The FAST "Seizure-Prone" Rat Strains; As a Possible Animal Model of Attention-Deficit Hyperactivity Disorder (ADHD)

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Abstract:

The FAST 'seizure-prone' rat strain has been a valuable tool in the study epilepsy over the past decades, recently it has been suggested that these animals may also display the behavioral characteristics of attention-deficit hyperactivity disorder (ADHD). The present study seeks to provide evidence suggesting the FAST rats as a model for ADHD. In order to suggest any animal model a validation criterion must first be met. In the current study the validation of the suggested animal model is carried out through the development of a novel behavioral paradigm. The test was designed to encompass a measure for each of the defining characteristics of ADHD, that being inattention, hyperactivity, and impulsivity. The current study sought to accomplish two main goals a) provide evidence that shows the ADHD characteristics of the FAST rats and b) validate the behavioral test as a reliable measure for ADHD in an animal.

The conclusions from the present study clearly display a higher activity level of the FAST rat when compared to the SLOW rats, however measures of attention failed to present any significant results. Furthermore, the tests of impulsivity were not performed as a result of the fact that the animals both FAST and SLOW failed to learn the task in a manner that would have allowed these measures to be realized.

Although the presented data shows the hyperactive nature of the FAST rats, hyperactivity alone does not warrant a diagnosis of ADHD, the failure of the behavioral test to accurately assess the defining characteristics of ADHD suggests that further validation of the FAST rats as a model of ADHD requires the use of previously established measures of hyperactivity, inattention and hyperactivity.

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Introduction:

Throughout history animal models of various diseases and disorders have continually been utilized in scientific research as an initial entry point to understanding the unknown, in discovering some element of a disorder that can then possibly be applied to the understanding of the human condition. However in order to make any parallels to the human condition, it must be shown that the animal model does, to the extent that it can, mimic the human state in question. In the context of the present study, the disorder that is begin examined is the behavioral disorder of attention-deficit hyperactivity disorder (ADHD) and the animal model proposed is the FAST 'seizure-prone' rat strain.

The challenge of the research presented here is to provide data that will argue the FAST seizure-prone rats as a plausible model for ADHD; this hypothesis is partly based on research indicating a substantially high co-morbidity between ADHD and epilepsy as well as other behaviors that have been observed in the FAST rats.

Given that our lab currently has an animal model of "seizure proneness" the FAST rats, the challenge of establishing them as an animal model of ADHD was carried out through a behavioral paradigm developed by our lab, which comprises a test for all three aspects of ADHD (inattention, impulsivity, and hyperactivity). To the best of our knowledge one behavioral test that encompasses a measure for each of the characteristics of ADHD in animal models fails to exist. With that being said, many tests do test for aspects of the disorder and thus the novel paradigm presented here does draw on aspects of the other test while at the same time interjecting features which make it an entirely new behavioral paradigm.

In order to establish the FAST seizure prone rats as a model for ADHD, an examination into the currently used models must be done to first establish the necessary criteria that must be fulfilled in order to suggest a new animal model. Second, an understanding of the current models allows for a presentation of parallels between our suggested model and the models presently utilized in ADHD research thus attaching predictive validity, and finally this then allows for a discussion involving the unique characteristics that the FAST rats posses that would present them as an entirely new model of ADHD.

ADHD: Attention Deficit Hyperactivity Disorder

The questions surrounding the behavioral disorder of ADHD are many and quite varied in the research literature. There is a large population of researchers that will argue that the disorder arises from a neurological dysfunction, which in many cases can be 'corrected' through the use of medication. Others, however, suggest that poor evaluation methods and the screening tools used in the diagnosis of ADHD have resulted in over-diagnosis, and medication has become a pharmacological answer to create a quiet classroom.

Given the large and increasing prevalence of ADHD in our society, considerable research now focuses on this disorder, which affects ~5-10% of the school age population (Faraone & Biederman, 1998; Faraone et al., 2003).

Countless articles indicate a high genetic heritably of ADHD (Coolidge et al., 2000; Edelbrock et al., 1995; Martin et al., 2002); however, as is the case of most behavioral and neurological disorders, biology alone cannot explain them completely. Environmental factors, such as food additives/diet, alcohol exposure, and smoking during

pregnancy (Biederman, 2005), must also be considered when attempting to understand this complex behavioral disorder. At the present moment, there are insufficient data to make any concrete conclusions as to the etiology of ADHD (Paule et al., 2000).

Characteristics of ADHD:

The DSM-IV-TR, The Diagnostic and Statistical Manual, sets out the diagnostic criteria for the disorder, and it indicates that six or more symptoms of inattention must be present for a period of six months and that these symptoms must be significantly different from the child's developmental level. The following is an example of some of the inattention criteria adapted from the DSM-IV-TR APA, 2000:

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities

(b) often has difficulty sustaining attention in tasks or play activities

(c) often does not seem to listen when spoken to directly

For an individual to be diagnosed with ADHD, they must present six or more of the hyperactivity- impulsivity symptoms for a period of six months and that these symptoms again be different from the individuals developmental age. The follow is an example of some of the hyperactivity-impulsivity criteria adapted from the DSM-IV-TR APA, 2000:

Hyperactivity

(a) often fidgets with hands or feet or squirms in seat

(b) often leaves seat in classroom or in other situations in which remaining seated is expected

(c) often runs about or climbs excessively in situations in which it is inappropriate (in

adolescents or adults, may be limited to subjective feelings of restlessness)

Impulsivity

(g) often blurts out answers before questions have been completed

(h) often has difficulty awaiting turn

(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

The assessment of the diagnostic criteria is based on behavioral observations put forth by parents and teacher ratings. Furthermore, there must also be evidence of a "clinically significant impairment", which impacts the individual's social, academic and/or occupational functioning (Paule et al., 2000). In a review paper by Paule et al., (2000), the authors put forward arguments that question the validity of this type of diagnosis.

First, a clinical setting presents a novel environment, where individuals are less likely to display the defining characteristics of ADHD in this type of setting, e.g., a doctor's office. Second, it may be very difficult to distinguish whether the symptoms are the result of an inability to maintain attention or the result of some other underlying co-morbidity.

Given the parameters outlined by the DSM-IV-TR, it is possible to take the outlined definitions of the characteristics of ADHD and operationally define them in a context that is applicable to the animal model.

The neurobiology of ADHD:

The hypothesis surrounding the neurobiology of ADHD has been concentrated on the actions of dopamine (DA) and norepinephrine (NE). This is impart due to the fact that the drugs used in the treatment of ADHD, i.e., amphetamine and methylphenidate exert

there effects on these neurotransmitters. Amphetamine increases DA by firstly promoting its release; the available DA is maintained in the synapse through amphetamine's second function, which prevents the reuptake of the transmitter through a blocking of the dopamine transporter. Methylphenidate also blocks the dopamine transporter. Preventing the reuptake of DA and NE in the synapse allows them to remain longer in the synaptic cleft and thus continually stimulating the postsynaptic membrane (Pliszka, 2005).

Norepinephrine (NE):

The main interest surrounding NE as a possible biological marker in ADHD is centered on the fact that many pharmacological agents used in the treatment of ADHD involve the noradrenergic systems, and furthermore some of these agents have either no affinity or a very low affinity for the DA system (Pliszka, 2005). For example, (Michelson et al., 2002; Michelson et al., 2003) found that Atomoxetine was an effective pharmacological agent in the treatment of ADHD in both the child and adult populations. Interestingly though, Atomoxetine is a potent NE reuptake inhibitor but the drug presents little effect on the reuptake of DA (Bolden-Watson & Richelson, 1993).

Another line of therapy in the treatment of ADHD has been the tricyclic antidepressants (TCAs), similar to Atomoxetine, TCAs are known to block the reuptake of NE while at the same time failing to block the reuptake of DA (Pliszka, 2005). Although it is important to note that these medications are typically used as a second line of therapy and that their efficacy is far below that of the traditional stimulant medications used in the treatment of ADHD (Pliszka, 2005).

The noradrenergic system further supports the role of NE in ADHD, as the locus coeruleus has been cited as an important area of the brain for the regulation of attention

and vigilance (Berridge and Waterhouse, 2003). However, the LC produces diffuse connections to a variety of brain regions, which can and do involve the DA systems.

Dopamine (DA):

Many of the theories regarding the role of DA in the disorder of ADHD have concentrated on the DA transporter (DAT) system. In a paper published in 2005, Madras et al., outline several lines of evidence that place the DAT at the forefront in the exploration of this behavioral disorder. Firstly they present the findings that the "dopamine transport inhibitors indirectly activate dopamine receptor subtypes; D4 and D5 dopamine receptors are implicated in ADHD and dopamine receptors activity enhances attention and experiential salience and engenders stimulation" (Madras et al., 2005). Secondly, they cite the fact that the DAT is the main target for the most often prescribed and efficacious medication in the treatment of ADHD, i.e., methylphenidate and amphetamine. Thirdly, it has been suggested that the DAT gene is associated with ADHD. And finally, the authors cite that various studies have presented data indicating abnormal levels of DAT in patients diagnosed with ADHD.

The theories presented here set the stage to move forward into a discussion concerning the current animal models used in the study of ADHD, due to the fact that some of the developed models are based on these above-mentioned hypothesis.

Criteria for Animal Models of ADHD:

In a review article by Sagvolden et al., (2005), the various animal models that are currently being used in the investigation of ADHD are outlined. In this article, the authors described the criteria for the classification of an animal model of ADHD developed by

(Sagvolden, 2000): first the model must possess face validity, where the animal displays the behavioral characteristics of ADHD.

Impulsivity should develop over time but should not be present initially. Hyperactivity should also develop over time and should not be observed in a novel or non-threatening environment, while deficits in sustained attention should be observed only when the stimuli are spaced in time.

Second, the model must possess construct validity and should conform to a theoretical rationale for ADHD. Altered reinforcement of novel behavior and deficient extinction of previously reinforced behavior also should be demonstrated, as these are the two main behavioral processes that are proposed to be major contributing factors in ADHD. Third, the model must have predictive validity in that it should predict novel aspects of ADHD behavior, genetics and neurobiology. And finally the model should be neurodevelopmental, and preferably a genetic model.

Current Animal Models of ADHD:

To date the most frequently invoked animal model of ADHD are the Spontaneously Hypertensive rat strains (SHR). These animals produce similar results to those seen in ADHD children when performing a maneuver that was designed to mimic a test performed with ADHD children with a multiple fixed interval/extinction schedule (Sagvolden, 2000). In terms of the three defining characteristics of ADHD, the SHRs have exhibited motor impulsivity, which has been demonstrated in the open-field test (Sagvoldgen, 1992; Wultz and Sagvolden, 1992, cited in Sagvolden et al., 2005). The animals when placed into the open field tend to display short runs that are not interrupted

by exploratory behavior or stopping. However this behavior is not initially present in a novel situation but does develop over time (Sagvolden, 2005).

