ABSTRACT

THE EFFECTS OF EXERCISE ON EXPLORATORY BEHAVIOR IN THE MALE SPONTANEOULSY HYPERTENSIVE RAT

By Amber B. Corry

Attention Deficit Hyperactivity Disorder (ADHD) is diagnosed in up to 12% of the grade-school population, and that number is continuing to increase. Symptoms of ADHD include impulsivity, hyperactivity and inattention. Children are treated for ADHD with stimulant medications such as Ritalin or Adderall, however the consequences of long-term use of these medications are unknown. Most physicians agree that it is time to consider an alternative course of treatment. Exercise is known to aid in the symptoms of depression, and it has overall health benefits as well. It may also be a useful alternative to medications commonly used to treat ADHD. Twenty Spontaneously Hypertensive Rats, an animal model of ADHD, were assigned to one of two groups. The experimental group (n = 10), was treated with an exercise regime of 30 min of access to a running wheel, three times per week for 43 days. The control group (n = 10) was not treated with exercise. The rats' exploratory behavior was observed in the open field prior to exercise (baseline), and every seven days after onset of the exercise regime. Dependent measures were number of interactions with objects placed in the open field and number of square crossings. Results showed that the treatment group had significantly longer object interaction times in the open field. There was no difference between the groups for the number of square crossings. This study suggests that exercise may increase exploratory behavior in the SHR. Future research on how exercise affects the symptoms of ADHD is needed

THE EFFECTS OF EXERCISE ON EXPLORATORY BEHAVIOR IN THE MALE SPONTANEOUSLY HYPERTENSIVE RAT

by

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TABLE OF CONTENTS

To Jeffery and Jeffery Jr., I appreciate all of your love, patience and encouragement throughout this entire process. I love you both.

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LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a behavioral disorder characterized by symptoms of impulsivity, inattentiveness, and overactivity that is typically of juvenile onset and carried through adulthood (Davids, Zhang, Tarazi, & Baldessarini, 2003). Researchers report ADHD diagnoses in the grade-school population in the range of 2 to12% (Bull, Reavill, Hagan, Overend, & Jones, 2000; Sagvolden, et al., 1992). ADHD is a neurobehavioral disorder that typically presents itself by the age of seven. The disorder can affect children's social and academic functioning. Clinical criteria established by the American Psychiatric Association (1994) are that "a child must display a collection of symptoms of hyperactivity/impulsivity or inattention for the past 6 months in at least two different settings (e.g. home and school)" (p 263).

Both males and females have been diagnosed with ADHD, however the disorder has been more prevalent in males with a male to female ratio ranging from 4:1 to 9:1, contingent upon the environment (Bull et al., 2000). An important factor to consider when interpreting this ratio is how each of the genders expresses symptoms of the disorder. Males typically express symptoms of hyperactivity and impulsivity, which can be physically observed. However, females express more symptoms of the inattentive subtype which can be characterized by dreaminess and therefore may be missed as a symptom of ADHD. These differences of expression are suggested to be the leading cause of under-diagnosis in the female population (Sagvolden et al., 2005).

ADHD has been divided into three different subtypes: a predominately inattentive subtype, a predominately hyperactive-impulsive subtype and a combined subtype.

Subtypes of ADHD

Inattentive Subtype

The inattentive subtype of ADHD can be characterized by children lacking the ability to remain focused for long periods of time. Inattention is nonspecific, meaning that inattention can occur in any situation and is associated with the lack of focused attention. Children diagnosed with the inattentive subtype are believed to have a lower information processing ability than other children (Taylor, Sandberg, Thorley, & Giles, 1991). The inattentive subtype of ADHD is more common in girls. Symptoms can often be misunderstood and the children with this subtype of ADHD are often categorized as "daydreamers." Again, this misinterpretation of the inattentive subtype of ADHD is believed to be why females tend to be under-diagnosed with ADHD.

Hyperactive/impulsive subtype

The hyperactive/impulsive subtype of ADHD can be characterized by inattention exclusively related to distractibility and a reduction in perseverance (Sagvolden et al., 2005). Children with this subtype of ADHD typically express problems associated with memory retrieval tasks and are prone to a cascade of emotions beginning with frustration and leading to aggression. Research has shown that, if left untreated, children with this

particular subtype of ADHD will often become delinquent adolescents and have a greater chance of substance abuse compared to children with other subtypes of ADHD (Barkley, 2004).

Combined Subtype

The combined subtype of ADHD is characterized by symptoms of both the inattentive and hyperactive/impulsive subtype. Children diagnosed with the combined subtype of ADHD display symptoms of inattention accompanied with high distractibility and poor information processing. These children also display hyperactive symptoms like reduced persistence, memory retrieval problems and inability to control one's impulses. Children with this diagnosis also display higher levels of aggression when compared to the other subtypes of ADHD (Taylor et al., 1998).

There is large debate regarding the best way to diagnosis and treat ADHD due to the large variability among individual symptoms. Currently, little is understood as to how factors like race, age, gender, and socioeconomic status affect this disorder. However, it is understood that if ADHD is left undiagnosed and untreated it can lead to social maladjustment, poor functioning, and/or psychiatric problems in adulthood (Johansen & Sagvolden, 2004).

Epidemiology of ADHD

Little is known about the epidemiologic background of ADHD. Many theories exist as to the possible causes of ADHD but due to the presence of other cognitive or

psychological conditions that often accompany ADHD researchers are challenged to discover the root dysfunction behind the disorder. Traditionally, it was believed that ADHD was evident by the age of seven, however ADHD diagnoses have been increasing in the adult population. It is unclear whether these adults have had the disorder from childhood or have developed it in their adult years (Barkley, 2004). There is far less research on adults and ADHD compared to the research available on childhood ADHD. What is known is that as the age of diagnosis rises the probability of another disorder coexisting along with ADHD also rises. It has been reported that up to 87% of clinically diagnosed children and teens with ADHD have another disorder. The two disorders most commonly diagnosed with ADHD are oppositional defiant disorder (ODD) and conduct disorder (CD). Oppositional defiant disorder is defined by frequent and consistent uncooperative, hostile and defiant behavior that stands apart from the behavior of other children of the same age group or developmental stage. This pattern of behavior will occur in multiple environments and is typically directed at authority figures or adults (American Academy of Child and Adolescent Psychiatry, 2004). Symptoms can include (but are not limited to): frequent temper tantrums, deliberate attempts to annoy or upset someone, seeking revenge on others, and excessive arguing with adults. Conduct disorder is defined as a group of behavioral and emotional problems in youngsters. Children with CD have problems following rules and are more physically aggressive than other children of their age group. Conduct disorder has four categories of symptoms: (a) aggression to people or animals characterized by being physically cruel to animals or people, initiating physical fights with others and even forcing people to engage in sexual activity; (b)

deliberate destruction of other people's property; (c) lying to obtain goods, stealing from others and using deception to obtain items that do not belong to you; (d) serious violation of rules, characterized by frequent truancy from school, breaking curfew and difficulty retaining a job due to poor attendance. Treatment for both ODD and CD include cognitive-behavioral therapy, individual psychotherapy, family therapy and possibly medication for aggression (American Academy of Child and Adolescent Psychiatry, 2004). Adolescents who undergo further testing after first being diagnosed with either ODD or CD are often consequently diagnosed with ADHD. Research has also begun to link various anxiety disorders with the existence of ADHD in both children and adults (Barkley, 2004). ADHD, ODD, CD and anxiety disorders all share symptoms that can sometimes present themselves in a similar manner as well as have similar root causes.

A pathophysiological theory of ADHD is widely accepted by researchers in this field. This theory states that ADHD is a dysfunction of the prefrontal cortex, however the exact causes of the dysfunction are still unknown (Davids et al., 2003). Support for this hypothesis comes from similarities within behaviors of clinically diagnosed patients with ADHD and behaviors of patients with injuries or disease to their frontal lobes (Arnsten, 1997, 2001). Research has focused on how the monoamines dopamine, serotonin and norepinephrine affect ADHD. Although there is little consensus on how each of the monoamines affect ADHD many researchers agree there is an interaction between them (Elam, Svensson, & Thoren, 1987; Meeusen & De Meirleir, 1995; Meeusen & Piacentini, 2001). Each of these monoamines affects functions of behavior, for example affect, attention, impulsivity or cognition. Since there are multiple symptoms that characterize

ADHD, and these monoamines affect multiple behaviors it is logical to assume that there is an interaction among these neurotransmitters.

An additional theory regarding the cause of ADHD relates to neurodevelopment. Termed the neurodevelopment hypothesis, this theory has correlated factors such as perinatal complications (toxemia), older maternal age, and premature birth with a diagnosis of ADHD. However, the research findings are inconclusive, and until the pathophysiology of ADHD is completely understood this research may have limited influence (Holloway, Anderson, Defendini, & Harper, 1993).

Spontaneously Hypertensive Rat (SHR) Model

Using animal models in research has many practical, financial and ethical advantages. Laboratory rats are genetically homogenous. This allows for more control over confounding factors of individuality as well as environmental control (Sagvolden, Russell, Aase, Johansen, & Farshbaf, 2005). Using an animal model to study ADHD is also more cost effective. Although there are many guidelines and procedures that must be followed in research with animal models, the ethics surrounding human participation, especially children or medicated individuals, are even more complicated.

The Spontaneously Hypertensive Rat (SHR) was developed by inbreeding the Wistar-Kyoto strain, originally intended for the study of hypertension. The SHR for use in studying ADHD was a serendipitous discovery. The SHR displayed unusually high

levels of spontaneous motor control and over the years was studied for its behavioral similarities with ADHD.

For an animal model to be most advantageous the model must satisfy the etiological, biochemical and symptomatological characteristics of the disorder in humans. Although there is much debate over several aspects of ADHD, researchers tend to agree on one principle: the spontaneously hypertensive rat is the closest model of ADHD researchers have available (Adriani, Caprioli, Granstrem, & Laviola, 2003; Davids et al., 2003; Sagvolden et al., 2005). Sagvolden et al., (2005) compared all of the available animal models of ADHD. The authors formulated a set of validation criteria to which all animal models can be compared. The proposed criteria set for the animal model of ADHD include face validity, construct validity, and predictive validity. Upon comparison with all the other available animal models of ADHD, the SHR is now the most widely excepted animal model of ADHD. It is the only model to fulfill aspects of all three types of validity.

Validity refers to the accuracy of a measure. It is the extent to which a measuring instrument actually measures the underlying construct it is supposed to measure. Face, construct, and predictive validity will be defined in a general sense, followed by how they relate to ADHD.

