disturbances typical in schizophrenia. The total crossing test also supports the efficacy of both haloperidol and risperidone in reducing impairments. The fact that significant differences were found between the *control* group and the *ketamine* group but not between the *control* group and the groups treated with either haloperidol or risperidone indicates that the motor disturbances evident in the *ketamine* group were reversed by the antipsychotic drug treatment. The total crossings test does not support the hypothesis that typical antipsychotic drugs induce more motor disturbances in individuals with schizophrenia than atypical antipsychotic drugs because no significant differences were found between the group treated with haloperidol and the group treated with risperidone.

The timed Swim Test yielded some valuable results both statistically and observationally. While the results from the Open Field Activity Task suggested that the ketamine induced increased locomotor activity and decreased anxiety, the results from the swim test indicate that the antispsychotic drugs themselves may have induced some motor disturbances as well. When analyzing how long it took the rats to reach the raised platform in the water tank, no significant differences were found between the *control* group and the *ketamine* group. A significant difference was found between the *control* group and the *ketamine/haloperidol* group, and while no significant difference was found between the *control* group and the *ketamine/risperidone* group, the p-value was only slightly above the significance level of 0.05. This indicated that the motor disturbances found in this test were due largely to the antipsychotic drugs rather than the ketamine. The results from this test may also indicate a higher prevalence of motor effects for the typical antipsychotic drug (haloperidol) than the atypical antipsychotic drug (risperidone). A significant difference was found between the *ketamine* rats and the *ketamine/haloperidol* rats but not between the *ketamine* rats and the *ketamine/risperidone* rats. The fact that haloperidol caused a significant detriment to locomotor activity and risperidone did not, may indicate that typical antipsychotic drugs exert more motor side effects than atypical antipsychotic drugs. In contrast, however, no significant results were yielded between the *ketamine/haloperidol* rats and the *ketamine/risperidone* rats. Therefore, it is also possible that the observed locomotor deficits were due to a *reaction* between the ketamine and the haloperidol rather than the haloperidol alone.

The time it took for the rats to climb onto the platform after reaching it was also analyzed. Rats will readily climb out of water if able, and any prolonged time spent in the water is indicative of possible motor or cognitive disturbances. The results from this test again supported the ketamine-model of schizophrenia because significant differences were found between the *control* group rats and the *ketamine/haloperidol* and between the *control* group rats and the *ketamine/risperidone* rats but not between the *ketamine* rats and either the *ketamine/haloperidol* rats or the *ketamine/risperidone* rats. No significant differences were found between the *ketamine/haloperidol* group and the *ketamine/risperidone* group.

Statistically significant results were not the only interesting results obtained from the Swim Test. Potentially valuable behavioral changes were noted among the rats treated with haloperidol. Nine out of the ten rats treated with the haloperidol did not reach the raised platform within the five minute allotted period. These rats would swim close to the platform but would never acknowledge that they noticed the platform. They would simply continue to swim for the entire five minutes. Three of the haloperidol-treated rats had to be rescued from drowning, and one of the haloperidol-treated rats drowned. In addition to the effects observed in the haloperidol rats, four other rats treated with ketamine had to be saved and one other rat drowned. The seven rats that had to be saved and the two rats that died would turn vertically and relax their bodies prior to sinking to the bottom of the tank. This is interesting due to the fact that the rats only had to swim for a period of five minutes before being removed from the tank. Rats can typically swim for much longer periods of time. It appeared as if these rats simply quit fighting and "gave up". This observation suggests that the ketamine-model of schizophrenia could possibly be utilized as a rat-model of depression.

This current research yielded valuable results that could potentially inspire future research. For instance, this current research would yield much more interesting results if designed as a longitudinal study. Only the acute effects of ketamine, haloperidol, and risperidone could be assessed through this research. Most, if not all, individuals with schizophrenia are on antipsychotic drugs for many years. By longitudinally studying the ketamine-model of schizophrenia, more applicable results could be obtained. In future studies of this type, it would also be beneficial to videotape the rats when tested. Doing this could allow the researcher to re-evaluate the rats for motor effects that could not be evaluated during the testing period. Another change that could improve this research would be to train the rats on the t-maze prior to testing the rats. In addition to training the rats, rewarding the rats on their first correct alternation could produce more reliable results. This has been shown to be effective in other research (Berachchea et al., 2004).

In addition to continuing this current research, it could be beneficial to examine the relationship between ketamine and depression. As previously mentioned, two of the ketamine-treated rats appeared to give up swimming prior to becoming physically exhausted and another seven rats had to be rescued. This could be indicative of depression. Ketamine is a common veterinary anesthetic and therefore is easily accessible. Utilizing a common drug for research on depression could make such research easier to conduct.

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Figures

<u>Open-Field Task:</u>

Figure 1.A: Mean Number of Grooming Behaviors in the Open-Field Activity Task per Treatment Group.

Figure 1.B: Standard Error of Measurement of Grooming Behaviors in the Open-Field Activity Task per Treatment Group.

Figure 2.A.: Mean Number of Total Crossings of the Open-Field Activity Task per Treatment Group.

Figure 2.B.: Standard Error of Measurement of Grooming Behaviors in the Open-Field Activity Task per Treatment Group.

Figure 3.A.: Ratios of Inside Crossings to Total Crossings in the Open-Field Activity Task per Treatment Group.

Figure 3.B.: Standard Error of Measurement of Inside Crossings to Total Crossings in the Open-Field Activity Task per Treatment Group.

<u>Swim Task:</u>

Figure 4.A.: Mean Swim Time (seconds) to the Raised Platform.

Figure 4.B: Standard Error of Measurement of Mean Swim Time.

Figure 5.A.: Mean Climb Time (seconds).

