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Changes in entorhinal cortical thickness and volume in young adults following an exercise intervention

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Thesis

CHANGES IN ENTORHINAL CORTICAL THICKNESS AND VOLUME IN YOUNG ADULTS FOLLOWING AN EXERCISE INTERVENTION

by

ANDRES VELEZ LOPEZ

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Approved by

First Reader Karin Schon, Ph.D.
Assistant Professor of Anatomy & Neurobiology

Second Reader Ron Killiany, Ph.D.
Associate Professor of Anatomy & Neurobiology

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ABSTRACT

One of the few areas in the brain that still exhibits experience-dependent neuroplasticity in adulthood is found in the medial temporal lobe (MTL) system. Within the MTL, this plasticity has been observed in the hippocampus in both humans and animal models. Rodent model studies focusing on the effect of aerobic exercise have shown a positive increase of neuroplasticity in the dentate gyrus subregion of the hippocampus. Another area in the MTL, the entorhinal cortex (EC), serves as a primary input to the hippocampus, and studies on environmental enrichment have reported greater EC volume in rodents supplied with toys and running wheels. Previous work in our lab working with healthy young adults showed a positive correlation between right EC volume, and aerobic fitness (VO_2 max). In this thesis, I examined two aims, first whether aerobic fitness predicts changes in thickness or volume of the MTL as well as performance in an MTL dependent task in healthy young adults. Additionally, whether the brain morphology measures of the MTL can predict performance on the memory task. The second aim looks at the longitudinal effect a 12-week exercise intervention has on thickness or volume in the MTL and performance on an MTL dependent task in the same population. Results indicate that there is a positive baseline correlation between aerobic fitness and thickness of the EC on the left hemisphere but there are no longitudinal changes in morphology after the exercise intervention. These data extend previous work on the effects aerobic exercise has on MTL structure and offer interesting venues to combat neurodegenerative diseases that affect the MTL memory system like Alzheimer's disease.

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LIST OF ABBREVIATIONS

ACSM	American College of Sports Medicine
ANOVA	Analysis of Variance
APOE	Apolipoprotein E
BDNF	Brain Derived Neurotrophic Factor
BUMC	Boston University Medical Center
DG	Dentate Gyrus
EC	Entorhinal Cortex
ET	Exercise Training Group
GCRU	General Clinical Research Unit
ICV	Intracranial Volume
MTL	Medial Temporal Lobe
MRI	Magnetic Resonance Imaging
fMRI	Functional Magnetic Resonance Imaging
sMRI	Structural Magnetic Resonance Imaging
ROI	Region of Interest
RT	Resistance Training Group
VO_2	Volume of Oxygen consumption

INTRODUCTION

At the time of birth, the human brain has developed to about 80% of its adult size. From birth to what is believed to be around 25 years old the brain will finish growing (Stiles and Jernigan 2010). While most of the connections in our brains have reached their targets, there are areas in our brain that continue to create new neurons after the brain is fully formed. One of these areas is the granular cell layer of the dentate gyrus (Eriksson 1998). This area is found in the hippocampus, a region of the brain associated with the formation of new contextual and spatial memories (Burgess, Maguire and O'Keefe 2002). It has been hypothesized that the prevalence of adult neurogenesis in the hippocampus is impart responsible for pattern separation, the ability to distinguish and store similar experiences as distinct memories (Aimone, et al. 2006, Nakashiba, et al. 2012).

