The College of Wooster

Spaced Training in the 5CSRTT Proves Beneficial in Early Levels

by

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Abstract

ADHD is a neurodevelopmental disorder characterized by inattentiveness, impulsivity, and hyperactivity. Due to these characterizations, children with ADHD typically exhibit lower academic performance which has been improved by spacing out academic training. Yet no study has performed spacing in an ADHD population. Spaced training involves studying over short periods for multiple days rather than multiple hours in one day, or massed training. Using a rat model of ADHD, known as the SHR strain, the present study assessed how spacing training from 90-trials a day to 45-trials a day in the 5CSRTT would improve performance abilities. Additionally, the impact of spaced training on object displacement was assessed. Lastly, activity levels confirmed the SHR hyperactive phenotype. It was found that spacing was beneficial during earlier levels of 5CSRTT training, that required less focused attention. In addition, during the earliest level of training, males in the spaced condition benefited more than females, closing the previously reported sex gap. Due to the hyperexploratory nature of the SHR, spacing did not influence the ability to recognize the displaced object, and spaced training in 5CSRTT did not impact hyperactivity in the open field. These findings imply that by simply spacing out training, the SHR rats demonstrate a significant improvement in some training levels of the 5CSRTT. Future studies should assess spacing academic work and attentiveness training in children with ADHD.

Introduction

When studying for a test, a student has two options; they can either study for five hours the night before the exam, or they can study an hour a day for five days before the exam. The first method is called massed practice and the second method is called spaced practice (Carey, 2015). Spaced practice is extremely beneficial for memory of new vocabulary, math problems, and working memory in general (Kornmeier et al., 2014; Rohrer & Taylor, 2006; Wang et al., 2014). Its beneficial effects can be seen across populations; from animals, to neurotypical and non-neurotypical people (Commins et a., 2003; Grassi, 1971; Kerfoot et al., 2007). Even though spacing is a popularly used method in the cognitive and behavioral neuroscientific field, it has yet to be assessed in a population with Attention Deficit Hyperactivity Disorder (ADHD) or its animal model, the Spontaneously Hypertensive Rat (SHR). Further, the effects of spacing have been limited to memory and there is potential to explore other areas of this training such as in attention. Compared to the amount of exploration on spacing and memory, the idea that giving individuals a break in between trials to heighten their focus and attention is relatively unexplored. Questions that remain include: does improving performance on an attention task improve general attentional abilities similar to how a working memory task improves memory abilities? Is there a bigger effect with spacing? More so, can spaced training reduce impairing ADHD-like symptoms in the SHR? Finally, can SHRs benefit from spacing in a spatial memory task such as object displacement? These questions have yet to be explored in the present literature and the current study aims to answer these questions.

Attention Deficit Hyperactivity Disorder, or ADHD, is a neurodevelopmental disorder that is impairing to many children's performance in school and overall well-being. The DSM-V describes ADHD as being characterized by inattention, impulsivity, and hyperactivity (American

Psychiatric Association, 2013). Patients can have a primarily inattentive type, meaning their level of inattention is greater than their hyperactivity, or a combined type, meaning there is a presence of both hyperactivity and inattention in the patient (Epstein & Loren 2013). The DSM-IV required ADHD symptoms to be present prior to age seven (2013). Yet Applegate et al. (1997) found that 43% of children that expressed the primary inattentive type for ADHD did not exhibit symptoms until after age seven. The updated DSM-V now requires that patients who exhibit ADHD must have had symptoms prior to twelve years of age rather than seven (2013). The current prevalence of ADHD in the United States is 5% or 1 in 20 children (Faraone et al., 2003). There is a similar prevalence in non-US countries as well (2003). Though individuals believe there has been an increase in prevalence since the disorder was first understood, there is no evidence of this increase (Polanczyk et al., 2014). Therefore, it can be assumed that ADHD is less the result of cultural practices in the United States and is more a valid behavioral and neurodevelopmental disorder that affects many children from differing races, ethnicities, and cultures. Furthering this claim, there are also many neurological differences associated with ADHD.

Brain Areas Associated with ADHD

The temporal lobe is an area of the brain that helps with long term memory consolidation, higher visual processing, and general auditory processing (Kolb & Whishaw, 2015). Its relationship with ADHD is substantial. Children and adolescents with ADHD showed less gray matter in their anterior temporal lobe areas than controls (Sowell et al., 2003). Gray matter is a part of the brain that mainly consists of the cell bodies and synapses on the neuron (2003). Largely, gray matter is where the neurons communicate with one another. Therefore, the temporal lobe in a brain with ADHD has less neuronal communication due to this lack of essential matter. This could explain why those with ADHD have difficulty putting new information into long-term memory. Less gray matter in the temporal lobe has also been significantly related with clinician ratings of ADHD symptom severity, thus emphasizing that the more severe the ADHD is, the smaller amount of gray matter in the brain (Castellanos et al., 2002). Finally, glucose metabolism in the temporal lobes is more abnormal in those with ADHD. Girls and boys with ADHD had less glucose in their temporal region than controls and therefore, more impaired neurochemical signaling (Ernst et al., 1994; Zametkin et al., 1993). This could explain some of the memory impairments those with ADHD face.

The parietal lobe is a part of the brain between the frontal lobe and occipital lobe that is essential for interpreting sensory stimuli (Mishkin & Ungerleider, 1982). Those with ADHD often have difficulty with tasks related to this neural function. Vance et al. (2007) administered an fMRI to children (8-12 years old) with combined-type ADHD and had them perform a mental rotation task. The mental rotation task involved observing a picture and identifying that picture in its rotated form. During the task, there was less activation in the right inferior parietal lobe and right parieto-occipital areas in children with ADHD than there was in controls. Even though the children with ADHD did not perform any differently on the task than the controls, they used less of their parietal lobe to reach their conclusions. More importantly though, is how the neural pathway between the temporal lobe and the parietal lobe are implicated in ADHD.

ADHD's relation to the temporo-parietal network is an important aspect of the attention problems seen in patients. When a visual attention task was given to medication naïve children with ADHD and their brains were scanned, the temporo-parietal regions were under-activated (Rubia et al., 2007). Specifically, this network has been found to play a role in detecting novel stimuli in a sensory environment which requires high amounts of attention and focus (Downar et al., 2000). Therefore, under-activation in this network indicates a deficit in allocating attention to higher-order vision processes. Children with ADHD may have difficulty focusing on certain stimuli because of the interaction between these two lobes. It has also been observed that both medication naïve children and medicated children with ADHD were more likely to have low activation in their temporo-parietal network when performing a cognitive flexibility task, specifically task-switching (Smith et al., 2006). This visual-spatial task uncovered that they had lower response inhibition—the ability to not respond when it is inappropriate— than controls and therefore lower attention to change in detail.

Another part of the brain implicated in ADHD is the frontal area. The frontal lobe and the prefrontal cortex are essential for judgement and decision-making along with executive functions such as working memory and attention (Robbins et al., 1996; Koechlin & Summerfield, 2007). Difficulties with executive function are often present in those with ADHD. Lawrence et al. (2004) compared how children (6-12 years old) with ADHD performed on neuropsychological versus real-world tasks that measured their executive functional abilities. This was to measure the external validity of neuropsychological testing, but also to further emphasize children with ADHD's impaired executive function. The results indicated that children with ADHD responded more slowly during the neuropsychological testing and took longer to complete the real-world task compared to the controls. This partially explains why a high positive correlation exists between an ADHD diagnosis in children and a smaller frontal lobe and prefrontal cortical volume (Filipek et al., 1997; Mostofsky et al., 2002). Similar findings have been made for adolescents and adults with ADHD (Almeida et al., 2010; Depue et al., 2010; Schulz et al., 2005). These findings are also sex-matched meaning the findings do not differ across sexes (Castellanos et al., 2002). This is important to note because ADHD research often focuses on boys with the diagnosis (“Gender in ADHD Epidemiology,” 2019). Yet, there is more evidence to suggest that the connections between the parietal lobe and frontal lobe are important to understanding deficits involved in ADHD.

A deficit in the fronto-parietal network often indicates a deficit in attention to visuospatial areas. Waldie & Hausmann (2010) used the line-bisection test to assess fronto-parietal dysfunction in children with ADHD and children with developmental dyslexia. The line-bisection test looks at whether a patient favors one side of their general space more than another by having them draw vertical lines to bisect a series of horizontal lines. Both children with ADHD and children with developmental dyslexia showed a rightward bias to the line-bisections, which emphasized deficits in the right fronto-parietal network. Additionally, using an fMRI during a Continuous Performance Test (CPT) to test the prolonged attention of adults with ADHD emphasized that symptom severity was highly correlated with decreased activity in the parietal cortical regions (Schneider et al., 2010). Essentially, the worse the person’s attention, the smaller the activation in their fronto-parietal network. Therefore, ADHD can be understood to be highly attention-based and there are neurological correlates to these behavioral differences. Finally, children with ADHD’s attention to visuospatial elements, and therefore their fronto-parietal network, has been studied through the usage of an fMRI and Raven’s Standard Progressive Matrices (Silk et al., 2008). Poorer performance on the Raven’s Standard Progressive Matrices was related to lower activation in the fronto-parietal network. The lower activation in these areas and networks are partially due to the neurotransmitters, dopamine and norepinephrine.

Neurotransmitters Associated with ADHD and Treatments

Dopamine is an important neurotransmitter in the reward pathway, nigrostriatal pathway, and prefrontal areas (Levy & Swanson, 2001). Volkow et al. (2011) used a PET scan to measure D2/D3 receptors in the reward pathway and found that those with ADHD who had less motivation to work hard, also had fewer D2/D3 receptors. This partially explains why maintaining focus on non-rewarding tasks for those with ADHD is difficult. Dopamine also plays a large role in motor control within the nigrostriatal pathway (Castellanos, 1997). Since those with ADHD have a dopamine deficit in the nigrostriatal pathway, they typically exhibit motor deficits, displaying longer response times on tasks that require sustained focus and general motor delays from birth to two years old (Brandeis et al., 1998; Johansen et al., 2002; Taylor, 1998). Finally, dopamine helps with working memory in the prefrontal areas. An experiment uncovered that after infusing antagonists for the D1 receptor in the prefrontal cortex of Rhesus Monkeys, their performance on working memory tasks decreased (Sawaguchi & Goldman-Rakic, 1991). The D1 receptor gene is often implicated in ADHD due to the transmission of Halotype 3, explaining why working memory may be impaired in those with ADHD as well (Misener et al., 2004). Yet it is not yet known whether the D1 receptor’s function is altered by Halotype 3, but its transmission has been found to correlate with inattention in ADHD (2004).

