GENETICALLY DETERMINED POOR AEROBIC CAPACITY IS DETRIMENTAL FOR FLEXIBLE COGNITION

Ekman Carita
Hjelm Sini
Master's thesis
Department of Psychology
University of Jyväskylä
April 2013

UNIVERSITY OF JYVÄSKYLÄ
Department of Psychology

EKMAN, CARITA & HJELM, SINI: Genetically determined poor aerobic capacity is detrimental for flexible cognition
Master's thesis, 19 p.
Supervisor: Jan Wikgren
Psychology
April 2013

Several studies have shown that physical exercise has positive impacts on both humans' and animals' cognitive abilities, such as learning. Especially the genome that underlies aerobic capacity has been found to have an effect on learning. However, it is unclear if the poor aerobic capacity impairs learning or if the good aerobic capacity enhances it. In this study we aim to find out if the HCR (high capacity runner) rats that have been selectively bred by their good aerobic capacity really perform better than Sprague Dawley (S-D) rats that have not been bred selectively for any special ability or phenotype. We also want to investigate if poor physical condition could affect learning. If this poor aerobic capacity has greater effect on learning than good aerobic capacity has the LCR (low capacity runner) rats that are selectively bred by their poor aerobic capacity learn significantly worse than the S-D and the HCR rats.

The data consisted of eight Sprague Dawley rats that participated in a discrimination-reversal experiment. In the discrimination phase two different auditory conditioned stimuli (CSs) were presented to the rats. After one CS the rats received food while the other CS signaled nothing. In the reversal phase the meaning of the CSs was reversed and the rats were supposed to learn a new rule in order to get the food reward. With this experiment we measured rats' flexible learning. We compared our results with Wikgren et al. (2012) study where the LCR and the HCR rats were trained in the same task.

Our results showed that the S-D rats' performance profile resembled that of the HCR rats and that they were significantly better learners than the LCR rats in the flexible cognition task. It can be inferred from these results that good fitness does not always predict better learning outcomes. Instead, it seems that genome coding for poor physical fitness may have a detrimental impact on flexible learning.

Keywords: Flexible cognition, aerobic capacity, learning, discrimination-reversal conditioning

JYVÄSKYLÄN YLIOPISTO
Psykologian laitos

EKMAN, CARITA & HJELM, SINI: Geneettisesti määräytynyt heikko aerobinen kapasiteetti heikentää joustavaa kognitiota
Pro gradu -tutkielma, 19 s.
Ohjaaja: Jan Wikgren
Psykologia
Huhtikuu 2013

Monet tutkimukset osoittavat, että fyysisellä harjoittelulla on myönteisiä vaikutuksia sekä ihmisten että eläinten kognitiivisiin kykyihin, kuten oppimiseen. Erityisesti aerobisen kapasiteetin taustalla olevan geeniperimän on todettu vaikuttavan oppimiseen. On kuitenkin epäselvää, johtuuko tämä geeniperimän ja oppimisen välinen suhde siitä, että huono aerobinen kapasiteetti heikentää oppimista vai siitä, että hyvä aerobinen kapasiteetti tehostaa sitä. Tarkoituksenamme onkin selvittää, suoriutuvatko aerobisen kapasiteetin perusteella jalostetut hyväkuntoiset HCR (high capacity runner) rotat todella paremmin joustavan oppimisen tehtävässä kuin Sprague Dawley (S-D) rotat, joita ei ole jalostettu minkään erityisen kyvyn tai fenotyypin mukaan. Tutkimme myös, voiko huonolla kunnolla olla suurempi vaikutus oppimiseen, jolloin heikon aerobisen kapasiteetin perusteella jalostettujen LCR (low capacity runner) rottien oppiminen olisi merkitsevästi heikompaa kuin S-D ja HCR rottien oppiminen.

Tutkimusaineistoon kuului kahdeksan Sprague Dawley -rottaa, joille tehtiin erotteluoppimiseen pohjautuva discrimination-reversal -koe. Kokeen discrimination-vaiheen aikana rotille esitettiin kahta erilaista ääniärsykettä, joista toisen aikana rotta sai ruokaa ja toisen aikana ei. Reversal-vaiheessa äänien merkitykset käännettiin toisinpäin, jolloin rotan tuli oppia uusi sääntö ruoan saamiseksi. Tällä kokeella mitattiin rottien joustavaa oppimista. Saamiamme tuloksia verrattiin Wikgrenin ym. (2012) aikaisempaan tutkimukseen, jossa aerobisen kapasiteetin perusteella jalostettujen rottien oppimiskykyä tutkittiin edellä mainitulla kokeella.