The SHRs also display attention deficits mostly involving sustained attention; this is seen in the extinction component, for the most part when the reinforcements are provided at a regular time intervals they do not appear to show any deficits in attention (Sagvolden, 2005). However in the extinction schedule the SHRs recommence responding after a brief time period (Sagvolden, 2000). Similar to the attention results, the SHRs are hyperactive when the reinforcements are infrequent but not when they are provided at regular time intervals (Sagvolden, 2005). The SHRs also do not display hyperactivity in a novel situation; this behavior given the right parameters will develop over time, in much the same way that the motor impulsivity does (Sagvolden, 2005). This evidence appears to strongly support the face validity component of the set out criteria.

Further research has provided evidence in support of the construct validity component of the criteria for an animal model of ADHD, however researches do note that it is too early to make any conclusions to the construct validity of the SHRs as an animal model of ADHD. This is due to the "limited agreement on the theoretical rationale for ADHD" (Sagvolden, 2005).

The research has shown that the SHRs display several variants in the dopamine transporter-1 (DAT-1) gene, which is important because several ADHD families show linkages to DAT-1 (Sagvolden, 2005). In terms of basic neurobiology Bendel & Eilam, (1992) showed that SHRs also present decreased brain volume, which is a neuroanatomical feature often observed in ADHD children.

The parallel to the human condition in terms of a gender difference is also seen in the SHRs males who tend to display more bursts of activity when compared to females in a lever pressing exercise. However the females tend to be less attentive than the males evidenced by the fact that they continue to press the lever after the reward has been provided (Sagvolden & Berger, 1996; Berger & Sagvolden, 1998).

The Coloboma mutant mouse has also been put forward as a model of ADHD. This particular animal displays hyperactivity and delays in reaching neurodevelopmental milestones (Davids et al., 2003). The Coloboma mouse has a mutation in the gene encoding the SNAP-25, an integral component in the release of neurotransmitter (Russell et al., 2005). Wilson (2000), found that the Coloboma mouse displayed hyperactivity in the open field much like the SHRs, and furthermore their behavior was reduced through the administration of d-amphetamine, but not with methylphenidate. Although this animal does represent various features of the disorder, it is not recommended as a fully valid model of ADHD. The diminished validity stems from the lack of impulsivity, although Brouno et al., (2006) found that these animals did show impulsivity in a delayed reinforcement task. Furthermore, the Coloboma mouse presents some neurobiological deficits that if present in a child would exclude them from the diagnosis (Sagvolden et al., 2005).

In the neurodevelopmental theory of ADHD, researchers suggest that anoxia can increase the risk of developing ADHD; Lou et al., (1996) found that children diagnosed with ADHD were found to have had more incidences of perinatal anoxia when compared to controls. Anoxia produced in a neonatal rat has also been used to create an animal model of ADHD. These animals display the hyperactivity characteristics of ADHD; but

as seen with the Coloboma mouse, the anoxia creates impairments in learning and memory (Davids et al., 2003), factors that would exclude a diagnosis of ADHD.

Further models have been created through exposure to toxins; one such model is the 6-hydroxydopamine-lesioned rats. These animals display the characteristic hyperactivity that is initially absent but will develop over time, and they also show impairments in learning within the context of spatial discrimination task, which was shown to improve with the administration of methylphenidate (Davids et al., 2003).

Many other models have been suggested as plausible models of ADHD, however they tend to display aspects of the characteristics rather than fulfilling all of the above-mentioned criteria. To date, the SHRs serve as the strongest model in studying ADHD.

Behavioral Paradigms in the Assessment of ADHD:

The behavioral disorder of ADHD encompasses three fundamental facets: an individual or in this case an animal must display aspects of impulsivity, hyperactivity, and inattention. To the best of our knowledge, a single behavioral test that invokes a test for each of these characteristics fails to exits. Many test as previously mentioned will test various aspects of the disorder, for example, the behavioral test known as the open field will measure levels of activity, which can then be interpreted as measures of hyperactivity. In such a paradigm, an animal is placed into an open box for a given time typically ten minutes. During this time the experimenter records measures of activity, scored as number of lines crossed, distance traveled, and standings. Taken together, the experimenter is able to gather data regarding the movement of the animals.

The behavioral test that is most commonly associated with the assessment of ADHD is the 5-choice serial reaction time task (5-CSRTT). This test was developed to

measure the effects of various drug treatments as well as other factors on the attentional processes of a rat (Robbins, 2002). The test was designed to at its most basic level mimic a clinical test developed by Rosvold & Mirsky known as the continuous performance tests (CPT) (Rosvold et al., 1956; Mirsky & Rosvold, 1960 cited in Robbins, 2002). The CPT is used to measure sustained attention, over a thirty-minute test session.

The 5-CSRTT was developed to display aspects of the CPT but with an added spatial component. In a review article by Robbins (2002), the author outlines the development as well as the various uses of this behavioral test. The test consists of a nine-hole box; the rat was required to attend to the location of a light, which is used as the target stimulus. The light would appear at the rear of one of the five holes. Infrared photocell beams located at the entrance of the entrance of the five holes monitored the nose-poke responses; a correct response was rewarded by the delivery of a food pellet in a magazine that is found at the rear of the chamber.

The animal's responses are recorded as either correct responses, or errors of commission, which would involve the animal responding to a hole where there was no stimulus presented. Also, Errors of omission, which would involve failing to respond to the presented stimulus, and premature responses, which would involve the animal responding prior to the presentation of the target stimulus. In summary, the author notes that at its most basic level the 5-CSRTT is designed to gather data related to the animals ability to sustain spatial attention, which is divided among a number of different locations.

A further test that is used to measure levels of impulsivity in the animal model is the stop signal reaction time task (SSRTT). This test again measures a facet of the ADHD

characteristics, the impulsivity subtype. The design of the test involves the assessment of an animal's ability to stop a behavior that is in the process of being carried out (Eagle and Robbins, 2003). In this procedure the animal is required to perform a response to a "go" signal. However on some trials a "stop" signal will be introduced after the "go" signal has been presented. The animal is then required to stop the behavior that was initiated by the "go" stimulus (Eagle & Robbins, 2003).

In a 2003 paper by Eagle and Robbins, the authors outline the SSRT procedure. The SSRT trials begin by the animal performing a nose poke into the central food holder. At this point the left lever was presented; when the animal presses on the left lever the right lever is then presented. The animals were trained to perform a rapid response of left to right level presses – this is the "go" response. During the "go" trials, the animals are rewarded with a food pellet after the right lever had been pressed. Twenty percent of the "go" trials involve the "stop" stimulus; the "stop" stimulus is presented as a tone that is delivered between pressing the left and right lever. If the animal failed to recognize the tone as the "stop" signal, they would not receive the food reward. However if the animal recognized the tone as the "stop" signal and therefore failed to press the right lever they would then be rewarded with the delivery of food. The design of this study was to test the ability of the animal to maintain behavioral inhibition, a problem that is commonly seen in those with ADHD.

Taken together, the open field, 5-CSRTT and the SSRT can measure all of the three key characteristics of ADHD. Hyperactivity can be measured through line crosses and rearing in the open field. Attention can be measured in the 5-CSRTT through the number of correct responses, and impulsivity can also be assessed using the 5-CSRTT as

well as the SSRT, by either noting the number of premature responses or failure to cease the behavioral response after the presentation of the "stop" signal, respectively.

FAST and SLOW rats: An Animal Model of Epilepsy:

As noted previously, the goal of the present thesis is to establish the FAST "seizure prone" rats as a model of ADHD; the behavior's observed in the Fast rats will be compared against our SLOW "seizure resistant" strains, thus using the SLOW rats as the control.

The development of rat strains based on their predisposition to seizure induction was predicated on the question as to whether such predispositions have a genetic base. To address that question, the FAST and SLOW rats were selectively bred, based on their differential rates of amygdala kindling to the development of the first stage 5 convulsive seizure (Racine et al., 1999; McIntyre et al., 2002). Two strains of rats (i.e., Wistar and Long Evans hood) were used as the parent population from which the selection proceeded. Specifically, male and female rats from the parent population that demonstrated the fastest kindling were selected and bred. Their offspring eventually established the FAST strain. A similar selection was done for rats with slower kindling to produce the SLOW strain (Racine et al., 1999).

When compared to SLOW rats, FAST rats show a propensity for hyperactive/impulsive behaviors, which has been observed in several contexts, including physical restraint. In restraint testing, the FAST rats tended to struggle assiduously, whereas the SLOW rats tend to develop an immobile posture (McIntyre et al., 1999; McIntyre et al., 2002). Other studies performed in our lab have displayed results

indicating a much higher activity rate in the FAST rats in such paradigms as open field (McIntyre et al., 2002).

Attention difficulties have also been observed in the FAST rats in their performance in the Morris Water Maze. Anisman & McIntyre (2002) noted that when an irrelevant cue was added as a distracter, it impaired the acquisition of the FAST rats but not the SLOW rats, suggesting that the attention of the FAST rats may be more readily distracted from salient stimuli.

The importance of an animal model to parallel the human condition is obvious; it lends validity to the model and allows for generalization and prediction from the model. Therefore it is the goal of the present study to further assess and document the ADHD characteristics of our FAST (seizure prone) rats, which will hopefully additionally validate them as an ADHD animal model.

Purpose of the present study:

The goal of the present study is to assess the characteristics of ADHD that being inattention, hyperactivity and impulsivity in our FAST seizure-prone rats. The idea that a model of 'seizure-proneness' could be useful in the study of ADHD has arisen firstly, due to a large number of studies that indicate a co-morbidity between the two disorders. Secondly, the FAST 'seizure-prone' display various behaviors that appear to mimic the defining characteristics of ADHD.

The assessment of the defining characteristics of ADHD will be carried out through the use of a novel behavioral paradigm developed by our lab. A novel behavioral test was designed to encompass a measure for hyperactivity, inattention and impulsivity achieved through different testing phases. Briefly, hyperactivity was measured through

line crosses, latency to entry and total trial time, for each trial. Inattention was measured by calculating the percentage of correct arm choices in each of the experimental phases. Impulsivity, was to be measured in later experimental phases, however this measure was not tested due to the fact that the animals did not meet the criterion to move to these testing phases.

Methods and Materials

Animals

20 FAST and 20 SLOW male rats at ~ 90 days of age were individually housed in plastic cages with stainless steel coverings. Animals were housed in controlled conditions on a 12-hour light/dark cycle (lights on at 8am and off at 8pm) with water *ad libitum*. All animal experimentation was performed in accordance with the animal research act. The experimental procedures were approved by the Carleton University Animal Care Committee under protocol P07-1.

Experimental Groups:

The animals were divided into different experimental groups. The group division was irrelevant to the testing procedure; it was simply done, because all 40 animals could not be tested at the same time. The groups were randomly chosen resulting in 5 SLOW and 5 FAST in each 'group' testing period.