Figure 5.B.: Standard Error of Measurement of Mean Climb Time.

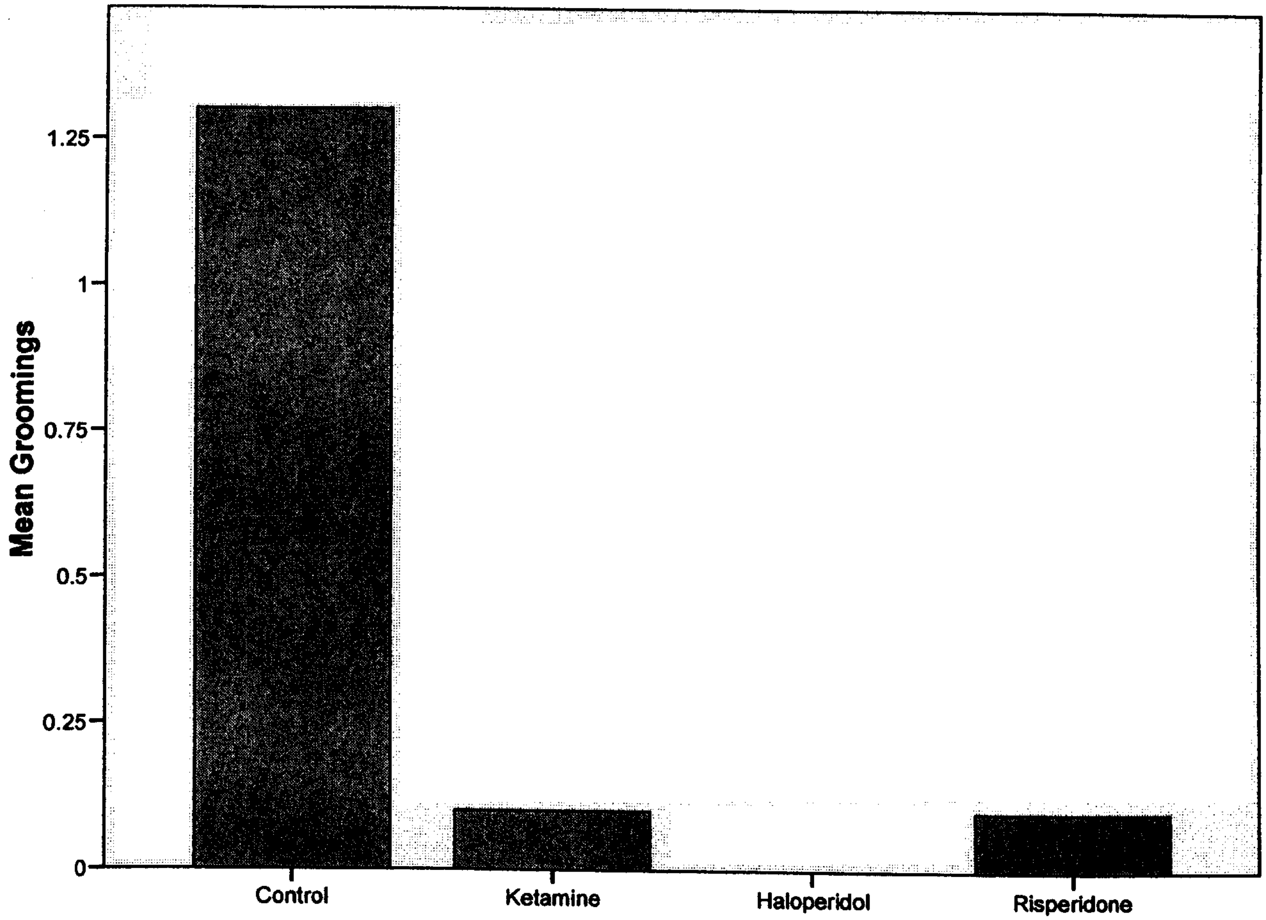

Figure 1.A- Mean Number of Grooming Behaviors in the Open-Field Activity Task per Treatment Group.