Tulokset osoittivat, että S-D rotat suoriutuivat joustavan kognition tehtävästä yhtä hyvin kuin HCR rotat ja huomattavasti paremmin kuin LCR rotat. Tästä voidaan päätellä, että hyvä kunto ei aina takaa parempia oppimistuloksia, vaan näyttäisi siltä, että huonokuntoisuuden taustalla oleva geeniperimä aiheuttaa vaikeuksia joustavassa oppimisessa.

Avainsanat: Joustava kognitio, aerobinen kunto, oppiminen, discrimination-reversal ehdollistaminen

CONTENTS

1. INTRODUCTION

It has been noticed in several studies that physical exercise has an effect on brain function and structure that underlie learning (Antunes et al., 2006; Colcombe et al., 2006; Cotman, Berchtold & Christie, 2007; Grace, Hescham, Kellaway, Bugarith & Russell, 2009; Hillman, Erickson & Kramer, 2008). It has been found both in humans and animals that exercise in infancy and adolescence can improve brain health and plasticity in general. For example, aerobic exercise in childhood could in later life enhance the resilience of the brain (Sibley & Etnier, 2003). This plasticity of the brain interrelates with learning and memory. Kim et al. (2004) studied how early-life exercise in rats induces neurogenesis in the dentate gyrus which locates in the hippocampus. This neurogenesis is most prevalent at young age. Snyder, Hong, McDonald and Wojtowicz (2005) suggest that hippocampal neurogenesis induced by exercise can enhance learning and memory potential in rats. This is why especially the early-life exercise is important to learning and other cognitive abilities. In other words the lack of exercise can make learning more difficult because thus the level of neurogenesis is lower when physical exercise is not boosting the emergence of new neurons.

Besides the physical exercise it has been noted that also a beneficial genome that promotes good physical condition can improve cognitive skills such as learning and memory (Wikgren et al., 2012). However, it has not been studied if the ones that are in good physical condition really have better cognitive abilities than the average population or are they equally good. Or could it be possible that the ones that have a detrimental genome that promotes poor physical capacity are worse than average? In the latter case, it would mean that there are no differences in learning between fit and average subjects but that the ones with inferior aerobic capacity are compromised in learning. In this study we compare

flexible learning in standard Sprague Dawley rats with previously studied rats (Wikgren et al., 2012) selectively bred for either low or high aerobic capacity.

Wikgren et al. (2012) studied how the above-mentioned variation of genomes and selective breeding affects flexible learning in rats. In their research they had two populations of rats that had been bred selectively by their running capacity. One population consisted of high-capacity runner (HCR) rats with the beneficial genome and the other of low-capacity runner (LCR) rats with the detrimental genome. Both rat populations were trained in two different kinds of tasks requiring flexible cognition. One of the tasks was the appetitive discrimination-reversal conditioning task in which rats were exposed to two auditory stimuli. In the discrimination phase the rats received food (two pellets) when conditioned stimulus (CS+) was presented while the other conditioned stimulus (CS-) was followed by nothing. In the reversal phase the assignment of stimuli was opposite. This means that now CS- was followed by food and CS+ predicted nothing. The other flexible cognition task was the alternating T-maze task in which the rats also had to learn two different kinds of rules in order to get food.

Wikgren et al. (2012) found out that the HCR rats learned the new rules quicker in the discrimination-reversal conditioning task and in the T-maze task so they were better in flexible learning than the LCR rats. The results of this study strongly support the idea that genome that regulates the aerobic capacity, is linked to flexible cognition but also better health and longevity. This better brain function, in this case the learning capacity, could rely on improved oxygen delivery to the brain. In conclusion, Wikgren et al. (2012) suggest that high aerobic capacity (i.e. beneficial genome) predicts better learning, but the study left it open whether the difference was because of enhanced learning ability of the HCR rats, worsened learning in the LCR rats, or both.

Also Green, Chess, Burns, Schachinger and Thanellou (2011) have examined the

effects of physical exercise on learning and memory but instead of selectively bred rats they used rats given physical activity in their study. They had two groups of rats: the first group had a possibility to exercise in a running wheel in their home cages and the other group did not have a chance to this kind of voluntary exercise. They found out that the rats without the possibility to work out performed worse in an eyeblink conditioning task than the exercise group. From these results it could be concluded that the lack of physical training can have a negative impact on eyeblink conditioning and maybe on learning and memory in general.

In our study we use the same above-mentioned discrimination-reversal design as Wikgren et al. (2012) and compare their results with Sprague Dawley (S-D) rats that have not been selectively bred for anything. In this way we try to find out whether the HCR rats are better or the LCR rats are worse than the S-D rats in the flexible cognition task. Thus, the idea is to study whether the S-D rats that represent "normal" rat strain perform similarly to the HCR or to the LCR rats that were studied by Wikgren et al. (2012). If the S-D rats outperform the LCR animals, we can conclude that genotype promoting poor aerobic capacity has a detrimental effect on flexible cognition. In contrast, if the HCR rats are superior to the S-D rats, it would suggest that genotype supporting high aerobic capacity is beneficial for learning.