Food Restriction:

Two days prior to training, all animals were weighed and food restriction enforced. The animals were given on average 4 pellets daily (~30g). Their individual weights were monitored daily, and their food was adjusted according to loss or gain. Their individual weights never dropped below 10% of their original body weight. All animals were weighed and fed one hour after the testing has finished for the day. Food restriction was carried out for the entirety of the experiment.

Behavioral Apparatus:

The behavioral apparatus used in this experiment was novel and designed by myself. The apparatus was constructed out of plywood and then painted black (see Figure 1). It consists of a semi-circle starting area (SA) with a height of 10 inches, maximum width of 30 inches and length from the rear wall to front wall of 23 inches.

Attached to the semi-circle area were three arms extending out, where a door blocks each of the 3 arms from the main entry area. The doors were 6 inches in height by 7 inches in width. Each of the doors had a white light in their center; the light was positioned 3 inches from the top and bottom of the doors. Each door opened into one of the arms of the maze. Each of the arms was 30 inches in length and had a height of 10 inches; the width of each of the arms was 8 inches.

A clear plastic food holder was at the end of each arm. The food holder was fitted into the back wall of the arm, where it could be slid in and out; it was 3.5 inches in length, 2 inches in depth and 2.5 inches in width.

The floor of the maze (the starting as well as each of the arms) was divided into equal size grids that were used for the assessment of line crosses, during habituation and throughout the testing phases.

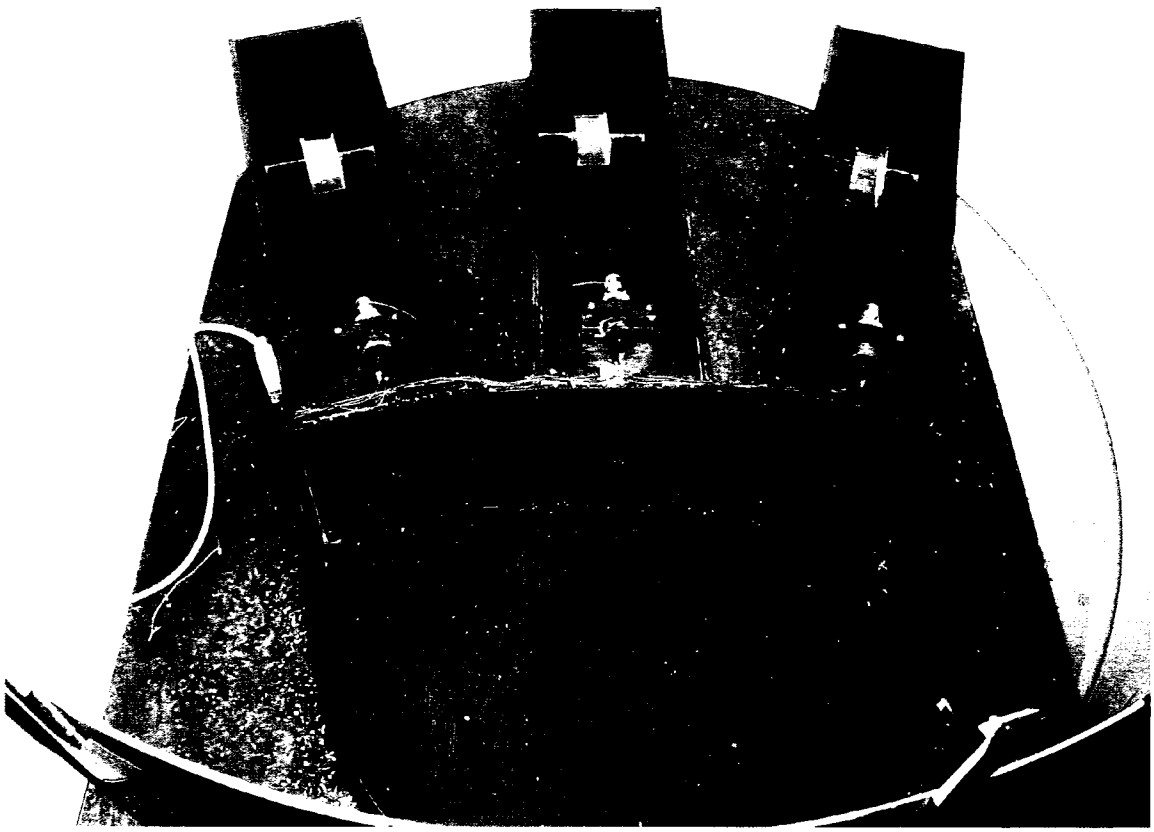
Training:

Day 1: Maze habituation

All testing was conducted under dim room lighting with the only source of light being a desk 60-watt incandescent lamp. This weak room lighting was done to make the maze door lights appear more salient. Each rat was placed in the at the back of the

semicircle facing the front wall with all doors closed, allowing it to habituate to the starting area. The rats were allowed

Figure 1: Behavioral Apparatus



to explore the starting area for a period of 5 min. During the habituation trials measures of activity were recorded these included line crosses and vertical rearing activity. After exposure on the first day, the rats were introduced to the food reward, i.e., honey nut cheerios cereal. This exposure allowed the rats to become habituated to the novel food.

Day 2: Maze habituation

Again all testing was performed under dim room light. The rats were placed in the starting area, with all three doors raised. The animals were given 5 minutes to explore the entire maze. None of the arms were baited with food; this phase was simply to allow the rats to familiarize themselves with the over-all maze. Line crosses and rearing were counted throughout the 5 minutes.

Day 3: Maze habituation

Testing followed the same procedure as day 2. Again measures of activity were recorded.

Day 4: Maze habituation

Subsequent training involved placing each rat in the starting area, with all of the doors opened and food was found at the end of each of the arms as well as along the arms. The rats were placed in the starting area and were allowed to explore for a period of 5 minutes. Measurements included line crosses, rearing, and the food reward eaten.

Day 5: Maze habituation

Again the rats were placed in the starting area with all doors open, but on this day, food was only found in the food holders. The rat was allowed to explore the maze freely for a period of 5 minutes. After it was clear that the rats knew where to find the food, the next phase of testing began.

Maze Training:

Maze training involved pairing the door light with the presence of food. The animals received six trails daily. During the training phase the animals received six light/food trails on Arm 1. For each trial the animal was manually restrained in the maze facing the three closed doors, at this point a light corresponding to arm 1 was turned on. After a period of 5 seconds the door was raised. A 6-volt motor located above the doors powered the opening of the doors. Once the door was opened the animal was free to enter the arm to retrieve the food reward. If the animal failed to enter the arm with the designated time of 60 the trial ended and a no entry score was recorded. If the animal entered the arm but failed to retrieve the food reward with 60 seconds a no food score was recorded. The trial was considered completed when either the animal received the food reward or when the trial exceeded the maximum time of 60 seconds.

Once the trial was completed the animal was removed from the maze and brought back to the starting area for the next trial. The training on Arm 1 continued until the animal was consistently retrieving the food on at least 5 out of the 6 daily trials. Once the animal had reached this criterion, they moved on to the same procedure on Arm 2, which was then followed by Arm 3. Following the training on Arm 3, the rats were exposed to a single day of randomized trials involving all three arms. On each of the 6 trials, once the animal had entered the open arm, the door was manually closed behind it, during the trial activity scores recorded were, number of lines crossed during the trial, latency to enter the open arm, and total trial time.

Testing:

Phase 1: Maze Testing:

Testing involved two doors, the rat was placed in the starting area, and the light in the center of one of the doors was turned on for only one of the 3 doors. Then two of the 3 doors were raised (one lit and one not). The animals received six trials daily, the trials were randomized for each day, with each rat receiving the same trials on that day. Once the 2 doors were raised, the rat had to choose between the lit and unlit open arms. Once the rat had entered either arm, the door was closed regardless of whether the rat selected the correct or incorrect arm. This phase continued until the rats were performing at 80% correct choices on three continuous days.

Phase Two: Maze Testing:

The second phase followed the same protocol as in phase one with one exception. The rats were placed in the starting area and one of the lights turned on, but after a period of five seconds was turned off, and two of the three doors are raised. The animal was required to have paid attention to the light and remembered which door/arm had been signaled and, thus, baited. This phase continued until the rats were performing at a criterion of 80% correct choices on three continuous days.

Phase Three: Maze Testing:

The third phase of testing, like the last phase, further measures sustained attention. In this phase, the rats were placed in the starting area and one of the lights turned on, again signaling the arm location of the food reward. The light was then turned off after five seconds, as before, but there was a delay of ten seconds between the light

turning off and the doors opening. This phase was the last phase in this portion of the experiment given that none of the animals ultimately could either get to or pass this test.

Amphetamine Vs H_20: Maze Testing:

The final experiment was to assess whether or not administration of amphetamine would affect the performance of these animals. Rats were assigned to groups based on their performance level at the time. The rats within each group were then randomly assigned to either an amphetamine or control condition. Thirty minutes prior to testing the rats received a 0.5 mg/kg i.p. injection of amphetamine or H_20, depending of their group assignment. The animals were exposed to three days of testing with drug treatment followed by a fourth washout day. The scores were then averaged across the three drug treatment days and compared to the fourth washout day.

Measurements of ADHD:

Relative 'hyperactivity' was measured in the FAST and SLOW rats through recording line crosses and rearing during and after habitation. Attention and impulsivity were measured throughout each of the experimental phases.

Statistics:

Most of the parametric results were analyzed using a repeated measures analysis of variance (ANOVA) with strains as the between -subjects measure and days as the within - subject variable. Where appropriate the data was analyzed using independent samples t-tests and a one-way ANOVA with strains serving as the between-subjects variable.

Results:

Habituation:

The initial experiment examined levels of hyperactivity during habituation. Line crosses and numbers of standings were recorded as a measure of activity between the FAST and SLOW animals. Habituation measures recorded over the first four days of exposure to the maze is shown in Figure 2. The FAST (n=20) rats made significantly more line crosses compared to the SLOW (n=20) rats $F(1, 38) = 21.98$ $p < .0001$. The repeated measure ANOVA also showed that the number of line crosses also changed over days $F(3, 38) = 6.26$ $p = .0006$, however the days X group interaction was just short of significance $F(2, 38) = 2.57$, $p = .0565$, suggesting that with more exposure to the maze, the SLOW tend to decrease their movement, this tendency is observed in Figure 2.

A second measure of initial activity displayed in Figure 3 was the amount of vertical activity displayed by rearing; again a repeated measures ANOVA indicated that the FAST animals showed a significantly higher level of rearing activity $F(1, 27) = 31.91$, $p < .0001$. There was also a significant difference in amount of rearing across days $F(3, 27) = 14.51$, $p < .0001$, while the days X group interaction was not significant $F(3, 27) = 1.34$, $p = .264$. The lack of a significant days X group interaction is suggestive of the fact that there is a tendency for the groups to decrease at similar rates over the four days.