Face Validity

Face validity refers not to what the test actually measures, but to what it appears superficially to measure. Face validity pertains to whether the test "looks valid" to the examinees who take it, the personnel who decide on its use and other technically

untrained observers. In other words, does the measurement/model appear to measure what it claims to measure? Face validity is achieved by having obvious similarities with the construct in question. For example, if an animal model representing human ADHD were to have face validity, the animal model would need to outwardly display symptoms typically observed in humans diagnosed with ADHD. Face validity is demonstrated by the animal model essentially mimicking the human behavioral-clinical characteristics of the disorder.

The criteria for face validity include behaviors of motor impulsiveness, deficient sustained attention and hyperactivity (Sagvolden et al., 2005). Motor impulsiveness is considered to be one of the most important criteria for an animal model to fulfill. Although motor impulsivity is a defining characteristic of children with ADHD, it is important to note that motor impulsivity is not present in novel situations, but that it progressively develops over time. For the animal model to demonstrate motor impulsivity, it must respond in a manner that is premature or burst-like. A short interresponse time during extinction schedules is one way that the SHR demonstrates this behavior.

Hyperactivity is the last of the face validity criteria. Hyperactivity is often displayed after a situation has lost its novelty and is characterized by an animal displaying overactivity in scheduled (fixed and variable) and extinction reinforcement schedules. Animal models that display hyperactivity would have a short and steep response gradient (Sagvolden et al., 2005). The animal seems unable to wait a long

period of time without responding. The longer the time between rewards the more the animal will perform the behavior.

The SHR displays impulsivity as brief sequences of action and hasty change (Sagvolden et al., 2005). For example, in the open field test, the SHR runs in a non-characteristic fashion defined by aimless running and not stopping to investigate objects in its path (Davids et al., 2003). The SHR also shows a deficit in sustained attention and hyperactivity during fixed-interval and extinction schedules of reinforcement. The SHR performs as well as controls in a schedule where the reinforcers were frequent. However, as in children with ADHD, the SHR's performance declines when reinforcers were infrequent and required inhibition of response (Metzger & Sagvolden, 1994).

Construct Validity

Construct validity requires that the measurement/model adequately represents the construct of interest. Regarding ADHD, the model should represent all aspects of ADHD-- pathophysiological, biochemical, and behavioral. Construct validity can be difficult to fully obtain since multiple theories exist for ADHD, however some have stronger evidence to support conformity to a theoretical rationale for the disorder, and therefore are frontrunners in the pathophysiological theories of ADHD.

Criteria included in construct validity include genetics, sex differences, neuropathology, neurotransmitter dysfunction, behavior variability, psychostimulant effects as well as the three criteria discussed in face validity (Sagvolden et al., 2005). Support for construct validity is limited due to the lack of a concrete understanding of many of the causes of ADHD. Again, hyperactivity, motor impulsiveness, and lack of

sustained attention have all been supported in the SHR model of ADHD. However, the similarities found when comparing children with ADHD to the animal model of ADHD, for example the impaired second-messenger systems within the dopamine and norepinephrine systems, are present within both samples. The dopamine system, which mediates reinforcement, is dysfunctional and is thus hypothesized to be the factor that modifies the behavior in the SHR strain (Sagvolden, 2005). The dopamine system is also hypothesized to be dysfunctional in children diagnosed with ADHD. Norepinephrine systems also appear to be dysfunctional in the SHR. The norepinephrine system is also a modulatory neurotransmitter and increases the strength of neuronal circuits that supports adaptive behavior in the SHR (Sagvolden, 2005). Again, this system is also hypothesized to be somehow dysfunctional within children with ADHD (Davids et al., 2003; Sagvolden et al., 2005).

One criterion that is consistent in both the SHR and children with ADHD is the response to psychostimulant treatment. The SHR has a reduction in behavioral symptoms when treated with either D-amphetamine or methylphenidate. Children show the same improvements with treatment. These medications increase the amount of dopamine available in the mesolimbic pathway, the reward pathway, which in turn enhances the effect of reinforcements in children and the SHR. Treatment with stimulants also reduces motor impulsivity and motor activity in both the SHR and children. This evidence further supports the SHR model's construct validity.

Predictive Validity

Finally, predictive validity is defined as the ability for the measurement/model to correctly predict future events associated with that construct. Thus a good model of ADHD would be able to allow predictions as to how a certain treatments would affect it.

Before the SHR model of ADHD existed little was known about altered reinforcement processes and their consequences (Sagvolden, 2000). Today, the SHR model of ADHD has provided understanding in the areas of exploratory behavior, development of motor impulsivity, hyperactivity and sustained attention. With continued research, the SHR model of ADHD will be able to provide validation in many of the areas that are currently being studied (e.g. genetics, neurotransmission) as well as develop an understanding of long-term effects of current treatments. The usefulness of the SHR as a model of ADHD will strengthen with further understanding of the pathology of ADHD. It is believed by many that the SHR will provide insight into aspects of ADHD behavior. However, the only limitation to the predictive validity of the SHR is the development of hypertension. The SHR does not develop hypertension until adulthood, at the same time the SHR stops resembling ADHD and takes on a new dysfunction, hypertension (van den Bergh et al., 2006). For this reason, there is a limited time for which the model can be used in the study of ADHD.

Treatment for ADHD

The two most widely-prescribed treatments for ADHD include methylphenidate and d-amphetamine. Other less successful treatments include a non-stimulant medication, atomoxetine and a depression medication called Bupropion (Barkley, 2004; Julien, 2005). Non-pharmaceutical treatments such as psychotherapy have been tried but with limited success (Barkley, 2004; Paule et al., 2000). It is important to understand how these treatments work and any long-term side effects that may occur with prolonged use. Finally, exercise has been suggested as a possible treatment or supplemental treatment. The effect of exercise on people diagnosed with depression has led researchers to believe that exercise can have some benefit for children diagnosed with ADHD (Meeusen, 2005; Meeusen & Meirleir, 1995; Meeusen & Piacentini, 2001; Tantillo, et al., 2000). It is known that exercise causes an increase in the neurotrasmitters DA, NE, and 5-HT. These same neurotransmitters are hypothesized to be deficient in ADHD, thus it is possible that exercise can have an effect on symptoms of ADHD.

Methylphenidate and d-amphetamine are both psychostimulants. Both psychostimulants have a similar molecular structure and effects on the central nervous system as well as on the autonomic nervous system. These stimulants cause an increase in the monoamines DA and NE and this action is believed to be the reason stimulants aid in the suppression of ADHD symptoms (Julien, 2005). Drawbacks to this class of treatment include the large variability in response to dose of the drug, the short half-life of each of the drugs (which, in turn, increases the number of doses needed throughout the day), and the range of side-effects, from loss of appetite to insomnia.

Non-pharmaceutical treatments like psychotherapy have been studied, however the results are disappointing. Psychotherapy requires an intensive treatment schedule for the child and usually requires that a parent partake in the sessions as well (Paule et al., 2000). These highly demanding treatments fall short of a pill-style therapy. However, combination treatments have shown greater success compared to pharmaceutical mono-treatment style therapies (Barkley, 2004).

The Effects of Exercise on SHR

One treatment option that has received limited attention regarding its effects on ADHD is exercise. Exercise has been studied for its effects on monoamine neurotransmission, and studies have found that exercise increases levels of dopamine and norepinephrine which, in turn, enhance cognitive functioning (Szabo, 2006). However the research available on the effects of exercise has limited ecological validity. Studies on the effects of exercise differ in design, the operational definition of exercise, the specified brain region of interest, the animal model, the stress factors, and the measurement methods (Meeusen & Piacentini, 2001). Interpretations of this research must consider these methodological discrepancies. Meeusen and Piacentini (2001) conducted two experiments to understand the effects of exercise on neurotransmission. These researchers address the downfalls of using postmortem methods to collect data on neurotransmitter concentrations. Using postmortem methods limits the possibility of concluding that neurochemistry affects behavior. The development and use of "*in vivo*"

neurochemical methods allows for collection of data from nervous tissue in living animals through sampling of the extracellular fluid. It is believed that an estimation of transmitter content in the synaptic cleft can be determined through sampling of the extracellular fluid in an intact living brain. Researchers have acknowledged "in vivo" methods as the most relevant measurement currently available.

In the first of two studies, Meeusen and Piacentini (2001) exercised rats on a treadmill (12 m/min) and used microbore liquid chromatography (LC) with electrochemical detection to analyze levels of DA, 5-HT, and NE. This procedure entails measuring the dialysates with a microbore liquid that allows detection of monoamine levels by using a fluorescent light. The monoamines are reflected and measurements can be taken from this. During the exercise interval of 20 minutes the researchers reported that concentrations of all three monoamines in the striatum where significantly higher than baseline. They also reported that concentrations were back to baseline around two and a half hours after exercise was terminated.

In their second experiment the researchers used the technique of "in vivo" microdialysis to collect samples of extracellular neurotransmitter levels in the striatum. This entails sampling the extracellular fluid from the nervous tissue of the living, exercising animal (Meeusen & Piacentini, 2001). In this study, both trained and untrained rats were used. The trained rats were given an exercise regime. The training consisted of the rats running on a treadmill for six weeks, five days a week for 30 min. The exercise regimen running time and speed were increased from 30 min at 19 m/minute (the first week) to 80 min at 26 m/min (the last week). To control for the effects of training,

Meeusen and Piacentini allowed the control group four "adaptation sessions" during which they exercised twice a week for 15 to 45 min at 26 m/min. To determine if training had an effect, they measured the soleus muscle citrate synthase in the two groups. There was a significant difference between the trained and untrained rats. This difference of muscle citrate between the trained and untrained rats simply indicates an effect of training. The trained rats were in better physical condition than the control rats: their muscles were more active. The researchers also found that with 60 min of exercise, extracellular levels of DA and NE were significantly higher in both trained and untrained rats (when compared to baseline).

Meeusen and Piacentini (2005) concluded from these studies that while exercise causes this temporary increase of certain neurotransmitters in specific brain areas, it is still too early to draw any firm conclusions as to the long-term effects of the interactions between the neurotransmitters. The authors suggest that more research is needed to understand how the neurotransmitter release contributes to the modulation of pre- and post-synaptic receptor binding, leading to changes in transmitter synthesis and release. Nevertheless, these studies support the notion that exercise can increase the release of neurotransmitters, and that exercise may cause the same effect as stimulant treatment, thus improving cognition and motor activity. Again, it is too early to draw any long-term conclusions, but these findings shed some light on the possibility of exercise relieving the symptoms of ADHD, even for a brief period of time.