Decreased Grooming

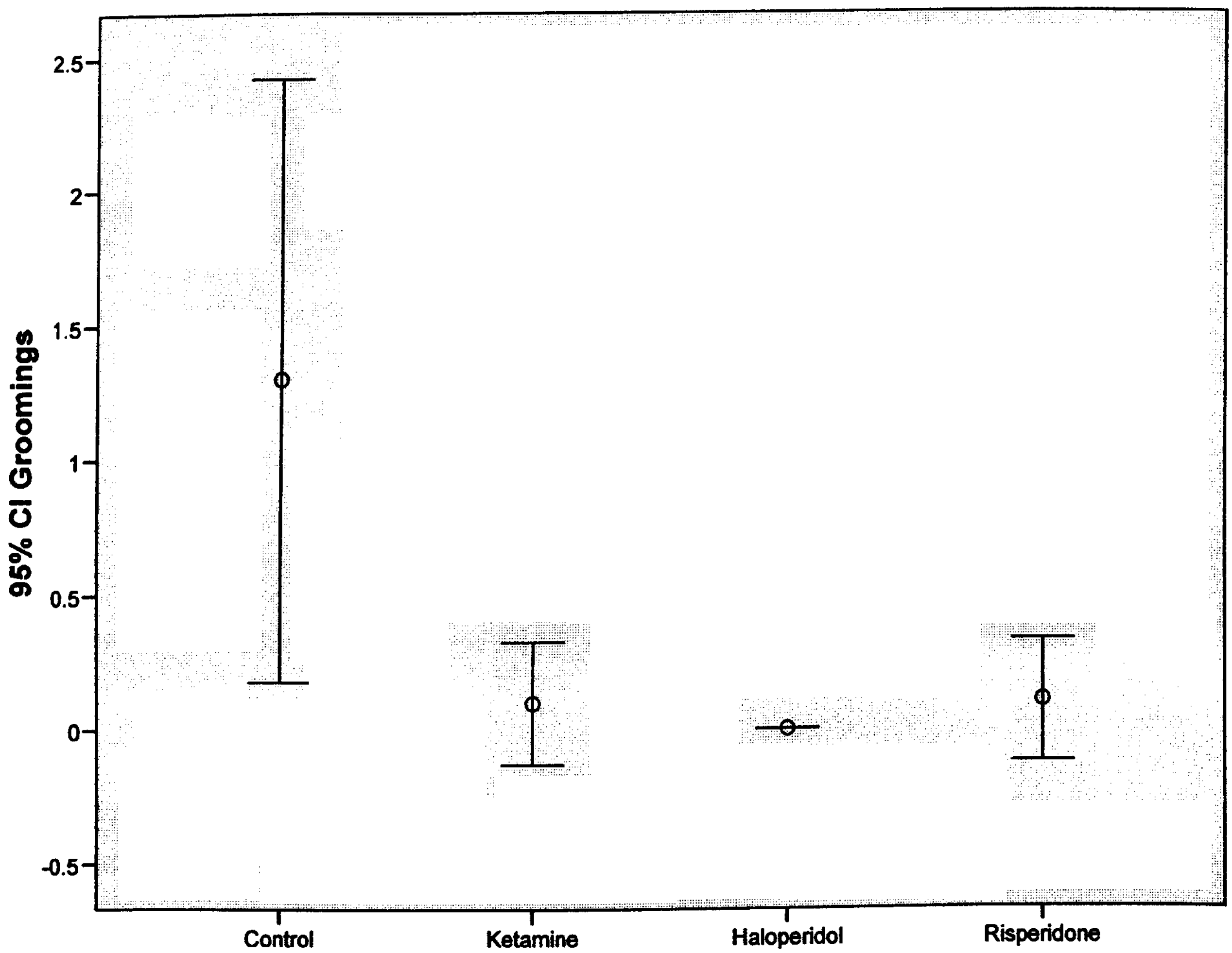

Figure 1.B- Standard Error of Measurement of Grooming Behaviors in the Open-Field Activity Task per Treatment Group.

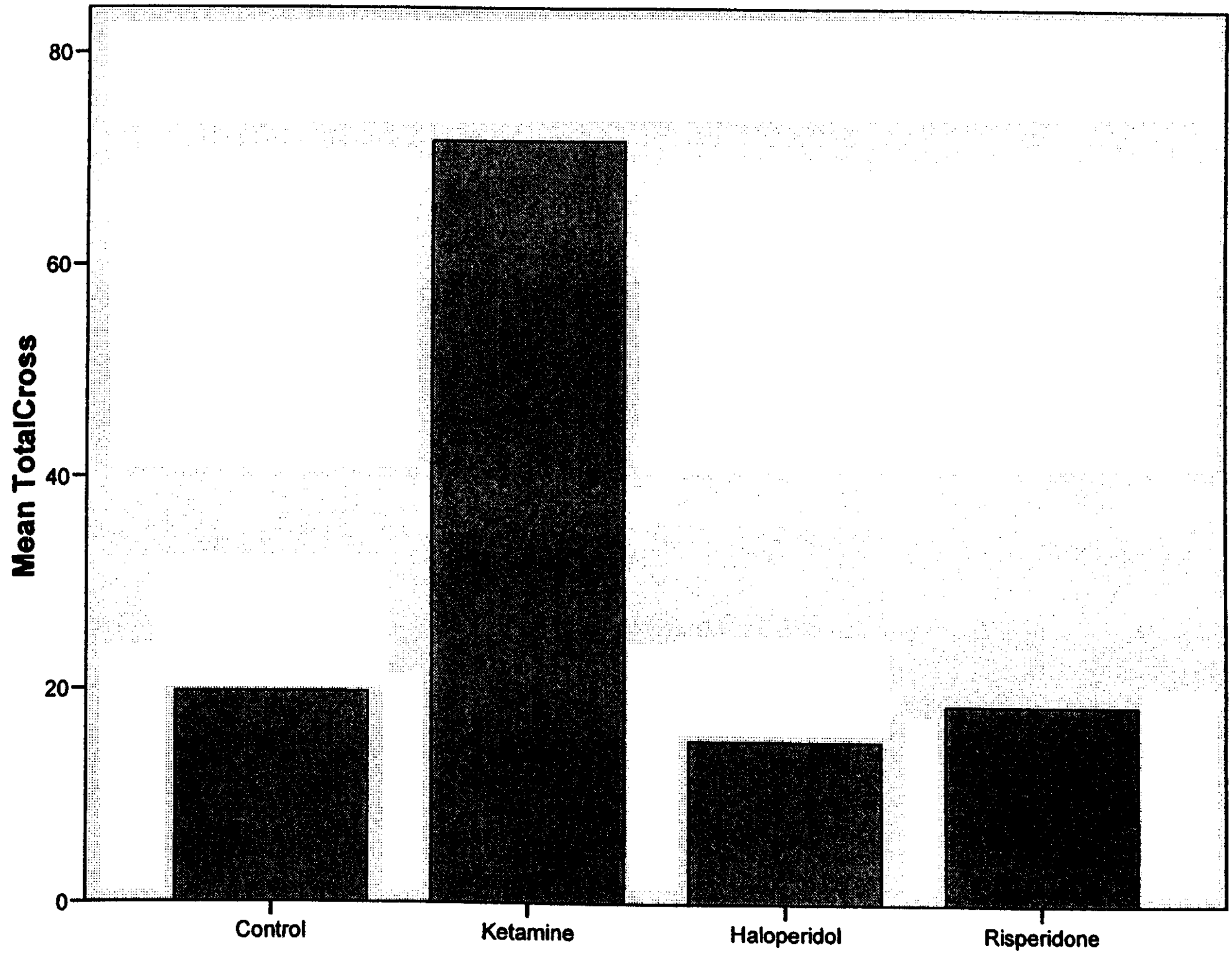

Figure 2.A- Mean Number of Total Crossings of the Open-Field Activity Task per Treatment Group.

