THE EFFECT OF STRESS ON SPATIAL LEARNING IN RATS

By

Rebecca Wyckoff Kim

Submitted to the

Faculty of the College of Arts and Sciences

of American University

in Partial Fulfillment of

the Requirements for the Degree of

Master of Arts

In

Psychology

Chair:

Maria Gomez, Ph.D.

David Kearns, Ph.D.

Alan Silberberg, Ph.D.

Dean of the College of Arts and Sciences

April 25, 2012

Date

2012

American University

Washington, D.C. 20016

THE EFFECT OF STRESS ON SPATIAL MEMORY IN RATS

BY

Rebecca Wyckoff Kim

ABSTRACT

Research investigating the effects of stress on spatial learning and memory in rats is conflicting and often unclear. Some research indicates that the length of time or frequency of stress induction has an effect on rats' ability to learn and remember a spatial memory task. Other research indicates that the type of stressor plays an important role. In this experiment, the role of housing, individual or group, along with induction of restraint stress was examined. Lew and F344 rats were divided in four groups based on housing (single v. grouped) and experimental condition (restraint stress v. non-restraint control) and tested on a Morris water maze. The results indicated that, in general, F344 rats learned and remembered the maze better than the Lew rats. In both strains, the group-housed rats performed better during the acquisition trials than the single-housed rats. These results provide interesting insight into how housing conditions and rat strain play a role in learning and memory tasks.

TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

CHAPTER 1

INTRODUCTION

Research on the effect of stress on learning and memory is often conflicting, as the results of different studies show that the cause and duration of stress, the strain of the rat and the housing conditions all play important roles in the outcome (Simpson & Kelly, 2011; Schwabe, Schächinger, & Oitzl, 2008; Sadowski, Jackson, Wieczorek, & Gold, 2009; De Quervain, Roozendaal, & McGaugh, 1998; Sunanda, Shankaranarayana, & Raju, 2000). It has been shown that stress increases blood levels of corticosterone (Sternberg, Glowa, Smith, Cologero, Listwak, Aksentjevich, Chrousos, Wilder, & Gold, 1992; Freed, Martinez, Sarter, De Vries & Bergdall, 2008; Wu & Wang, 2010) and that this increase in corticosterone influences cognitive functions, such as learning and memory (Nooshinfar, Akbarzdeh-Baghban & Meisami, 2011; Harrison, Hosseini & McDonald, 2009).

Certain housing conditions, such as being housed in cages with wire bottoms, being housed singly, or overcrowded housing have been shown to be a source of stress (Freed et al., 2008; Simpson & Kelly, 2011; Sternberg et al., 1992; Wu & Wang, 2010). For example, Freed et al. (2008) demonstrated that animals housed in wire cages, as compared to rats housed in solid bottom cages, had "enhanced and prolonged responses" to acute restraint stress as measured by levels of corticosterone. Another possible source of stress is the number of rats housed together. Simpson and Kelly (2011) showed that the number of animals per cage itself could be considered a stressor. Individually housed rats often show "social isolation syndrome" with hyperactivity, poor adaptability, less exploration of new objects, and more anxiety (Simpson & Kelly, 2011). Whereas, rats housed in groups of between two and four performed between the levels of individually housed rats and rats that are housed in enriched environments (Simpson & Kelly, 2011).

Fischer (F344) and Lewis (Lew) inbred rats are commonly used in research to study stress. These two strains are characterized by their different response to stressors. Whereas F344 rats are hyper-responsive to stress, Lew rats are hypo-responsive to the same stimuli as expressed by lower levels of plasma corticosterone, plasma ACTH and hypothalamic CRH mRNA as compared to the F344 strain (Sternberg et al., 1992).

The effect of housing conditions in stress response was studied in F344, Lew and Sprague-Dawley rats (Wu & Wang, 2010). In this study, rats were doubly or singly housed. After rats were exposed to chronic mild stresses (e.g., small cage, a crowded cage with two extra rats in it, overnight water deprivation), F344 and Sprague-Dawley strains were found to have significantly higher corticosterone levels than the controls. The authors additionally found that the corticosterone levels were elevated in the singly-housed control groups for both Sprague-Dawley and Fischer rats as compared to the corresponding doubly-housed control groups (Wu & Wang, 2010). Lewis rats showed no significant difference in corticosterone levels between the singly-housed control, the doubly-housed control or the experimental group. In addition to demonstrating that both the strain and housing environment are important in the outcome, this study indicates that the corticosterone levels of F344 and Sprague-Dawley rats were affected by housing and chronic mild stress. Although there is a large amount of research done with these strains on stress, there is less research addressing the relationship between strain differences and learning and memory.