Aside from natural neurogenesis in the hippocampus, there are various factors that enhance the growth of the DG. Running or aerobic exercise has been shown to increase neurogenesis and cell proliferation in the dentate gyrus of mice (Praag, Kempermann and Cage 1999) Additionally, this change translated to better performance in the Morris water maze, a task which has been shown to recruit the hippocampus in mice (Morris 1984). More closely, populations of dentate granule cells activate during pattern separation in mice (Deng, et al. 2013). The connection between running and the hippocampus has been theorized to be a result of a variety of hormonal and inflammatory factors including neurotrophins, proteins that play roles in growth and maintenance of the nervous system (Cotman, Berchtold and Christie 1997). Brain Derived Neurotrophic Factor (BDNF) is a neurotrophin that is associated with synaptic plasticity, the ability of neurons to create new connections, has been shown to be upregulated in the hippocampus in response to exercise in mice (Schinder and Poo 2000). The neurotrophin hypothesis proposes that increased neuronal activity enhances neurotrophins at the synaptic level in three ways: synthesis, secretion and signaling. Neuronal activation of glutamatergic synapses increases the expression of mRNA's encoding for various neurotrophins in slices of rat hippocampi and this expression is decreases if synapses are blocked (Ernfors, et al. 1991, Zafra, et al. 1991). Neurotrophins like BDNF then carry out housekeeping functions necessary for the modification of synapses.

These findings have intrigued laboratories to be able to replicate this work in humans given that added to the benefit exercise has on cardiovascular health, memory might also be enhanced. Work in our laboratory has begun to look at translating this observation in mice to humans by using MRI, fMRI and performance on cognitive tasks to track changes in healthy adult participants after an exercise intervention. Results of our previous studies have shown that BDNF and aerobic fitness interactively predict memory performance in young adults (Whiteman, Young and Schon 2014). Additionally, a different study from our lab has shown that the volume of the entorhinal cortex on the right hemisphere correlates with fitness and on recognition memory task performance (Whiteman, Young and Budson, et al. 2016). The entorhinal cortex is the major input relay to the hippocampus, and our laboratory has predicted that the observed association between entorhinal volume and fitness might be due to the connection this region has with the DG (Witter, et al. 2000). Additionally, aerobic exercise also enhances angiogenesis in the MTL and this can account for increases in volume and thickness (Clark, et al. 2009).

The current study has taken these findings and expand on them by looking at healthy young adults in an ongoing exercise intervention study. Participants underwent a 12-week exercise intervention where they were placed randomly in either an aerobic exercise group or a resistance and balance exercise group. A 12-week program was chosen because previous studies have shown a 6-week exercise intervention is enough time to significantly change fitness capacity as well as memory performance in young adults and is as effective as longer interventions in enhancing cognition (Stroth, et al. 2009, Colcombe and Kramer 2003). Structural MRI and fitness capacity were measured before and after the exercise intervention. Aerobic fitness was measured using a modified Balke treadmill protocol, a submaximal walking test to estimate maximal oxygen uptake at the predicted maximum heart rate of the participant based on age and sex (Cooper and Storer 2001).

The Freesurfer software was used to study the entorhinal cortex and hippocampus before and after the exercise intervention. Freesurfer is a MR image analysis software that uses T1 weighted images and makes surface based models to compute cortical thickness and curvature (Fischl and Dale 2000). In addition, the software calculates volume for the cortex and subcortical structures using volumetric segmentation (Fischl, Salat, et al. 2004). The Freesurfer software also subdivides the cortex as well as the subcortical regions to predefined regions of interest (ROI). Freesurfer software was used to directly compare the findings in Whiteman et al. 2016 that used voxel based morphometry with SPM8 software and manual tracings to calculate cortical volume and but not cortical thickness. Cortical thickness is believed to be a better measure of structural change in great matter dimensions as it more clearly defines it compared to volumetric approaches. (Winkler, et al. 2010).

To parallel the finding in mice of an improved performance in the Morris water maze, I used a task that also recruits the hippocampus in humans. Studies show that voluntary wheel running enhances the pattern separation ability of adult mice (Creer, et al. 2010). The pattern separation task is used to evaluate the participant's ability to pattern separate or distinguish very similar stimuli with one another. (Yassa and Stark 2011). The circuitry for this computation is believed to be in the hippocampus which establishes discrete networks by separating overlapping representations arriving from the entorhinal cortex (Treves and Rolls 1994). Using two faces as the stimuli, the pattern separation ability of the participants was tested by differing degrees of similarity between the faces and asking the participant if a third face or test face was more similar to the previous stimuli or a new face. Increasing the similarity between the faces increases the difficulty of the task and enforces the use of pattern separation.