More Crossings for Ketamine Rats

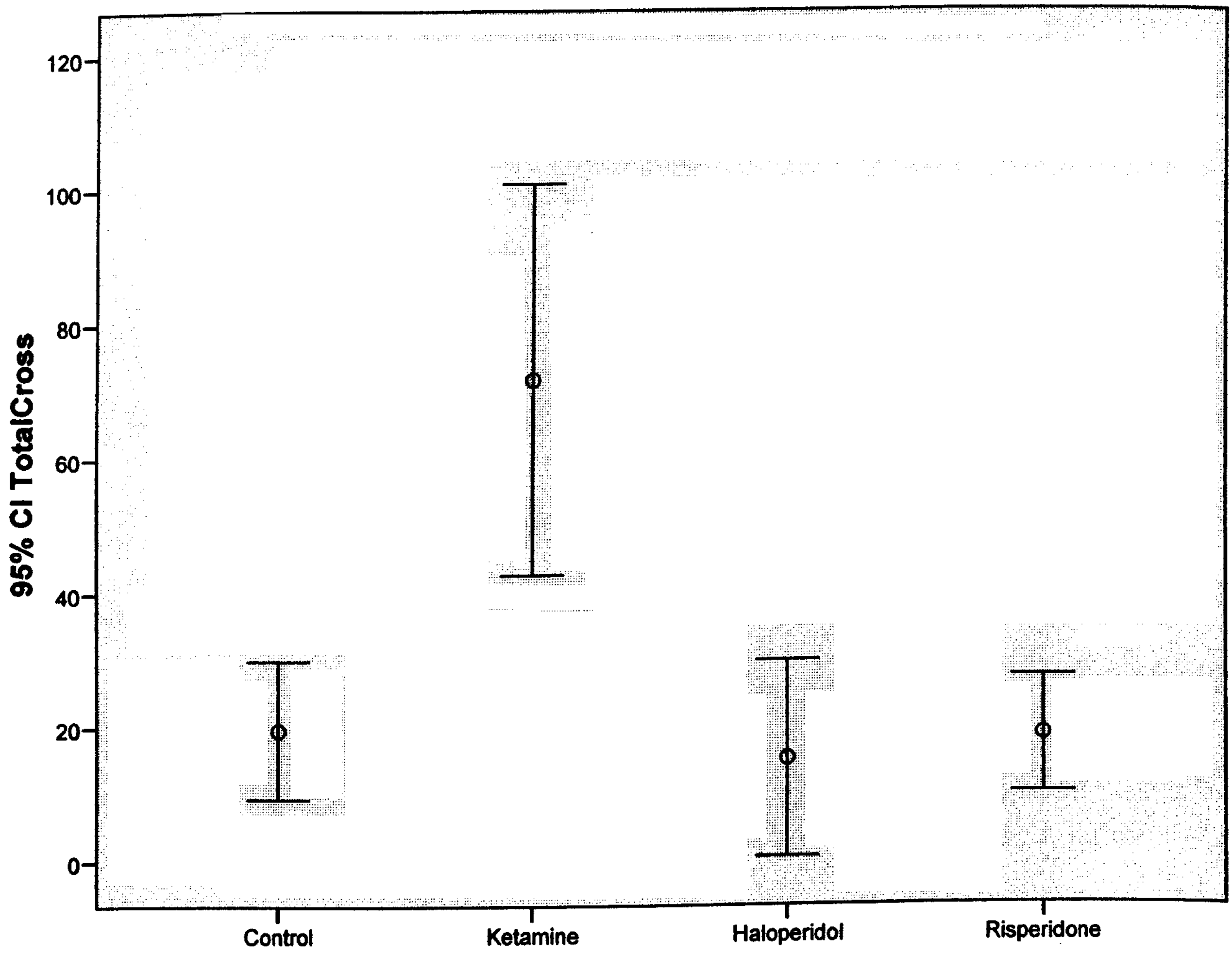

Figure 2.B- Standard Error of Measurement of Grooming Behaviors in the Open-Field Activity Task per Treatment Group.