Based on this research, it is apparent that housing conditions affect the stress levels of the animals as indicated by their higher levels of corticosterone. The question of how higher levels of corticosterone effect memory and learning tasks remains. By using these different strains of

rats, this study will be able to examine how inherent sensitivity to stress affects the learning and memory.

Conrad et al. (2007) showed that chronic elevation of glucocorticoids can increase neurotoxin-induced damage to CA3 cells in the hippocampus. These results indicate that long-term glucocorticoid elevation may make CA3 damage by chronic stress worse (Conrad et al., 2007).

Studying how corticosterone affects memory performance in rats, McLay, Freeman, and Zadina (1998) examined rat performance in the Barnes maze. The authors exposed the rats for 80 days to corticosterone through CORT-secreting pellets (controls received control pellets). This administration of corticosterone was thought to elevate corticosterone levels similar to those of chronic stress (McLay et al., 1998). After 16 trials, the authors demonstrated that both control and experimental rats were capable of learning the Barnes maze, however, a significant difference was observed between CORT-treated and control animals as measured in errors, distance to escape, ambulatory time to escape and time to escape. In all cases, CORT-treated animals performed worse than the controls (McLay et al., 1998). The authors concluded that the poorer performance in Barnes maze after corticosterone treatments is due to cognitive impairment. The authors further argue that, because of HPA-axis activation due to stress such as the Morris water maze or other external stressors, it is possible that over shorter periods of time stress can improve learning and memory (McLay et al., 1998).

Thus far, I have described how a chronic artificial increase in corticosterone levels negatively affects the performance maze tasks. Corticosterone levels can also be elevated by immobilization (both chronic and acute) (Nooshinfar et al., 2011). Nooshinfar et al. (2011) exposed male Wistar rats to either acute immobilization (1 hour, 3 hours or 5 hours) or chronic

immobilization (2 hours a day for a week) to study the effects of immobilization on corticosterone levels and learning. Learning was evaluated through step-through latency in a passive avoidance procedure. The authors found that both the 5-hour and the long-term exposure immobilization stress caused significant increases in corticosterone levels. Learning was positively affected by 3- and 5-hour immobilization but was negatively affected in the chronically immobilized group. These results demonstrate that immobilization can increase corticosterone secretion and also may decrease memory.

The objective of the present experiment is to assess how stress induced by restraint and housing conditions affects learning and spatial memory of rats as tested in a water maze task.

CHAPTER 2

METHODS

Subjects

Twenty-four F344 rats and twenty-four Lewis male rats approximately 8 months old were obtained from Harlan Sprague-Dawley (Indianapolis, IN). The rats were housed in two different conditions: individually (n=24, 12 F344 and 12 Lew) or in groups of 3 (n=24, 12 F344 and 12 Lew). The individually housed rats were in stainless steel, wire-mesh hanging cages (24.3 X 19 X 18cm). The group-housed rats were in plastic bins (48 cm X 27 cm X 20 cm). All animals were maintained on a 12/12 hr light/dark cycle, with lights off at 1000 h and on at 2200 h and at an ambient temperature of 23°C. Rat chow and water were available ad libitum at all times in the home cage. Guidelines established by the Institutional Animal Care and Use Committee at American University were followed.

Procedure

Acquisition Trials

Rats in all conditions were transported to the testing room in their home cages. For those who were group-housed, their grouping was maintained throughout training and testing in the Morris water maze task and during restraint (if in the experimental group). Rats were trained and tested on the water maze task between 1100 h and 1500 h. In the group-housed rats, rat 1 was placed into the water maze and allowed to explore and search for the hidden platform for 60 seconds. The other rats from the grouping remained in their home cage during this first acquisition trial. At the conclusion of that time, if the rat had not found the platform, it was placed on the platform for ten seconds. The rat was then dried off and allowed to rest during the first acquisition trials of the other two rats from the same housing bin. Rat 2 was then introduced

to the maze following the same procedure as with Rat 1. Once Rat 2 had completed acquisition trial 1, it was dried off and allowed to rest alongside Rat 1 while Rat 3 completed its first acquisition trial. This cycle was continued until each rat had completed six acquisition trials to allow for learning and memorization of the maze.