Since ADHD typically indicates high inattention and impulsivity, its relationship with norepinephrine is unsurprising. Norepinephrine is a neurotransmitter that is largely involved in response-inhibition and learning from feedback (Aston-Jones & Gold, 2009; Chamberlain et al., 2006). Cognitive tests have discovered that children with ADHD often exhibit low response-inhibition (Kollins et al., 2008; Schwartz & Verhaeghen, 2008). A family study looking at the heritability of ADHD found that a single nucleotide polymorphism (SNP) in the norepinephrine transporter gene (NET), a transporter that reuptakes extracellular norepinephrine, was correlated with errors on a task that measured response-inhibition (Kollins et al., 2008). This SNP changed the expression of the NET gene and led to higher correlations with poor response inhibition. The SNP in the NET gene has also been found to influence binding of the norepinephrine neurotransmitter in certain areas of the ADHD brain. For example, children with ADHD's hyperactivity was found to highly correlate with lower binding of norepinephrine in the cerebellum due to the presence of an SNP in the NET (Sigurdardottir et al., 2016). This lower binding indicates that the NET is overactive and removes too much norepinephrine from the synapse when this SNP is introduced. Effectively, the SNP leads to different expression of the NET gene in ADHD brains. This causes norepinephrine to spend less time in the synapse and leads to a more hyperactive child with less response inhibition. Dopamine and norepinephrine's implication in ADHD have led to the creation of medications that influence them in the synapse.

The most well-known treatment for ADHD is stimulant medication due to its exceptional effects on the neurochemistry in the ADHD brain. Methylphenidate, a common stimulant used to treat ADHD, has been shown to modify the norepinephrine transporter gene and thus reduce hyperactive and inattentive symptoms in children with ADHD (Yang et al., 2004). It has also been shown to have an effect on the fronto-striatal circuitry, a system widely affected by norepinephrine, of the ADHD brain, leading to an improvement in response-inhibition (Shafritz, Marchione, Gore, Shaywitz, & Shaywitz, 2004; Vaidya et al., 1998). Methylphenidate also directly influences dopamine. When given medication, controls were found to have more extracellular dopamine in their brain than prior to treatment (Volkow et al., 2001). There are also major neurological benefits those with ADHD experience during the usage of methylphenidate. Specifically, children with ADHD who start stimulant use early have been shown to have thicker cortices than those who do not take medication at all (Castellanos et al., 2002). Behaviorally, parents and teachers were more likely to see a reduction in ADHD symptoms when stimulants were administered compared to a placebo (Handen et al., 1999). Stimulants are not always the best route for treatment though. The side effects of stimulant medications primarily involve headaches, appetite loss, and insomnia (The Understood Team, 2019). Multiple studies have found that children with ADHD may not experience many detrimental or severe side effects though, besides appetite loss (Barkley et al., 1990; Efron et al., 1997; Firestone et al., 1998), and that long term usage does not lead to more detrimental side effects (Charach et al., 2004). Yet the idea of giving stimulants to children can be fearful for a parent so it is natural to consider alternative treatments.

Effective alternative treatments often involve a certain form of therapy for the child. One form of therapy that is effective is movement therapy. Movement therapy involves getting the child active and encouraging exercise to stimulate the mind and body. Two different pilot studies found that ADHD symptoms decreased, and motor control increased in cases that used movement therapy (Grönlund et al., 2005; Majorek et al., 2004). A more common therapy used is cognitive-behavioral therapy (CBT). CBT is meant to use talk-sessions to change negative or impairing thought-processes and behaviors an individual may exhibit. For ADHD, its main focus typically involves help with problem-solving, instructing oneself on how to do something, reinforcing oneself to do a task, and coping with errors (Toplak et al., 2008). This type of treatment has been found to be effective in all age groups, specifically in increasing attentiveness and decreasing off-task behaviors (Antshel et al., 2012; Bloomquist et al., 1991; Froelich et al., 2002; Weiss et al., 2012). Even with treatment though, learning can still be impaired.

ADHD Learning Difficulties and Associated Rodent Model

Those with ADHD often perform worse on memory tests and have poorer learning skills than the average individual. Yet people with ADHD do not have lower IQs than those without ADHD. Schuck & Crinella (2005) argued this point through a comparison of general intelligence with executive function in children with ADHD. Even though children with ADHD performed below average on the executive function tasks, their scores on these tasks did not correlate with their performance on varied IQ tests. Therefore, a lack in executive function ability does not determine an individual's general intellect. Poorer executive function can, however, determine one's ability to study, plan, and memorize new information. This is partly why children and adolescents with ADHD perform more poorly in school (Ek et al., 2011).

Brand et al. (2002) analyzed learning preferences of primary and secondary school children with ADHD. They discovered that both age groups had a high difficulty with persistence, meaning they could not stay focused on one topic for a long period of time. When observing college students with ADHD, they were found to have more trouble with time management than their neurotypical peers and those with learning disabilities (Reaser et al., 2007). Even though better time management (Reaser et al., 2007) and breaks between studying (Brand et al., 2002) are assumed to be helpful for those with ADHD, no study on spaced studying and its effect on those with ADHD have been published. There have also been no published studies that look at the effects of spacing on SHRs.

Spontaneously Hypertensive Rats, or SHRs, are a common animal model used to assess ADHD due to the similar attributes they share with patients with ADHD. Specifically, this strain has been found to have inattentiveness, impulsivity, and hyperactivity on similar levels to children with ADHD (Sagvolden et al., 2009; Sagvolden et al., 1992). SHRs also show similar performance on delayed reinforcement tasks to children with ADHD. In particular, SHRs responded less once a delayed reinforcement was introduced, but had higher responses when the reinforcement was consistent (Johansen et al., 2005). This means that SHRs gave up on responding and could not stay consistently focused and interested in the task if there was a delay between rewards. Children who had hyperactive tendencies were also more likely to go for a small reward than wait a period of time for a big reward similar to the SHRs (Sonuga-Barke et al., 1992). This highlights how the SHR is a good model to observe the effects of spacing because it may be easier for SHRs to learn under conditions where focus does not need to be extended. Since spaced training is a widely studied topic in the behavioral neuroscience field, it should also be studied in SHRs.

Spaced Memory Training in Humans

Spaced and massed training are two types of training that differ in the amount of rest between training intervals. Massed training involves training continuously without significant rest while spaced training involves rest between training intervals (Lindsay, 2012). Spaced training is hypothesized to create a spacing effect which results in a higher retention of information and therefore, higher performance (Roediger & Pyc, 2012). Many human studies have found memory to benefit from spacing.

In a neurotypical population, spacing has been shown to have incredible benefits for learning. Math is often a difficult subject to learn, so Rohrer & Taylor (2006) had college students practice a math problem. The spaced group practiced five problems and then had a one-week interval before the next five problems while the massed group practiced ten problems all in one session. There was either a one-week or four-week interval before the final test. Though there was no difference on the final test between the spaced and massed group at the one-week interval, there was at the four-week interval. Therefore, since the spaced group was more likely to successfully retrieve the skill after a longer period of time there is emphasis for spacing leading to higher consolidation and memory for the task. These results were also present for remembering medical information (Kerfoot et al., 2007) and new German and Japanese words (Kornmeier et al., 2014). Spacing training in a working memory task has also been observed to transfer to performance on a fluid intelligence task in fifth grade children (Wang et al., 2014). The working memory task was spaced over either 2, 5, 10, or 20 days. The children who had the greatest space between training experienced the largest training transfer to, and therefore the greatest performance on, the fluid intelligence task. This further supports higher memory consolidation when spacing is present, but it also supports a carry-over effect of spacing affecting intelligence.

Studies on non-neurotypical individuals have found memory results similar to those done on neurotypical people. Children 11-15 years old with brain-damage, behavioral disorders, or no present disorders all received training in auditory and visual memory (Grassi, 1971). Their training was either spaced or massed. Though children without any present disorder had higher overall achievement scores, the spaced condition, no matter the grouping condition, showed a higher level of performance on both the visual and auditory tasks. This effect has also been seen in children with specific language impairment (SLI). Spacing helped with verb-learning in children with SLI at five to six years old (Riches et al., 2005). Specifically, they found that children with SLI were able to recall more verbs after spacing their practice than children who did not, along with this, the control group did not show this recall effect. This provides further evidence to the spacing effect because working memory was improved in children who presented impairments. Though there are no studies on whether spacing benefits those with ADHD, children with SLI have similarities to children with ADHD in language, social skills, and executive functions such as working memory (Cohen et al., 2000; Bruce et al., 2006). Therefore, the benefits seen in spacing for children with SLI could be achieved in children with ADHD. Animal studies may be a good way to test the potential benefits of spacing in an ADHD population.

Spaced Memory Training in Rats

Multiple studies have observed the spacing effect in rat populations when spreading training out over multiple days. Goodrick (1973) assessed mature-young and aged rats on a T-maze test with a 24-hour break between each trial. The T-maze test measures spatial memory and has a start box and a goal box with a reward in it. The main goal for the rats is to make as few errors as possible before reaching the goal box. Mature-young rats displayed fewer errors in the spaced condition than in the massed condition, emphasizing a learning effect correlated to spacing. More recent spatial memory tests have been spaced such as the Morris-water maze, a test in which a rat learns where a platform is while submerged in water, then, in another condition, performs the same task with the platform removed. Male Wistar rats were trained in the Morris-Water Maze by either having them perform 16 consecutive trials with 20-minute intertrial intervals or four trials per day for four days (Commins et al., 2003). Rats in the spaced condition swam in the platform area longer than those in the massed condition, thus highlighting a main effect of spacing on higher spatial memory performance. Finally, desensitization to fearful stimuli benefits more from spacing. While observing female hooded rats' avoidant responses to foot shocking, it was found that distributing the shocks over three minutes for three days (one minute per day) helped extinguish avoidant behaviors (Baum & Myran, 1971). Therefore, the spaced group learned more easily than the massed group.

A task that has been used consistently with spacing is the object displacement task. The object displacement task involves placing a rat in a field with four novel objects, allowing them to explore the field. Seven days after training an object in the field is displaced and researchers record whether the rat recognizes that the object has moved. This task tests for spatial memory ability. In a study by Commins et al. (2001), they used object displacement, but spaced out the training to one trial per day for four days. They found that spaced rats made more nose contacts with the displaced object than the massed rats. They also found that spaced rats spent more time exploring the objects compared to massed rats, meaning they did not habituate to the environment as easily. Other studies have found similar results in exploratory behaviors and nose-contacts with object displacement (Bello-Medina et al., 2013). It is important to add that no sex differences have been found in this task due to rats not showing a sex difference in their ability to recognize whether an object has been displaced (Seib et al., 2018). It would be interesting to replicate the object displacement findings in SHR rats since an effect of spacing has been seen with other rat strains. SHRs have been found to be hyperexploratory in the presence of novel objects as well, so their memory retention when spaced could be notably larger than in other rats (Knardahl & Sagvolden, 1979). Through this, we could find out whether spacing is helpful in SHRs during an exploratory based task.

Studies that have used short intertrial intervals as a form of spaced practice have also been used. When observing male Sprague-Dawley rats during a radial arm maze, a task that presents rewards on different arms and requires the rat to remember where the reward is located, researchers spaced the trials for 10 minutes rather than over a day (Elmes et al., 1979). Reference memory errors were found to decrease but working memory errors did not. This meant that spaced practice was beneficial in a problem-based situation, but in a learning situation, performance did not increase. This goes against the theory that spaced practice is supposed to improve learning and therefore memory. It also presents counterintuitive results to another finding that used a reward-based methodology in male Sprague-Dawley rats. Classical conditioning, where a neutral stimulus becomes a conditioned stimulus, was used and a difference in learning but not in performance was found when training was spaced (Lattal, 1999). Largely, the rats did not show better performance during conditioning, but during testing they did better. This is more in line with current theories surrounding spacing's benefits, but these reward-based studies did not look at 24-hour intertrial intervals. Therefore, a study observing this should be conducted.