2. METHODS

In this study we had 16 Sprague Dawley rats. They were all male and 7 months old. During the experiments the rats were on limited diet: the amount of food was restricted but water was always available. The rats' weights were observed during the experiments and it was taken care of that the weight did not reduce more than 15 % from the *ad lib* weight which was 350-420 grams. The rats were always fed after the daily experiments so that they would be hungry and motivated during the experiments. The animals were housed in separate cages in a room in which the lights were on for 12 hours per day. The experiments were conducted every day around noon when the lights were on. Before this study the rats had been subjects in another conditioning experiment.

For the appetitive discrimination-reversal conditioning task we used two aluminum chambers (24.5 x 23.0 x 20.0 cm) in which the rats were placed individually. There was a pellet magazine on one wall of each chamber and behind the magazine there was a speaker which delivered the conditioned auditory stimuli (CS+ and CS-). The intensity of the stimuli was 80 dB. In the discrimination phase for the half of the rats the CS+ stimulus was a continuous white noise and the CS- was a series of bursts of 50 ms sine tones that were repeated at 200 ms intervals. For the other half the CS+ was the bursts of sine tones and the CS- was the white noise. Thus the experimental design was counterbalanced between the animals. The duration of the CSs was 12 seconds. In the reversal phase the stimuli were presented in the exactly opposite way than it was in the discrimination phase. This means that the sound that predicted food in the discrimination phase now predicted nothing in the reversal phase and vice versa.

Before the actual experiments the rats were familiarized with the chamber and the pellet magazine by two daily magazine training sessions. Both sessions lasted for 20

minutes during which the rat received two pellets in the magazine every two minutes. After the magazine training eight rats with robust responses to the pellet delivery were selected for discrimination-reversal training.

The conditioning took 25 days (10 days for discrimination and 15 days for reversal). Each daily training session took about 50 minutes per rat and CS+ and CS- trials were randomly presented in 90-180 second intervals. The experiments consisted of 20 trials of which 10 were CS+ and 10 CS-. After the CS+ two pellets were delivered in the magazine while after the CS- nothing happened. Thus, in the discrimination phase the rats must learn a rule (which of the auditory stimuli predicts food) in order to get the food and in the reversal phase extinguish this old rule and learn a new one. The time the animal spent with its nose in the food magazine during the CSs was recorded as a measure of conditioned responding. This was measured by the breakage of the infrared beam inside the pellet magazine. The breakage was caused by the rat's nose when the rat came looking for food. AxoScope 9.0 was used to record magazine behavior and E-prime 1.2 was used to control for the stimulus timing.

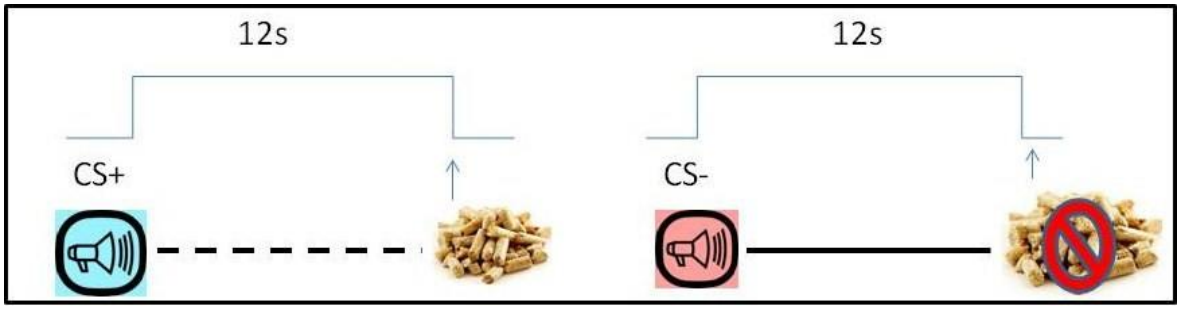

FIGURE 1. Experimental design of the discrimination phase (the design was counterbalanced between the groups)