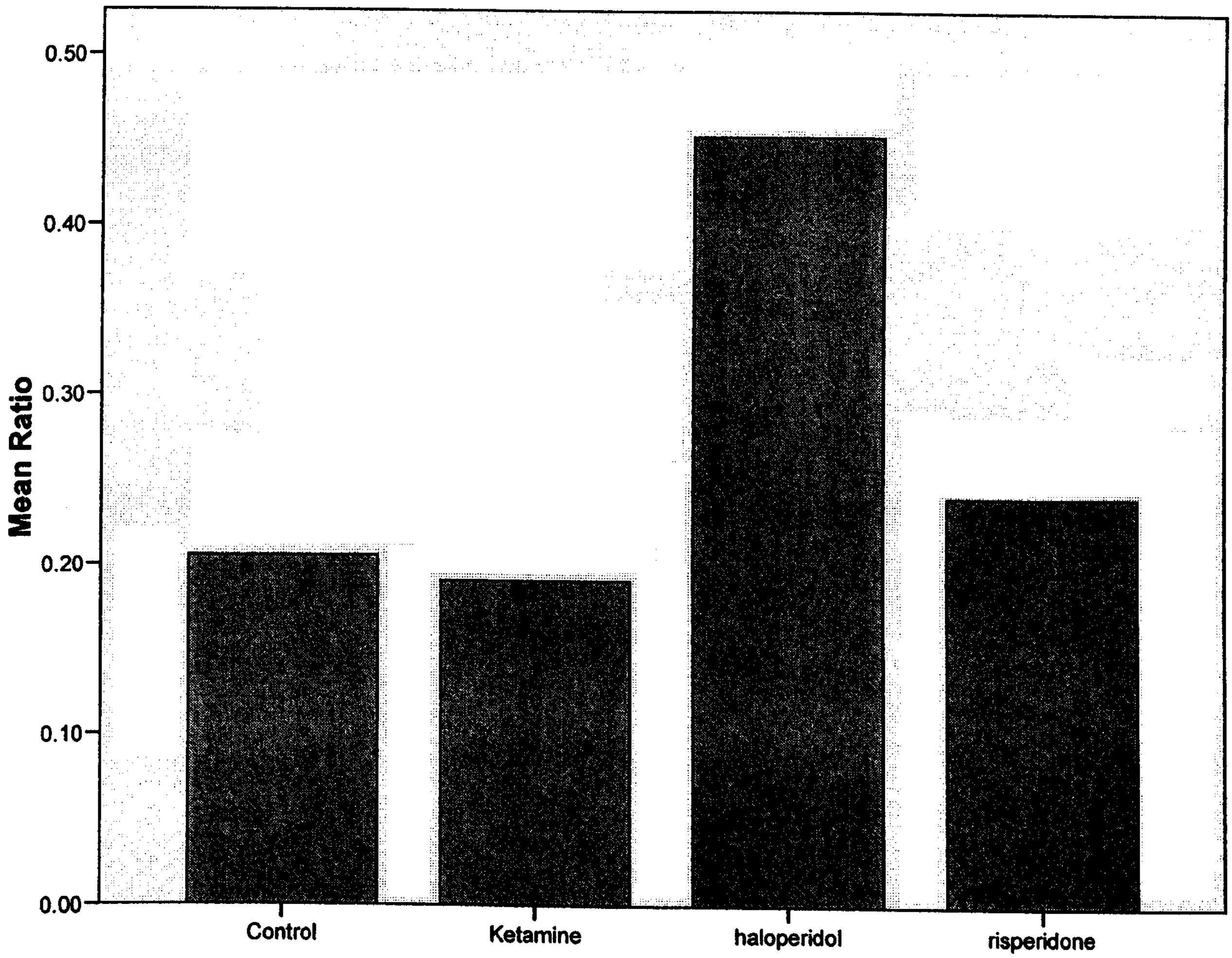

Figure 3.A- Ratios of Inside Crossings to Total Crossings in the Open-Field Activity Task per Treatment Group.