The same procedure was followed for individually housed rats and their six acquisition trials. Rats were given the same amount of time between acquisition trials as were given to the group-housed rats.

Restraint

One week after the rats were trained in the Morris water maze, rats in the experimental group were subjected to one hour of restraint in a transparent plastic restrainer (68 mm diameter). Control rats were left undisturbed in their home cage.

Post-restraint water maze test

After restraining, the rats were removed from the tube and immediately placed into the water maze. They were given 60 seconds to locate the platform. Upon locating the platform or the conclusion of the 60 seconds, the rat was removed from the water maze, dried off and returned to the home cage.

Control rats were maintained in their home environments until testing time where they were also given 60 seconds to locate the platform and then returned to the home cage.

Data analysis

For determination of statistical significance, $\alpha = 0.05$. To assess strain differences in learning, data was analyzed using a 2 X 2 X 6 repeated measures ANOVA with the between-subjects variable of Strain (F344 and Lew) and Housing Condition (Single and Group-housed)

and the within-subjects variable of Trial (1-6) followed by t-tests when appropriate. To investigate the effects of stress on memory, a 2 X 2 X 2 ANOVA was used with the between-subjects variable of Strain (F344 and Lew), Housing Condition (Single and Group-housed) and Condition (Stressed and Control) followed by t-tests when appropriate.

CHAPTER 3

RESULTS

Trials

A 2 X 2 X 6 repeated measure ANOVA performed on these data revealed significant effects of strain ($F(1,44)=16.183$, $p<0.001$), housing ($F(1,44)=40.867$, $p<0.001$) and trial ($F(1,44)= 40.496$, $p = 0.000$). There was a significant interaction between strain, housing and trial ($F(1,44)= 7.974$, $p = 0.007$) with the F344 rats being faster than the Lew rats to find the platform and housed group rats being faster than their single-housed counterpart. Moreover, in general, all groups except Lew single-housed rats showed a reduction in the time to find the platform across acquisition trials. Specifically, the Lew single rats were significantly slower than the Lew grouped rats in trial 3 ($p=0.034$), trial 5 ($p=0.0015$), and trial 6 ($p=0.000068$). Moreover, whereas Lew single rats did not show an improvement across trials, Lew grouped rats became faster in locating the platform across trials, showing significant improvement in trial 4 ($p=0.0097$), trial 5 ($p=0.00005$), and trial 6 ($p=0.00013$). (See Fig. 1)

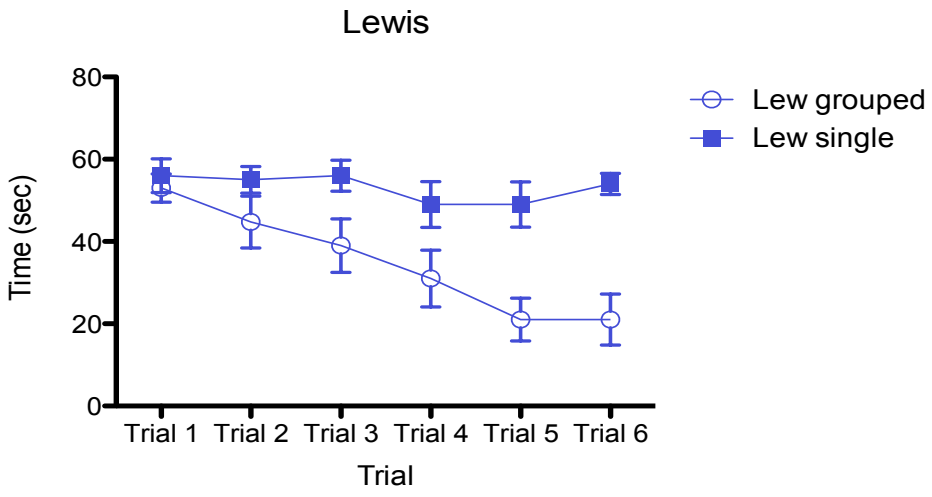

Figure 1. Time (sec) for Lewis rats to locate the platform in Morris water maze over six acquisition trials.