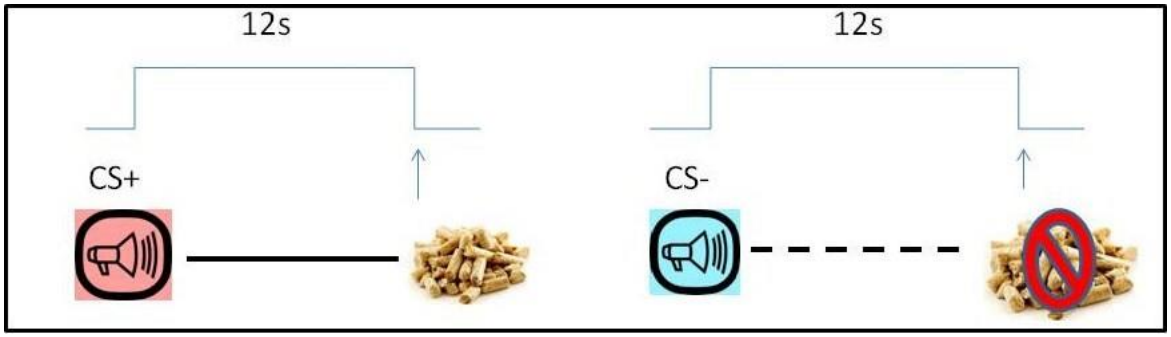

FIGURE 2. Experimental design of the reversal phase (the design was counterbalanced between the groups)

The raw data was first processed with MatLab 7.11 to extract the magazine behavior. After that the data was fed to the IBM SPSS Statistics 20 and analyzed by the analysis of variance for repeated measures (ANOVA) with the session and the trial type as within-subjects variables and the time the rats spend in the pellet magazine during the CSs as a dependent variable. By this we examined how the conditioning affects learning. In the analysis the trial type had two levels (CS+ and CS-) and the session had 10 levels in the discrimination phase and 15 levels in the reversal phase.

Our data was compared with the earlier data that Wikgren et al. (2012) collected and presented in their study. In this part of analysis we used ANOVA for repeated measures with discrimination ratios (DRs) of the reversal phase as a within-subjects variable, having 15 levels, and the group (S-D, HCR and LCR rats, three levels) as a between-subjects factor. This discrimination ratio (DR) which consists of the rats' responses to the CSs is one possible way to define the learning. These responses consist of the total time that the rats spend in the pellet magazine during the last nine seconds of the CSs. The discrimination ratio is formed as follows:

$$DR = \frac{R^+}{R^+ + R^-}$$

R+ stands for the duration of the response to the CS+ and R- is the duration of the response to the CS-. So, the DRs value varies between 0 and 1. If the DR value approaches 1 the discrimination is near perfect and the rat would show maximal responding in the presence of the CS+ and minimal responding during the CS-. This means that the rat has learnt to discriminate the sounds from each other and thus goes more often to the pellet magazine when the food is available. If the DR value is 0.5 (chance level) the rat has not learnt to discriminate the stimuli and goes to the pellet magazine equally often during both sounds. In this case the rat has not learnt which stimulus predicts food and which does not. When the DR value approaches 0 the rat goes to the pellet magazine mostly during the "wrong" stimuli, CS-, and not during the CS+. By comparing these DR values between the groups we tried to find out if there are any differences in reversal learning outcomes between the S-D rats and the rats that are selectively bred by their aerobic capacity.

Finally, we did the planned pairwise comparisons between all of the three groups in order to find out how the groups differed from each other in reversal learning. In this part of analysis we used the ANOVA for repeated measures with the discrimination ratios (15 levels) as within-subjects variables and group (S-D, HCR and LCR, three levels) as a between-subjects factor.

3. RESULTS

3.1. Discrimination-reversal learning in the S-D rats

In the discrimination phase the main effects of the trial type [$F(1,7) = 6.67$; $p < 0.05$] and the session [$F(9,63) = 2.83$; $p < 0.05$] were significant in the S-D rats. This means that the rats learnt to discriminate between the auditory stimuli (see Figure 3). The interaction between the session and the trial type was not significant [$F(9,63) = 0.85$; $p = 0.572$].

In the reversal phase the main effects of both session [$F(14,98) = 2.16$; $p < 0.05$] and trial type [$F(1,7) = 20.08$; $p < 0.05$] were significant, as was the interaction between the session and the trial type [$F(14,98) = 5.77$; $p < 0.001$]. These results show that the S-D rats were successfully discriminating between the tones and spent more time at the pellet magazine during the CS+.