A further study supports the idea that long-term running is associated with increased neurotransmission production. Elam et al. (1987) conducted research using the

progenitor species of SHR, the Wistar Kyoto rat. The rats were allowed free access to a running wheel and running time was recorded by a microprocessor system. The rats developed a spontaneous running behavior that stabilized after four weeks. (The rats ran an approximate distance of 5 km per 12 h.) After an additional seven days of steady-state exercise of approximately 5 km per 12 h, the rats were sacrificed. One group of rats was sacrificed immediately after running and another group of rats was sacrificed 24 h after running. The brains of both groups were analyzed for levels of DA and 5-HT, as well as metabolites in the limbic forebrain (nucleus accumbens), striatum, and brain stem regions.

The results suggest that the rats sacrificed immediately after their last running session had significantly lower levels of the DA metabolite in the limbic forebrain and striatum. However, DA metabolite levels were at significantly higher levels in the brainstem (typically a NE rich area). The authors reported no significant findings in the rats that were sacrificed 24 h after exercise. This indicates that some time within the 24 h period after exercise the levels of the monoamines and their metabolites had returned to baseline levels. The effects of exercise had worn off. To conclude, the findings of a decrease in DA synthesis in the limbic and striatum areas support previous research. This decrease is attributed to lower aggression levels in rats following exercise. The limbic system is associated with emotional behavior, while the striatum is associated with motor activity. A lower level of DA synthesis within both of these brain areas is associated with lower levels of aggression (Gazzaniga et al., 2002). As previously stated, aggression, whether a primary deficit or secondary deficit, can be a defining symptom of ADHD.

Researchers have not yet conducted a study to test the long-term effects of exercise on the brain. It is possible that longer-term effects will be found with continued exercise.

Study Overview

The current study focused on the effects of an exercise regimen on exploratory behavior through non-invasive methods. While no subjects were sacrificed after the regimen had concluded, the goal was to determine whether SHRs could display exploratory behavior in the open field that were more investigative in nature than is typically observed in SHRs that were not exposed to exercise. These exploratory behaviors were operationally defined as the animal stopping at an object or objects within the open field to sniff them, make contact with them using one, two, or four paws, biting them, licking them, dragging, pushing, or engaging in any bodily contact with the object. This type of investigative behavior is reduced in the SHR. Exercise, which is believed to increase concentration, improve mood and lower aggression (Elam et al., 1987; Meeusen, 2005; Meeusen & De Meirleir, 1995 and Tantillo et al., 2000) will theoretically allow the SHR to function with a decrease in ADHD symptoms. Again, while levels of DA, NE, and 5-HT will not be analyzed it is important to understand the connection between exercise, neurotransmitters and how they can influence ADHD.

Hypotheses

Hypothesis 1: The exercise group will display more investigative behavior, as determined by more time spent interacting with the objects in the open field compared to the control group.

Hypothesis 2: The control group will cross more squares in the open field compared to the exercise group.

METHODS

Subjects

Twenty male Spontaneously Hypertensive Rat (SHR) |Harlen, U.S.A.| weanlings (21 days old) were housed in two Plexiglas cages measuring 70 cm x 70 cm x 46 cm, ten rats per cage. The rats were randomly assigned to either the control or treatment group and assigned a letter (A through J). However, rat H from the treatment group died and therefore rat H from the control group was not used. The rats were housed in a room maintained on a reversed 12 h light/12 h dark cycle. Red light illuminated the room from 19:00 h to 7:00 h. The rats had free access to food (standard rat chow) and water in the home cage. Food and water was not available in the exercise box or the open field. The experimental procedure was approved by the University of Wisconsin-Oshkosh Institutional Animal Care and Use Committee (IACUC).

General Procedure

All acclimation, exercise and observation procedures for the open field were conducted in red light. Following acclimation to their new home for four days, the animals (age 29 days) were acclimated to the open field apparatus for three days. At age

32 days, the animals were observed and baseline data were recorded in the open field. At age 33 days the exercise regime began and continued for six weeks. The exercise regime lasted 43 days and was conducted every Tuesday, Thursday, and Saturday. A total of 20 exercise sessions were recorded. The animals were observed for ten min every seven days (Sunday) in the open field. Activity of each rat was recorded by a video camera and later was coded to be used in further analysis.

PROCEDURE

Exercise Regimen

The day after baseline data were collected in the open field the exercise regimen began. Each rat from the treatment group (n = 9) was randomly chosen and placed in a box that was approximately 10 cm x 10 cm x 15 cm. Each box contained a running wheel (Wodent Wheel model number 8397-4) of approximately 9 cm in diameter attached to a device (Sigma Sport Wodometer model number 05304) that recorded the time spent on the wheel as well as total distance ran (km). Exercise was provided 3 days a week (every Tuesday, Thursday, and Saturday) for 30 min/day and lasted approximately six weeks (43 days). A total of 20 exercise sessions were conducted.

The exercise regimen was given in the same room in which the animals were housed. The order in which the rats exercised was randomly determined each week. Each treatment rat was placed in the exercise box for 30 min and was allowed to run on the

wheel. To control for extra handling, the presence of the running wheel, and time outside of the cage the corresponding rat from the control group (e.g. Rat A) was also placed into an identically sized box with a running wheel that was locked to prevent exercise. The exercise and control boxes were cleaned with vinegar and water solution after each rat's session. Both groups were tested on the seventh day (Sunday) in the open field to determine if exercise had any effects on exploratory behavior.

Apparatus

The Open Field

The open field is a wooden circular observation area measuring 111.76 cm in circumference, with wooden walls measuring 43.18 cm high. The open field was painted grey on the outside. The floor was black with white lines dividing it into 25 squares. Circular pieces of untreated plywood were placed within the square (Appendix A). At age 29 days the animals were acclimated to the observation area (an empty open field) for three consecutive days, 5 min/day. Two objects were placed in the open field with the rats: a wooden spoon and a cardboard toilet paper roll. The wooden spoon was placed in the lower right square of the box whereas the cardboard toilet paper roll was placed in the upper left square of the box. Both objects were placed in the center of their respective squares and were reset after each of the rat's observations. At age 32 days the rats were observed in the field and a baseline interaction was established. The placement of the objects remained consistent each week, however the objects were exchanged for a new

spoon and roll each week since they are made of porous materials that could retain a scent. The order in which each rat was placed in the open field was random. Each rat was placed in the bottom middle square in the open field at the beginning of each session. Recorded observations took place once each week: each session lasted ten min. A total of seven observations were recorded. The observation area was cleaned using a vinegar and water solution after each rat's session. Animals were observed one last time 43 days following the beginning of the exercise regimen (at age 82 days). All animals were videotaped in the open field using a Sony HandyCam model CCD-TRV 138 and a Panasonic time-date generator and recorder model number WJ-810. See Appendix B for a timetable of the procedure.

RESULTS

Coding of Open Field Behaviors

The camera was placed directly above the open field (facing down). Exploratory behaviors were operationally defined as any contact between an object and any part of the rat's body. Once contact was observed the length of the interaction was recorded. An interaction ended as soon as bodily contact between the object and rat terminated. The interactions were timed in milliseconds. Any interaction lasting more than 50 ms was rounded up to the next second.

Square crossings were also recorded from the videotapes. A rat crossed a square when three of four paws crossed the white line demarking the squares within the open field. Because rats have the ability to elongate themselves, it is possible for the rat to stretch itself into another square without crossing any lines. Therefore, it was necessary to set the criterion of a square crossing to three paws within a square since that would require the rat to have crossed the white line. The number of square crossings was tallied for the ten min of observation.

An alpha level of .05 was used for all statistical tests. Table 1 presents the average weights of the treatment and control groups at each observation. An independent samples t-test revealed no significant difference between the control group ($M = 209.59$, $SD = 61.94$) or treatment group ($M = 209.73$, $SD = 63.24$), ($t\ (14) = -.004$, $p > .05$).

A three-factor (group, object, and observation) mixed analysis of variance (ANOVA) was conducted on the time spent interacting with the objects. The amount of time each group interacted with the objects during each of the observations is graphed in Figure 1. The main effect for group was significant (F (1, 32) = 7.85, $p < .01$). The treatment group (M = 60.84, SD = 38.54) spent more time interacting with the objects than the control group (M = 46.74, SD = 32.25). The main effect for object was also significant (F (1, 32) = 20.59, $p < .01$). The rats spent more time exploring the roll (M = 65.21, SD = 44.15) than the spoon (M = 42.38, SD = 20.40). The main effect for observation was significant as well (F (7, 26) = 13.22, $p < .01$). These data are graphed in Figure 2. Observations that are significantly different from each other, as determined by planned comparison tests, are shown in Table 2. There was also a significant interaction between observation and objects (F (7, 26) = 5.62, $p < .01$). Figure 3 graphs the treatment and control group mean interaction time (in seconds) with the roll and spoon for each observation. Planned comparison tests revealed that the interaction times for spoon and roll significantly differed for Observations 1, 2, and 4.

The interaction between observation and group was not significant (F (7, 26) = 1.51, $p > .05$), nor were the interactions between group and object (F (1, 32) = 1.08, $p > .05$) or the interaction between observation, group and object (F (7, 26) = 1.96, $p > .05$).

A one-factor (group) ANOVA was conducted to compare the number of squares crossed for the two groups. No significant differences were found (F (1, 16) = .436, $p > .05$) Table 3 displays the treatment and control groups mean number of square crossings across all observations.

The treatment group (n = 9) exercised for a total of 20 sessions across a 49-day period. Past studies have suggested that rats may achieve a consistent running distance after a period of approximately 4 weeks (Elam, et al., 1987). However, none of the rats within the treatment group achieved a consistent running distance. A degree of variability existed in the exercise group. Table 4 presents the total running distance, mean, and range for each SHR's exercise regimen. Appendix C presents the distance ran for each individual rat.

A Pearson's product moment correlation coefficient was calculated to examine whether a relationship existed between time spent on the wheel and distance ran on the wheel. The two variables were positively correlated (r (207) = .93, $p < .01$). A second correlation coefficient was computed to examine the relationship between object interaction time and number of squares crossed in the open field. The correlation was not significant (r (144) = .42, $p > .05$). Finally, we correlated distance ran and object interaction time. The correlation was not significant (r (196) = -.13, $p > .05$).