In the case of the F344 strain, we observed that the single-housed animals were significantly slower than the grouped housed ones in trial 1 (p=0.028), trial 2 (p=0.0016), trial 3 (p=0.0195), and trial 5 (p=0.031). Interestingly, both the single-housed (p=0.027) and the group-housed F344 rats (p=0.035) showed a significant improvement in performance over the six trials in locating the platform. (See Fig. 2)

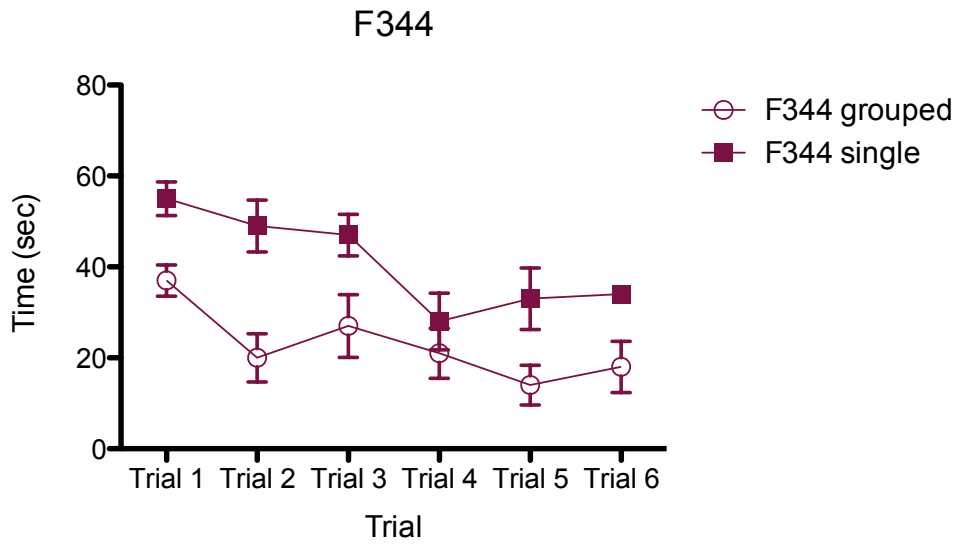

Figure 2. Time (sec) for Fischer rats to locate the platform in Morris water maze over six acquisition trials.

Test

A one-way ANOVA performed on this data revealed significant effects of strain ($F(1,40)=20.926$, $p = 0.00$) at test with the F344 rats of both housing condition performing better at test than the Lew rats in both housing conditions. There was not significant effect of housing and stress condition (all p's > 0.05). There was no significant interaction between strain, housing and stress condition ($F(1,40) = 1.189$, $p = 0.185$).

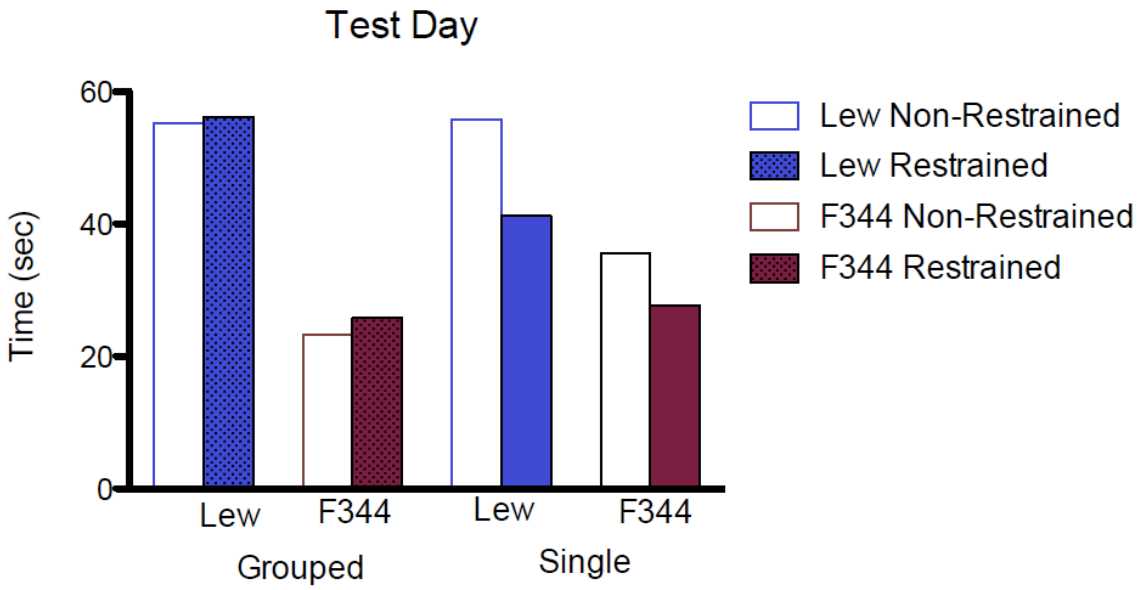

Figure 3. Time (sec) for Lewis and Fischer rats to locate platform in Morris water maze on test day. Groups divided by housing condition and by restrained vs non-restrained control condition