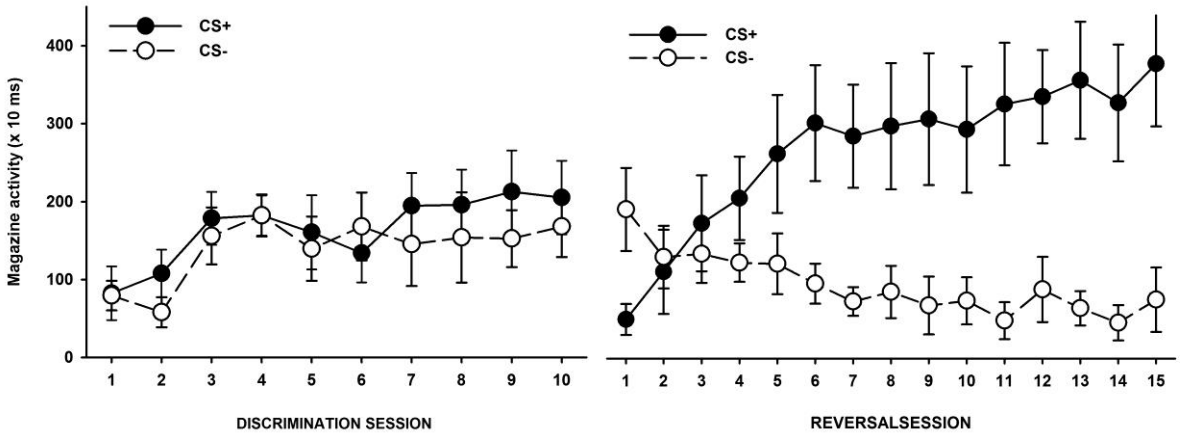

FIGURE 3. Learning outcomes (i.e. the average time that rats spent in the pellet magazine during the conditioned stimuli) of the S-D rats in the discrimination-reversal task

3.2. Comparison of reversal learning between the S-D, the HCR and the LCR rats

When comparing the discrimination ratios (DRs) of the reversal phase between our results and the earlier results of Wikgren et al. (2012) there was a significant interaction between the session and the group [$F(28,294) = 2.32$; $p < 0.001$]. As it can be seen from the Figure 4 the S-D rats learnt to discriminate the sounds as well as the HCR rats and better than the LCR rats. The LCR rats did not perform better than the chance level (DR=0.5, the red line in the Figure 4) at their best.

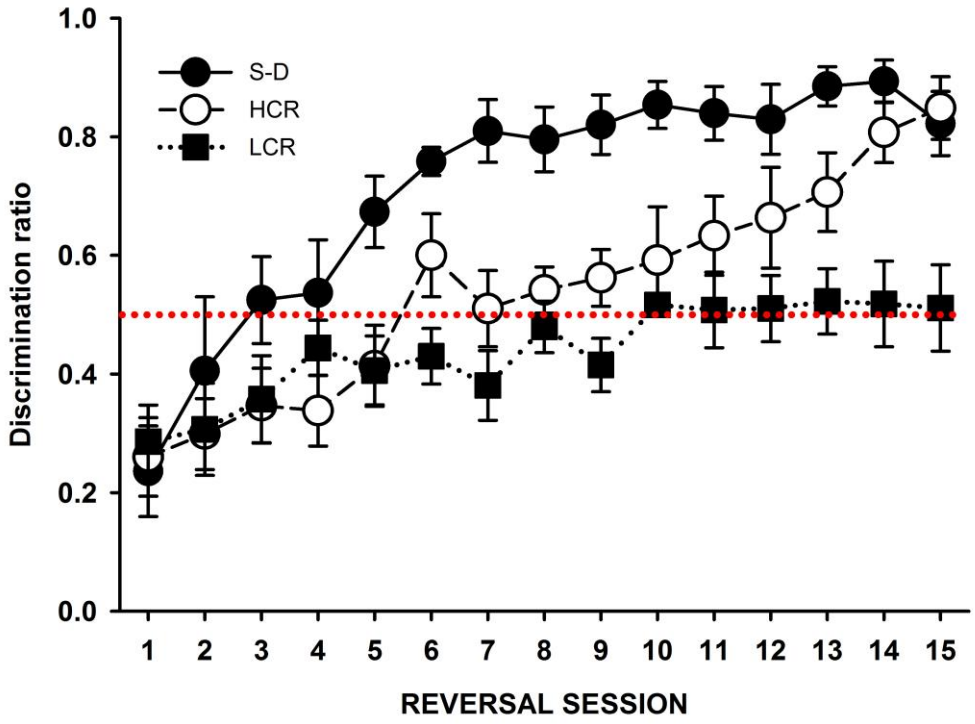

FIGURE 4. The discrimination ratio (DR) values of the reversal learning of the S-D, the HCR and the LCR rats

Planned pairwise comparisons between the strains (S-D vs. HCR, S-D vs. LCR, HCR vs. LCR) revealed that the interaction between the group and the session between the S-D and the HCR rats was not significant [$F(14,196) = 1.50$; $p = 0.112$] which means that

both groups learnt as well and with similar pattern. The main effect of the group was significant [$F(1,14) = 14.29$; $p < 0.01$]. Judging from the Figure 4 this is probably due to quicker learning in the S-D rats. The S-D and the LCR rats differed from each other in learning outcomes: both interaction between the group and the session [$F(14,196) = 3.00$; $p < 0.001$] and the main effect of the group [$F(1,14) = 43.01$; $p < 0.001$] were significant. Also the difference between the HCR and the LCR rats was significant as Wikgren et al. (2012) had found in their study. The interaction between the group and the session [$F(14,196) = 2.53$; $p < 0.05$] and the main effect of the group [$F(1,14) = 4.67$; $p < 0.05$] were both statistically significant.