Figure 2: Average number of line crosses across habituation days. FAST animals made many more line crosses across habituation days $F(1, 38) = 21.98$, $p < .0001$. The number of line cross also showed a significant difference across the testing days $F(3, 38) = 6.26$, $P = .0006$. The groups X days interaction was nearly significant $F(2, 38) = 2.57$, $p = .056$. The n was 20 per group.

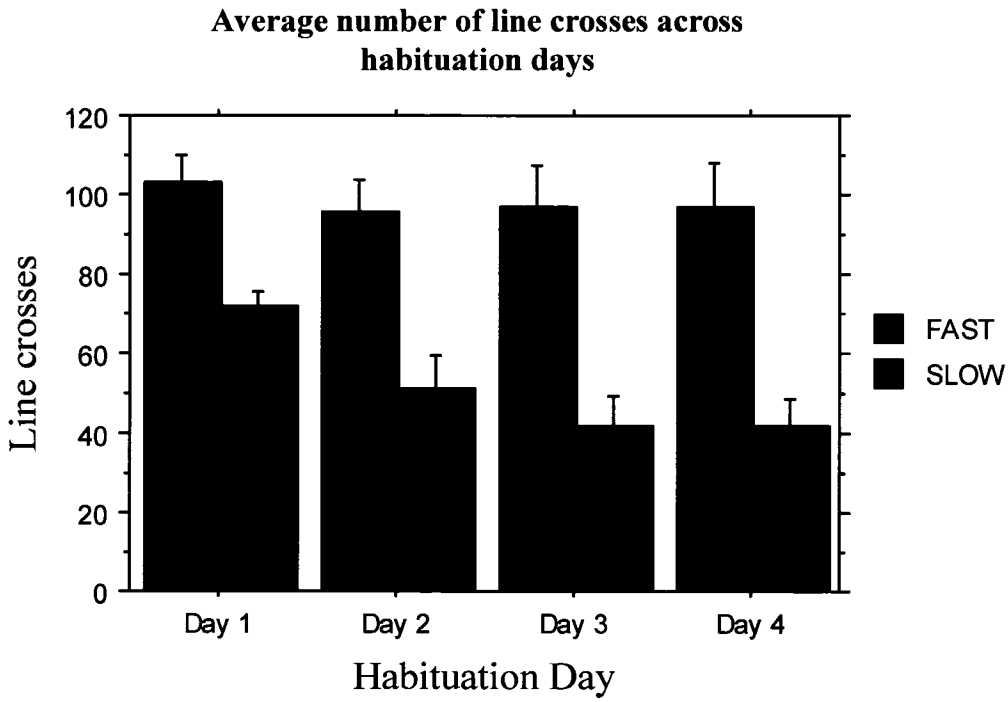
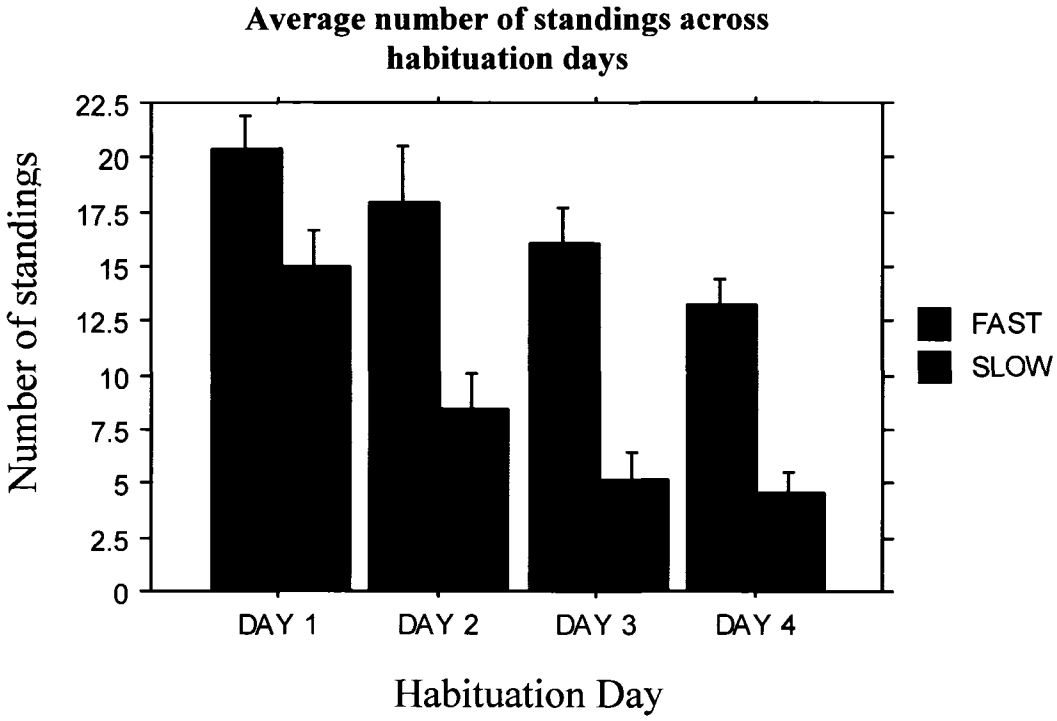


Figure 3: Average number of standings across habituation days. The FAST animals displayed a higher rate of vertical rearing activity $F(1, 27) = 31.91$, $p < .0001$. A significant effect of days was also observed $F(3, 27) = 14.51$, $p < .0001$. The days X group interaction failed to reach significance $F(3, 27) = 1.34$, $p = .264$.

The n was 20 for each group.



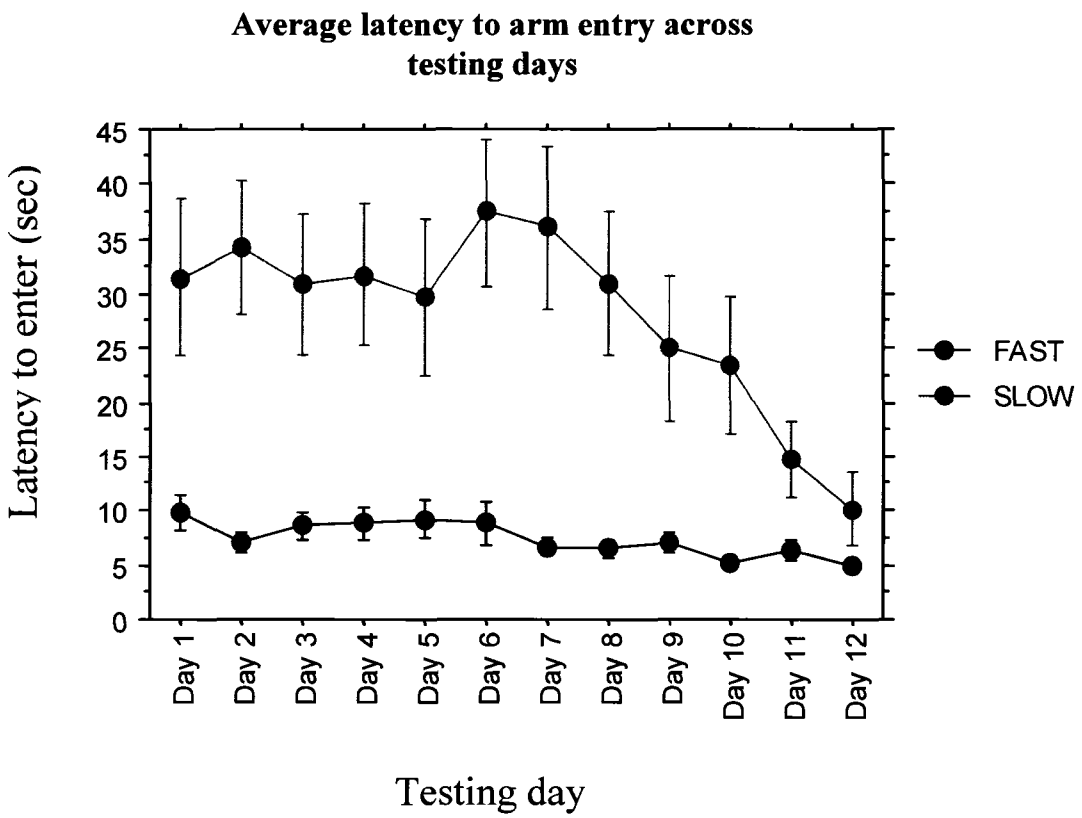
Testing: Hyperactivity

Various measures of activity were recorded throughout all phases of the experiment. All of the data collected was done in a way to present a clear picture of the differences between the FAST and SLOW rat strains in terms of their activity rates. The activity measures that were deemed important to the assessment of this characteristics of ADHD are as follows: (a) Latency to entry an arm: this score was the amount of time it took the animal to entry an arm regardless of whether or not the arm was the correct choice; (b) Line crosses: the amount of line crosses during each trial recorded until the animal retrieved the food reward or to a max of 60 seconds; (c) Trial time: this is the amount of time for the animal to complete the trial, determined by the either getting the food reward or to a max of 60 seconds. The data presented in this section does not include the initial 4 days of habituation. The displayed data and the analysis are done on only the first 12 days because this was the time when the majority of the animals were performing reliably. Although the presented data does include animals that are in different testing phases their activity levels over time regardless of phase is what was deemed important.

Figure 4 shows the data for latency to entry; the graph displays the mean latency to entry scores for the first 12 days. A repeated measure ANOVA showed that latency times changed across the 12 testing days $F(11, 275) = 10.65$, $p < .0001$. The ANOVA results also indicate that the SLOW rats had significantly longer latency to entry times $F(1, 25) = 35.50$, $p < .0001$. Furthermore, the latency to entry results showed a significant day X groups interaction $F(11, 275) =$

Figure 4: Average latency to arm entry across testing days. The FAST (n = 18) showed a lower entry time across the testing days compared to the SLOW(n = 8) $F(1, 25) = 35.50$, $p < .0001$. A difference in entry time was also observed across days $F(11, 275) = 10.65$, $p < .0001$. A significant days X group interaction was also observed $F(11, 275) = 6.61$, $p < .0001$.

The presented data includes animals in different experimental phases, however their activity level was independent of the experimental phase.



6.61, $p < .0001$, indicating that the groups changed differently over time in terms of the entry scores across the testing periods (days).

One of the more interesting findings to this point was the analysis of line crosses between the FAST and SLOW. Figure 5 shows the data involving the mean number of line crosses for the first 12 days. The graph clearly shows the extreme difference during the initial testing; however, the two groups become similar during the final phases of the experiment. This shift in activity in the SLOW rats resulted in a non-significant days effect $F(11, 275) = .840$, $p = .600$. Although the FAST rats still maintained significantly more line crosses across the 12 testing days $F(1, 25) = 14.63$, $p = .001$. The significant interaction is indicated in Figure 5 $F(11, 275) = 3.76$ $p < .001$ where the SLOW rats increase their line crosses over days while the FAST rats decrease their crosses.