Table 1

Mean Weight Distribution for Both Groups Across All Observations

	Mean (SD)
Observation BL[a]	
Treatment	98.3 (9.5)
Control	96.9 (5.7)
Observation 1	
Treatment	144.2 (11.5)
Control	148.6 (8.7)
Observation 2	
Treatment	182.3 (15.3)
Control	184.7 (10.8)
Observation 3	
Treatment	218.8 (21.4)
Control	220.1 (13.9)
Observation 4	
Treatment	235.1 (16.5)
Control	235.8 (12.5)
Observation 5	
Treatment	260.5 (17.6)
Control	256.6 (18.3)
Observation 6	
Treatment	263.8 (16.6)
Control	263.2 (14.6)
Observation 7	
Treatment	275.1 (16.5)
Control	271.4 (16.1)

Note. Values indicate weight in grams. Standard deviations are given in parentheses.

[a]Baseline measure.

Table 2

Observation Comparisons

	BL	1	2	3	4	5	6	7
BL	--	*	**	--	*	**	*	*
1	*	--	--	--	**	**	**	**
2	**	--	--	**	--	*	**	**
3	--	--	**	--	--	*	**	**
4	*	**	**	--	--	--	**	**
5	**	**	**	*	--	--	--	--
6	**	**	**	**	**	--	--	--
7	**	**	**	**	**	--	--	--

* $p < .05$, ** $p < .01$

Table 3

Mean Square Crossing Totals for Both Groups Across All Observations

	Treatment	Control
Observation		
Baseline	255.7 (50.6)	239.7 (32.1)
Observation 1	231.8 (57.9)	208.3 (30.1)
Observation 2	247.8 (53.9)	261.9 (33.3)
Observation 3	220.3 (66.7)	204.3 (41.5)
Observation 4	191.6 (73.7)	218.9 (20.2)
Observation 5	166.6 (69.3)	211.8 (30.2)
Observation 6	158.4 (97.3)	194.2 (50.7)
Observation 7	160.3 (99.0)	191.6 (57.3)

Table 4

Individual SHR Running Distance Total, Mean and Range

Rat	Total	Mean	Range
A	2.13	.11	.22
B	2.33	.12	.12
C	3.39	.17	.17
D	1.94	.10	.14
E	2.76	.14	.11
F	1.52	.08	.11
G	2.51	.13	.18
I	2.98	.15	.13
J	1.78	.09	.16

Note: Measurements in kilometers. Range was calculated by subtracting the shortest running distance from the longest running distance.

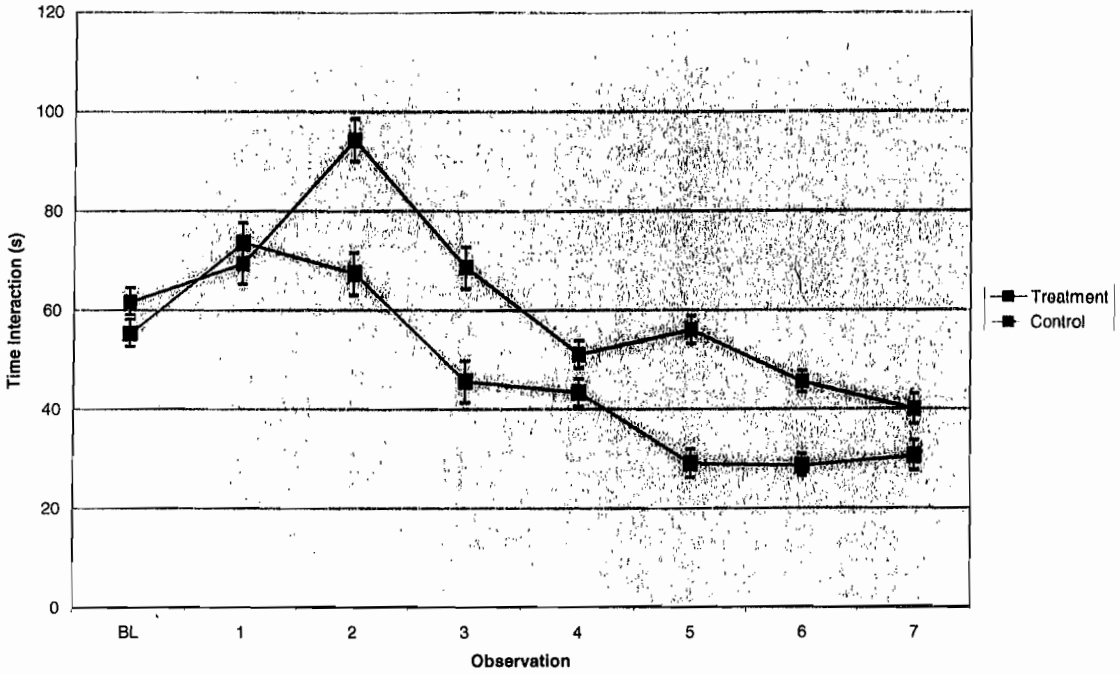


Figure 1. Object interaction time by group across all observations.

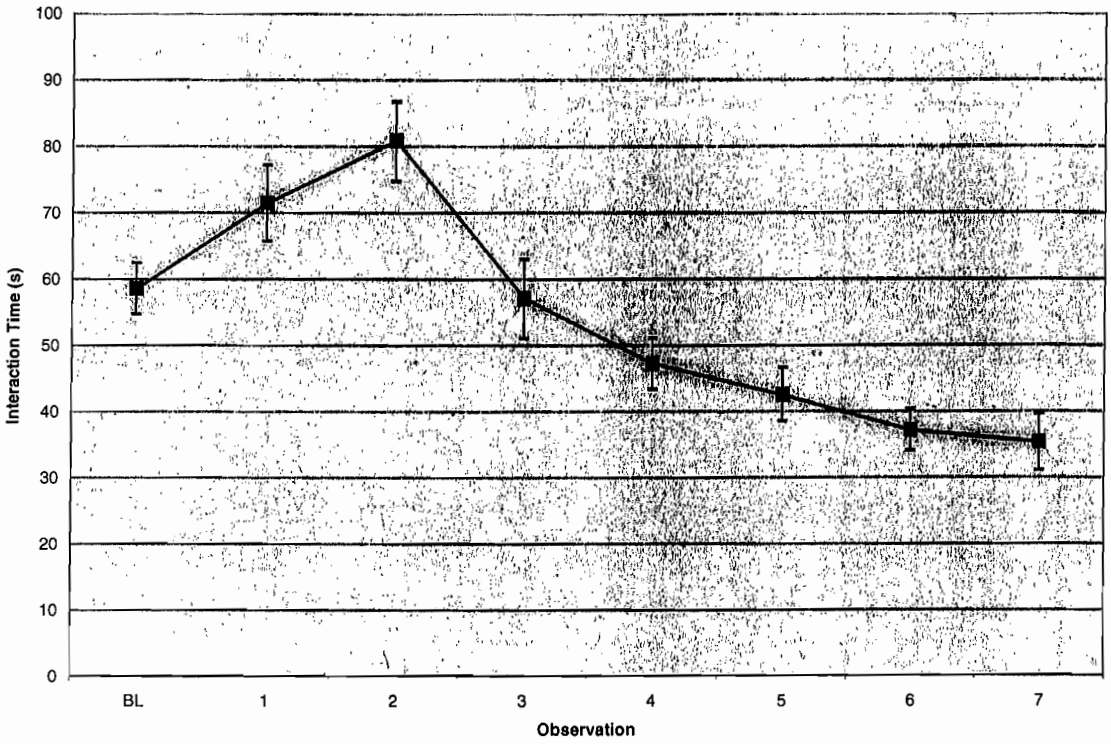
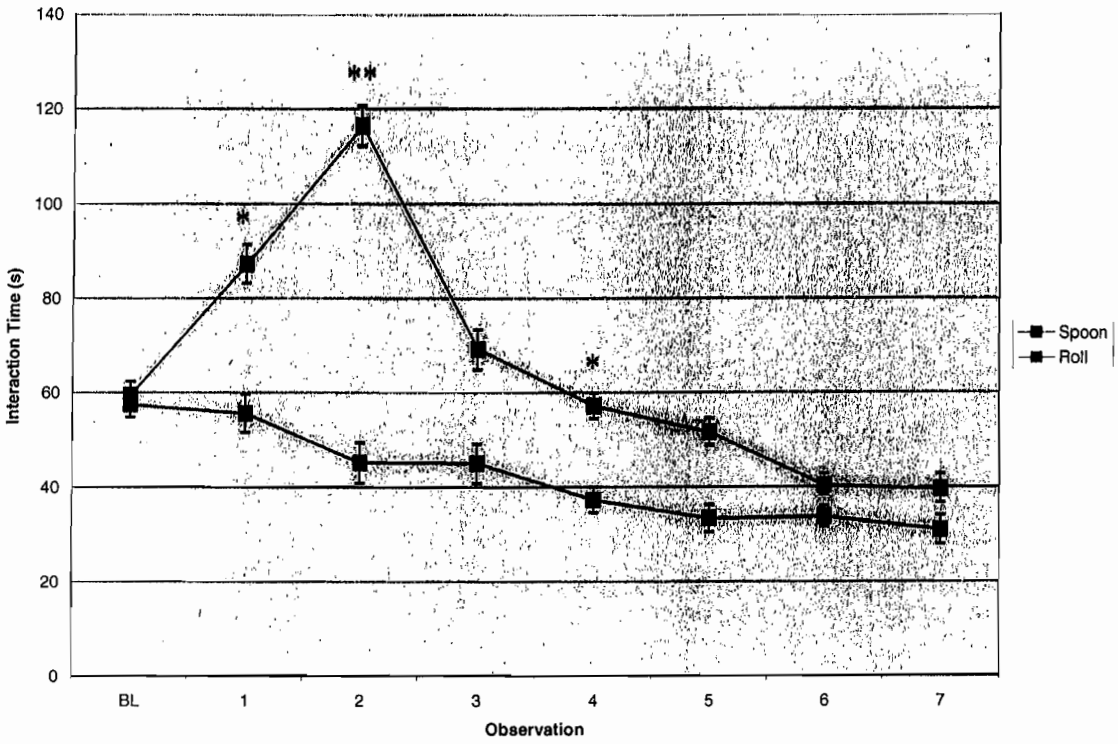


Figure 2. Total interaction time across observations.



* $p < .05$, ** $p < .01$

Figure 3. Interaction time for roll and spoon across observations.