More Inside/Total for Ketamine and Haloperidol

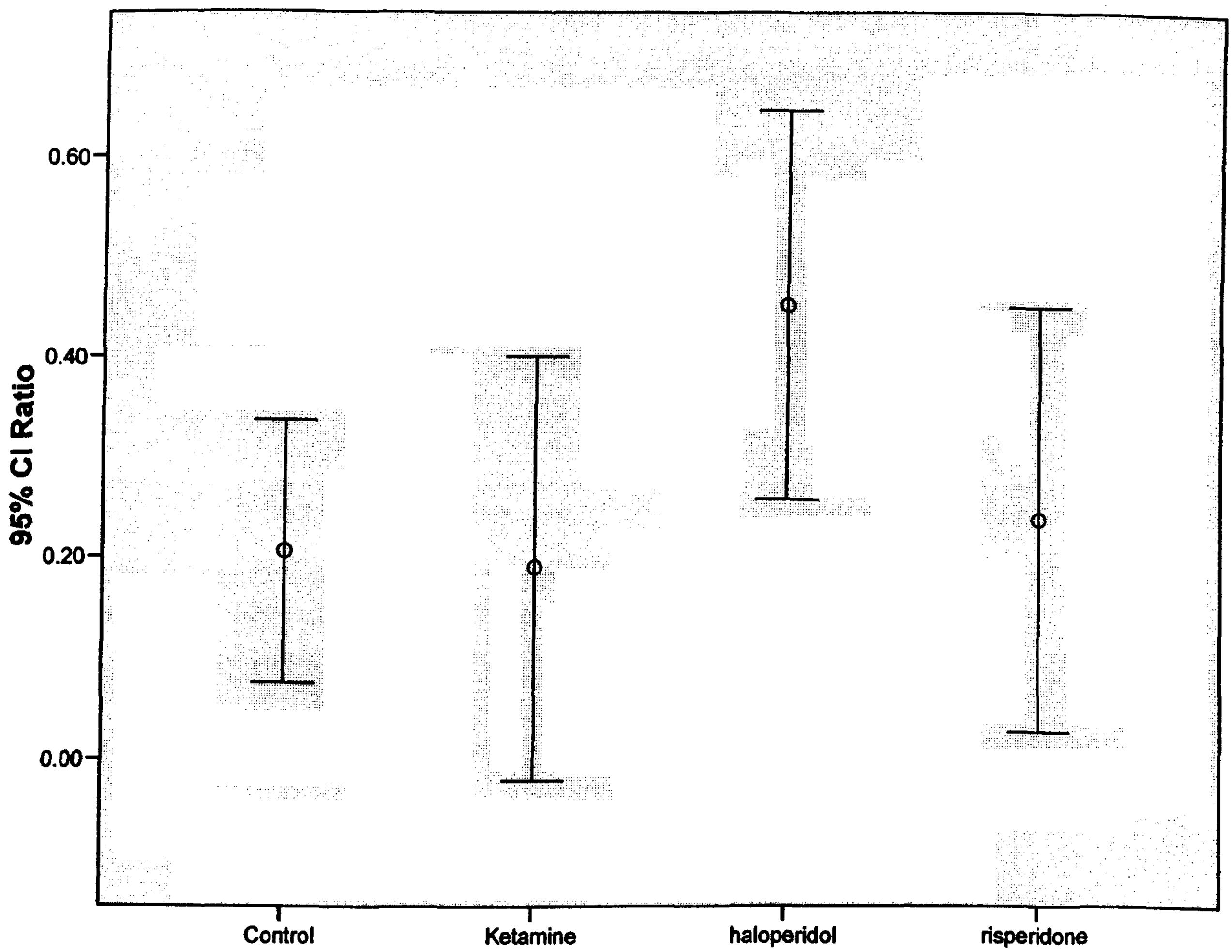

Figure 3.B- Standard Error of Measurement of Inside Crossings to Total Crossings in the Open-Field Activity Task per Treatment Group.

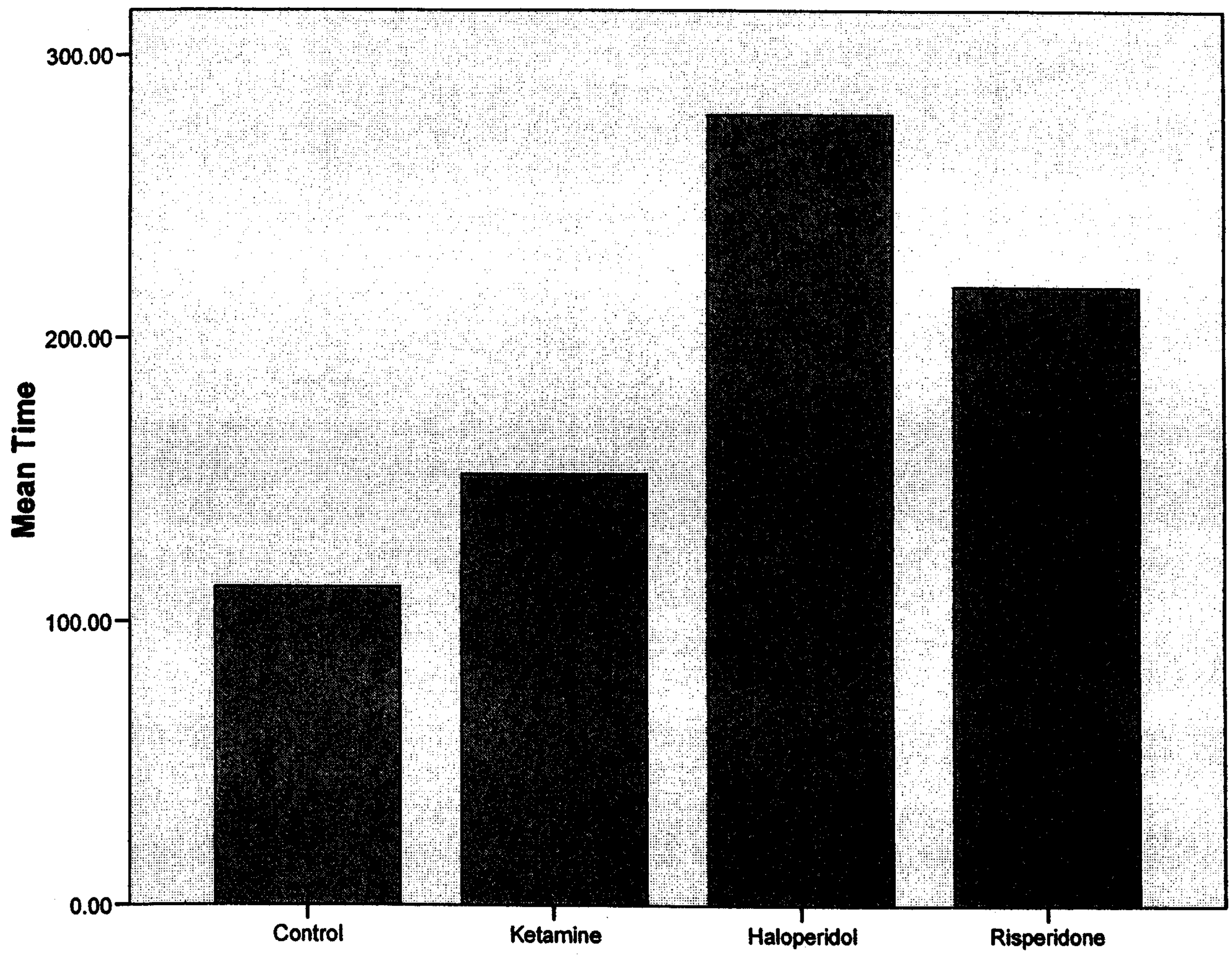

Figure 4.A- Mean Swim Time (seconds) To the Raised Platform.