Conflicting studies are also present when short intertrial intervals are used in massed and spaced conditions (Martasian et al., 1992; Schiff et al., 1972). A review article observed that spacing over longer periods of time, specifically over 24 hours, led to the highest performance on reinforcement tasks (Smolen et al., 2016). Finally, having SHRs focus for fewer trials spaced over 24 hours may be more beneficial to their attentional abilities. This is because not as much extended focus is being demanded of them and they can complete the task without getting too distracted. There have also been neurochemical benefits to spacing at longer intervals.

Though researchers can behaviorally and cognitively measure the effects of spacing, some of spacing's real benefits and optimum spacing intervals can be seen in recent neurochemical research. These benefits are specifically seen in increasing long-term potentiation (LTP) in the hippocampus. LTP is the strengthening of synapses after completing a recent task or activity, typically it is associated with increasing learning and memory ability. When hippocampal slices of Sprague Dawley brains were stimulated one hour or more apart, there was an increase in dendritic connections made with synapses (Kramár et al., 2012; Lynch et al., 2013). Therefore, long-term potentiation was increased. Further, this supports that spacing for one hour or longer is more beneficial for long-term memory and learning because more synaptic connections are made compared to when they are massed together. If short intertrial intervals are used, these new connections may not be achieved as easily. Differences in memory consolidation after specific time periods have also been studied. Using a multitude of memory tests including the Morris Water Maze, inhibitory avoidance training, and contextual fear conditioning, researchers reduced synthesis of BDNF, a protein important for memory, by injecting half the rats with anisomycin, a drug that induces amnesia, before or after the tasks' completion (Bekinschtein et al., 2007). Protein synthesis in the hippocampus was explicitly focused on. Those who received the injection at 12 hours, experienced significantly more trouble remembering the task seven days after training than the group given a vehicle, or control, injection. Therefore, restricting BDNF specifically at 12 hours most likely restricts a significant period for memory consolidation. Additionally, spacing should be done to allow for memory consolidation to occur. Though spacing has notable effects, the benefits of massed training are important to focus on as well.

Massed training is helpful for perfecting motor skills. When product usage was observed under massed and spaced conditions there was an increased speed and quality of usage under massed conditions (Lakshmanan et al., 2010). Massing motor abilities allowed for quicker acquisition of skills that could not be achieved in a spaced condition. This could infer that spaced training may be better for remembering explicit information, or conscious remembrance, while massed may be better for remembering implicit information, unconscious remembrance. For example, one can have an explicit memory of their favorite type of car but have an implicit memory about how to drive a car. This unconscious remembrance of a task specifically relating to massed training has also been seen in volleyball skills. Women who massed their volleyball training were more likely to show greater acquisition and retention of those skills later on than women who spaced their volleyball training (Ahmadvand et al., 2016). This shows further support for massed training being better for unconscious motor memory than conscious semantic memory. Additionally, these findings support that spaced training will be better in terms of explicit memory of how to perform a task correctly. Even though memory is a large part of spacing, there is a large question of whether spacing can help with maintaining focus.

Breaks of Attention and Training Attention in ADHD

People with ADHD have lower attention spans which inhibits their ability to learn. During both passive and active listening tasks, children with ADHD had lower arousal, and therefore a lower attention span, than controls did (Shibagaki et al., 1993). Thus, focusing on improving attention spans is essential to helping those with ADHD. Many studies have attempted to improve attention spans in neurotypical children and children with ADHD by giving them “brain breaks” or moments where they do not have to focus (Chaney, 2005; McGinley, 2011; Reiber & McLaughlin, 2004; Weslake & Christian, 2015). These breaks can either be physical or non-physical. Yet, non-physical breaks have been shown to be more beneficial. Relaxation breaks in children led to less off-task behavior more quickly than movement breaks did (Weslake & Christian, 2015) and mental breaks for college students led to higher performance on a memory task than taking physical breaks (McGinley, 2011). Thus, breaks, especially ones with low physical activity, are beneficial for both the attention span and, therefore, memory. Often, teachers will institute more breaks for children with ADHD to help increase attention span and also set realistic goals the child feels they can meet. Ultimately, if the child has to focus for a shorter period of time, they will become more encouraged to continue later because less is being asked of them (Busch, 1993; Reiber & McLaughlin, 2004). Cognitive tasks that involve attention and working memory have also been proven to increase these abilities.

The carry-over effect seen when attention and working memory are cognitively trained is well-researched. Carry over is defined as the ability to take skills gained from one task and applying those skills to a new task or harder version of the same task. Cognitive training involves performing tasks that exercise and stimulate the brain. Those with ADHD who received memory and attention training through activities like cognitive video games showed improvement in working memory and attention. Multiple studies have found that after training occurred, a reduction in ADHD symptoms were seen (Gray et al., 2012; Halperin et al., 2013; Lim et al., 2012). Yet, Gray et al. (2012) also found that those who had more impairing inattention and hyperactivity scored worse on working memory tasks after training compared to those whose symptoms were less severe. Even though an overall increase in working memory was seen, it is notable that working memory training was not as useful for everyone. Training attention has also been shown to reduce inattentiveness in those with ADHD, but these effects were only seen in the case of an eight-week intensive training and no spacing was performed (Lim et al., 2012). Thus, it is possible that improving attention spans could be even more possible if training was spaced out. This is why we plan to directly space-out behavioral tasks that measure ADHD-like symptoms and, thus, observe whether limiting required attention decreases these impairing symptoms.

Tasks to Measure ADHD Symptoms

The Five-Choice Serial Reaction Time Task (5CSRTT) is a task that conditions a rat to poke their nose in a slot with a light over it to receive a reward. It is often used with SHR rats to measure their symptoms and general performance on attention based tasks (Hunziker et al., 1996). There are different levels to the task that involve the light being on for shorter intervals (Asinof & Paine, 2014). This task specifically tests for impulse control and attentional ability by necessitating focus from the rat when the light comes on so they can receive the reward. Sex differences have been found during this task. When SHRs' baseline performance in this task was compared to WKYs', the SHR control, male SHRs were less attentive than female SHRs, even though they were equally impulsive (Bayless et al., 2015). Yet, spacing could alleviate this gender gap by allowing the male SHRs to pay more attention and thus score higher in attentiveness. Females may not benefit from the spacing as much as the males, but they still may benefit more than the females receiving massed training.

Essentially, spacing this out would allow for the SHRs to sustain their attention for a shorter period of time, and an increase in performance could potentially be seen. Asinof and Paine (2014) mention in their paper that the rat can take months to properly learn the 5CSRTT, but they do not mention the duration of training levels, which are typically thirty minutes long, as a possible hindrance to their performance. If an SHR rat already has a low focus and attentional ability, it would only be logical to make the task shorter so they do not have to pay attention for an extended period of time. Since the 5CSRTT is a great way to test for ADHD-like symptoms such as inattention and impulsivity, it is possible to measure if spreading out trials over multiple days has an effect on ADHD-like symptoms. Impulsive responses are seen as faulty inhibitory responses or premature responses that involve answering before the light comes on (Fox et al., 2008; Asinof & Paine, 2014). Inattentive responses are categorized as a low number of correct responses. Attentiveness overall is categorized as a high number of correct responses and a low number of premature responses. (Asinof & Paine, 2014). Thus, these measures can help researchers determine whether the subject is displaying ADHD-like symptoms while also assessing if the rat is becoming more focused and less impulsive as training goes on. Yet, the ADHD symptom this task does not measure is hyperactivity.

SHRs are hyperactive during the open field. The open field is a task in which a rodent is placed in an empty box for five minutes and their activity levels are measured. SHR activity, when compared to their control rat, WKY, were found to travel greater distances in the open field, meaning they were more hyperactive than their control counterpart (Knardahl & Sagvolden, 1979). Within their strain though, female SHRs typically traveled further distances than male SHRs in the open field (Chelaru et al., 2012; Cierpial et al., 1989). In the present study this sex difference was predicted to occur, and the open field was used to see if training in the 5CSRTT would have an effect on both male and female activity levels. In a previous experiment in our lab that used both the 5CSRTT and the open field in SHRs, a secondary data analysis was run to compare activity levels to performance on the 5CSRTT. There was a significant correlation in the SHRs with high activity levels and lower performance on the 5CSRTT, specifically for TR-5. Essentially, the more hyperactive the SHRs, the more difficult the task was for them in this specific TR-level. Therefore, it is important to look at whether spacing has an indirect effect on hyperactivity in the open field through training in the 5CSRTT. Another way to measure activity in the open field is to record the SHR's rearing activity. Rearing is characterized by the rat standing on its hind legs at any angle, supported or unsupported by a wall (Sturman et al., 2018). Rearing has been found to highly correlate with activity levels in the open field and is therefore a good secondary measure to observe when looking at SHR activity levels (Díaz-Morán et al., 2014). Thus, by measuring ADHD-like symptoms with the 5CSRTT and the open field, a potential carry-over effect of spaced-training on activity level can be measured.

Hypotheses

The present study aimed to discover if spacing attentiveness training affected ADHD symptoms including inattention, impulsivity, and hyperactivity. An overall improvement in performance on the 5CSRTT and an overall decrease in hyperactivity was expected to be seen in both groups due to the positive benefits cognitive training can lead to in humans with ADHD (Gray et al., 2012; Halperin et al., 2013; Lim et al., 2012). An increase in performance in the 5CSRTT was expected to lower activity levels and rearing in the open field for both groups. This is due to decreases in hyperactivity also being affected by simply training memory or attention (Gray et al., 2012; Lim et al., 2012). Yet, females were expected to exhibit higher hyperactivity and rearing because in the past, females have been found to be more active in the open field (Chelaru et al., 2012; Cierpial et al., 1989).

This decrease in inattention, impulsivity, and hyperactivity was hypothesized to be more significant in the spaced condition because of spacing's well-known effect on memory and attention in both rodents and humans (Commins et al., 2003; Grassi, 1971; Kerfoot et al., 2007; Kornmeier et al., 2014; Riches et al., 2005; Wang et al., 2014). A higher carry over effect for SHRs who were in the spaced condition was also predicted. For example, if a rat had a high attentiveness score one week, they would be able to maintain that score when they moved to a harder level. There was evidence this carry over effect would occur because training in cognitive video games has led to higher attentiveness in other tasks (Gray et al., 2012; Halperin et al., 2013; Lim et al., 2012). Moreover, males in the spaced condition were expected to experience a larger improvement in their 5CSRTT attention scores than females in the spaced condition. Bayless et al. (2015) found a strain difference in attentiveness scores for SHR males, but not for females in baseline measures. Spacing was predicted to therefore close this gap by improving attentiveness.