The third measure of activity is trial time, indicated in Figure 6. The graph again shows the total trial time scores for the first 12 days of testing. Total trial time was the time required for an animal to either retrieve the food reward, or recognizing that the reward was not there – indicated by the rat looking for the reward in the food holder. A repeated measure ANOVA showed that total trial time significantly decreased across days $F(11, 275) = 19.60$ $p < .0001$. The ANOVA also shows that the FAST rats had significant lower trial times $F(1, 25) = 28.54$ $p < .0001$. The analysis further suggests that the groups trial times change differently between the two groups throughout the testing period, indicated by a significant days X group interaction $F(11, 275) = 2.11$, $p = .020$.

Figure 5: Average number of line crosses across testing days. A non-significant effect of days was found $F(11, 275) = .840$, $p = .600$. A significant group effect was noted $F(1, 25) = 12.63$, $p = .001$ as well as a significant days X group interaction $F(11, 275) = 3.76$, $p < .001$.

FAST (n=18), SLOW (n = 8)

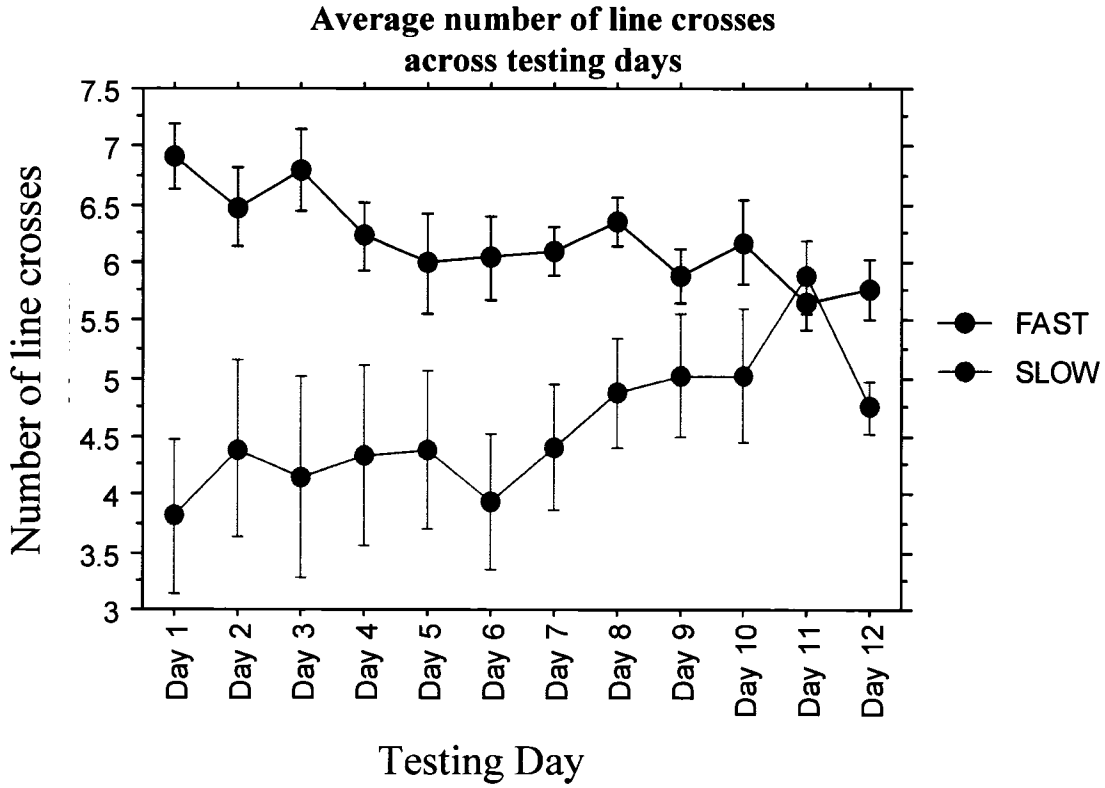
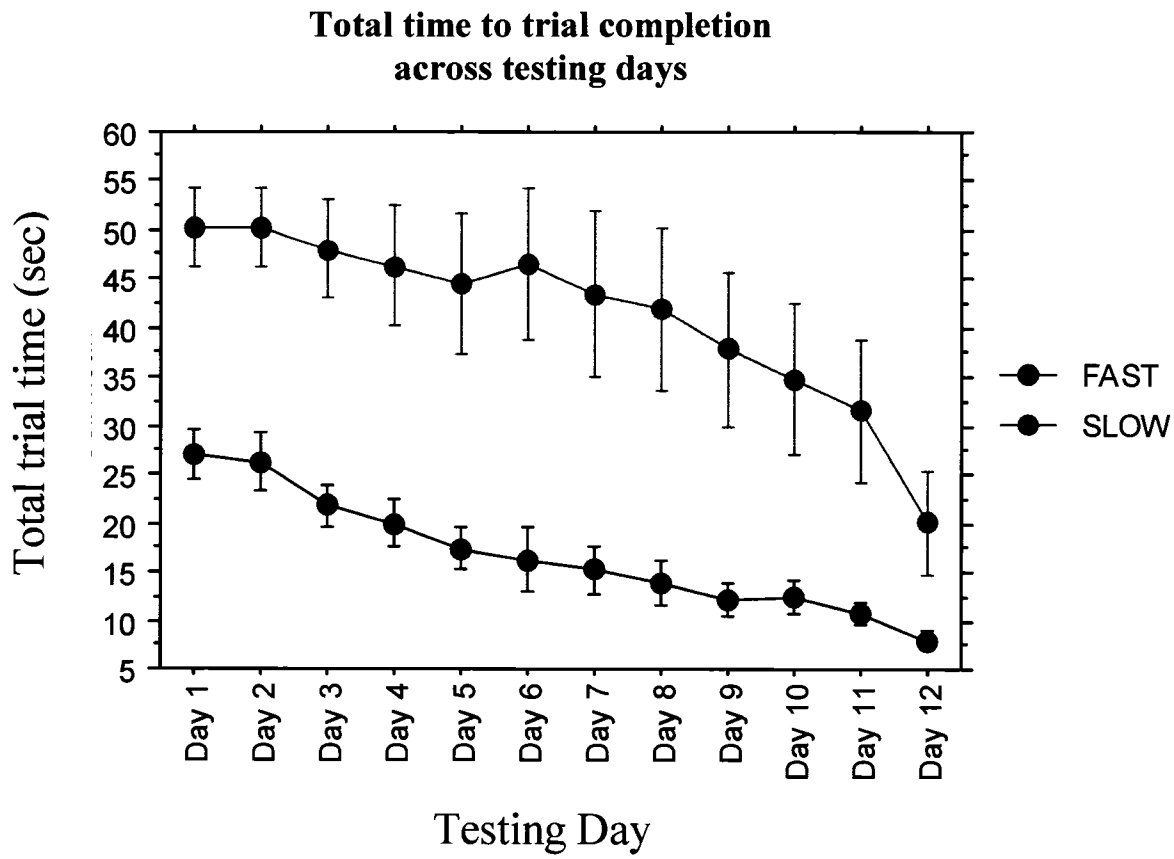


Figure 6: Total time to trial completion. The FAST (n=18) animal showed faster trial time across testing days compared to the SLOW (n=8) $F(1, 25) = 28.54$, $p < .0001$. A significant days effect was also noted $F(11, 275) = 19.60$, $p < .0001$. There was also a significant days X group interaction $F(11, 275) = 2.11$, $p = .020$.



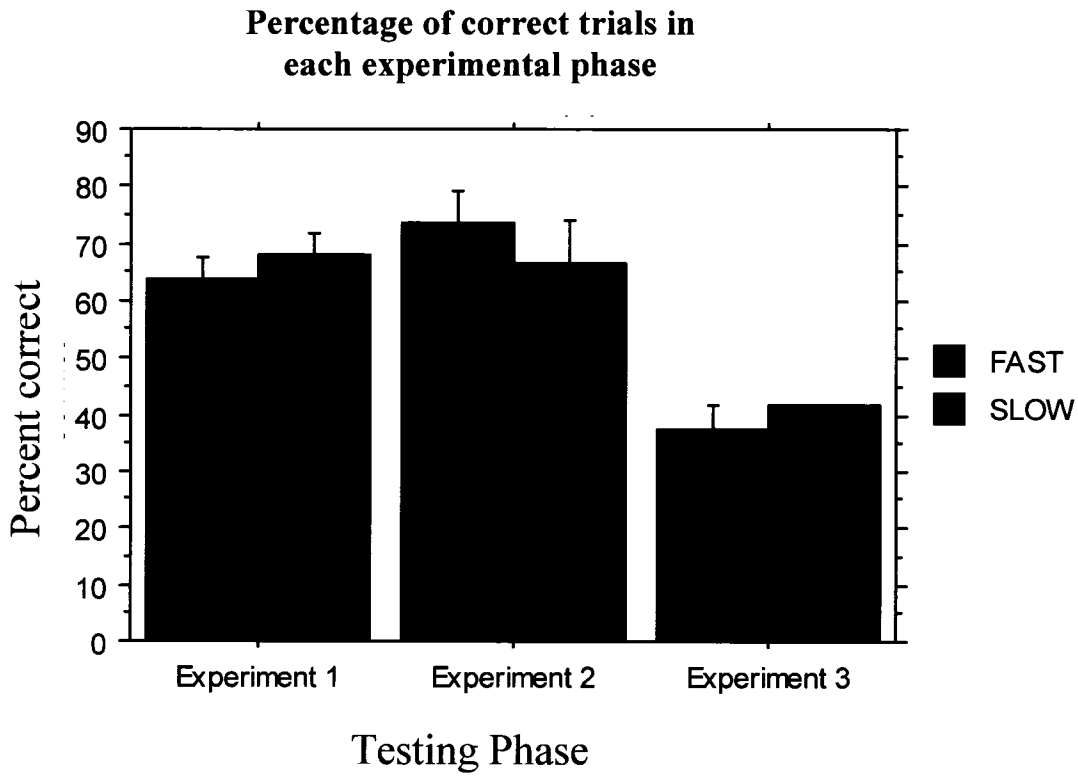
Testing: Inattention:

The measures for inattention were calculated based on the each experimental phases. In the first experiment, the light indicating the location of the food, remained on during the trial. An independent samples t-test indicated a non-significant difference between the FAST (n = 18) and SLOW (n = 8) rats in terms of the overall percent of correct choices in experiment 1, $t(24) = -.683$, $p = .501$. In the second experiment, the light on the door was turned off and the door rose immediately. Only a few of the FAST (n = 7) and SLOW (n = 4) rats moved on to this phase, and again an independent samples t-test indicated a non-significant difference between the two groups $t(9) = .791$, $p = .449$ in their performance. The final experiment involved two doors raised after a light had been turned off for 10 seconds; only three animals two FAST and one SLOW, moved to this stage of testing and therefore analysis on these data could not be performed. Figure 7 shows the mean percentage correct scores for the two groups (FAST and SLOW), for all three experimental phases.