Increased Latency for Ketamine, Ketamine/Haloperidol, Ketamine/Risperidone

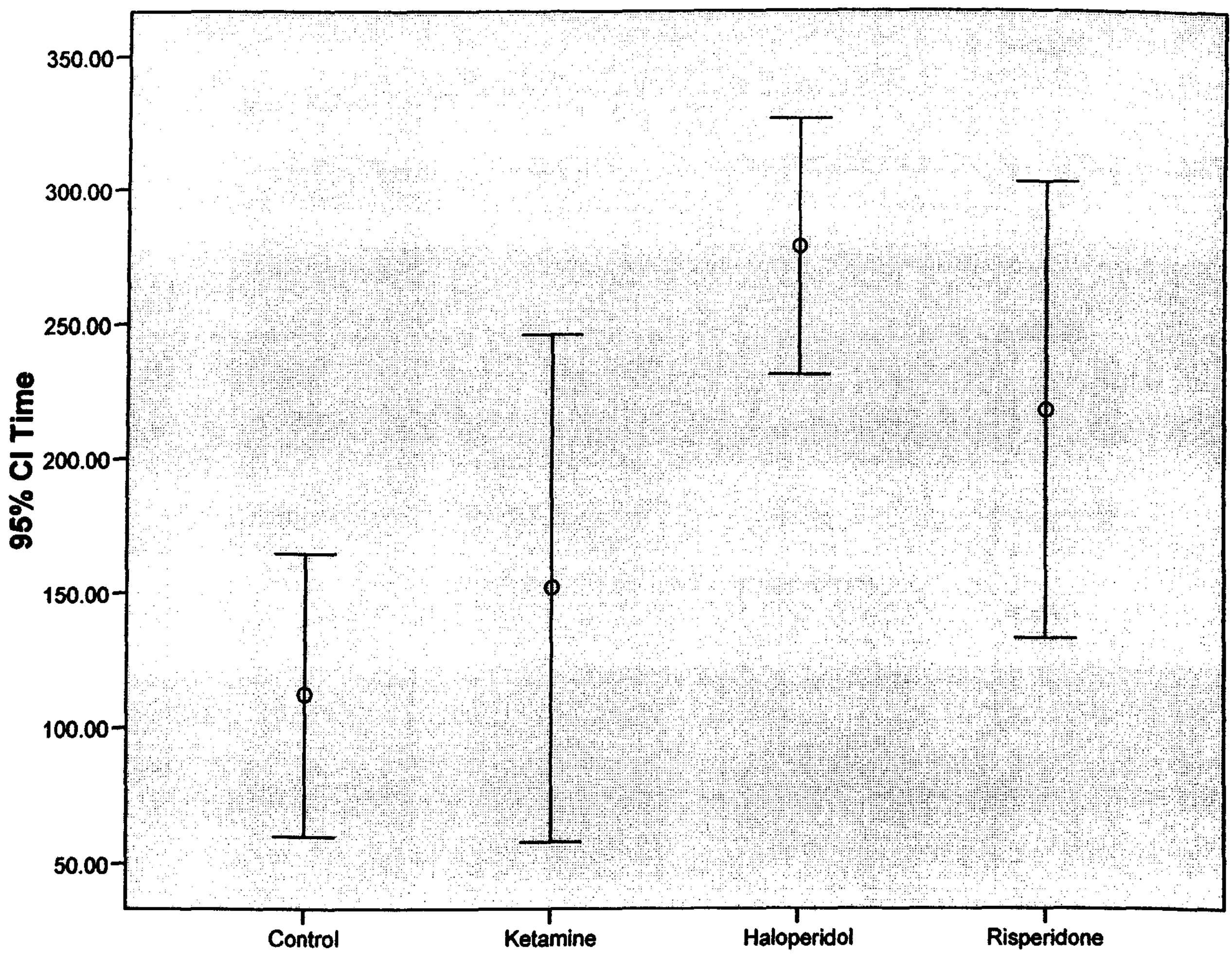

Figure 4.B- Standard Error of Measurement of Mean Swim Time.