CHAPTER 4

DISCUSSION

The present study found that housing conditions and strain are significant factors in the ability of rats to learn a Morris water maze. Further, the results indicate that F344 rats learned faster over trials than Lew rats and that group-housed rats of each strain learn faster than single-housed rats of each strain.

Additionally, the study showed significant effects of strain at test in the Morris water maze. As compared to the prior results examining learning of the water maze task, these results showed that F344 rats are better able to remember the Morris water maze task at test than the Lew rats. With regard to the induction of stress, there were mixed results. For the Lew rats, the single-housed rats that were exposed to restraint stress performed better than the control group.

Strain

It has been well established that F344 and Lew rats differ in their HPA-axis response to stress. Specifically, F344 rats are hyper-responsive to stress whereas Lew rats are hypo-responsive to the same stimuli (Sternberg et al., 1992) as measured by their lower corticosterone levels, hypothalamic CRH mRNA expression and plasma ACTH levels. Sternberg et al. (1992) also measured the different behavioral responses to stressors such as open field test and swim test, finding that Lewis rats have a significantly more difficult time than the Fischer rats in a swim test in which the rats were placed in the water to evaluate if they would stay afloat for the twenty minute test period (Sternberg et al., 1992). It is of note that the behavioral differences were directly correlated to the detected hormonal differences, with Lew rats having significantly lower plasma corticosterone, plasma ACTH, and hypothalamic CRH mRNA levels than the F344

in response to the stressor. Sternberg et al. (1992) data suggested that differential endogenous CRH levels in Lew and F344 rats might contribute to behavioral differences.

In the present study, we observed that F344 rats are faster in the water maze than Lew. These results are not surprising given that the Morris water maze itself is considered a stressor (McLay et al., 1998) and it has been shown that short periods of stress can in fact improve learning (Harrison et al., 2009). Given that F344 rats are hyper-responsive to stress and Lew rats are hypo-responsive to the same stimuli, the task itself (with the stress associated with it) may have facilitated the learning in F344 rats but not in the Lew rats. Moreover, while conducting the experiment the researcher observed that F344 rats are in general better swimmers than Lew rats. This phenomenon has been also described by Sternberg et al., (1992). The current research does not examine how speed of swimming acted as a factor in the results of learning and memory. This limitation could be further investigated by evaluating distance swam to platform or number of errors in a future study. It is possible that the differences observed between strains are not only caused by the HPA-axis but also by a natural predisposition to swim in the F344 strain.

F344 rats were not only better than Lew in the learning phase of the maze task; they were also better at remembering at test. Further, the results indicate while that the Lew group-housed rats had learned the maze during acquisition trials, it appears that they forgot the solution at trial. F344 rats of both housing condition not only learned the maze during acquisition trials but also appeared to remember the solution at test. This issue of forgetting in the Lew rats is an interesting finding of the current study and could serve as a model of aging and memory.

Corticosterone has been shown to have a profound effect on both the structure and the function of the hippocampus and, therefore, corticosterone can modulate memory formations

(Schaaf, De Kloet, & Vreugdenhil, 2000). Although there are not studies in mature (up to 10 months) F344 and Lew rats on how the hippocampal changes due to stress affect learning; there have been studies with old F344 rats (31 months). These older rats remember the water maze task better when they were exposed to higher levels of corticosterone for periods of two weeks (Hebda-Bauer, Morano & Therrien, 1999). It is possible that corticosterone has the same effect on mature F344 and Lew rats in remembering the water maze task.

Housing

The results indicate additionally that the group-housed rats performed better in the learning aspects of the task across strains. Although initially these results may seem surprising given that isolated animals are more stressed than grouped house animals. For example, Wu and Wang (2010) found that the corticosterone levels of F344 rats were affected by housing, with those who were single-housed having higher corticosterone levels than double-housed groups. In the aspect of housing, higher corticosterone levels cannot be surmised as an explanation for better performance as the group-housed rats, who would have had lower corticosterone levels, performed better.