DISCUSSION

The results of the present study suggest that exercise does have an effect on exploratory behavior defined as object interaction for the Spontaneously Hypertensive Rat. It was hypothesized that exercise would decrease ADHD symptoms while increasing the treatment group's exploratory behavior. The treatment group had a significantly higher interaction time with the objects while in the open field. The literature suggests that SHRs display behavior that is less exploratory in nature (Savolden et al., 2005). Typically, the SHR runs aimlessly within the open field and does not stop to explore objects (Davids et al., 2003). The results of this study do not support these findings (see Figure 1). Although both groups appear to have habituated to the objects over time, both groups explored the objects in the open field throughout the study. Furthermore, the current study suggests that exercise may increase exploratory behavior in the SHR, in that the difference between the treatment and control groups' object interaction time was significant. However, exercise does not appear to affect hyperactivity. There was no difference between the two groups for square crossings.

The SHRs displayed a preference for the roll over the spoon in the open field. During Observations 1, 2 and 4 the treatment group interacted with the roll significantly longer than they interacted with the spoon (see Figure 3). The videotapes showed the rats using the roll like a tunnel. They would enter the paper roll and roll across the open field. As the rats grew individuals from both groups would get stuck in the roll and have

trouble getting out of it. Some rats would stay inside the roll for over 20 s before coming out. This behavior was particularly evident during Observation 2. While this was counted as interaction time, the rats were not exploring the object, rather trying to escape from it. The rats then changed their behavior during Observation 3 and did not use the roll as a tunnel but instead would push it with their noses, like a ball. Some rats would follow the roll, others would just move on. This may suggest that these rats began to lose interest in the roll. Literature suggests that once the novelty of an object is gone the SHR will stop interacting with that object. Figure 3 suggests the SHRs in this study displayed behaviors typical of other rats while in the open field.

The treatment group had a higher mean interaction time with the roll for 7 out of the 8 observations. Other than the baseline observation, the control group also had a higher mean interaction time with the roll for 7 out of 8 observations. The rats did interact with the spoon, and many times would straddle the spoon and lie on it for a period of time. Many of the rats would bite onto the spoon and drag it from one end of the open field to the other. Although this study cannot determine why the rats had a preference for one object over another, one could speculate that the rats interacted with the roll longer than the spoon because it was more mobile.

The second hypothesis was that the control group would cross more squares in the open field compared to the treatment group, due to their reduced exploratory behavior and increased aimless running. Informal observations taken from the videotape showed that the rats did explore their surroundings and the objects. Their running behavior did not seem random and many times they would run from one object to the next. In addition,

the treatment group was expected to cross fewer squares because the exercise regimen would increase the rats' ability to stop and investigate the objects. This hypothesis was not supported. The results indicated that both groups crossed a high number of squares (Table 3). The videotape showed rats from both groups dragging the objects across numerous squares, thus producing high numbers for both the treatment and control groups. The SHR still interacted with the objects, but in a different manner than expected. As stated above, in the earlier observations rats would use the paper roll as a tunnel and roll across numerous squares. As the rats grew in size they would have trouble getting out of the roll, and many had to forcefully wiggle (or maneuver) their bodies to exit the roll. This forceful motion often caused the roll to cross into one or more other squares. Another behavior that led to the high number of square crossings was chasing the roll. Thus, all rats were interacting with the objects while crossing many squares, with the treatment group showing more object exploration than the control group. A significant main effect for observation was present for interaction time (Figure 2). The later observations (i.e., observations 5, 6, and 7) were significantly different from the earlier observations (i.e., BL, 1, 2, and 3). This may be due to either habituation to the objects, or to the high number of "jumpers" in these later observations. Five rats, four from the control group and two from the treatment group, jumped out of the open field. Observations 2 and 3 had a total of two jumpers, Observations 5 and 6 had a total of four jumpers and Observation 7 had a total of 5 jumpers. Knardahl and Sagvolden (1979) stated that the SHR may perform an escape response rather than exploratory behavior in forced-exploration open field studies. It is believed that a rat is more likely to explore a

new environment or object when it has access to a familiar environment (free choice exploration). This escape behavior may help explain why the rats in the current study jumped out of the open field. Once a rat jumped out of the open field it continued to do so every subsequent observation period, with the exception of treatment rat A, which only successfully jumped out of the open field in Observation 3. Several rats attempted to jump out of the open field but were unsuccessful. Those that succeeded would jump out at different times during the observation period and from different places within the open field. This created outliers in both groups. Removing the outliers from the analysis did not produce different main effect results. The main effect for group was still significant (F (1, 18) = 13.58, $p < .01$) with the treatment group having a higher mean interaction time than the control group. The main effect for object was still significant as well (F (1, 18) = 27.82, $p < .01$). As before, the roll still had a higher mean interaction time than the spoon. The main effect for observation was also still significant (F (7, 12) = 14.35, $p <$ .01). However, removing the outliers did change the results of some of the interactions. Previously, the interaction between group and object was not significant. However, removing the outliers made this interaction significant (F (1, 18) = 6.24, $p < .05$). The treatment group interacted with the roll (M = 79.64, SD = 46.55) significantly more than the spoon (M = 47.36, SD = 19.36). The control group also interacted significantly more with the roll (M = 53.94, SD = 36.87) than the spoon (M = 42.47, SD = 18.08). Again, it is believed that the rats preferred the roll because it was a more mobile object. The interaction between observation and group also was significant once the outliers were removed (F (7, 12) = 3.46, $p < .05$). Post-hoc independent samples t-tests revealed a

significant difference between Observations 5 and 6. The treatment group had a higher mean interaction time in Observation 5 (M = 54.94, SD = 28.95) and in Observation 6 (M = 49.00, SD = 18.88) compared to the control group (M = 34.42, SD = 16.80) and (M = 31.42, SD = 11.39, respectively). It should be noted that the interaction between observation, group and object was not changed by removing the outliers.

A source of added stress was present during the duration of the experiment. Construction was taking place within the building where the animal colony is located. Maintenance crews were remodeling the bathrooms on all three floors. The rats were thus exposed to noise every Monday through Friday from 8 AM until 4 PM from the very first day that they arrived at the colony. The rats did not display any obvious signs of stress, but it is unknown if this exposure had any effect on their exercise or open field performance.

A strong positive correlation was found for time spent on the wheel and distance ran. This result is logical, since it is unlikely that a rat would spend a long amount of time on the wheel and only travel a short distance. However, it is not known whether a rat ran the entire distance at once and then rested, rested and then ran the entire distance, or if it ran consistently throughout the entire exercise session. Future research should record how each rat patterns its exercise in order to determine if possible differences in exploratory behavior are due to exercise regimen variations.

The treatment group exercised every Tuesday, Thursday and Saturday for a total of 20 exercise sessions within a 49-day period. There was a high degree of variation in the amount of time spent on the wheel and running distance. Some research has

suggested that rats exposed to a running wheel will progressively increase their running and then stabilize after about 4 weeks. (Elam et al.,1987). A study conducted by Bucinskaite et al., (1996) exposed SHRs to a similar structured exercise regimen. Their median running distance for week one was .17 km: our median was .15 km. However, in week 5 Bucinskaite et al.'s median was .26 km while our's decreased to .11 km. The current data show that individual rats had a semi-consistent running distance, but as a group the distances varied. (See Appendix C for graphs of each rat's running distance.) Although exercise was voluntary it was still surprising that some rats chose not to run while in the wheel. Rats F and J were the only non-runners, rat F failed to exercise 2 out of the 20 sessions, while rat J failed to exercise only once. Some of the rats did run the same distance a few times within the exercise regimen but not enough to be considered consistent. (Hoffman, Elam, Thoren, & Hjorth, 1994).

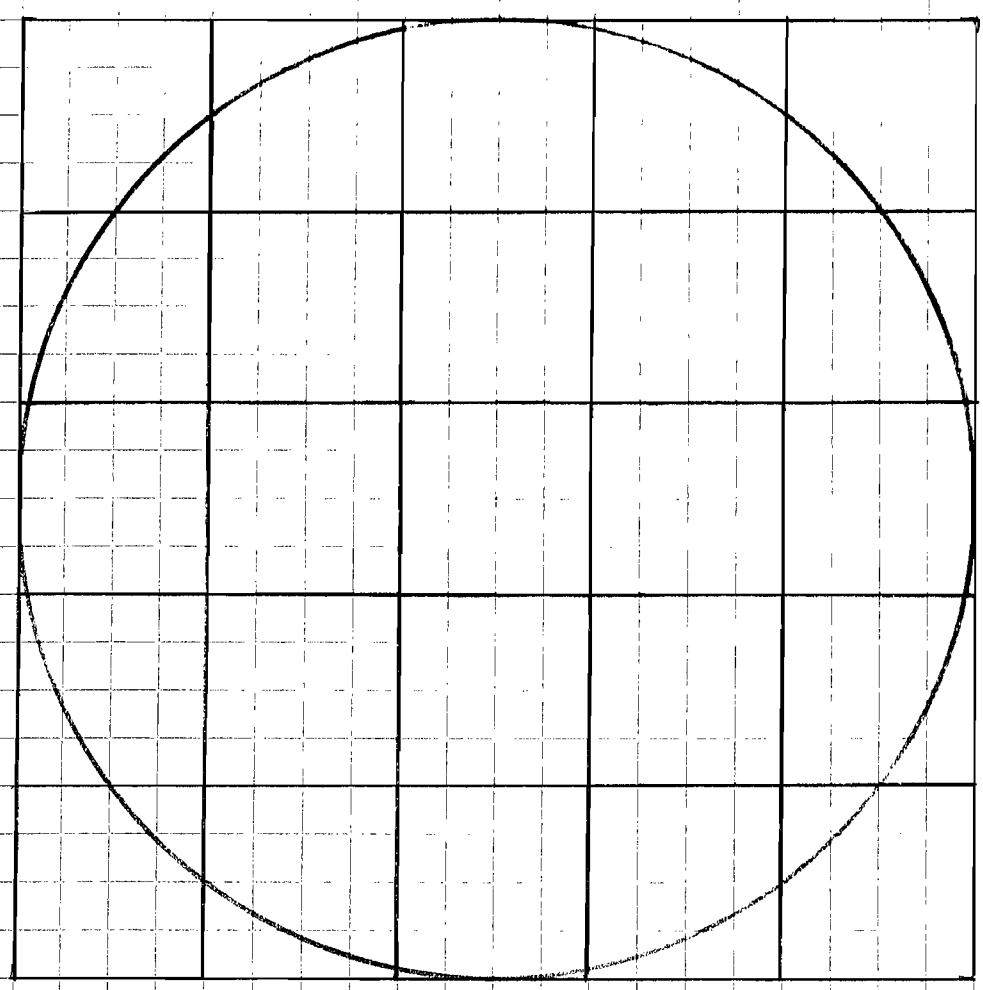
One goal of the current research was to test the notion that exercise may help relieve the behavioral symptoms of ADHD. This study partially supported this idea in that rats exposed to exercise showed more exploratory behavior in the open field than control rats. The number of square crossings, however, did not differ between groups, suggesting that exercise may not decrease hyperactivity. Exercise is known to elevate mood and improve concentration as well as cognitive functioning (Szabdo, 2006). While a direct connection between exercise and relief of ADHD symptoms in children cannot yet be confirmed, these results do warrant future research. Exercise may provide an alternative to a drug regimen that has unknown consequences.