Finally, a replication of the literature by Commins et al. (2003) was observed during the object displacement task. SHRs in both conditions were hypothesized to show similar exploratory patterns due to their hyperexploratory nature (Knardahl & Sagvolden, 1979), but it was expected that the spaced condition would not habituate as quickly and therefore recognize the displaced object more than the massed condition. No sex differences were predicted to be observed in the object displacement task. Commins et al. (2003) study only used male rats, but other studies have also found no sex differences in rats that perform object displacement (Seib et al., 2018). Yet sex differences were still measured for due to SHR females having higher exploratory behaviors than males (Chelaru et al., 2012; Cierpial et al., 1989).

Methods

Subjects

Twenty-four SHRs (12 females, 12 males) participated in this experiment. Rats were placed into one of two conditions: massed (M) or spaced (S) training. These conditions were equal in sex and number and were balanced across litters. Also, all of the rats lived in the same type of environments throughout the duration of the study (pair-housed in standard cages). Strain analyses of the SHR vs WKY, in our lab on 5CSRTT, a previous IS student using an N of 9 and 15 found a marginally statistically significant difference $F(1, 22) = 2.106$, $p = 0.092$, $\eta_2 = 0.124$. Therefore, to increase power, we boosted the N to 12 in each group. Finally, no control was used for this experiment due to the already available data surrounding spaced training in other rats and the desire to mainly focus on whether spaced training has an effect on ADHD symptoms.

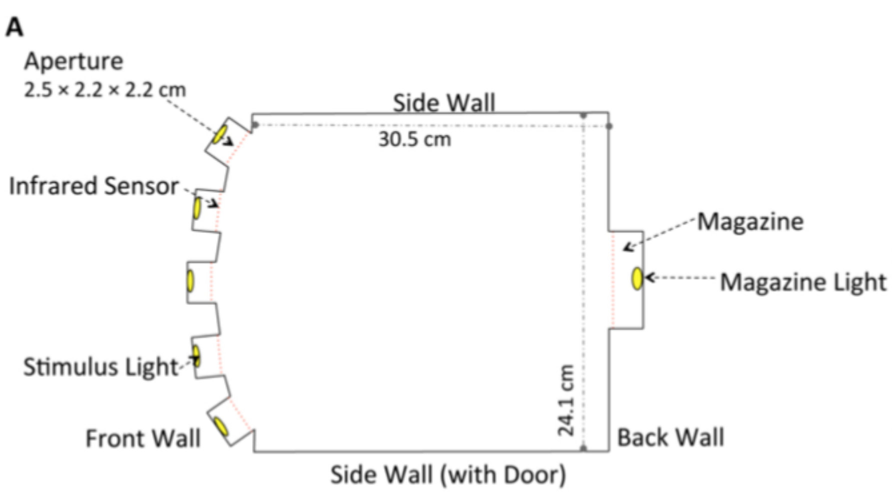
Materials

5-Choice Serial Reaction Time Task (5CSRTT)

There were three Med Association chambers used to train the rats on increasing their attention and decreasing their impulsivity. Twenty-four hours before the task was conducted, rats were food deprived to 85% of their body weight (Asinof & Paine, 2014). During the task, the rats were rewarded via sugar pellets. Each chamber contained five slots for the rats to poke their noses in and the interiors of the chambers were all 23.5" x 22" x 14" (Figure 1). Before each training session, chambers were wiped down with 70% ethyl alcohol and quilted paper towels were placed underneath the SHRs to catch any droppings.

Figure 1

5CSRTT Diagram



Note. This diagram was taken directly from Asinof & Paine (2014). It shows how the 5CSRTT was set up for the rat. The rat would respond to the stimulus light by poking their nose in the hold under the light and then get their reward from the magazine area. The infared sensor would let researchers know that the rat had interacted with each area.

Open Field (OF)

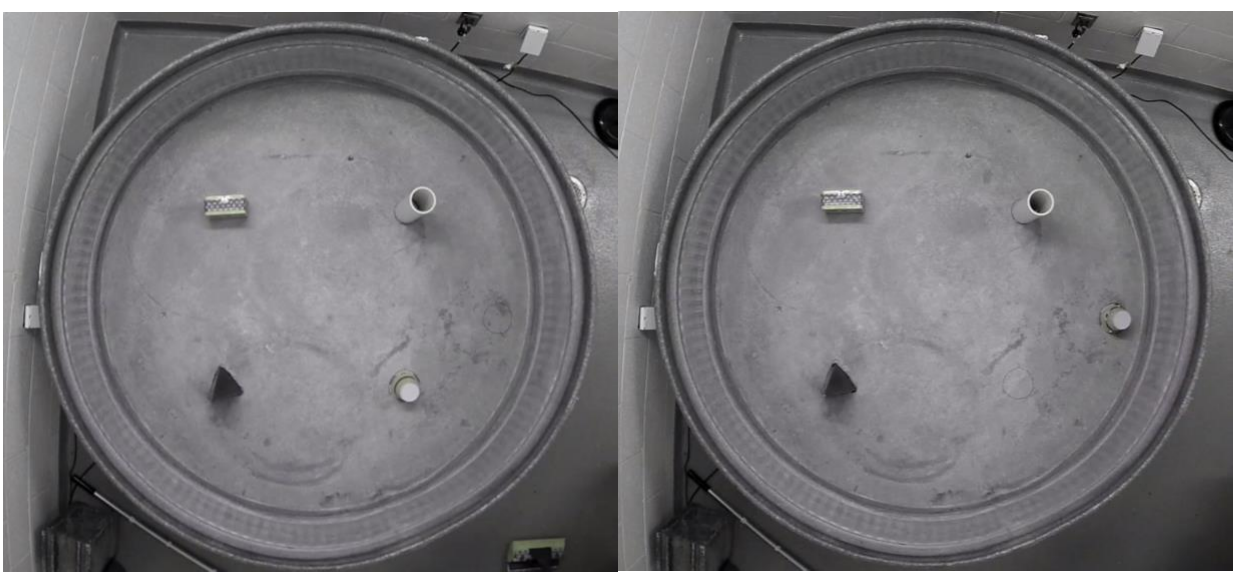
The SHRs performed the open field task in a 3’x 3’x 18” wooden open field. It contained a painted black bottom and painted white sides. This allowed for the experimenter to be able to see the white rat clearly on the video feedback. Activity levels, such as distance traveled and rearing, were recorded with an overhead video camera. A mixture of ½ Nature’s Miracle and ½ water was used to wipe down the open field and remove any odor. A start box was placed in the open field for the initial 10 seconds of the task. This allowed for the SHR to start the trial in the same location. A stopwatch was used to measure how long the rat had been in the open field for.

Object Displacement

The methodology for this task is being replicated from Commins et al. (2003). SHRs were placed in a circular arena that was 160 cm in diameter and 58.4 cm in height (Figure 2).

Figure 2

Pictures of Object Displacement Task



Note. The left picture indicates the arena when the SHRs were in their training condition. The right picture indicates the arena when the SHRs were testing. The cup in the lower right-hand corner was the object that was displaced.

Four different objects that the SHRs had no prior experience with were used. The objects included a metal yellow lunchbox (14.6 cm x 14.6 cm x 6.4 cm), a large yellow cup (11.4 cm x 11.2 cm), a white cylinder (8.9 cm x 30.5 cm), and a black pyramid (35.6 cm x 12.7 cm) (Figure 2). The experimenter stayed in the same place for the duration of the task and experiment.

Procedure

5CSRTT

All SHRs received Consistent Reinforcement (CRF) training before they began the open field and received regular training, this involved teaching them how to receive the reward by having all lightbulbs remain on. The rats in the massed condition and spaced condition were tested separately. The massed condition was trained 90 trials per day for four days. Training for the spaced condition was 45 trials per day for eight days. Testing lasted eight weeks. Rats progressed through the training levels in increasing order. Once the training for each TR schedule (4 x 90 or 8 x 45) was completed all rats moved to the next training level (Table 1). This way, researchers could focus on which training was more effective based on performance improvement during that training level and across training levels. The day before testing, rats were food deprived to ensure motivation to complete the food-based task. Each rat was handled, and pet while being transferred into the 5CSRTT chambers to reduce possible stress from being picked up. To perform the task correctly and get a reward, the rat had to poke their nose into the correct slot. The correct slot was indicated with a lightbulb. If the rat picked the correct slot, they received a reward. Performance on the task was recorded by the number of correct responses and improvement on the task over time. Inattention was measured by the accuracy of the rat's response and their number of omitted or unanswered responses. Impulsivity was recorded by the number of premature responses made by the rat (Figure 3). At the end of the task, all of the chambers were wiped down with 70% ethyl alcohol and a new quilted paper towel was placed underneath the chamber's platform. They were also immediately fed after they completed the task. They fed for one hour and then had their food removed again to prepare for next day's trials. If the rats were finished training for the week or were in a different condition, they were fed a regular diet.

Table 1

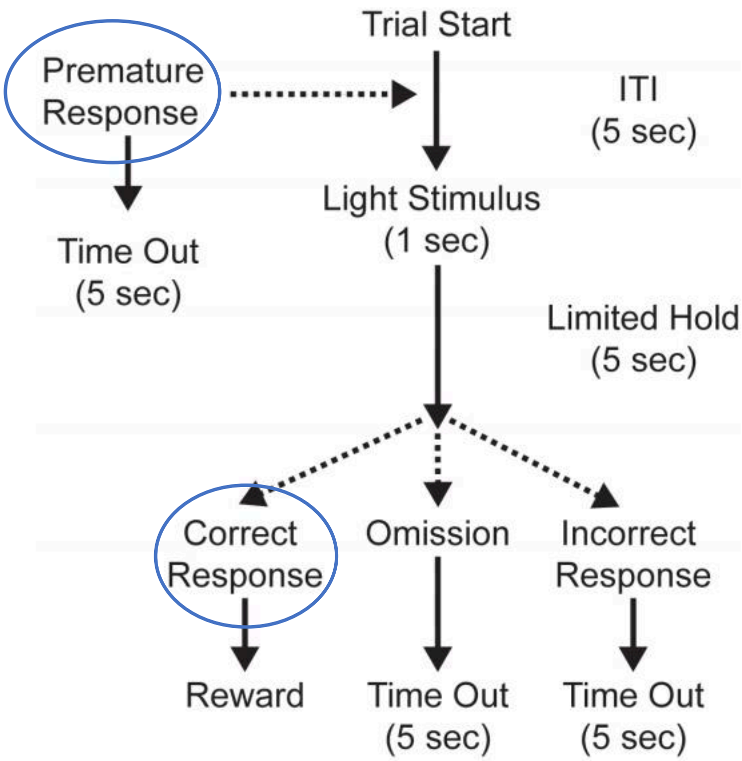
Training Schedule for Massed and Spaced SHRs

Training Stage	Trials/Session	Stimulus Duration (SD)	ITI Duration	Limited Hold (LH)	Time Out (TO)
TR-1	Massed (90 trials or 30 min)	30	2	30	2
	Spaced (45 trials or 15 min)				
TR-3	Massed (90 trials or 30 min)	15	3	15	3
	Spaced (45 trials or 15 min)				
TR-4	Massed (90 trials or 30 min)	5	3	10	3
	Spaced (45 trials or 15 min)				
TR-5	Massed (90 trials or 30 min)	2	3	5	3
	Spaced (45 trials or 15 min)				

Note. This table was adapted from Asinof & Paine's (2014) paper on the 5-Choice Serial Reaction Time Task and was modified to include spaced training. The stimulus duration (SD) indicates how long the lightbulb was on in seconds. The ITI or the intertrial interval was the amount of time between each trial. Limited hold (LH) was the amount of time the SHR had to respond. Time out (TO) was the amount of time the SHR had to wait after giving an incorrect response. SD, ITI, LH, and TO were all recorded in seconds.