Within the scope of the current research examining how housing condition affect learning and memory, it is acknowledged that the use of two different housing cages poses a limitation. The group-housed rats were housed in plastic cages while the single-housed rats were housed in wire-mesh bottom cages. It is not known how this discrepancy in cage type affected results or if the discrepancy confounded the results at all. A follow up study using the same type of cage could be conducted to confirm the results of this study.

Filipovic, Zlatkovic, Pavicevic, Mandic, and Demajo (2012) showed that chronic isolation for 21 days caused unaltered corticosterone levels in Wistar rats. Moreover, the authors

showed that chronic isolation caused reduced response to a novel acute stressor, such as immobilization, as measured by corticosterone levels (Filipovic et al., 2012). Given that our rats were individually housed for 6 months, it is possible that their HPA-axis stopped or decreased the response to the particular stressor of isolation. This concept of the HPA axis, along with other adaptive systems in the body, becoming over or under active is called allostatic load (McEwen, 1998). Allostasis, an essential part of the maintenance of homeostasis, is the system that responds to the body's current state and to the external environment and promotes adaptation to the surroundings (McEwen, 1998). The HPA axis is very sensitive to allostatic changes. McEwen (2000) argues that unaltered corticosterone response to stressors is not healthy and can be caused by a general deregulation of the HPA-axis.

Moreover, this overexposure to stress or allostatic load, could also desensitize the rats' ability to respond to the acute stressor that was the Morris water maze task and affect their ability to learn the escape route. Furthering this idea and helping to explain why the singly housed rats are unable to learn the water maze task, McEwen (1999) indicates that repeated stress produces dendritic atrophy in the CA3 region of the hippocampus and can impair hippocampal-dependent learning. Even looking at human brain, recent evidence indicates that the human hippocampus is particularly sensitive and shows greater changes in response to stress than other brain areas do (McEwen, 1999).

While both Wu and Wang (2010) and Sternberg et al. (1992) found that Lew rats do not demonstrate significant differences in corticosterone levels with respect to stress levels, including those induced by housing condition, it may still follow that the group housing condition positively affected the Lew rats' abilities to perform in the learning task, explaining the results of this experiment.

Acute Stress

At test, it was found that the singly-housed rats in the restrained experimental condition performed better than the non-restrained control singly-housed rats for both strains. In the group-housed condition, the non-restrained control group performed better than the restrained experimental condition for both groups.

Little research has been found on the long-term effects of single housing of rats in terms of stress levels but research has demonstrated that single housing does cause elevated corticosterone levels (Wu & Wang, 2010). Von Frijtag et al (2000) looked at individual housing as a chronic stressor and saw the effects of this stressor up to three months after induction.

Further examining how single housing effects the behavior of rats, de Jong, van der Vegt, Buwalda, and Koolhaas (2005) demonstrated that animals housed alone after exposure to social defeat reacted more strongly than group-housed rats to various behavioral tests and also showed an increase in HPA activity. The authors speculated that social isolation may induce hyper-responsiveness to relatively mild stressors (de Jong et al, 2005). If this was true, it could be extrapolated that, in this experiment, the singly housed rats were more sensitive to the restraint stress, which then positively affected their performance in the water maze, perhaps through an increase in corticosterone levels which enhanced their memory retrieval.

Other explanations

In reflecting on the results of this experiment, it is possible that other biological factors are being affected by stress exposure and could play a role in the memory storage and retrieval. Das, Rai, Dikshit, Palit, and Nath (2005) showed that acetyl cholinesterase activity in the brain areas and memory function of rats was dependent on the nature of the stressors. The authors found that chronic-unpredictable stress was more effective in decreasing the AChE activity in all

areas of the brain except in the hippocampus than the chronic-predictable and acute stressor paradigms (Das et al., 2005). AChE raises acetylcholine levels in the brain, which help maintain cognitive functions. Additionally, in these rats, there was a degeneration of the hippocampal cholinergic neurons that are important in cognitive behavior. If there is no AChE activity in the hippocampus in the chronic-unpredictable paradigm resulting in the impairment of memory, it could indicate that AChE is an important factor in stress and learning and memory paradigms.