It should be noted that the SHR has a limited age window during which their behaviors resemble ADHD. At adulthood, the rats' behaviors resemble those of hypertension rather than ADHD. The exercise regimen used in the current study ended when the rats were 82 days of age, which by most is considered adulthood.

Much of the research used to develop the current study was based on open field experiments conducted in the late 1970's and 80's. The SHR was mainly an animal model for hypertension, not hyperactivity, and the variables studied were different from those examined in previous research. The dependent variables examined in prior studies of the SHR as an animal model of ADHD are typically delayed response tasks, serial choice tasks and extinction behavior tasks. These tasks may be better representative of ADHD symptoms in humans than the tasks utilized in the current study. Future research could focus on using both pharmaceutical treatments in conjunction with exercise. It may be worth investigating whether exercise could help stabilize the dose of medication needed to treat ADHD. The effects of long-term stimulant use are not known. Perhaps coupling exercise with medication will reduce the dose of medication necessary for the relief of some of the symptoms of ADHD. Because up to 12% of our grade school children are medicated with stimulants, understanding the effects of exercise on inattention should be a priority.

APPENDIX A

Sketch of Open Field.



APPENDIX B

Time Table of Events.

Time Table of Events

Table B-1

Age(Days)	25-28	29-31	32	33	40	47	54	61	68	75	82
Acclimation: to new home	X										
Acclimation: open field		X									
Observation: open field			X								
Exercise regime begins				X							
Testing: open field					X----------						----------X

APPENDIX C

Graphs of Exercise Patterns for Individual Rats.

Exercise Patterns for Individual Rats

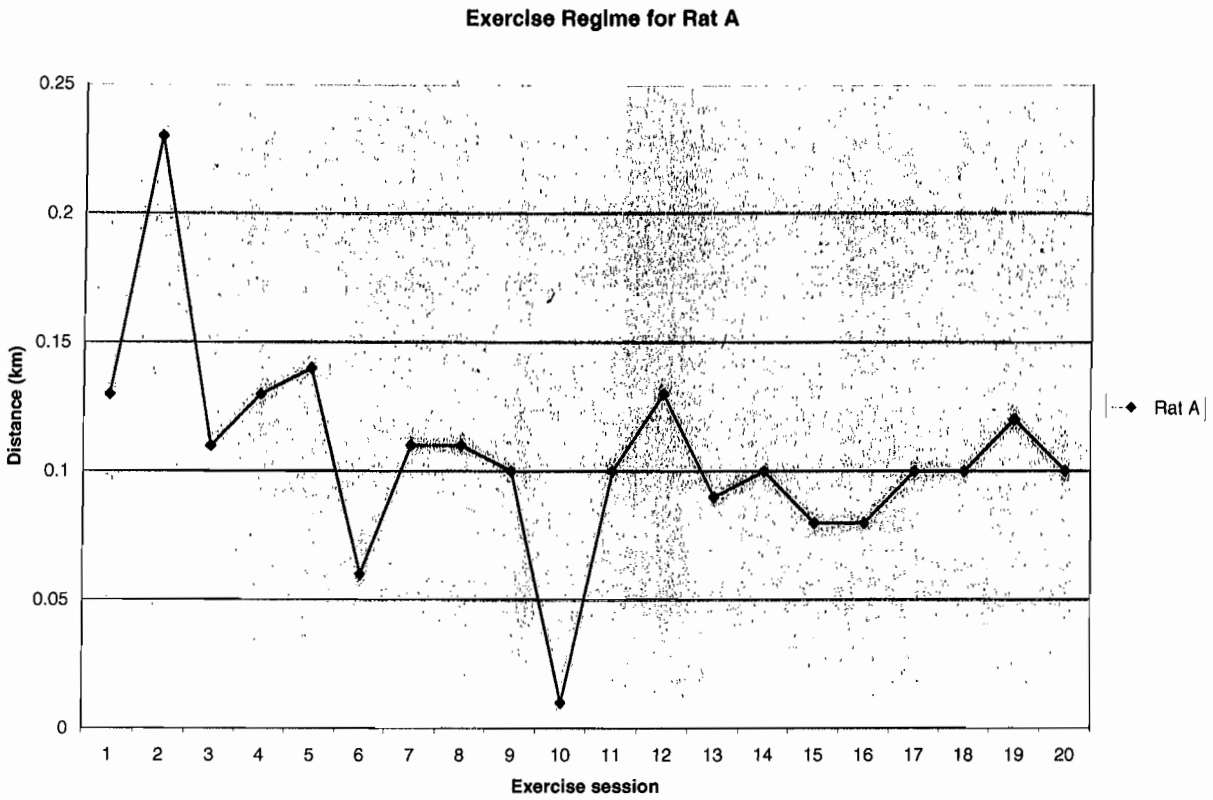


Figure C-1.

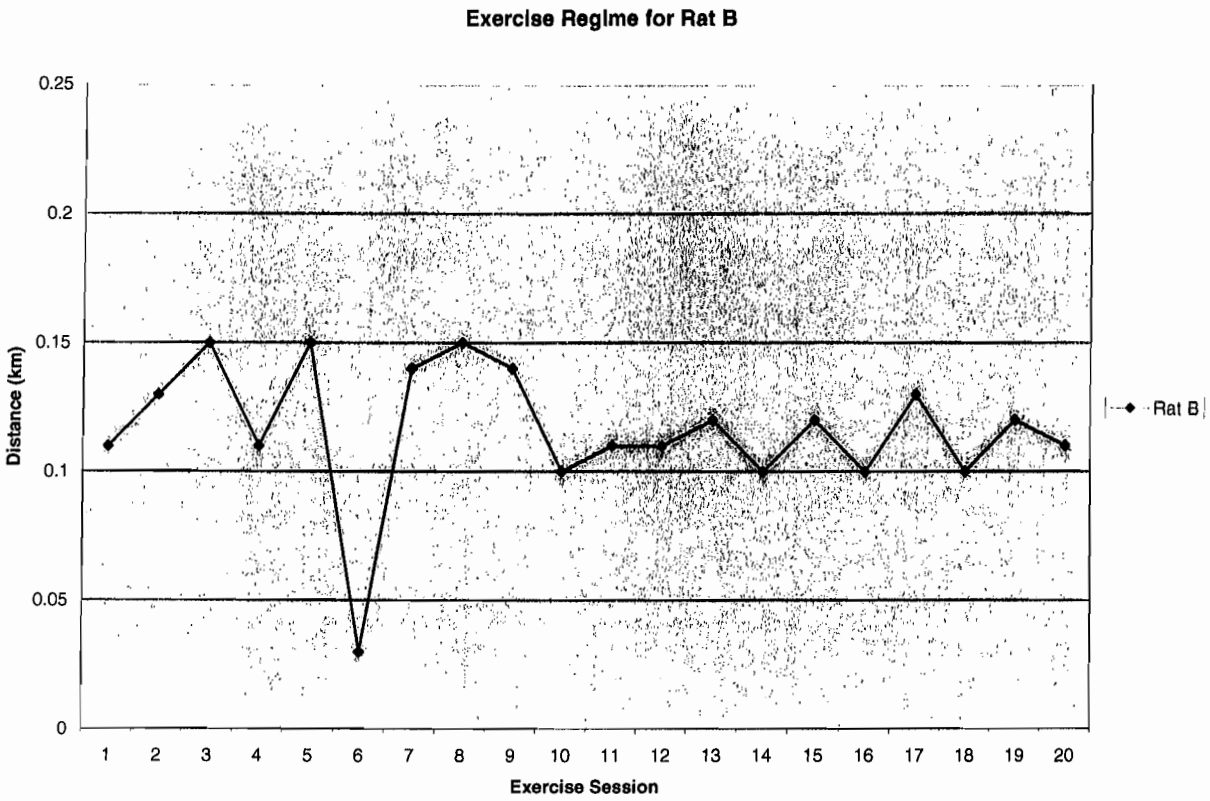

Exercise Regime for Rat B
0.25
0.2
0.15
0.1
0.05
0
Distance (km)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Exercise Session
Rat B

Figure C-2.

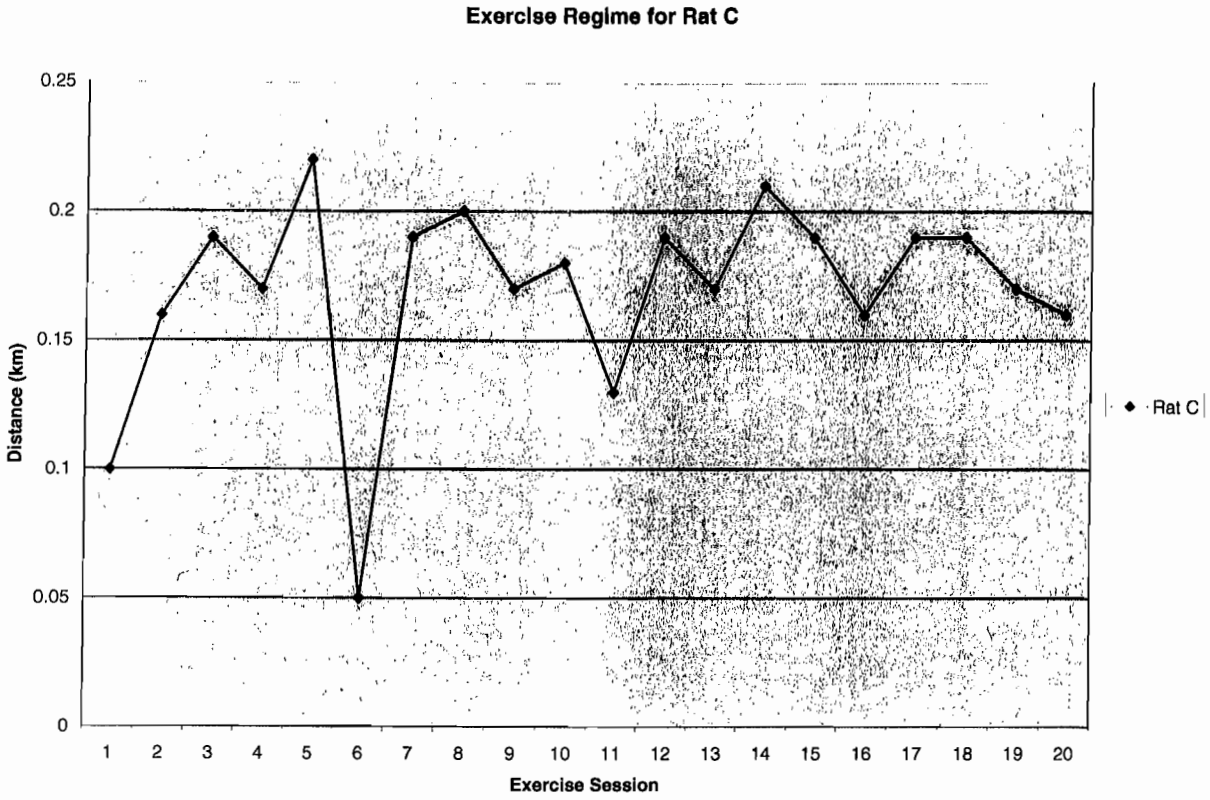

Exercise Regime for Rat C
0.25
0.2
0.15
0.1
0.05
0
Distance (km)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Exercise Session
Rat C

Figure C-3.