Testing: Amphetamine Vs H_20:

In this experiment, the rats were assigned to different drug treatments. The FAST rats that had not yet moved on from experiment 1 (n = 8) were randomly assigned to either an amphetamine (n = 4) or control (H_20) (n = 4) group. The animals were tested for three days with drug treatment, followed by a fourth 'washout' day that involved no injection.

Figure 7: Percentage of correct trials in each experimental Phase. A non-significant result was found for each of the experimental phases. Experiment 1 FAST (n=18), SLOW (n=8). Experiment 2, FAST (n=7) SLOW (n=4). Experiment 3, FAST (n=2), SLOW (n=1).



To analyze the three days compared to the fourth, the three drug treatment days were averaged. Using the same measures of hyperactivity and inattention as used in the initial experiment that being latency to entry, line crosses, total trial time and choice accuracy. The results showed that entry times significantly changed over days $F(1, 6) = 7.35$ $p = .035$. However the results fails to show a significant difference between the drug and control group $F(1, 6) = 2.22$ $p = .186$. The group X days interaction was also non-significant $F(1, 6) = .015$ $p = .906$. Figure 8 displays the data for the latency to entry data averaged over three days compared to the fourth.

The next measure analyzed in the experiment was the mean number of line crossed; again the three drug treatment days were averaged together allowing for a comparison to the fourth. These data are shown in Figure 9, where a repeated measures ANOVA again indicated that there was a significant difference in the number of line crosses over days $F(1, 6) = 99.63$ $p < .0001$. Similar to the results seen in the latency to entry data analysis of line crosses showed that the drug and control group did not differ significantly $F(1, 6) = .153$ $p = .709$. The interaction was also non significant $F(1, 6) = 3.73$ $p = .102$.

The final measure of activity level in this experiment is trial time; the data for this measure are shown in Figure 10. Here the repeated measures ANOVA indicated that the total trial time did not change significantly over days $F(1, 6) = 2.83$, $p = .144$. Total trial time did not significantly differ between the drug and control group $F(1, 6) = 2.33$, $p = .178$ and not surprisingly a non-significant days X group interaction $F(1, 6) = 1.98$, $p = .210$.

Figure 8: Effect of amphetamine on latency to arm entry in FAST (n=4) rats compared to FAST (n=4) controls. The results showed a significant days effect $F(1, 6) = 7.35$, $p = .035$. A non-significant result was noted for both the group effect and the days X group interaction.

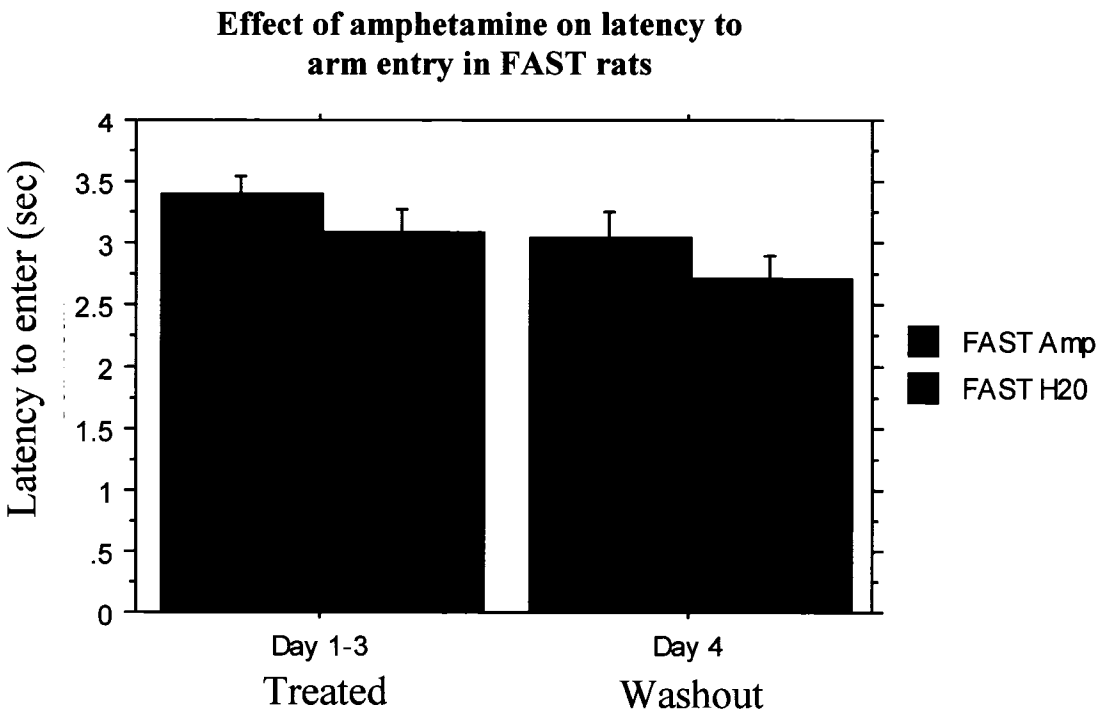


Figure 9: Effect of amphetamine on number of lines crossed in FAST (n=4) rats compared to FAST controls (n=4). A significant days effect was found $F(1, 6) = 99.63$, $p < .0001$. Although both the group effect and the days X group interaction failed to reach significance.

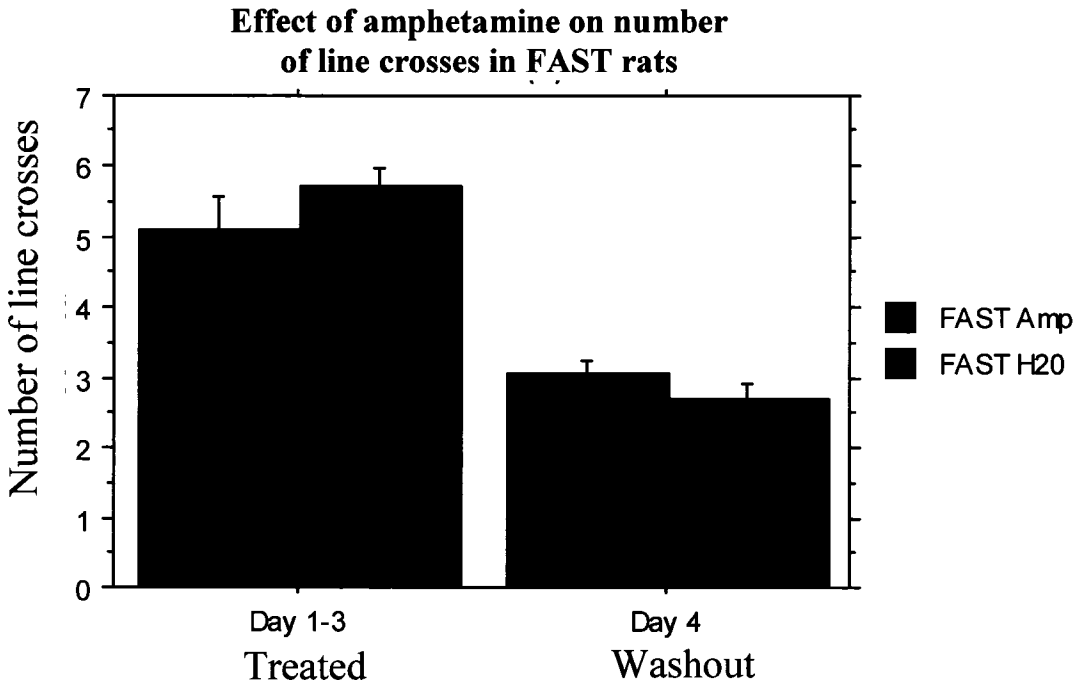
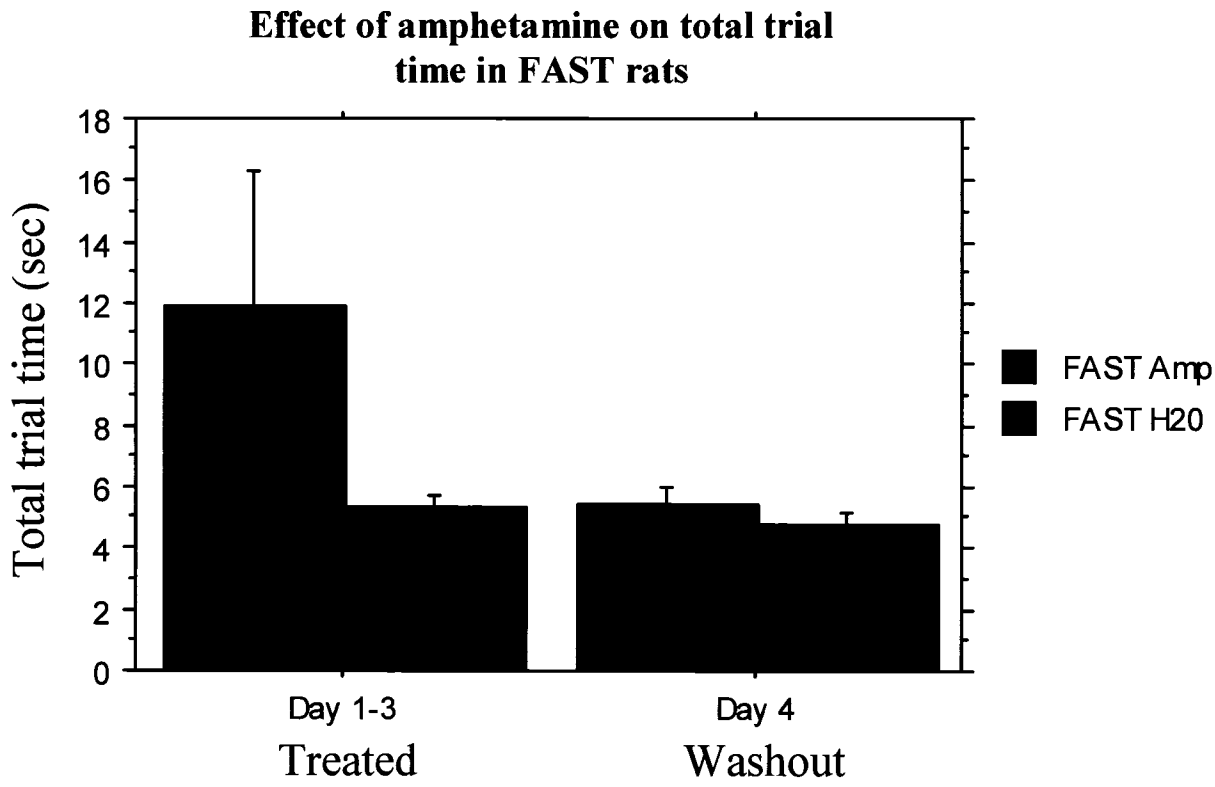


Figure 10: Effect of amphetamine on total trial time in FAST (n=4) rats compared to FAST (n=4) controls. No significant results were found.