4. DISCUSSION

Our purpose in this study was to find out if Sprague Dawley rats which are not selectively bred by their aerobic capacity perform better or worse in the flexible cognition task compared to rats with either the beneficial or detrimental genome. We found that the S-D rats learnt the first rule in the discrimination phase, in other words they learnt to wait for food during the CS that predicted food and ignore the other CS. In the reversal phase, the S-D rats successfully extinguished the first rule and acquired a new one in which the assignment of the stimuli was reversed. In the discrimination phase the S-D rats learnt to discriminate the sounds not until the seventh session as it can be seen from the Figure 3. This may affect the fact that in the reversal phase the learning was quicker than it was in the discrimination phase: the old rule was easier to extinguish because it had been learnt reasonably late and the extent of discrimination was not very high.

When comparing our results to the results of Wikgren et al. (2012) study we noticed that our S-D rats performed as good as the HCR rats in the reversal phase of the flexible learning task. This means that the S-D and the HCR rats did successfully learn to discriminate the sounds and thus spent more time in the pellet magazine during the CS+ which predicted food. As it can be inferred from the Figure 4 learning of the S-D rats was quicker than that of the HCR rats. This could result from the above-mentioned slower learning of the S-D rats in the discrimination phase. Even though the S-D rats acquired the new rule quicker their learning was still parallel and similar with the HCR rats. The LCR rats did significantly worse than the S-D and the HCR rats because they did not learn the new rule at all in the reversal phase. In other words, the LCR rats went to the pellet magazine equally often during both CSs because they did not learn which of the sounds predicted food in the reversal phase. As it can be seen from the results, learning in the LCR

rats is inferior to learning in the other rats and that the S-D and the HCR rats learn in a similar way.

According to our and the results of Wikgren et al. (2012) we could infer that the detrimental genome is more significant when it comes to the flexible learning. Wikgren et al. (2012) found that high aerobic capacity of the HCR rats predicts better learning, but we discovered that this is because of the impaired learning of the LCR rats caused by the detrimental genome. So, the genome that promotes good condition does affect learning outcomes but in our point of view the detrimental genome has a greater effect on flexible learning than the beneficial genome has. This can be concluded from the fact that the S-D rats performed as good as the HCR rats in the flexible cognition task even though the HCR rats had the beneficial genome for aerobic capacity. These findings are new in the research field and emphasize the connection between poor aerobic capacity and poor learning outcomes instead of good aerobic capacity and better learning.

As our study and other studies have shown there is a correlation between aerobic capacity or physical activity and cognitive functions. For example, in many animal studies it has been found that good aerobic capacity has a positive impact on cognitive abilities as learning and memory (Wikgren et al., 2012; Gomes da Silva et al., 2012; Cotman & Engesser-Cesar, 2002; Powell, 2005). The relation between physical activity and cognition has been studied also in humans (Sibley & Etnier, 2003; Salis, 2011; Weuve et al., 2004; Heyn, Abreu & Ottenbacher, 2004) and it has been found that exercise has a beneficial influence on different cognitive tasks, especially on executive processes such as planning, inhibition and scheduling of mental procedures (Colcombe & Kramer, 2003). These findings combined with our results give reason to assume that poor physical condition and detrimental genome could impair learning outcomes also in humans.

As mentioned, it has been shown that the aerobic capacity and learning have a

strong connection. However, there are only few studies of the neural mechanism of this connection. For example, memory systems of basal ganglia (particularly the dorsal striatum) and medial temporal lobe (including the hippocampus) have been found to be implicated in flexible cognition and activated in parallel. In certain learning situations competitive interference exists between these two systems (Packard & Knowlton, 2002). Thus, the dorsal striatum and the hippocampal system are interconnected but still specialized on different kind of learning. For example a lesion in the dorsal striatum indicates impairment in stimulus-response (S-R) learning but not in spatial learning while lesions of the hippocampal system produce the opposite pattern of results. Knowlton, Mangels and Squire (1996) studied this same phenomenon in humans and found out that Parkinson's and Huntington's diseases affect negatively the striatal activity. It appears that in both disorders the circuitry that is required for learning the stimulus outcome associations is distracted. According to these results the hippocampus is more responsible for spatial learning as for striatum runs the S-R learning. These results give reason to assume that the LCR rats could have some kind of anatomical anomaly or functional deficit in the striatum because they did not learn to connect the right response with the specific stimulus in the reversal phase of Wikgren et al. (2012) experiment. This phenomenon could be an interesting theme for further research. By combining the brain research with the studies of aerobic capacity and learning it is possible to get information about how aerobic capacity and genome that underlies it affect brain function and structure.