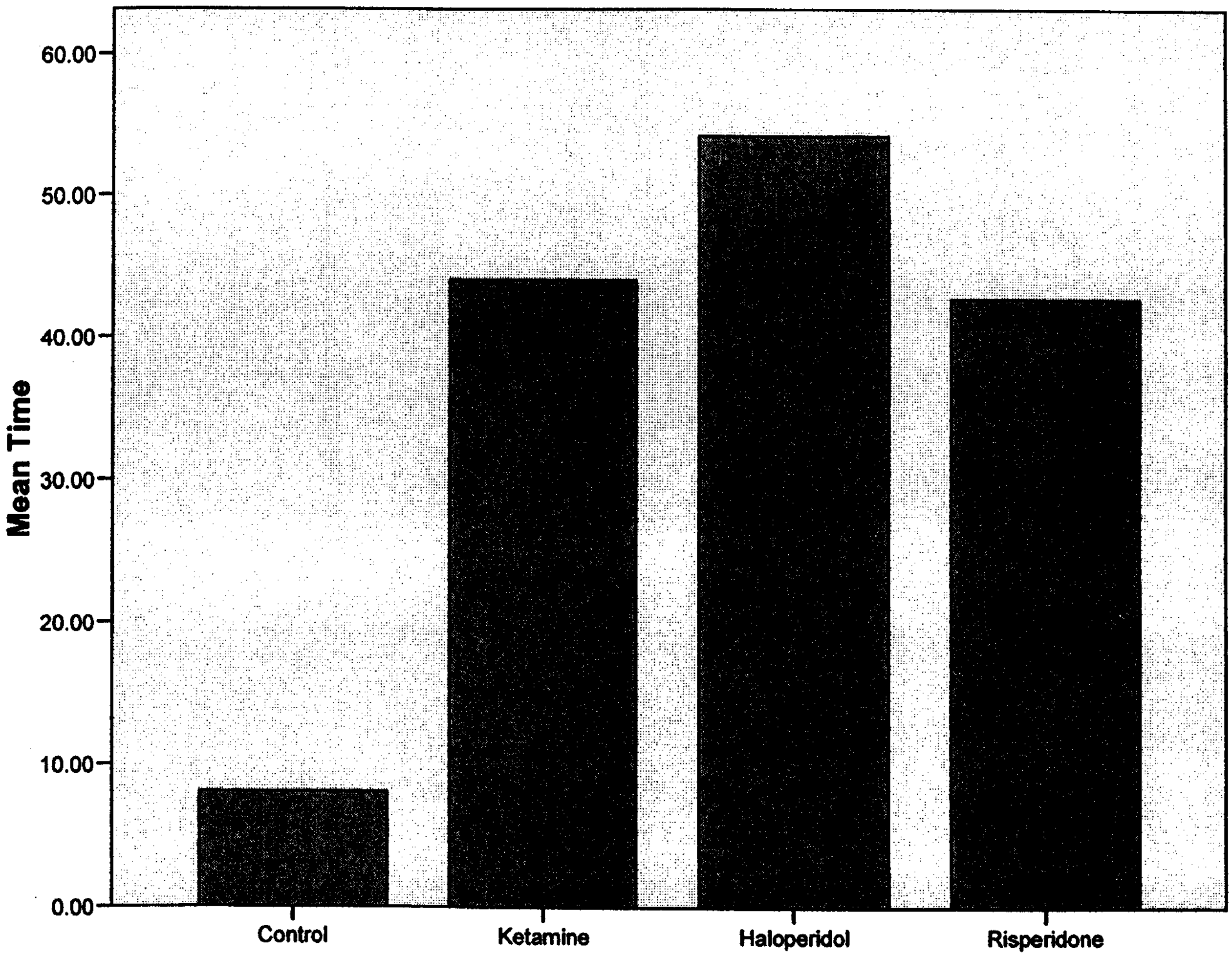

Figure 5.A- Mean Climb Time (seconds).

Increased Latency for Ketamine, Ketamine/Haloperidol, Ketamine/Risperidone

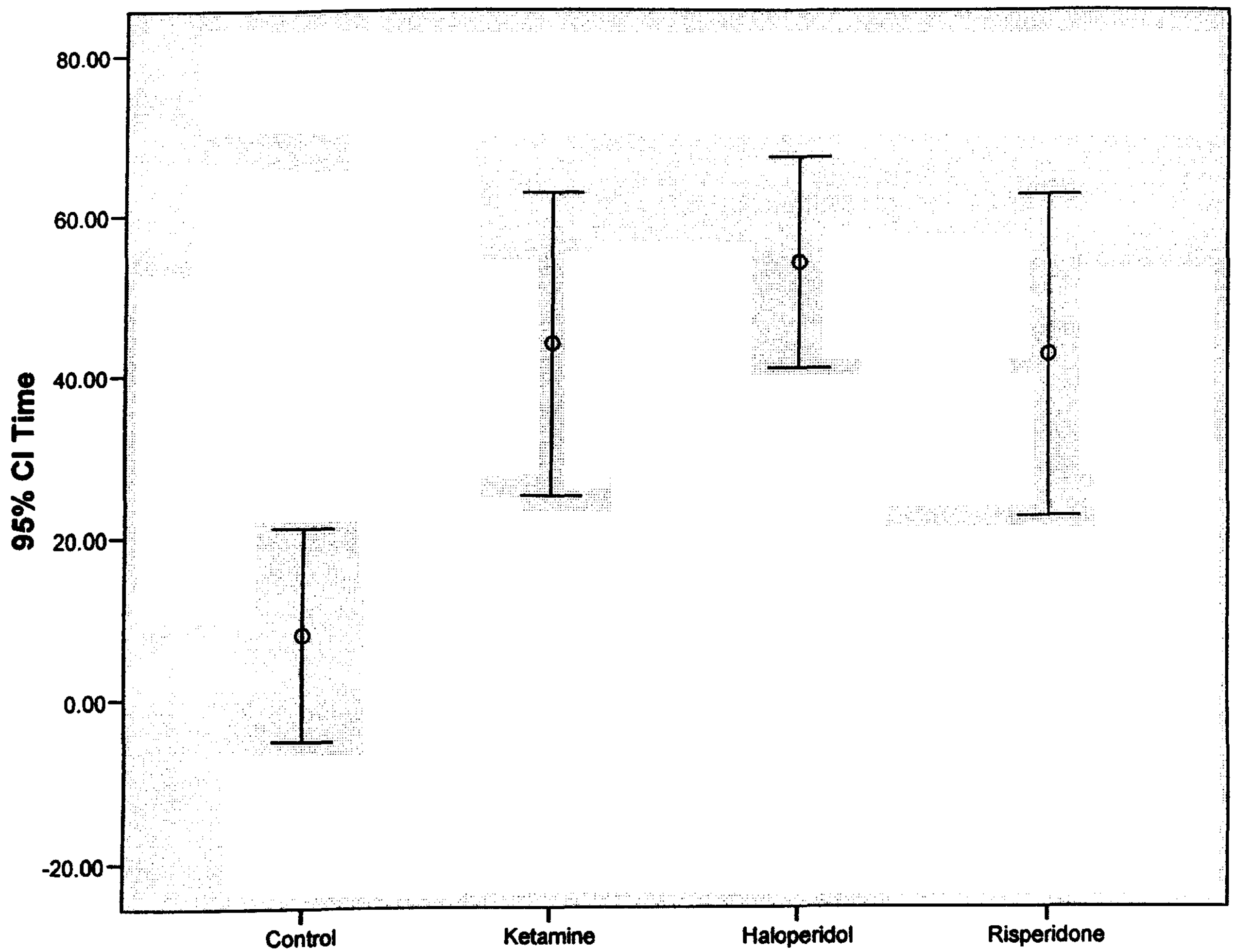

Figure 5.B- Standard Error of Measurement of Mean Climb Time.