The same attention measures were analyzed for drug compared to control condition; this was measured by the percent of correct choices averaged over the three drug days and compared to the fourth wash out day. The repeated measures ANOVA indicated that the drug treatment had no effect on the animal's ability to improve their choice accuracy. The results showed a non-significant days and group effect $F(1, 6) = .002$, $p = .968$, $F(1, 6) = 2.73$, $p = .150$, respectively. A non-significant days X group interaction was also found $F(1, 6) = 2.35$, $p = .177$. The observed data for the three averaged drug days and the fourth wash out day can be seen in Figure 11. Overall the amphetamine treatment failed to change the behavior of the FAST rats.

The SLOW rats that had not moved past habituation (n=6) were also randomly assigned to either drug or control. As a result of remaining in habituation only activity scores in the form of line crosses were recorded. Again the data here is averaged across the three days of the drug and then compared to the fourth wash out day. Figure 12 displays the mean number of lines crossed for the averaged and the fourth wash out day. The ANOVA results are in accordance with the drug treatment results observed in the FAST animals, indicating a non-significant group effect $F(1, 4) = .455$, $p = .537$, a non-significant days effect $F(1, 4) = 1.31$, $p = .316$. The results further indicate a non-significant days X group interaction $F(1, 4) = 2.89$, $p = .164$. Therefore as observed in the FAST rats, the amphetamine treatment failed to change the behavior of SLOW animals.

Figure 11: Effect of amphetamine on percentage of correct trials in FAST (n=4) rats compared to FAST (n=4) controls. No significant results were found.

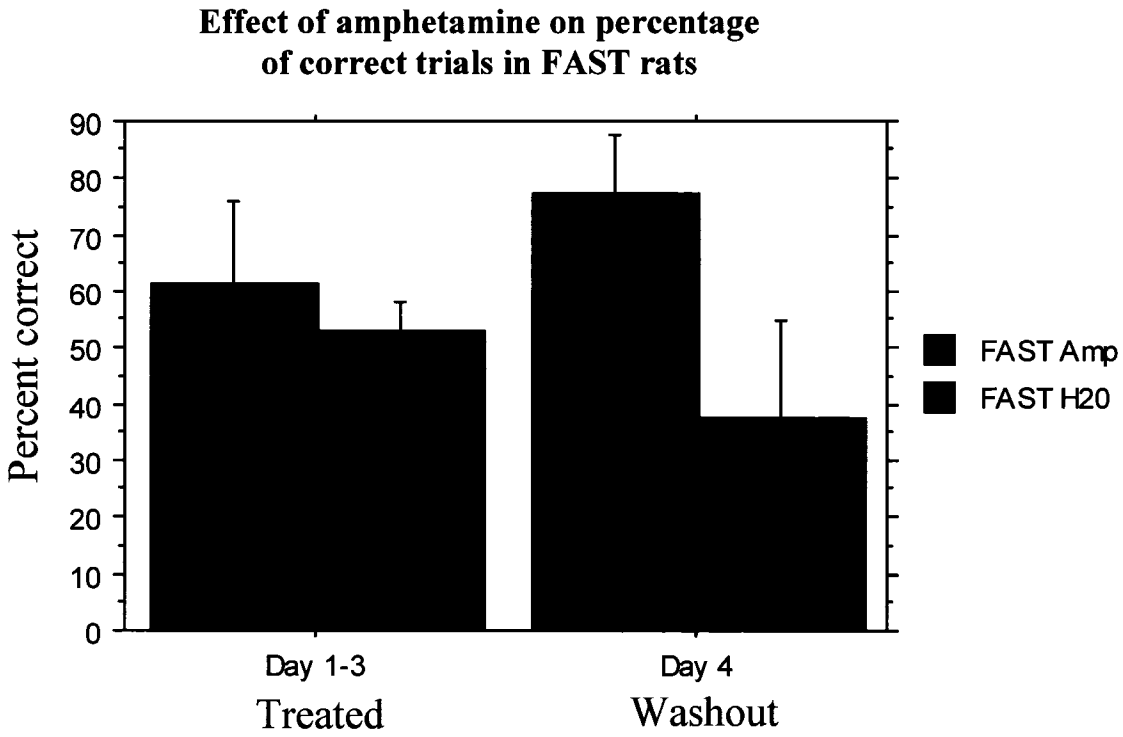
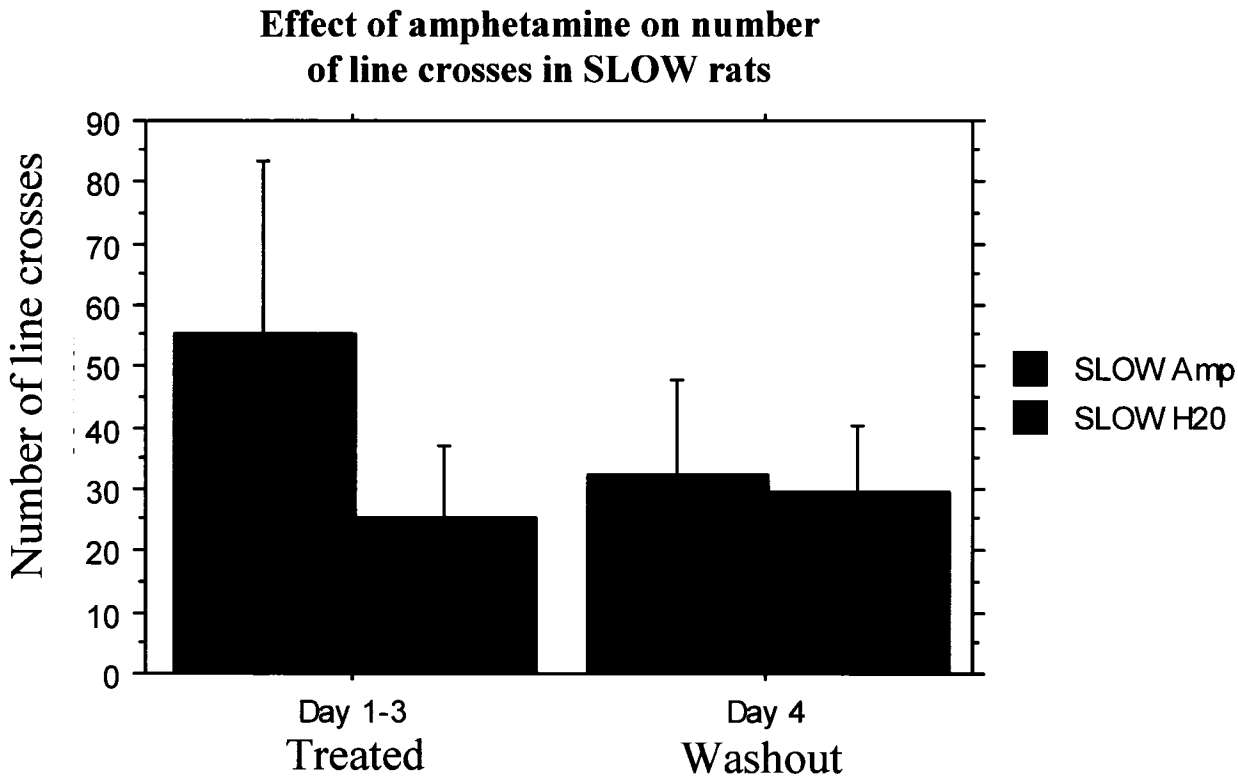


Figure 12: Effect of amphetamine on number of lines crossed in SLOW (n=3) rats compared to SLOW (n=3) controls. No significant results were found.



Testing: Impulsivity:

Measures of impulsivity could not be performed due to the fact that none of the animals reached the phase of the experiment that was designed to assess this particular characteristic.

Experimental Phases:

The experiment outlined here consisted of many different mini experiments, all of which provided an aspect of each of the characteristics in question. Figure 13 shows the amount of days that each strain spent in a given experimental stage. One-way ANOVA's were performed on each stage; the results indicated that the SLOW rats (n=15) spent much longer in habituation compared to the FAST rats (n=15) $F(1, 28) = 17.15$ $p = .0003$.

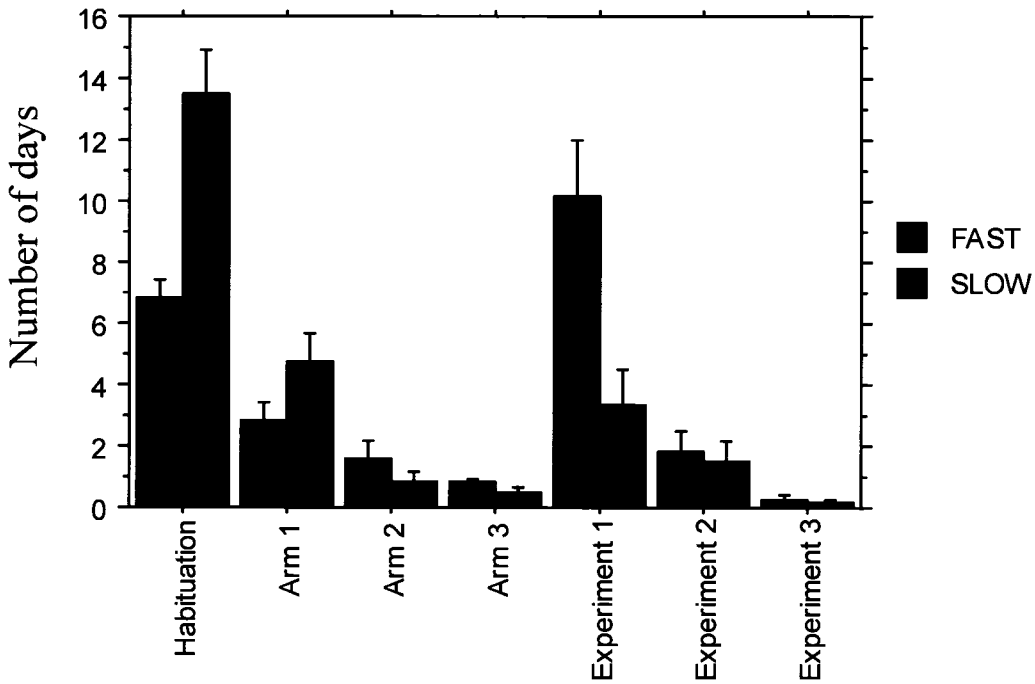
The next three analyses reflect the training portion of the experiment, where each animal was exposed to only one arm at a time. The ANOVA results confirmed what is suggested by the graph, the FAST (n=15) and SLOW (n=9) did not differ significantly in the time spent in each training phase, $F(1, 28) = 3.02$, $p = .093$, $F(1, 28) = 1.36$, $p = .254$, $F(1, 28) = 3.13$, $p = .088$, respectively.