Figure 3

Impulsivity and Attentiveness Measurements



Note. This figure is directly taken from the Asinof & Paine (2014) paper on how to measure inattention and impulsivity using the 5-Choice Serial Reaction Time Task. The circled variables are what will be measured during this study. If the SHR answers prematurely (premature response), they get a time-out for five seconds, this is considered an impulsive response. The measure of attention is the number of correct responses. See Table 1 for explanations on SD, ITI, LH, and TO.

Open Field

At the end of each training session (four or eight days), the rats would be placed in the open field to measure their activity levels. Only the group that had trained that week would complete this task. Incandescent and indirect lighting was used to not stress the animals (Katz et al., 1981) and an overhead camera was turned on. The open field was wiped down before and after usage with ½ Nature's Miracle and ½ water. Rats were picked up by the anterior side of the tail and put behind the start block for ten seconds. A reduced variability in handling allowed for the SHRs to be put in the same condition throughout the entirety of the task. The start block was removed after 10 seconds and the camera began recording the SHR's activity. Rearing was recorded by tallying every time the researcher observed it occur. Both supported and unsupported rearing was recorded, but it was not differentiated between for statistical analysis. After five minutes elapsed the recording was stopped, and the rat was taken out of the open field from the anterior side of their tail. Any defecation was cleaned before the next subject began the task. Distance traveled was then analyzed with the Noldus Ethovision 12 software program.

Object Displacement

The procedure for this experience is adapted from Commins et al. (2003). Rats were placed in the center of the arena and had one minute to explore in an empty maze before the first trial only. Once the objects were positioned, the rat was placed into the arena and recorded by an overhead camera for three minutes. When being placed into the arena, rats were handled like they were in the open field task. EthoVision was used to measure percent of time spent with the object. The spaced condition performed one trial per day for four days while the massed condition had four consecutive trials with an intertrial interval of 35 minutes. After each trial, the arena and objects were wiped down with ½ Nature's Miracle and ½ water. After all of the rats had been trained, their spatial memory was tested seven days later. During this test trial, the large yellow cup was displaced next to the cylinder. If the rat made more contact with the displaced object, they were aware it had been moved.

Results

The main purpose of this study was to determine whether spacing training would improve performance by increasing attentiveness and lowering hyperactivity and impulsivity scores in the SHR strain of rat. In addition, we sought to replicate the literature that spaced training can improve performance in object displacement, a spatial memory task. No published research study has looked at spacing training in SHRs.

5CSRTT

Hypotheses

It was predicted that across both groups, percent correct scores would increase, and premature responses would decrease as a result of training in the 5CSRTT. It was also hypothesized that spacing out training by reducing the number of trials to 45 each day, would increase percent correct scores and decrease premature responses more substantially. Finally, spacing out attentiveness was expected to close a gap in sex differences typically exhibited; males would benefit more from spacing than females. Sex differences in premature responses were not expected due to males and females not exhibiting a difference in previous literature (Bayless et al., 2015). Therefore, this variable was not included in the analysis of premature responses.

A series of 2 x 2 x 4 repeated measures were run for each training level to observe changes across group (spaced and massed) and sex (male and female) in percent correct and for only group for premature responses over four days. Attentive behavior was characterized by high percent correct responses and low premature responses. For the spaced condition, two complete 45 trials sessions were averaged together to match the 90 trial sessions of the massed group. (should I have something for premature responses)

TR1

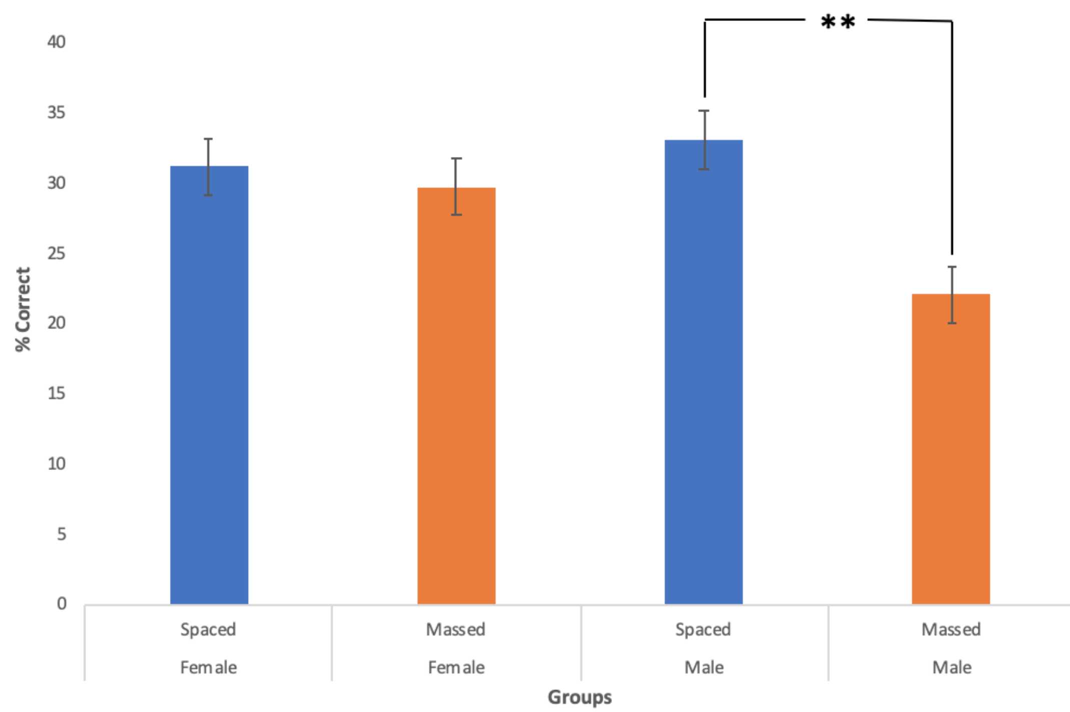
TR1 is the first training level the SHRs were taught after the CRF training. This training level is considered the easiest, with the stimulus duration being 30 seconds and the amount of time given to respond, or limited hold, being 30 seconds (Table 1). Attention is necessary to do well on this level, but it is also the least demanding of all the training levels.

The spaced group exhibited higher percent correct scores than the massed group in this training level, $F(1, 20) = 9.443$, $p = 0.006$, $\eta^2 = 0.321$. There was no main effect of sex in this training level, $F(1, 20) = 1.980$, $p = 0.175$. There was, however, a significant interaction between group and sex, $F(1, 20) = 5.592$, $p = 0.028$, $\eta^2 = 0.219$. A secondary independent t-test was run and it was found that males in the spaced group performed significantly better than males in the massed group, $t(10) = 3.923$, $p = 0.003$, $d = 0.975$. Females, based on treatment, did not differ in their performance, $t(10) = 0.491$, $p = 0.634$ (Figure 4). Therefore, males in the spaced group benefited more from spacing than females. There was also a significant within subject effect of days for percent correct scores, $F(3, 60) = 63.835$, $p < 0.001$, $\eta^2 = 0.761$ meaning that both groups improved significantly over the days they trained. There was no significant interaction between days and group, days and sex, or between sex, group, and days (all *ps* > 0.084) (Figure 5).

There was no difference in group for premature responses, $F(1, 22) = 0.197$, $p = 0.662$ meaning no group was more impulsive than another. A day effect was seen in premature responses as well, but instead of significantly decreasing their premature responses over training days, indicating lower impulsivity, an increase in premature responses was observed for both groups, $F(3, 66) = 37.686$, $p < 0.001$, $\eta^2 = 0.631$. There was no significant interaction between days and group, $F(3, 66) = 0.479$, $p = 0.698$.

Figure 4

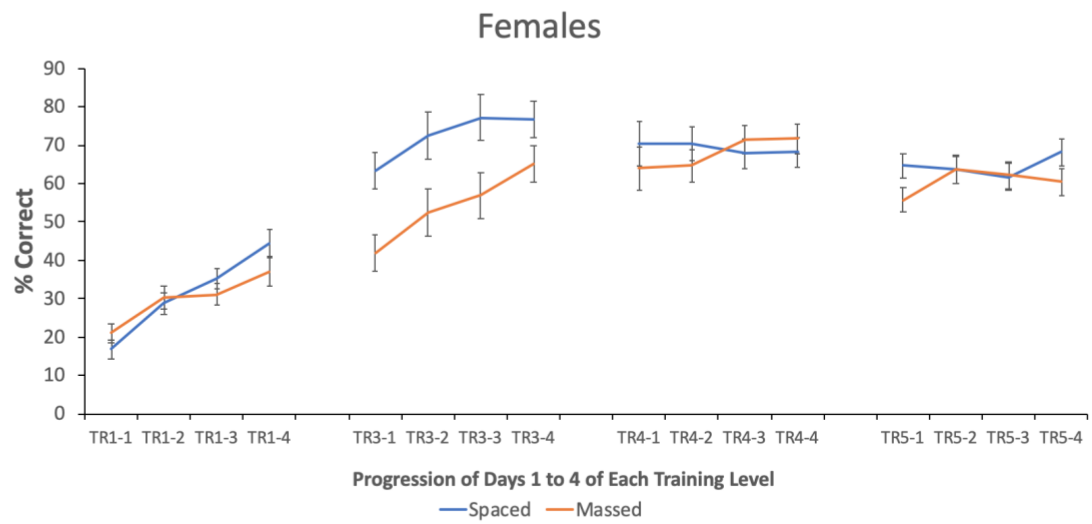
Spaced Training is More Beneficial for Males in TR1



Note. Males in TR1, specifically in the massed group, performed significantly worse than males in the spaced group while females in both groups did not significantly differ. Thus, spacing benefited males more than females. (** = $p < 0.01$)

Figure 5

Spaced Training is Beneficial in TR1 and TR3



Note. Figure 5 demonstrates that the spaced condition performed significantly better than the massed condition during TR1 ($p = 0.006$) and TR3 ($p < 0.001$) in their percent correct scores. It also demonstrates that both groups substantially improved over days during TR1 ($p < 0.001$), TR3 ($p < 0.001$), and TR5 ($p = 0.023$), but not during TR4 ($p = 0.181$). It is also seen in TR3 that the spaced group reached their optimal level of performance by day two while the massed group was still improving ($p = 0.008$).

TR3

TR3 is the second training level the SHRs were taught after completion of TR1. It is also considered a fairly simple training level with the stimulus duration being 15 seconds and the limited hold also being 15 seconds (Table 1). Yet there is a significant decrease in the amount of time the rat sees the light and can respond, so this training level puts a higher tax on attention than the previous one.