The current study uses the morphological data, exercise data as well as the performance data on the pattern separation task to address the two aims. The goal of the first aim is to investigate whether aerobic capacity from an initial (baseline) fitness assessment can predict MTL morphology (cortical thickness, volume of the entorhinal cortex and hippocampal volume) as well as pattern separation task performance and if MTL morphology can predict performance as well. The goal of the second aim then is to investigate whether MTL morphology and performance on the pattern separation task change after a 12-week aerobic exercise intervention compared to control participants undergoing resistance and balance training. Although the focus of this research is on healthy young adults, increased volume and thickness following aerobic exercise training might translate to combating effects of degenerative diseases that show atrophy in the MTL memory system, such as in Alzheimer’s disease. Some the earliest affected areas in Alzheimer’s disease are located in the MTL including the hippocampus and the entorhinal cortex (Smith 2002). An exercise intervention could be used to slow the progression of Alzheimer’s disease from mild cognitive impartment into Alzheimer’s amnesia or help maintain healthy levels of brain structure and cognitive ability before symptoms arise.

METHODS

Participant Recruitment

The participants for the study were recruited from the greater Boston area community including the Boston University undergraduate and graduate population. Initially, participants were screened through a phone interview before undertaking the first study visit. Participants were native English speakers in the age range of 18 to 35 years and lead a sedentary lifestyle. Sedentary is defined as a person who does not participate in at least thirty minutes of moderate intensity activity on at least three days per week for at least three months (guidelines per the American College of Sports Medicine, Thompson, Gordon and Pescatello 2010). Participants were also screened out for diagnoses of neurological, psychiatric, cardiovascular, or respiratory condition s and musculoskeletal impairments. Additionally, participants diagnosed with diabetes mellitus, obesity and under prescription for cardio-active and psycho-active medications were not included in the study. MRI procedure required participants to not have any metal in or around their body that cannot be removed.

Study Structure an Pre-intervention Phase

The study was organized into three phases; the pre-intervention phase, the intervention phase and the post intervention phase. The pre-intervention phase included four study visits with each individual participant before the start of the exercise intervention. If the participant passed the initial phone interview, then the first study visit was scheduled to take place in the general clinical research unit (GCRU) of the Boston

University School of Medicine. The initial visit includes an overview of the study and the written informed consent of the participant to participate. Additionally, a battery of neuropsychological tests was used to ensure the participants met standard benchmarks for their gender and age. Table 4 found in the appendix gives a list of all the neuropsychological tests used in the initial visit. After the first visit, the participant's performance in the tasks was evaluated and if under normal levels, they qualified to take part in the study and were scheduled for the second visit.

The following two visits were used to establish the fitness baseline of each participant before the beginning of the intervention. The fitness visits included measurements of vital signs and percent body fat, a cardio-respiratory fitness test and a strength assessment test to target various muscle groups. These visits took place in the Fitness and Recreation Center (FitRec) at Boston University. At the beginning of each of the two fitness visits the resting vital signs of the participants were taken including blood pressure and heart rate. These measurements follow the procedures published by the American College of Sports Medicine (ACSM; Thompson, Gordon and Pescatello 2010). The participants undertook one of two cardio-respiratory fitness tests; an incremental work rate test on the first fitness visit and a constant work test on the second fitness visit. The incremental work rate test is a submaximal exercise test that will not push the participant to more than 85% of their age-predicted maximum heart rate (Cooper and Storer 2001; Thompson, Gordon and Pescatello 2010). The known linear relationship between heart rate and of oxygen uptake (VO_2) allows us to estimate maximum VO_2 at the participants 100% age-predicted heart rate (Dalleck and Kravitz 2006). During the test, the participants walked on a treadmill equipped with a heart rate monitor and blood pressure cuff. Heart rate was recorded every minute while blood pressure was taken every three minutes during the test. The test follows a modified Balke treadmill protocol (Hanson 1984). Initially, participants warmed up for 3 to 4 minutes, then at a fixed speed the incline increased every minute until the participant reached 85% of their age and sex predicted maximum heart rate. A cooldown period followed for 7 to 10 minutes. The speed at which the participants were tested was chosen individually to ensure safety and comfort (Cooper and Storer 2001). During the three minute intervals where blood pressure is recorded, the participants were also asked to express their perceived exertion. The standard 15-grade scale for ratings was used to estimate perceived exertion (Borg 1982). Lastly, the first fitness visit included a strength assessment of major muscle groups of the upper body using a chest press and a latissimus dorsi pulldown.