In our research there were a few limitations that may have affected the results. One of the limitations could be the S-D rats' previous experiences as laboratory animals. Before our study the rats had been subjects in a fear conditioning experiment where they received electric shocks during specific auditory stimuli. Although the rats had been extinguished

with the connections between the sounds and the shocks it could be possible that this experience could affect learning in our experiment. This could appear in the rats' behavior for example as immobility or freezing which is rats' typical defense mechanism towards a danger (Brandão, Zanoveli, Ruiz-Martinez, Oliveira & Landeira-Fernandez, 2008; Bouton & Bolles, 1980). In this case the rats are afraid to move towards the pellet magazine because they are expecting the electric shock and this might be one reason why the S-D rats learnt to discriminate the sounds quite late in the discrimination phase. Another fact that could have affected the learning outcomes is the S-D rats' previous anesthesia to implant electrodes for the fear conditioning experiment.

Other limitations on our research could be the differences between the features of our rats and the rats of Wikgren et al. (2012). First of all, our S-D rats were males and the HCR/LCR rats were females. Secondly, the S-D rats were different breed than the HCR/LCR rats. Thirdly, the S-D rats were housed individually while the HCR/LCR rats were housed in pairs. In addition it is possible that the diet of our animals was not limited enough which could have affected the rats' motivation to do the experiment. If the S-D rats were not hungry during the test it could have been another reason for the slower learning in the discrimination phase. It may have also been essential to test the S-D rats' running capacity before the actual learning experiment. This way we would have found out if the rats that were not selectively bred really interposed between the HCR and the LCR rats by their aerobic capacity. In the future research these above-mentioned factors should be controlled more carefully.

In addition to the above-mentioned suggestions for the future research it would also be good to take notice of the research frame. Our study was a cross-sectional study such as many other studies in this field. However, it would be interesting to conduct a longitudinal study about if beneficial genome affects learning throughout life. This way it could be

found out if the genome that promotes good aerobic capacity protects the cognitive abilities from age related cognitive decline. At the same time it would be discovered if the genome that promotes poor aerobic capacity speeds up the declining process. In future studies it would be good to consider the possibility that the LCR rats might age faster than average in which case their cognitive abilities, including learning, start to degenerate earlier in life. This might be one of the reasons why the LCR rats performed poorly in the discrimination-reversal task. One example of a cross-sectional study about how physical training affects cognitive functions throughout life is the research of Gomes da Silva et al. (2012). They investigated in rats if daily treadmill exercise during the adolescent period has an effect on later brain function, especially on hippocampal formation. They found out that early-life exercise results in positive changes both in structure and function of the hippocampal formation, for example it can increase hippocampal plasticity and improve spatial memory in adult life. So, there has been discovered correlation between physical activity in childhood and cognitive benefits throughout life. Because it has been noticed that the beneficial genome itself has parallel effects on cognitive abilities as physical training (Wikgren et al., 2012) it could be possible that this beneficial genome protects cognitive functions from declining as well as physical exercise on Gomes da Silva et al. (2012) study.

Finally, it would be important to study also in humans how aerobic capacity affects flexible learning and cognition. In future it would be interesting to study for example if our results would apply also to humans. In other words: do people that are in good condition and in average condition perform as good in flexible cognition task and if people with poor condition perform worse than these two other groups. In humans, the research in this field has considered more the effects of physical activity and exercise instead of the genetic aspects. It would be essential to study the genetic background of the aerobic capacity in

order to eliminate the factors that affect learning besides physical exercise such as motivation, social interaction and stimulating environment. This way it would be possible to study purely the effects of the beneficial and detrimental genomes on cognitive functions and find out how the aerobic capacity itself without any other background factors affects learning in humans.

4.1. Conclusions

Most of the studies in this research field consider the positive effects of physical activity but not so much the negative impacts of physical inactivity on learning and memory. However it is as important to study how poor physical capacity affects cognitive abilities as it is to study the positive impacts of good physical capacity. According to our results the lack of exercise combined with the detrimental genome could possibly impair flexible learning and that is why the future research on this very perspective is reasonable. To conclude the message of our research it is essential to take care of one's well-being, as Hillman et al. (2008) wrote: “Be smart, exercise your heart”, because physical inactivity and detrimental genes might impair cognitive functions.

REFERENCES

Antunes, H. K. M., Santos, R. F., Cassilhas, R., Santos, R. V. T., Bueno, O. F. A., & Túlio de Mello, M. (2006). Reviewing on physical exercise and the cognitive function. *Revista Brasileira de Medicina do Esporte,12(2),* 97-103.