REFERENCES

Amir, N. & Bomyea, J. (2011). Working Memory Capacity in Generalized Social Phobia. *Journal of Abnormal Psychology*, 1-6. doi: 10.1037/a0022849

Belda, X., Márquez, C., & Armario, A. (2004). Long-term effects of a single exposure to stress in adult rats on behavior and hypothalamic-pituitary-adrenal responsiveness: comparison of two outbred rat strains. *Behavioural Brain Research*, *154*, 399-408.

Bentz, D., Michael, T., Dominique, J.F.Q., & Wilhelm, F.H. (2010). Enhancing exposure therapy for anxiety disorders with glucocorticoids: From basic mechanisms of emotional learning to clinical applications. *Journal of Anxiety Disorders, 24*, 223-230.

Conrad, C.D., McLaughlin, K.J., Harman, J.S., Foltz, C., Wieczorek, L., Lightner, E., & Wright, R.L. (2007). Chronic glucocorticoids increase hippocampal vulnerability to neurotoxicity under conditions that produce CA3 dendritic retraction but fail to impair spatial recognition memory. *The Journal of Neuroscience, 27* (31), 8278-8285.

Das, A., Rai, D., Dikshit, M., Palit, G., & Nath, C. (2005). Nature of stress: Differential effects on brain acetylcholinesterase activity and memory in rats. *Life Sciences, 77*, 2299-2311.

de Jong, J.G., van der Vegt, B.J., Buwalda, B., & Koolhaas, JM. (2005). Social environment determines the long-term effects of social defeat. *Physiology and Behavior, 84*, 87-95.

de Quervain, D. J.-F., Roozendaal, B., & McGaugh, J.L. (1998). Stress and glucocorticoids impair retrieval of long-term spatial memory. *Nature, 394*, 787-790.

Duclot, F., Hollis, F., Darcy, M.J., & Kabbaj, M. (2011). Individual differences in novelty-seeking behavior in rats as a model for psychosocial stress-related mood disorders. *Physiology & Behavior*, 1-10. doi:10.1016/j.physbeh.2010.12.014

Duncko, R., Johnson, L., Merikangas, K., & Grillon, C. (2009). Working memory performance after acute exposure to the cold pressor stress in healthy volunteers. *Neurobiology of Learning and Memory, 91*, 377-381.

Eysenck, M.W., Santos, R., Derakshan, N., & Calvo, M.G. (2007). Anxiety and cognitive performance: Attentional Control Theory. *Emotion, 7*(2) 336-353.

Filipovic, D., Zlatkovic, J., Pavicevic, I., Mandic, L., & Demajo, M. (2012). Chronic isolation stress compromises JNK/c-Jun signaling in rat brain. *Journal of Neural Transmission*, DOI 10.1007/s00702-012-0776-0.

Freed, C., Martinez, V., Sarter, M., De Vries, C., & Bergdall, V. (2008). Operant task performance and corticosterone concentrations in rats housed directly on bedding and on wire. *Journal of the American Association for Laboratory Animal Science, 47*(5), 18-22.

Harrison, F.E., Hosseini, A.H., & McDonald, M.P. (2009). Endogenous anxiety and stress responses in water maze and Barnes maze spatial memory tasks. *Behavioral Brain Research, 198*, 247-251.

Hawley, W.R., Grissom, E.M., & Dohanich, G.P. (2011). The relationship between trait anxiety, place recognition memory, and learning strategy. *Behavioural Brain Research, 216*, 525-530.

Hebda-Bauer, E.K., Morano, M.I., & Therrien, B. (1999). Aging and corticosterone injections affect spatial learning in Fischer-344 x Brown Norway rats. *Brain Research, 827*(1-2), 93-103.

Joëls, M., Pu, Z., Wiegert, O., Oitzl, M.S., & Krugers, H.J. (2006). Learning under stress: How does it work? *Trends in Cognitive Sciences, 10*(4), 152-158.

Katz, R.J., Roth, K.A., & Carroll, B.J. (1980). Acute and chronic stress effects on open field activity in the rat: Implications for a model of depression. *Neuroscience and Biobehavioral Reviews, 5*, 247-251.

Kirschbaum, C., Pirke, K.M, & Hellhammer, D.H. (1993). The 'Trier Social Stress Test'- a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology, 28*(1-2), 76-81.

McEwen, B.S. (1998) Stress, adaptation and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences, 840*, 33-44.

McEwen, B.S. (1999). Stress and hippocampal plasticity. *Annual Review of Neuroscience, 22*, 105-122.