The spaced group performed significantly better than the massed group in percent correct responses, $F(1, 20) = 19.219$, $p < 0.001$, $\eta_2 = 0.490$. There was no main effect of sex or interaction between treatment and sex in this training level (all *ps* > 0.05). Thus, sex did not play a role in influencing percent correct scores in either group, unlike in TR1. However, a significant within subject effect of days was seen for their percent correct scores, indicating that both groups improved significantly over the days they trained, $F(3, 60) = 41.250$, $p < 0.001$, $\eta_2 = 0.673$. Yet, there was also a significant interaction between days and group, where the spaced group hit their optimal level of performance while the massed group was still improving, $F(3, 60) = 4.345$, $p = 0.008$, $\eta_2 = 0.178$ (Figure 5). A pairwise sample t-test was run to compare the slopes of performance during TR3 between the massed and spaced groups. When day one versus day four was looked at, both the spaced, $t(11) = -5.051$, $p < 0.001$, $d = 0.933$ and massed group, $t(11) = -10.045$, $p < 0.001$, $d = 0.997$ had a significant difference. Yet when scores were compared between day two and day four, the massed group still significantly differed in their percent correct scores, $t(11) = -5.856$, $p < 0.001$, $d = 0.470$ while the spaced group did not ($p = 0.163$). Therefore, it can be assumed that the spaced group hit their optimal performance on day two and did not improve from there, while the massed group continued to improve (Figure 5). There was no significant interaction between days and sex or sex, days, and group (all *ps* > 0.05) (Figure 5).

The spaced group also exhibited significantly lower premature responses than the massed group, $F(1, 20) = 16.661$, $p = 0.001$, $\eta^2 = 0.454$. Therefore, spacing led to the rats responding less impulsively. There was also a significant decrease in premature responses over the days they trained, $F(3, 60) = 12.736$, $p < 0.001$, $\eta^2 = 0.389$ unlike in TR1 where a significant increase in premature responses was observed. There was a group by day effect for premature responses as well, $F(3, 60) = 4.792$, $p = 0.005$, $\eta^2 = 0.193$. A paired sample t-test was run to compare the slopes of premature responses between the massed and spaced groups. Between day one and day four, both the massed, $t(11) = 4.440$, $p = 0.001$, $d = 0.847$ and spaced groups, $t(11) = 3.201$, $p = 0.008$, $d = 0.858$ significantly decreased in their premature responses. Between day two (M= 76.27, SD= 49.58) and day four (M= 56.36, SD= 42.97) though, the massed group significantly decreased in their premature response, $t(10) = 2.440$, $p = 0.035$, d= 0.182, while the spaced group did not significantly decrease ($p = 0.520$). Therefore, similar to their percent correct responses, the spaced group had already hit their optimal level of performance for premature responses by day two and did not decrease much further. The massed group, on the other hand, still had room to decrease.

This highlights that rats were more attentive in the spaced condition than in the massed condition because they not only performed better, but they were also acting less impulsively and focusing on making the correct answer.

TR4

TR4 is the third training level that was taught to the SHRs. It is considered much harder than TR3 with the stimulus duration only being five seconds and the limited hold being 10 seconds (Table 1). Given that the rat has very little time to focus on the light and only some time to respond, high attentiveness is essential to performing well during this training level.

There was no main effect of spacing, sex, or interaction between group and sex for this training level (all *ps* > 0.05). There was also no significant within subject effect of days, meaning both groups did not change in their percent correct scores during this training level perhaps indicating that four days is not enough time for the animals to learn the task parameters. However, there was an approaching significant interaction between days and group in percent correct scores $F(3, 60) = 2.188$, $p = 0.099$. Similar to TR3, this interaction suggests that the massed group still demonstrates improving scores while the spaced group has hit their optimal level. However, this seemed to be a result of low day one scores for the massed group only and given that the interaction was only marginally significant, this was not explored further in another test (Figure 5). Finally, there was no days and sex interaction or sex, group, and days interaction (all *ps* > 0.05).

There was no group $F(1, 18) = 0.683$, $p = 0.419$ or day $F(3, 54) = 1.884$, $p = 0.143$ effect on premature responses. There was an approaching interaction for day and group and premature responses $F(3, 54) = 2.220$, $p = 0.096$. Similar to TR3, and in line with percent correct scores, this interaction suggests that the massed group still demonstrates decreasing impulsivity scores while the spaced group has hit their optimal level. Yet, this was most likely the result of high impulsivity scores on day one for the massed group only and given that the interaction was only marginally significant, this was not expanded on in another test.

TR5

TR5 was the last training level taught to the SHRs. It is not the hardest training level that can be implemented, but it is the most difficult one we administered. It has a stimulus duration of two seconds and a limited hold of five seconds. This training level requires more attentiveness than all the training levels prior given that the rat has very little time to focus on the light and very little time to respond.

Similar to TR4, there was no main effect of group, sex, or interaction between group and sex on percent correct scores or premature responses (all *ps* > 0.05). Although, there was a significant effect of days, with percent correct scores increasing over training days $F(3, 60) = 3.395$, $p = 0.023$, $\eta_2 = 0.145$. Finally, there was no days and group interaction (Figure 5), days and sex interaction, or sex, group, and days interaction (all *ps* > 0.05).

Premature responses did not change significantly across days, meaning both groups did not change in their levels of impulsivity $F(3, 60) = 0.972$, $p = 0.412$. There was also no group difference in premature responses, showing that both groups had similar levels of impulsivity, $F(1, 20) = 1.430$, $p = 0.246$. There was an approaching significant interaction for days and group for premature responses $F(3, 60) = 2.222$, $p = 0.096$. Similar to the reasoning in TR4, further testing was not conducted.

Carry Over Effects

It was hypothesized that carry over effects would occur more in the spaced group as training levels were increased. Carry over is defined as the ability to take skills gained from one task and being able to apply those skills to a new task or harder version of the same task. Carry over was considered to have occurred if a group, after performing well in one TR, performed just as well on the next TR's first day of training. In this case, the spaced group is expected to do better because they will most likely be able to learn the task more easily.

Paired sample t-tests helped measure for carry-over effects by comparing day four scores to the first day scores during TR1 to TR5. When comparing percent correct responses on day four of TR1 (*M*= 45.00, *SD*= 9.26) to the first day of TR3 (*M*= 61.57, *SD*= 12.31) , the spaced group had a significant increase in their scores, $t(11) = -7.700$, $p < 0.001$, $d = 0.961$ while the massed group did not, $t(11) = -1.279$, $p = 0.227$. Essentially, the spaced group remembered more from their previous training and were able to perform better than the massed group on the first day back.

When comparing day four of TR3 (*M*= 75.93, *SD*= 7.45) to the first day of TR4 (*M*= 70.28, *SD*= 11.87), the spaced group had an approaching significant decrease in their percent correct scores, t(11) = 2.001, p = 0.071. In the massed group however, percent correct responses on day four of TR3 (*M*= 62.04, *SD*= 13.98) and the first day of TR4 (*M*= 60.56, *SD*= 14.83), did not significantly differ, t(11) = 0.457, p = 0.657. The approaching significant decrease for the spaced group decrease indicates how difficult TR4 was in comparison to TR3. The massed group most likely did not experience a significant decrease because TR3 and TR4 may have been comparable in difficulty for them.

When comparing day four of TR4 (M= 69.09, SD= 6.17) to the first day of TR5 (M= 59.91, SD= 7.59), the spaced group significantly decreased in their percent correct scores, $t(11)= 4.510$, $p = 0.001$, $d = 0.902$. The massed group also had significantly different percent correct responses on day four of TR4 (M= 68.85, SD= 11.28) versus the first day of TR1 (M=55.55, SD= 9.00), $t(11) = 5.544$, $p < 0.001$, $d = 0.891$. An independent t-test was run to compare day four percent correct scores at for TR4 and the first day percent correct scores for TR5. Neither groups scores on either day significantly differed from one another (all *ps* > 0.213). Therefore, the spaced and massed group were performing at similar levels by the end of training in TR4. The groups not performing differently highlights the difficulty of TR4 and the continuing difficulty of TR5.

For premature responses, when comparing day four of TR1 (M= 55.17, SD= 12.02) to the first day of TR3 (M= 112.50, SD= 46.75), premature responses significantly increased in the massed group, $t(11) = -4.080$, $p < 0.001$, $d = 0.984$. In the spaced group however, premature responses on day four of TR1 (M= 51.58, SD= 26.52) and the first day of TR3 (M= 51.67, SD= 25.77) did not significantly differ, $t(11) = -0.016$, $p = 0.988$. This indicates that the spaced group did not respond more prematurely when switching levels, indicating higher attentiveness overall. This also indicates that they learned to have lower premature responses in TR1 and maintained those low levels in TR3.

For day four of TR3 (M= 25.58, SD= 15.00) and the first day of TR4 (M= 28.00, SD= 25.45), the spaced group did not significantly differ in their premature responses, $t(11) = -0.448$, $p = 0.663$. For the massed group, day four of TR3 (M= 58.58, SD= 41.68) and the first day of TR4 (M= 34.92, SD= 25.40) significantly differed, $t(11) = 2.750$, $p = 0.019$, $d = 0.389$. These are similar results to the comparison between TR1 and TR3. Therefore, it can be assumed that the spaced group, when switching levels, learned to make low premature responses during TR3 and maintained them into TR4. The massed group, on the other hand, were still learning how to become less impulsive in their responses, emphasizing the decrease.

Finally, for day four of TR4 (M= 31.17, SD= 12.97) and the first day of TR5 (M= 24.50, SD= 13.24), premature responses did not significantly differ for the spaced group, $t(11) = 1.604$, $p = 0.137$. Day four of TR4 (M= 22.27, SD= 13.80) and the first day of TR5 (M= 28.73, SD= 16.27) also did not significantly differ for the massed group, $t(10) = -1.462$, $p = 0.175$. Since both groups had low premature responses overall, it can be assumed that they could not decrease much further once they hit this level.

Open Field

Hypotheses

It was predicted that hyperactivity in the open field would decrease as training in the 5CSRTT increased. Specifically, the hyperactivity in the spaced condition was expected to decrease significantly more than the hyperactivity in the massed condition. Finally, hyperactivity was expected to be higher in the females than in the males. A 2 x 2 x 5 repeated measure assessed hyperactivity between groups (spaced and massed) and sex (male and female) over five days in the open field. One day occurred before training and the others occurred after each training level was complete.