The constant work rate test of the second fitness visit is similar in structure to the incremental work rate test. The participants walked on a treadmill and their heart rate, blood pressure and perceived exertion were monitored. The major difference between the two tests is that the constant work test only has a single stage and measures endurance. A predefined work rate was selected using the incremental work rate test results from the first fitness study visit. Like the incremental work rate test, a comfortable walking speed was used for the duration of the study. The incline was increased during the warm up period until the participant's heart rate is between 75% to 80% age and sex predicted hear rate. The test will then last between 6 to 8 minutes depending on the endurance of the participant and their heart rate increasing above the 75% to 80% range. The strength test in the second fitness visit focused on the major muscle groups of the lower body. The protocol for the strength assessment in the second fitness visit is identical to the first except the use of the leg press and leg curl machines.

The final visit of the pre-intervention phase included the MRI and blood draw protocols. Before the participants undertook the MRI procedure, they were given a practice condition of the tasks they would undertake while in the MRI as to familiarize themselves with them.

MR Image Acquisition

The protocol for the MRI portion of the visit includes various activities including a structural scan, fMRI while performing the cognitive tasks and a resting state scan. The only activities that are concerned with in this study are the initial structural scan, T1 weighted MR images, and the cognitive tasks performed in the MRI but not the fMRI BOLD response. The MRI used was a 3.0T Phillips magnet which is located at the Boston University Medical Center (BUMC) Center for Biomedical Imaging. Participants were asked to perform several tasks while in the MRI, these tasks included a delay matching to sample task and a pattern separation task. For this study, only the performance on the pattern separation was used. After the MRI scan, the participants were asked to complete an array of cognitive tasks to test their cognitive ability in memory, visuospatial ability and general intelligence. Table 5 in the appendix has a list of all the cognitive tasks completed in the 4th visit. None of these measures were used in the current study.

Exercise Fitness Intervention

Once the four initial visits were completed and more than 3 participants were recruited, the intervention phase could begin. Participants were organized in either a morning group (7:00-8:00 am) and/or an evening group (6:30-7:30 pm) depending on their schedule of availability and randomization to exercise training group. The intervention program ran three times a week (Monday, Wednesday and Friday) for 12 weeks. Participants were randomly placed in one of two groups; an aerobic endurance exercise training (ET) group and a resistance training (RT) or control group. The aerobic group routine focused on walking on a treadmill similarly to the constant work rate test. Each participant had an individualized exercise program that was tailored to them using the comfortable walking speed from the pre-intervention phase constant work rate test. As the intervention progressed the incline on the machine was increased regularly while keeping below 85% of their age and sex predicted heart rate. For the resistance group, the routine included training exercises targeting all major muscle groups. Participants lifted weights on different machines similarly to the fitness visits in the pre-intervention phase. As the intervention continued, the repetitions and weight used on each machine increased. Heart rate was monitored during the intervention visits and a personal trainer was available to guide and monitor the participants. During the intervention, the participants were asked not to partake in extraneous exercise outside of the study and if they do so, to record it on the exercise diary supplied to them. If the participants missed any of the sessions, a homework assignment was supplied to the participant to do on their own time.