McEwen, B.S. (2000). Protective and damaging effects of stress mediators: central role of the brain. *Biological Basis for Mind Body Interactions, 122*, 25-34.

McGuire, J., Herman, J.P., Horn, P.S., Sallee, F.R., & Sah, R. (2010). Enhanced fear recall and emotional arousal in rats recovering from chronic variable stress. *Physiology & Behavior, 101*(4), 474-482.

McLay, R.N., Freeman, S.M., & Zadina, J.E. (1998). Chronic corticosterone impairs memory performance in Barnes maze. *Physiology & Behavior, 63*(5), 933-937.

Meerlo, P., Overkamp, G.J.F., Benning, M.A., Koolhaas, J.M., Van Den Hoofdakker, R.H. (1996). Long-Term changes in open field behaviour following a single social defeat in rats can be reversed by sleep deprivation. *Physiology & Behavior, 60*(1), 115-119.

Nooshinfar,E., Akbarzdeh-Baghban, A., & Meisami, E. (2011) Effects of increasing durations of immobilization stress on plasma corticosterone level, learning and memory and hippocampal BDNF gene expression in rats. *Neuroscience Letters, 500*, 63-66.

Park, C.R., Campbell, A.M., & Diamond, D.M. (2001). Chronic psychosocial stress impairs l earning and memory and increases sensitivity to Yohimbine in adult rats. *Biological Psychiatry, 50*, 994-1004.

Sadowski, R.N., Jackson, G.R., Wieczorek, L., & Gold, P.E. (2009). Effects of stress, corticosterone, and epinephrine administration on learning place and response tasks. *Behavioral Brain Research, 205*, 19-25.

Schaaf, M.J., De Kloet, E.R., & Vreugdenhil, E. (2000). Corticosterone effects on BDNF expression in the hippocampus. Implications for memory formation. *Stress, 3*(3), 201-208.

Schutsky, K., Ouyang, M., Castelino, C.B., Zhang, L., & Thomas, S.A. (2011). Stress and glucocorticoids impair memory retrieval via β_2-Adrenergic, $G_{i/o}$-coupled suppression of cAMP signaling. *The Journal of Neuroscience, 31*(40), 14172-14181.

Schwabe, L., Dalm, S., Schächinger, H., & Oitzl, M.S. (2008). Chronic stress modulates the use of spatial and stimulus-response learning strategies in mice and man. *Neurobiology of Learning and Memory, 90*, 495-503.

Schwabe, L., Oitzl, M.S., Philippsen C., Richter, S., Bohringer, A., Wippich, W., & Schächinger, H. (2007). Stress modulates the use of spatial versus stimulus-response learning strategies in humans. *Learning & Memory, 14*, 109-116.

Simpson, J. & Kelly, J.P. (2011). The impact of environmental enrichment in laboratory rats – Behavioural and neurochemical aspects. *Behavioural Brain Research, 222*, 246-264.

Sternberg, E.M., Glowa, J.R., Smith, M.A., Cologero, A.E., Listwak, S.J., Aksentjevich, S., Chrousos, G. P., Wilder, R.L., & Gold, P.W. (1992). Corticotropin releasing hormone related behavioral and neuroendocrine responses to stress in Lewis and Fischer rats. *Brain Research, 570*(1-2), 54-60.

Sunanda, B.S., Shankaranarayana, R., & Raju, T.R. (2000). Chronic restraint stress impairs acquisition and retention of spatial memory task in rats. *Current Science, 79*(11), 1581-1584.

van der Harst, J.E., Baars, A., & Spruijt, B.M. (2003). Standard housed rats are more sensitive to rewards than enriched housed rats as reflected by their anticipatory behavior. *Behavioural Brain Research, 142*, 151-156.

Von Frijtag, J.C., Rijmers, LG.J.E, Van der Harst, J.E., Leus, I.E., Van den Bos, R., & Spruijt, B.M. (2000). Defeat followed by individual housing results in long-term impaired reward- and cognition-related behaviours in rats. *Behavioural Brain Research, 117*, 137-146.

Woodson, J.C., Macintosh, D., Fleshner, M., &Diamond, D.M. (2003). Emotion-induced amnesia in rats: Working memory-specific impairment, corticosterone-memory correlation, and fear versus arousal effects on memory. *Learning and Memory, 10*, 326-336.

Wu, H.H., Wang, S. (2010). Strain differences in the chronic mild stress animal model of depression. *Behavioural Brain Research, 213*, 94-102.