Rearing & Distance Traveled Correlates and Main Effect of Days and Sex

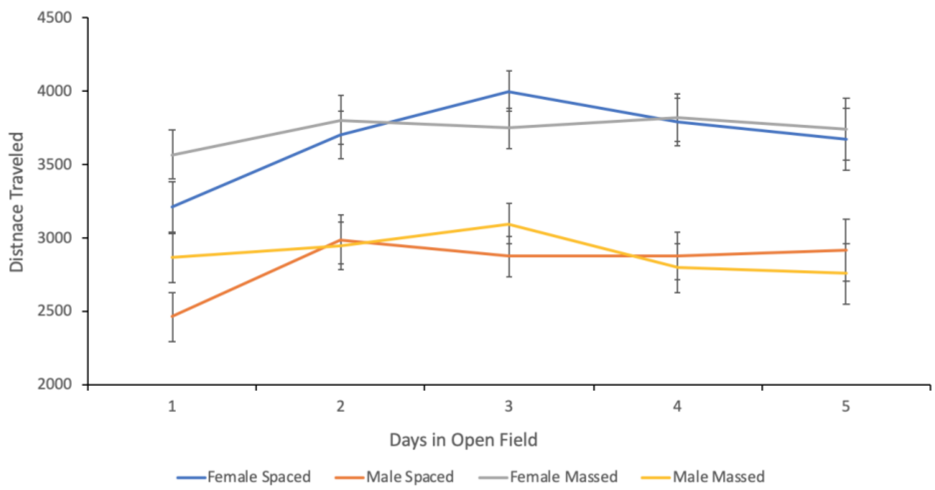
There was a significant positive correlation with rearing and distance traveled, $r = 0.720$, $p < 0.001$. This indicates that the rats who traveled the furthest distance also performed the most rearing. This also highlights that rearing was tallied correctly and is a valid measure for activity in the open field. To test whether hyperactivity in the open field and performance in the 5CSRTT were related and to replicate findings found in our lab, another correlation was run. This correlation compared the percent correct scores for day four of TR5 to the distance traveled in the open field after training in TR5. No significant correlation was found, $r = 0.169$, $p = 0.431$, which did not replicate earlier findings in our lab.

There was no significant main effect of group on distance traveled (all *ps* > 0.492) in the open field indicating that spacing in the 5CSRTT did not affect hyperactivity through carry over overall. In addition, there was a significant effect of sex. Females traveled a higher distance, $F(1, 20) = 57.665$, $p < 0.001$, $\eta_2 = 0.742$ and reared more, $F(1, 20) = 45.127$, $p < 0.001$, $\eta_2 = 0.693$ than males in the open field. There were no sex interactions for either rearing or distance traveled meaning that being in the spaced or massed condition did not benefit one sex more than the other, even over days (all *ps* > 0.05).

There was a statistically significant change in distance traveled over days, $F(4, 80) = 4.583$, $p = 0.002$, $\eta^2 = 0.186$. In order to explore the effect of early spaced training on activity we compared only day one and day two through a 2 x 2 x 2 repeated measure. There was a significant effect of days indicating an increase in distance traveled from day one to day two, $F(1, 20) = 7.852$, $p = 0.011$, $\eta^2 = 0.282$ (Figure 6). There was also an approaching group effect with the spaced group traveling an overall shorter distance than the massed group over these two days, $F(1, 20) = 2.994$, $p = 0.099$. There was also a main effect of sex across day one and day two, with females traveling a higher distance, $F(1, 20) = 41.487$, $p < 0.001$, $\eta^2 = 0.675$, but no sex interactions occurred (all *ps* > 0.05). Rearing also had a statistically significant change, with it generally decreasing over all days, $F(4, 80) = 12.611$, $p < 0.001$, $\eta^2 = 0.387$. In order to further explore the effect of early spaced training on activity we compared only day one and day two through a 2 x 2 x 2 repeated measure. A main effect of sex was discovered $F(1, 20) = 19.124$, $p < 0.001$, $\eta^2 = 0.489$, with females rearing more than males, but there was no group effect, days effect, or interaction effects (all *ps* > 0.05).

Figure 6

Open Field Indicates Sex Difference, But No Group Difference



Note. Figure 6 indicates that over all days, there were no group differences in distance traveled. There was however a large difference in sex, with females traveling significantly more. This was not modified by group, days, or days and group though. A large increase can also be seen from day 1 to day 2 for both groups, with the spaced group increasing slightly more.

Object Displacement

Hypotheses

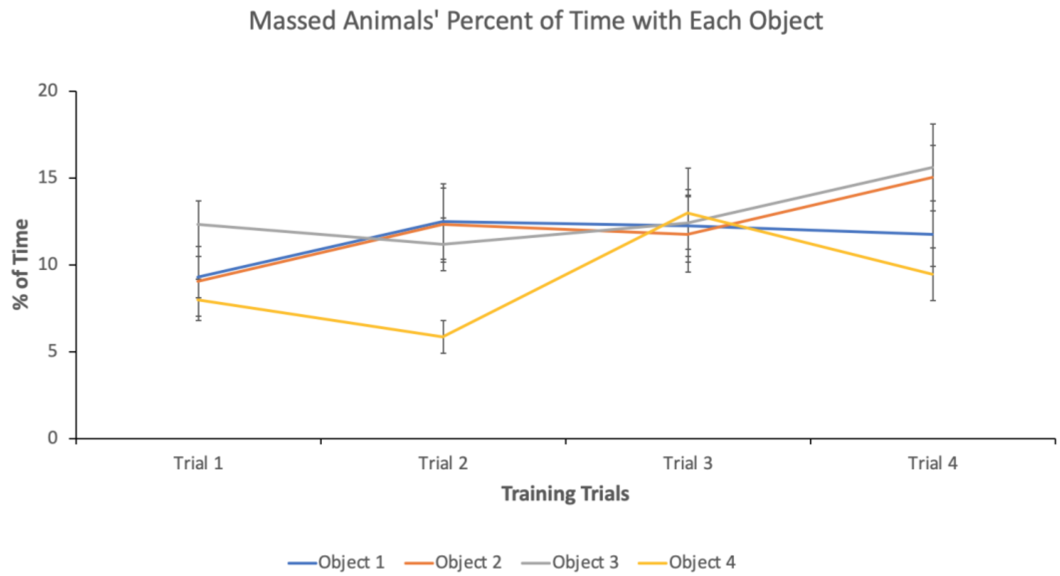
It was expected that the spaced condition would spend more time with the displaced object than the massed condition due to the spaced condition not habituating as quickly. Though no sex effect was expected to be found in ability to recognize the displaced object according to the present literature (Seib et al., 2018), we assessed sex because SHR females were more exploratory than males in the open field, meaning an exploratory memory task has the potential to favor females more. The object displacement task involved a 2 x 2 x 4 repeated measure to measure if habituation to the objects occurred. Habituation was considered to occur if there was a significant decrease in percent of time spent with the objects over four trials. A 2 x 2 x 2 repeated measure was also used to see which group interacted more with the displaced object during the training compared to the test trial.

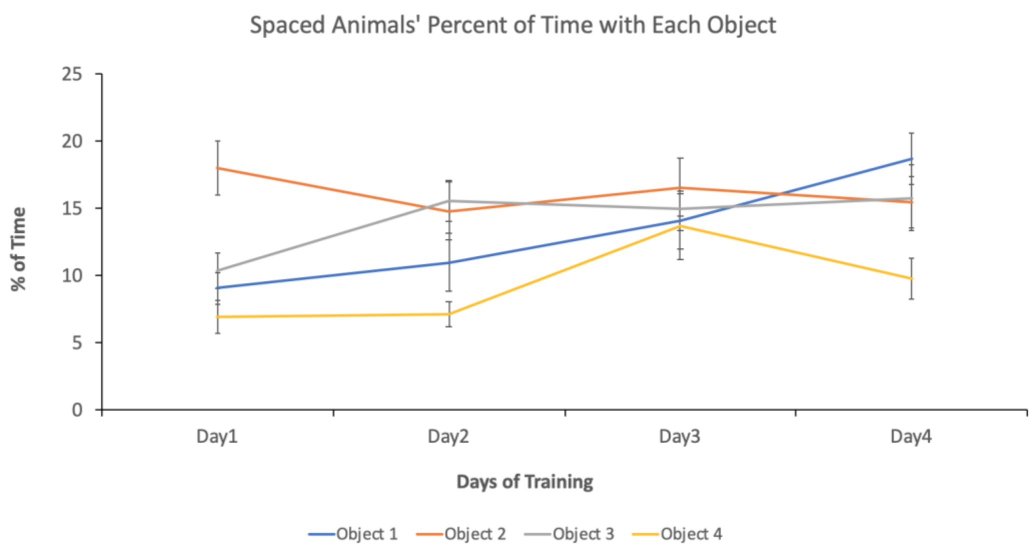
Main Effect of Displacing Object

There was no significant habituation in the object displacement task. The animals spent a similar amount of time with each object throughout all learning trials. For example, there was no group, sex, or day effect in the amount of time they spent with object one over days (all *ps* > 0.05) (Figure 7). There was a significant impact of displacing the object though (Figure 8). Both groups spent more time with the displaced object when it was displaced compared to the last learning trial (trial 4), meaning they recognized that the object had moved, $F(1, 19) = 11.973$, $p = 0.003$, $\eta_2 = 0.387$. In opposition to the hypothesis, there was no difference across groups for recognizing if the object was displaced, $F(1, 21) = 0.215$, $p = 0.647$. Matching our expectations, no main sex differences were found in ability to recognized the displaced object, $F(1, 19) = 0.686$, $p = 0.418$. Along with this, there was no interactions of sex and group, trials and sex, trials and group, and trials, sex and group, emphasizing that neither sex was influenced more heavily by their group or prior trials in their ability to recognize whether the object was displaced (all *ps* > 0.05).

Figure 7

Percent of Time with All Objects Does Not Differ Across Groups

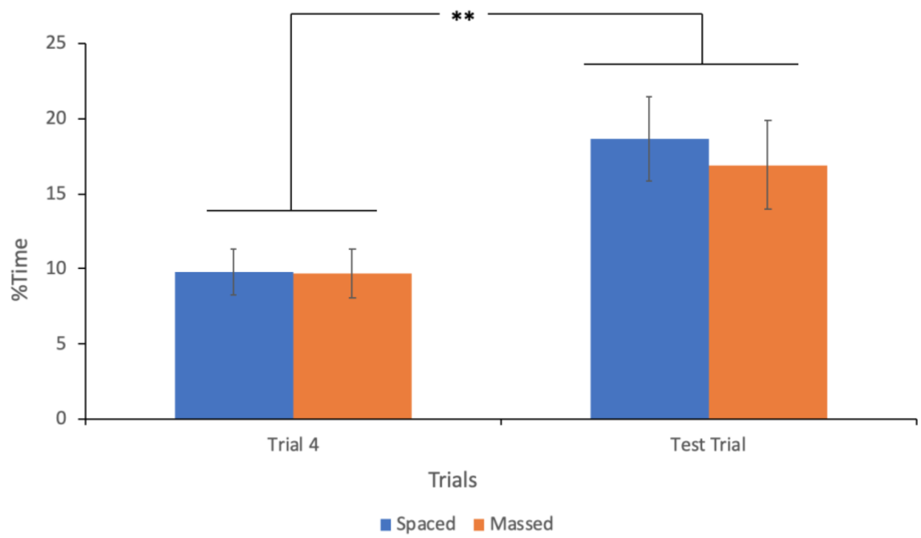




Note. This figure represents the amount of time each group spent with each object over either four trials (massed) or four days (spaced). It was expected that by trial three or trial four, the massed group would begin to decrease their interactions with all objects, but this effect was not seen. Thus, no habituation was seen to occur in the massed group. The same effect was seen in the spaced group.