The ANOVA results also showed that the FAST rats (n=13) spent significantly more time in experiment 1, compared to the SLOW rats (n=7), $F(1, 28) = 10.360$, $p = .003$; this results can be observed in Figure 13.

The results from experiment 2 indicated a non-significant difference in the amount of days spent in experiment 2, between the FAST (n=7) and SLOW (n=4) rats $F(1, 28) = .119$, $p = .733$. A non-significant difference was also found for days spent in experiment 3 between the FAST (n=2) and SLOW (n=1) rats $F(1, 28) = .350$, $p = .559$.

Figure 13: Number of days spent in each experimental phase by the FAST and SLOW rats. The SLOW animals spent many more days in habituation $F(1, 28) = 17.15$, $p = .0003$. No significant results were found for the training phases. The FAST rats spent many more days in experiment 1 $F(1, 28) = 10.36$, $p = .003$.

Number of days spent in each experimental level by FAST and SLOW rats.



Discussion:

The first phase of this experiment involved habituation to the apparatus, thus allowing the animals to familiarize themselves with the novel environment. The measures taken during this time indicate a much higher activity level in the FAST compared to the SLOW rats. It was also observed that the activity, measured by line crosses, decreased across the habituation days. This effect, however, was seen mostly in the SLOW rats. The lack of habituation in the FAST rats is consistent and relative state of hyperactivity. However, there is a fundamental problem here related to Sagvolden et al.,'s (2005) argument that for an animal to be considered hyperactive in the context of ADHD, the hyperactivity is not present initially in a novel environment, but develops over time. Our data clearly indicate that the FAST rats remain at a consistent, and relatively high level of activity throughout the habituation period. Not only is the activity level of the FAST rats held throughout habituation, this tendency is seen in all of the various experiments. In fact, the data from the line crosses suggests that the SLOW rats are a better fitted for that particular definition of hyperactivity, i.e., the SLOW rats tend to increase their activity over days, as observed in Figure 5.

The lack of habituation observed in the FAST rats appears to be a common theme when testing with this strain. Mohapel and McIntyre (1998) observed the same behavior in FAST rats when testing in the elevated plus maze, as well as in the open field, compared to the SLOW rats. This differential responding observed in both the present experiment and Mohapel and McIntyre (1998) suggests that not only is the behavior of the FAST different from the SLOW rats, it appears to be quite different from most other rat strains (Archer, 1973; Walsh & Cummins, 1976; cited from Mohapel and McIntyre,

1998). Nonetheless, the behavioral characteristics observed here appear to be typical of the FAST rats. Although these findings may not fit Sagvolden's model of hyperactivity completely, it undoubtedly suggests some clear differences between not only the FAST and SLOW rats, but also between the FAST and most other strains. To fully quantify the exact activity level of the FAST rats within the context of ADHD, the FAST rats should be compared to a different, previously established animal model of hyperactivity.

The data from the latency to entry also showed much higher activity levels of the FAST rats; however, again the graph does not indicate a steady increase in activity, rather a consistent level, observed in Figures. These data once again fail to fit the criteria set out by Sagvolden et al., (2005), where the authors state that motor impulsiveness is not present in a novel environment but will develop over time.

Line crosses during testing may not have provided the most valuable information due to the fact the rats were forced to leave from one point and go to another, therefore no matter how long it took them, the line crosses were typically the same; it is the speed to which they completed the trial that holds more information concerning their activity levels. Thus, by this argument, the FAST rats fit the stated criteria for hyperactivity, although it is far too early to make any definitive conclusions.

The results for the choice accuracy failed to reach significance; therefore the test failed to shows any attention differences between the FAST and SLOW rats. Problems with attention have been noted previously in FAST rats. Anisman and McIntyre (2002) found that initially introducing an irrelevant cue into the Morris Water Maze testing impeded the learning of the task in the FAST but fail to effect the acquisition in SLOW rats. This suggested that FAST rats are easily distracted, which may have affected their

acquisition in the present study. However, differential susceptibility to distraction cannot explain the poor performance of the FAST in this test because the SLOW rats also failed to learn the task.

Further evidence involving both hyperactivity and choice accuracy in the FAST rats comes from work performed by McLeod and McIntyre (1995). This experiment involved an alternating t-maze learning paradigm. Here they found that the FAST rats would run quickly down the maze to the choice point and choose the arm to which they were oriented. By contrast, the SLOW rats, who were ultimately equally as fast to reach the choice point, displayed a much higher degree of choice accuracy at the choice point. Much the same behavior was observed in the present study, where FAST rats appeared to enter the door to which they were closest and ran directly to the end of the arm for the reward. The SLOW rats, on the other hand, were much more methodical in their choice selection. This resulted in longer latencies to entry in SLOW rats but no difference in the number of line crosses, since the distance to reach the goal box was the same. Nonetheless the choice accuracy data produced a non-significant finding, which can be argued resulted from the very low number of SLOW rats that reached these testing phases.

The exact reasons why so few of the SLOW rats reached the later testing phases are unknown. The SLOW rats, however, have been known to exhibit a higher levels of anxiety than FAST rats (McIntyre et al., 2002), which has been seen in their tendency to become completely immobile in a fear situation, such as the elevated plus maze (McIntyre et al., 2002) or shuttle avoidance paradigm (Mohapel and McIntyre, 1998). This 'freezing behavior' in SLOW rats was typical throughout the present study and

resulted in the lower number of SLOW rats progressing to higher experimental levels. In many cases, these animals failed to move past the stage of habituation. The anxious behavior of the SLOW rats in other studies has been shown to be present initially, but they appear to overcome the fear with longer exposures (Mohapel and McIntyre, 1998). Their fearful nature was apparent in this test and was evidenced by their excessive freezing behavior as well as the lack of food consumed by them during the experiment. However, their fearful disposition alone cannot answer the question of why so few of the SLOW rats reached various acquisition criteria. All rats received the same food reward, and had weights that were maintained in the same range. Given that some of the SLOW rats did reach later criteria, it may simply be a lack of motivation on the part of these particular animals that controlled their lack of progress.

Validation of any animal model of ADHD is without a doubt enhanced by showing an improvement with medication. For the most part, interest here was on the performance of the FAST rats, although drug testing with SLOW was also carried out to serve as a comparison. The results from the present study failed to find any significant difference between or within the two strains on amphetamine days versus the 'washout' or no drug day.

Studies examining the ability of stimulant medication to improve performance or reduce activity levels are quite varied, although this is not surprising given that there are few widely excepted animal models of ADHD. Returning to the most often cited ADHD model, the SHRs, mixed results have surfaced concerning the effectiveness of these drugs. Van Den Bergh et al., (2006) found that the administration of methylphenidate failed to affect the behavior of the SHRs within the open field or the 5-CSRTT, whereas

Ueno et al., (2002), found that methylphenidate significantly reduced hyperactivity in an open field. Other studies have found that low doses of methylphenidate increase motor behavior, whereas high doses reduced the activity level of both the SHRs and controls (Wyss et al., 1992).

Given that the evidence surrounding the effectiveness of stimulant medications to improve performance in the SHRs is varied, it appears plausible that given different parameters, the drug administration may in fact alter the behavior of the FAST rats. This argument is based on the trial time data present above, which although were non-significant statistically, there appeared to be a difference in tendency, which may have been confirmed statistically had the sample size been larger. However, another factor, which may have affected the trial time length, may not have been the ability of the amphetamine to reduce motor activity measured by the time required to enter and retrieve the food reward, but the simple fact that amphetamine is a known appetite suppressant. Thus it was not a reduction in movement associated with the drug, but simply a lack of motivation to retrieve the food reward that was observed. Future studies should consider this important side effect of amphetamine and use a paradigm that does not require a food reward.

The present hypothesis was tested in the presence of a new behavioral test in an effort to further valid the FAST animal and the behavioral paradigm as relevant to ADHD. Given that the present experiment was the first to use this behavioral test, it remains unclear as to whether the test actually measured the variables for which it was designed. Other tests currently used in the assessment of various facets of ADHD, such as the open field and the 5-CSRTT, have been utilized and validated numerous times.

Although the present design did draw on many aspects of these tests, it did not posses the known reliability, thus making it difficult to confirm the FAST rats as a model of ADHD using this paradigm. Further, the data presented here are similar to the results seen in McLeod and McIntyre (1995) studies, and therefore the same results may be arrived at by using a T-maze; this would require much less training, as well as produce results from a behavioral test that is widely accepted. Further validation of the behavioral test should use other previously accepted animal models of ADHD, and the results should be in-accordance with the hypothesized theories of the testing outcome.

The goal of the current study was to argue that the FAST 'seizure-prone' rats are a valid animal model of ADHD. In order to do this, the results should speak to the measures of validity established by Sagvolden et al., (2005). The first being face validity: the animal must mimic the characteristics that are associated with the disorder, including hyperactivity, inattention and impulsivity (Sagvolden et al., 2005). In the context of the current study, it is clear that the FAST rats do show a motor impulsiveness and a higher level of hyperactivity than SLOW rats; however, as mentioned earlier, the activity does appear to be present in a novel environment, although the total trial time data suggests an increase in the activity level of the FAST animals. Unfortunately, fully useful data relating to the attention component was never quite indicated, given the small numbers of rats that progressed to these further testing stages. Sagvoldgen et al., (2005) also suggested using an extinction procedure as a form of measuring sustained attention; this was not applicable to the current study. Given that a large number of the rats could not learn the initial procedure, there was very little point to collect data on extinction.

The second criteria for validation of a model set out by Sagvolden et al., (2005) was construct validity, where he indicated that the model should be a genetic model and possess features that are similar to those observed in the human condition, particularly involving the dopaminergic systems. Although this criterion was not assessed in the current study, McIntyre et al., (2002) pointed out that to date no large differences have been found between the FAST and SLOW rat strains in terms of their monoaminergic systems, however, subtle differences do exist. Current studies are investigating the possibility that the FAST rats possess a smaller pre-frontal cortex compared to the SLOW rats, demonstrating a feature that has been linked to ADHD (Russell et al., 2005).

The third facet of Sagvolden's validity criteria is predictive validity; the model must possess the ability to predict unknown aspects of the disorder (Sagvolden et al., 2005). Given that it is to earlier to confidently present the FAST rat strain as a model of ADHD, this criterion cannot be fully assessed at the present time.

In summary, the present study serves as support for further investigations into the FAST rats as a model for ADHD; whether or not the behavioral paradigm used here should be used again would be dependent on additional testing to develop reliable training and testing procedures that will allow our previously designed tests to be successfully completed.

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