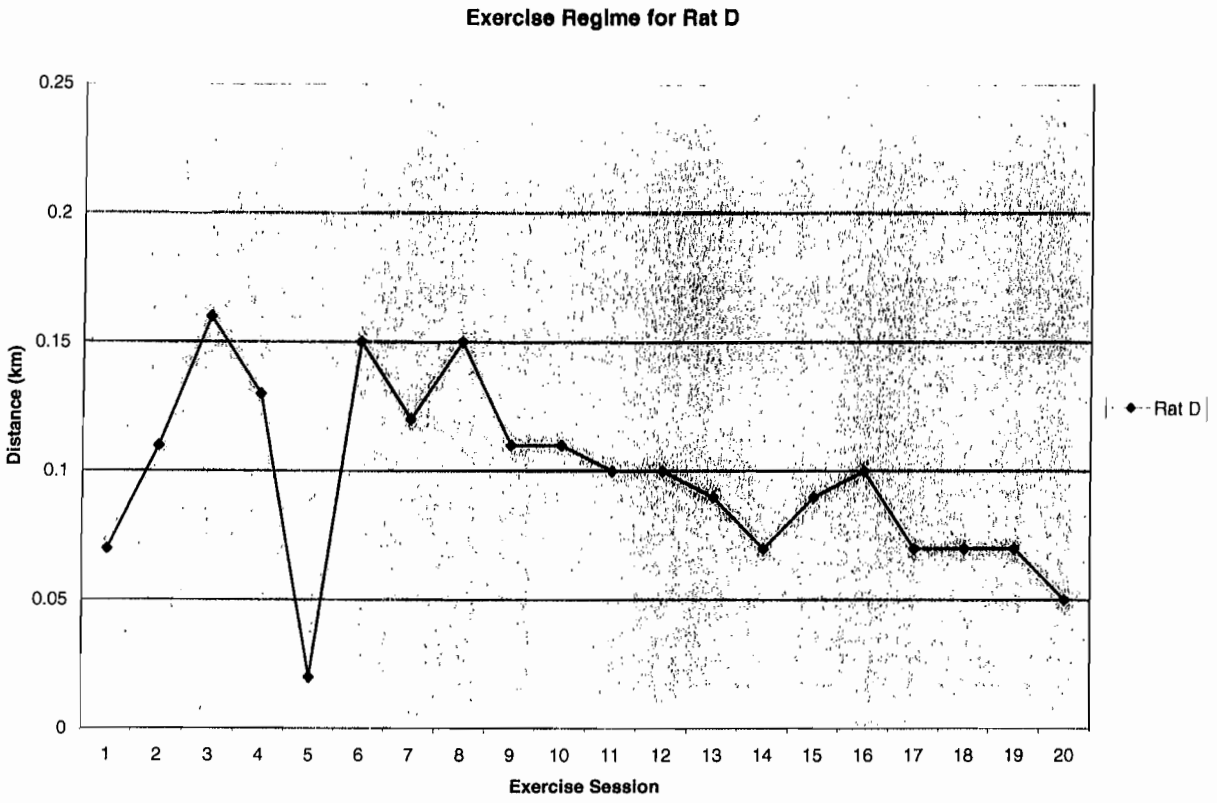

Exercise Regime for Rat D
0.25
0.2
0.15
0.1
0.05
0
Distance (km)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Exercise Session
Rat D

Figure C-4.

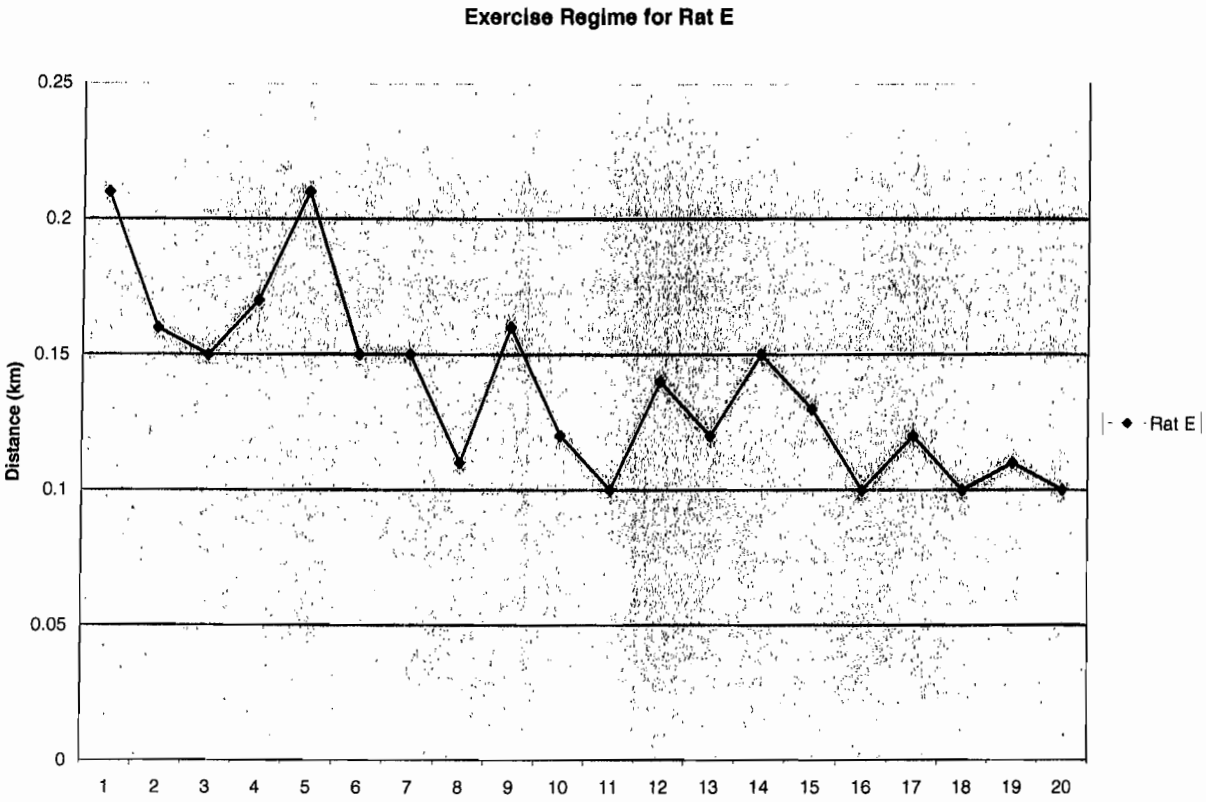

Exercise Regime for Rat E
Distance (km)
0.25
0.2
0.15
0.1
0.05
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
Rat E

Figure C-5.

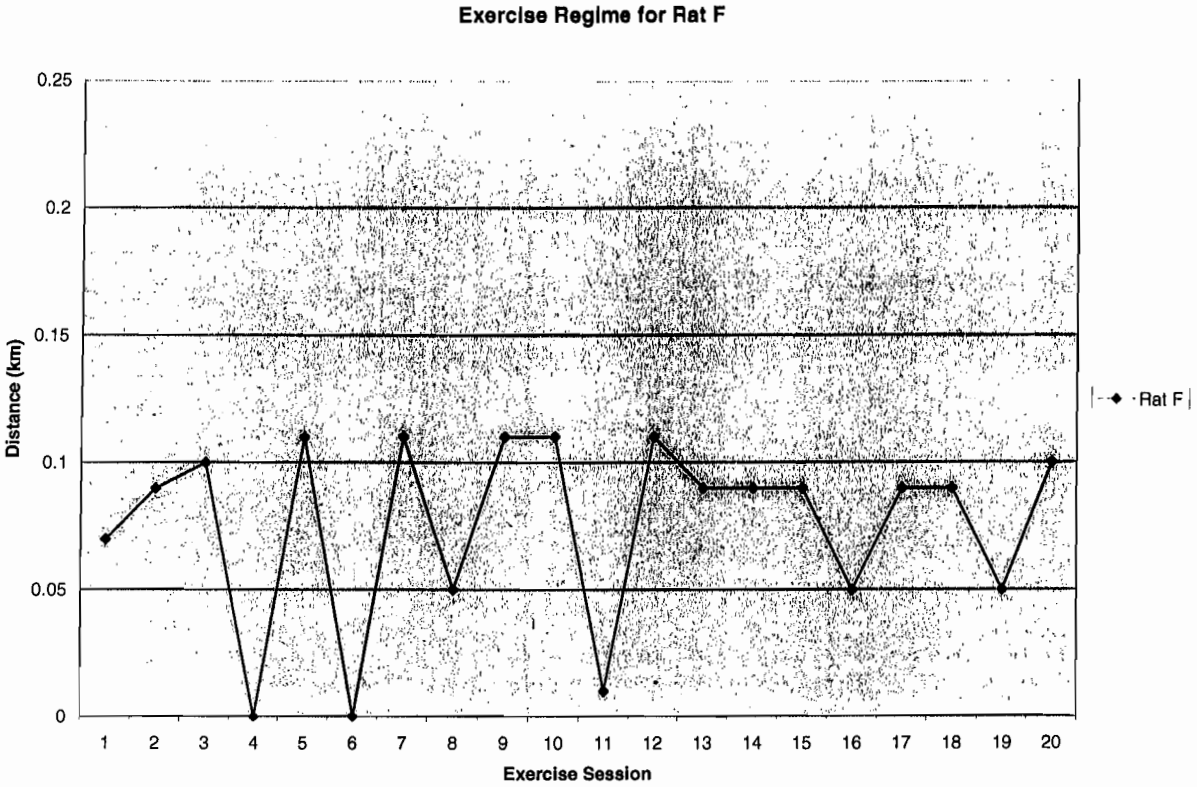

Exercise Regime for Rat F
0.25
0.2
0.15
0.1
0.05
0
Distance (km)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Exercise Session
Rat F

Figure C-6.