Figure 8

Significant Difference in Recognizing Displaced Object



Note. It was found that both groups were able to recognize that the object was displaced. This is seen in the increased percent of time with the displaced object in the test trial than they did in the final trial of their training. (** = $p < 0.01$)

Discussion

5CSRTT

Benefits of Spaced Training Mainly Seen in TR1 and TR3

It was predicted that spacing out training in the 5CSRTT by having 45 trials over eight days instead of 90 trials over four days would increase percent correct scores and decrease premature responses. Human studies have shown that attentiveness training leads to better attentiveness (Gray et al., 2012; Halperin et al., 2013; Lim et al., 2012) and that spacing in human and rats is more beneficial for long-term memory (Commins et al., 2003; Grassi, 1971; Kerfoot et al., 2007; Kornmeier et al., 2014; Riches et al., 2005; Wang et al., 2014). Therefore, spacing and attentiveness training together was expected to lead to optimum attentiveness abilities. Overall, all animals improved in percent correct responses for TR1, TR3, and TR5, and improved in impulsivity during TR3 and almost TR4 and TR5. In TR1 and TR3 though, spacing led to higher percent correct responses and during TR3, spacing led to less premature responses. Along with this, in TR3, the spaced group's percent correct scores and premature responses were at their optimum level by day two while the massed group was still catching up (Figure 5). This provides evidence that spaced training during TR3 was more beneficial in keeping performance consistent. It also highlights why there was a high difference between the spaced and massed group on day one of TR3 in percent correct scores and impulsivity performance.

The spaced group performing better in fewer days than the massed group leads into our hypothesis surrounding carry-over. Carry-over, once again, is defined as being able to take skills from one task and being able to apply it to another task or a harder version of that task. It was hypothesized that if a group, after performing well in one TR, performed just as well on the next TR's first day of training, carry-over had occurred. Literature on carry over effects has found that training attentiveness via cognitive video games has led to higher attentiveness in children with ADHD (Gray et al., 2012; Halperin et al., 2013; Lim et al., 2012). This study was able to replicate that literature from TR1 to TR3 for percent correct responses and premature responses.

Between day four of TR1 and the first day of TR3, the spaced group performed significantly better in their percent correct scores and also did not decrease in their premature responses, which were already quite low. The massed group on the other hand, performed the same in their percent correct scores and significantly increased in their premature responses. Therefore, it can be assumed since the spaced group was not performing too impulsively and was also performing better, the skills they gained at the end of TR1 carried over to TR3. The massed group though, was most likely still guessing how to perform correctly, highlighting their increased premature responses, but no increase in performance.

Yet percent correct scores began to decrease from day four of TR3 to the first day of TR4 and day four of TR4 to the first day of TR5. This indicates that TR4, for both groups, was much harder to train in, which is why little carry-over was seen into TR5 as well.

Premature responses, on the other hand, generally decreased until TR5. Therefore, both groups were continuously learning how to perform the task in the best way. The spaced group learned that less premature responses were better more soon though. This can be seen between day four of TR3 and the first day of TR3, where the spaced group's premature responses were already at their optimum level, and therefore unchanging, while the massed group started at a relatively higher point and caught up to the spaced group.

Overall, these findings highlight that spacing out attention by having a fewer number of trials necessary to complete in the 5CSRTT created a higher ability to pay attention, specifically during the simpler levels. Thus, there is support for the idea that spacing out training does not only have to revolve around memory it can revolve around attention.

Spacing attention should be instituted in future studies that use the 5CSRTT. If SHRs have the chance to perform more optimally more quickly, a lot of the time typically spent on training the rats to optimal performance could be alleviated (Asinof & Paine, 2014). Typically, rats train for weeks before they are able to move on to the next TR, but some of our spaced rats reached this optimal level well within four averaged days (Figure 5) (Asinof & Paine, 2014). Finally, spacing out attentiveness training in children or adults with ADHD could prove to be extremely beneficial. Future research should conduct a replication of this study with humans by spacing out cognitive training and seeing if attentiveness increases more effectively. Other learning tasks with SHRs should also be spaced out if researchers want SHRs to learn tasks more efficiently and for a longer period of time.

Sex Differences During TR1

It was originally predicted that males' percent correct scores would benefit more from spaced training than females due to literature indicating that male SHRs typically perform lower in this area (Bayless et al., 2015) and that spaced training can lead to higher performance (Commins et al., 2003; Grassi, 1971; Kerfoot et al., 2007; Kornmeier et al., 2014; Riches et al., 2005; Wang et al., 2014). The present study discovered that during TR1, spacing led to males performing significantly better on their percent correct scores than males who were massed while females did not significantly differ at all (Figure 4). Since spacing closed this gap, it can be hypothesized that males in the spaced condition did not lose focus as easily and were able to perform as consistently well as the females. There was also an approaching interaction during TR1 indicating that males in the massed condition were not performing as well across days of training than females in either condition or males in the spaced condition (Figure 5). Thus, further indicating that spacing was more beneficial for males' performance. Yet these findings were not significant across TRs, so sex only truly played a role in the beginning of training. Consequently, since this study only observed these sex differences when the rats were first introduced to the task, future studies should ask whether these sex and group interactions still occur after mastery of the task is attained. By instituting spacing at the highest level, both sexes and groups can enter with mastery versus no experience.

TR4 and TR5: Where Spacing was Ineffective

Spacing was expected to benefit training throughout all conditions. This is because, as training continues, attentional skill levels in the 5CSRTT have to increase to keep performance high. Furthermore, since spacing has been shown to increase retention of information after learning, we predicted that spacing attention during simpler levels would increase attention during harder levels (Kerfoot et al., 2007). Yet once TR4 and TR5 were reached, the main effects of spacing went away. Both groups during TR4 did not significantly change over days, so it is possible that both groups needed more time to train, especially since TR4 is highly different from TR3 in stimulus time and limited hold (Table 1). Along with this, TR5 showed a significant difference across days, but not as significant as TR1 and TR3. So, though they did improve, the amount at which they did improve was not as high. Therefore, some learning had occurred in TR4 in relation to how the new test would work, but it was not effective enough in creating an effect of spacing or a carry-over into TR5.

Therefore, future studies should space out trials over more days during the harder TRs. For example, a study could institute 45 trials per day for 16 days instead of eight days during TR4 to see if spacing could increase performance. This may also lead to higher carry-over during the open field or other exploratory memory tasks. Along with this, many reward-based tasks have used shorter intertrial intervals of about 10 minutes when doing spacing in rats (Elmes et al., 1979; Lattal, 1999). Since the 5CSRTT is also reward-based, it is possible these short intertrial intervals could be more beneficial. Additionally, short intertrial intervals are more similar to giving a child with ADHD a break (Chaney, 2005; McGinley, 2011; Weslake & Christian, 2015; Reiber & McLaughlin, 2004).

Open Field

Females were expected to be more active in the open field (Chelaru et al., 2012; Cierpial et al., 1989). We replicated these findings with the females displaying higher activity in the open field than males in both rearing and distance traveled. If future studies plan to use both female and male SHRs, this significant sex difference in activity should be taken into account.

There was also an expectation that cognitive training in the 5CSRTT would decrease hyperactivity because human studies that instituted cognitive training saw a decrease in hyperactivity and ADHD symptoms (Halperin et al., 2013; Lim et al., 2012). No published study prior to this one had looked directly at whether hyperactivity symptoms decreased in SHRs after instituting training in the 5CSRTT. Along with this, in our lab it has been found that more hyperactive SHRs took longer to reach criterion levels of performance in the 5CSRTT. Fundamentally, if hyperactivity influences attention, it was predicted that attention may also influence hyperactivity. Unexpectedly, the distance traveled in the open field was found to significantly increase after training occurred in 5CSRTT while rearing significantly decreased. Though rearing did decrease, it was essential for both to decrease to emphasize a decrease in hyperactivity. Most importantly, no group differences were found in rearing or distance traveled, meaning spacing did not decrease hyperactivity levels as it was expected to. Also, being in the spaced or massed condition did not decrease hyperactivity more in one sex than another. Largely, attention training did not carry-over to influence hyperactivity.

Yet, it is also possible that carry-over from attention to hyperactivity in SHRs is not relevant. When a follow up statistic was run to compare performance on the 5CSRTT to open field activity, no correlation was noted. The original data that correlated performance and activity in the open field looked at days the rat spent mastering the training level against distance traveled. Our correlations, differing in how we measured performance, could explain why significance was not found. Yet, it is also possible hyperactivity did not influence learning scores at all. On the other hand, we did replicate the literature that emphasizes how the SHR's hyperexploratory nature in the open field leads to a lack of habituation and therefore no decrease in activity (Knardahl & Sagvolden, 1979). If future studies wish to decrease hyperactivity or this hyperexploratory nature, then it would make sense to institute more intense cognitive training to see if this decrease occurs. Yet future studies may also choose to not use the open field since hyperactivity in the SHR may not significantly influence performance.

Object Displacement

It was hypothesized that the spaced group would be able to recognize the displaced object better than the massed group. This effect was expected to occur due to the massed group habituating over the four trials more quickly than the spaced group (Bello-Medina et al., 2013; Commins et al., 2003). Spreading out introduction to the arena for the spaced rats was supposed to make it equally stimulating each time, while repeated exposure to the arena was supposed to decrease stimulation for the massed rats. Also, no sex differences were expected to occur due to no sex differences in object displacement being found in previous literature (Seib et al., 2018). However, previous studies that have instituted spacing have also mainly observed male Sprague-Dawley rats (Bello-Medina et al., 2013; Commins et al., 2003). This is one of the first studies to give SHRs spaced practice in the object displacement task and to explicitly look for sex effects.

Both groups were able to recognize that the object was displaced (Figure 8). Therefore, the rats' memories were functional, and they were able to properly perform the task. As expected, females and males did not differ in the percent of time they spent with each object, highlighting that both sexes explored the objects equally and, therefore, remembered their placement equally. Yet the massed and spaced rats did not differ in their ability to recognize that the object was displaced. Since the massed and spaced group both lacked habituation during the task, both groups got equal exposure to each object. Typically, the massed group experiences habituation during the third and fourth trials while the spaced group does not, but this has only been shown in non-ADHD type rats (Commins et al., 2003). Yet since the SHRs had low habituation, they spent about the same amount of time with each object across all four trials (Figure 7). Future studies should use a memory task that does not rely on exploratory behaviors to control for this aspect of the SHRs.

Conclusions

Spacing was beneficial during 5CSRTT learning. Giving the spaced group fewer trials to focus on in each session increased their ability to pay attention and therefore improved their overall score. ADHD is a disorder that pervades many children's academic lives because of their difficulties with maintaining focus (American Psychiatric Association, 2013; Ek et al., 2011; Schneider et al., 2010; Smith et al., 2006). Right now, there are few published studies that look at spacing out a child's focus to increase their academic performance. If spacing is instituted in school settings, an increase in academic performance for children with ADHD could be observed. Furthermore, if spacing is given during attentiveness training, training that has been proven to reduce ADHD symptoms, there is a high possibility the training could be more effective (Gray et al., 2012, Halperin et al., 2013, Lim et al., 2012). Helping children with ADHD does not have to preferentially involve giving medication, it can also circulate around changing systems or practices that currently do not benefit those with ADHD.

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