Bouton, M. E., & Bolles, R. C. (1980). Conditioned fear assessed by freezing and by the suppression of three different baselines. *Animal Learning & Behavior, 8(3),* 429-434.

Brandão, M. L., Zanoveli, J. M., Ruiz-Martinez, R. C., Oliveira, L. C., & Landeira-Fernandez, J. (2008). Different patterns of freezing behavior organized in the periaqueductal gray of rats: Association with different types of anxiety. *Behavioural Brain Research, 188(1),* 1–13.

Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., Elavsky, S., Marquez, D. X., Hu, L., & Kramer, A. F. (2006). Aerobic exercise training increases brain volume in aging humans. *The Journals of Gerontology, 61(11),* 1166-1170.

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychological Science, 14(2),* 125-130.

Cotman, C. W., Berchtold, N. C., & Christie, L.-A. (2007). Exercise builds brain health: key roles of growth factor cascades and inflammation. *TRENDS in Neurosciences, 30(9),* 464-471.

Cotman, C.W., Engesser-Cesar, C. (2002). Exercise enhances and protects brain function. *Exercise & Sport Sciences Reviews, 30(2),* 75-79.

Gomes da Silva, S., Unsain, N., Masco, D. H., Toscano-Silva, M., de Amorim, H. A., Silva Araujo, B. H., Simoes, P. S., da Graça Naffah-Mazzacoratti, M., Mortara, R. A., Scorza, F. A., Cavalheiro, E. A., & Arida, R. M. (2012). Early exercise promotes

positive hippocampal plasticity and improves spatial memory in the adult life of rats. *Hippocampus, 22(2),* 347–358.

Grace, L., Hescham, S., Kellaway, L. A., Bugarith, K., & Russell, V. A. (2009). Effect of exercise on learning and memory in a rat model of developmental stress. *Metabolic Brain Disease, 24(4),* 643-657.

Green, J. T., Chess, A. C., Burns, M., Schachinger, K. M., & Thanellou, A. (2011). The effects of two forms of physical activity on eyeblink classical conditioning. *Behavioral Brain Research, 219,* 165-174.

Heyn, P., Abreu, B. C., & Ottenbacher, K. J. (2004). The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis. *Archives of Physical Medicine and Rehabilitation, 85(10),* 1694–1704.

Hillman, C. H., Erickson, K. I., Kramer, A. F. (2008). Be smart, exercise your heart: exercise effects on brain and cognition. *Nature Reviews. Neuroscience, 9(1),* 58-65.

Kim, Y. P., Kim, H., Shin, M. S., Chang, H. K., Jang, M. H., Shin, M. C., Lee, S. J., Lee, H. H., Yoon, J. H., Jeong, I. G., & Kim, C. J. (2004). Age-dependence of the effect of treadmill exercise on cell proliferation in the dentate gyrus of rats. *Neuroscience Letters, 355(1-2),* 152–154.

Knowlton, B. J., Mangels, J. A., & Squire, L. R. (1996). A neostriatal habit learning system in humans. *Science, 273(5280),* 1399-1402.

Packard, M. G., & Knowlton, B. J. (2002). Learning and memory function of the basal ganglia. *Annual Review of Neuroscience, 25,* 563-593.

Powell, S. K. (2005). The effects of aerobic exercise on spatial learning in the rat. *Dissertation Abstracts International: Section B: The Sciences and Engineering, 65(7-B).*

Salis, A. S. (2011). The effects of cardiovascular exercise on college students' learning,

recall, and comprehension. *Dissertation Abstracts International Section A: Humanities and Social Sciences, 71(11-B).*

Sibley, B. A., & Etnier, J. L. (2003).The relationship between physical activity and cognition in children: A meta-analysis. *Pediatric Exercise Science, 15(3),* 243-256.

Snyder, J. S., Hong, N. S., McDonald, R. J., & Wojtowicz, J. M. (2005). A role for adult neurogenesis in spatial long-term memory. *Neuroscience 130(4),* 843–852.

Weuve, J., Kang, J. H., Manson, J. E., Breteler, M. M. B., Ware, J. H., & Grodstein, F. (2004). Physical activity, including walking, and cognitive function in older women. *The Journal of the American Medical Association, 292(12),* 1454-1461.

Wikgren, J., Mertikas, G. G., Raussi, P., Tirkkonen, R., Äyräväinen, L., Pelto-Huikko, M., Koch, L. G., Britton, S. L., Kainulainen, H. (2012). Selective breeding for endurance running capacity affects cognitive but not motor learning in rats. *Physiology & Behavior, 106(2),* 95–100.