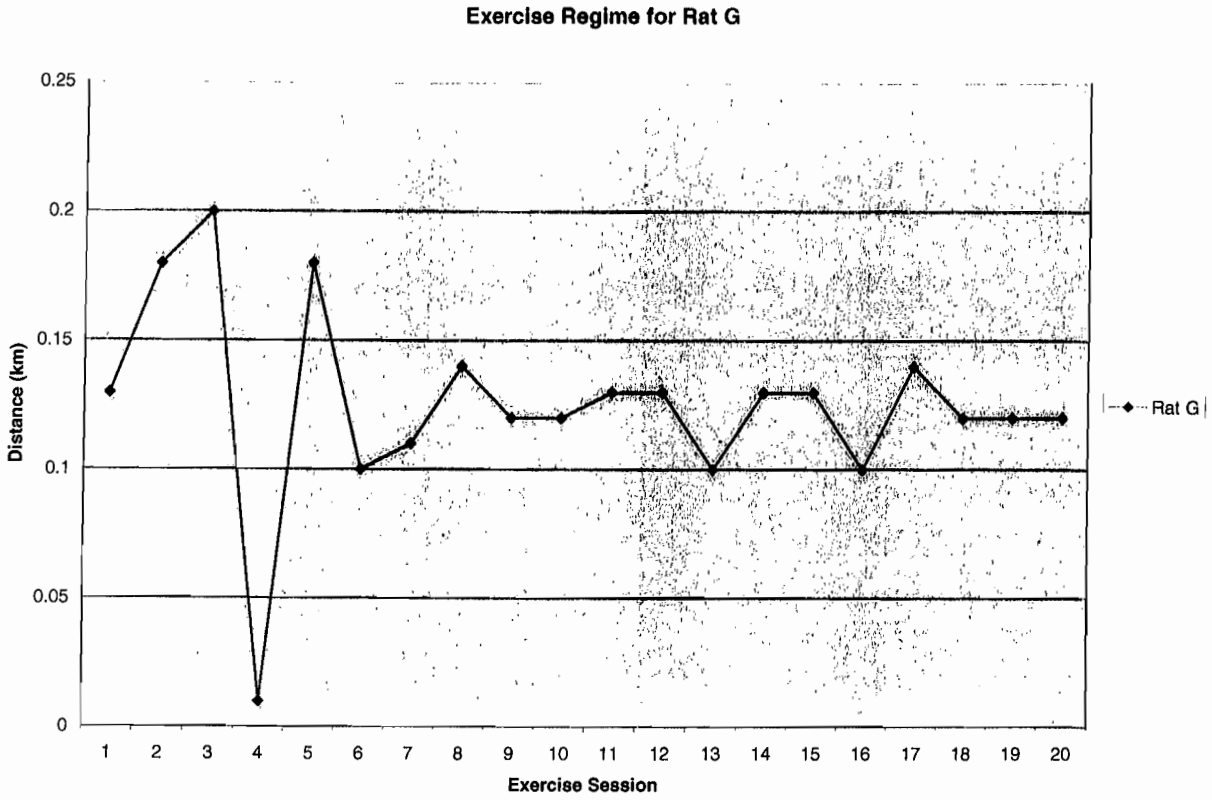

Exercise Regime for Rat G
0.25
0.2
0.15
0.1
0.05
0
Distance (km)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Exercise Session
Rat G

Figure C-7.

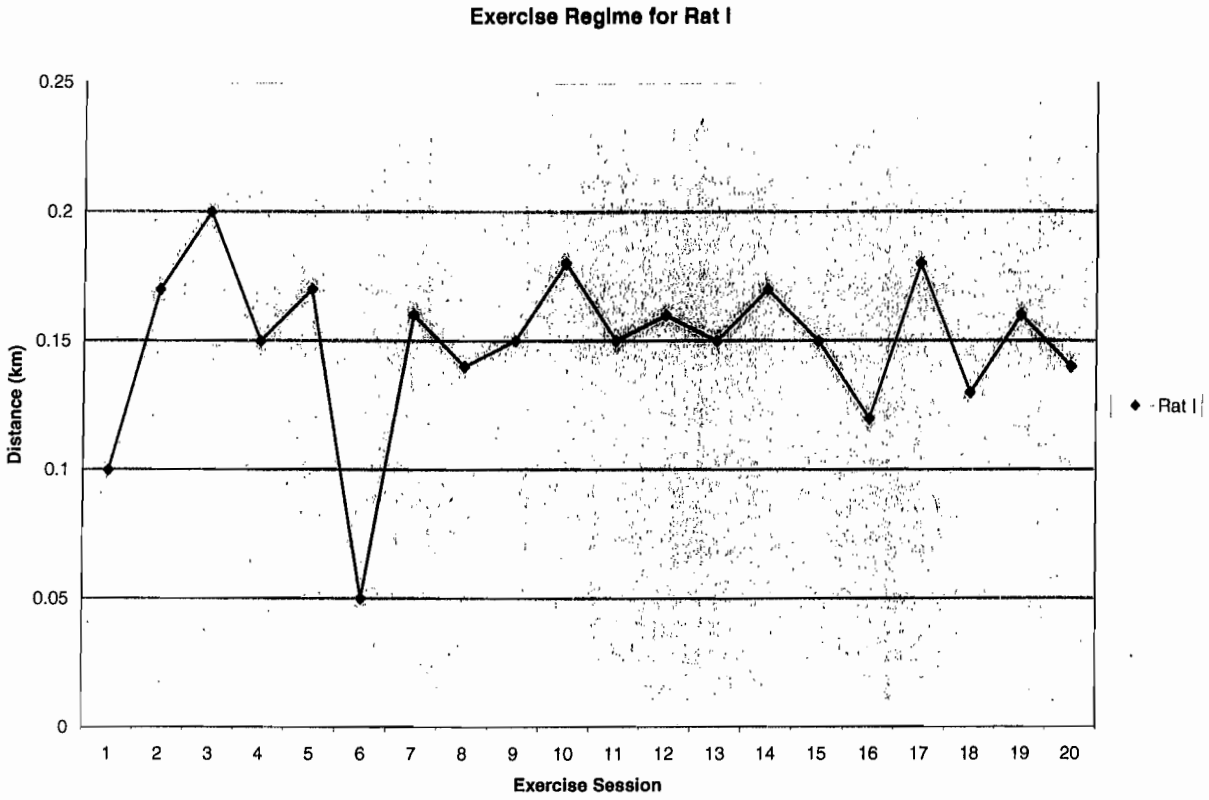

Exercise Regime for Rat I
Distance (km)
0.25
0.2
0.15
0.1
0.05
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Exercise Session
Rat I

Figure C-8.

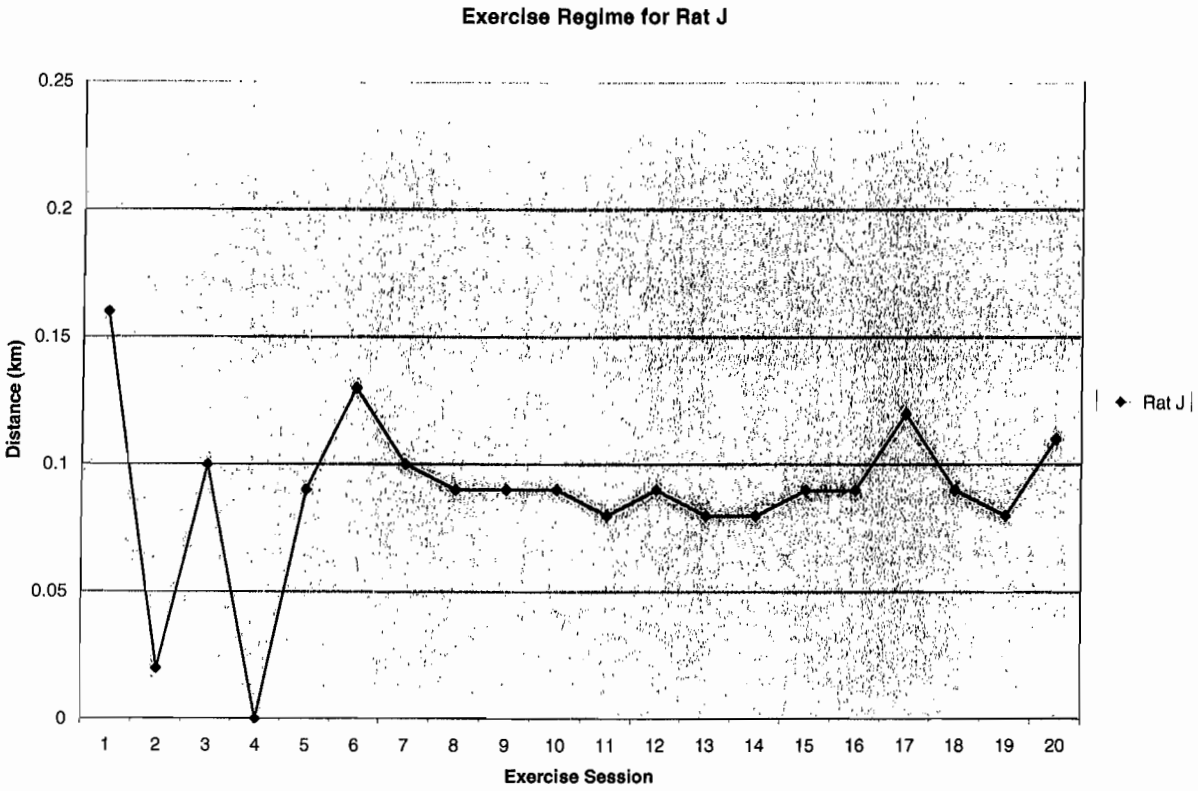

Exercise Regime for Rat J
Distance (km)
0.25
0.2
0.15
0.1
0.05
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Exercise Session
Rat J

Figure C-9.

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