Post-intervention Phase

Participants who finished the intervention moved on to the post-intervention phase. This phase consists of repeating the same visits used in the pre-intervention phase except the first visit that included informed consent and neuropsychological testing. The two fitness visits were repeated using the same protocol as in the pre-intervention phase. The final visit of the post-intervention phase used an identical protocol to the final visit in the pre-intervention phase including the MRI scanning and blood draw. Cognitive ability was also measured using the same list of tasks found on Table 5.

Pattern Separation Task

While in the scanner, the participants undertook a pattern separation task to test their ability to differentiate similar stimuli from one another. Participants were asked to observe and remember two faces from famous individuals shown each for two seconds individually and after a ten second delay, were then shown a third test face (Figure 1). The participant then answered if the third face were identical to face 1, face 2, or if it was a new face. The task has three levels of difficulty that morph the two faces to create three condition s for the new faces (Figure 2). The composition of the faces in the test, using random faces a and b, were either 10% face a and 90% face b, 30% face a and 70% face b or 50% of each face. Morphing of the faces was achieved by using the FaceGen software.

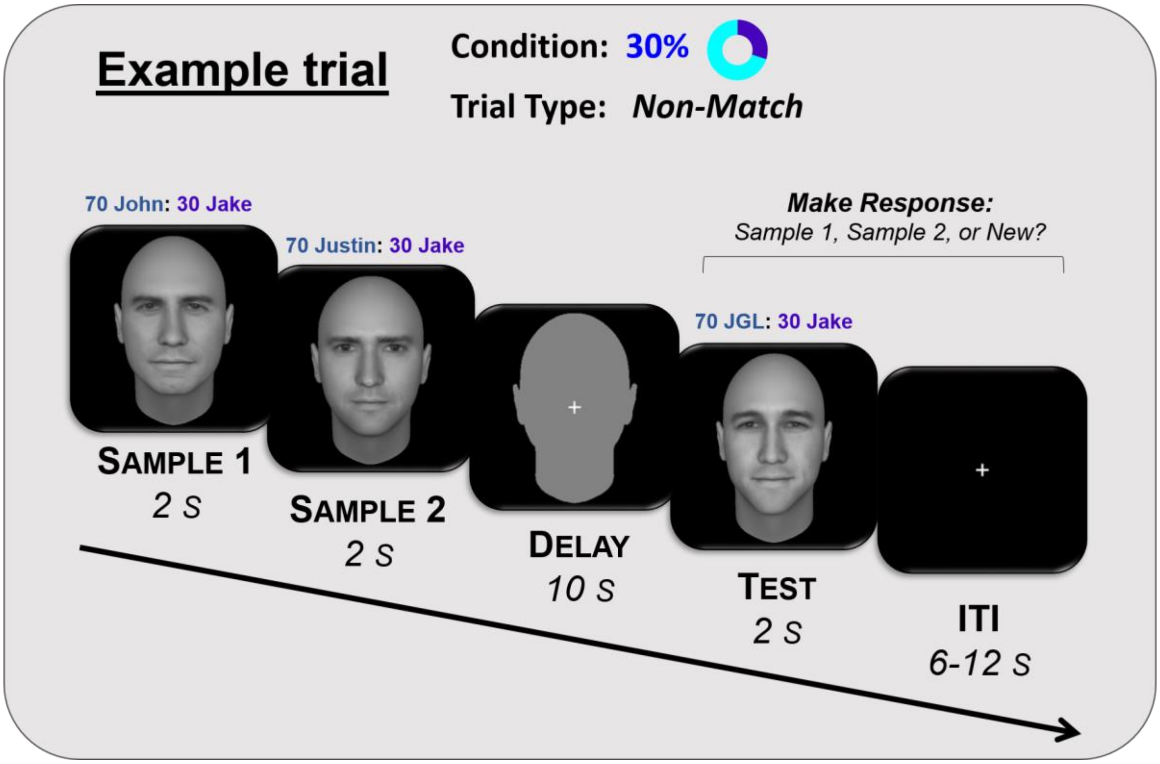


Figure 1. Design of Pattern Separation task. See text for details.

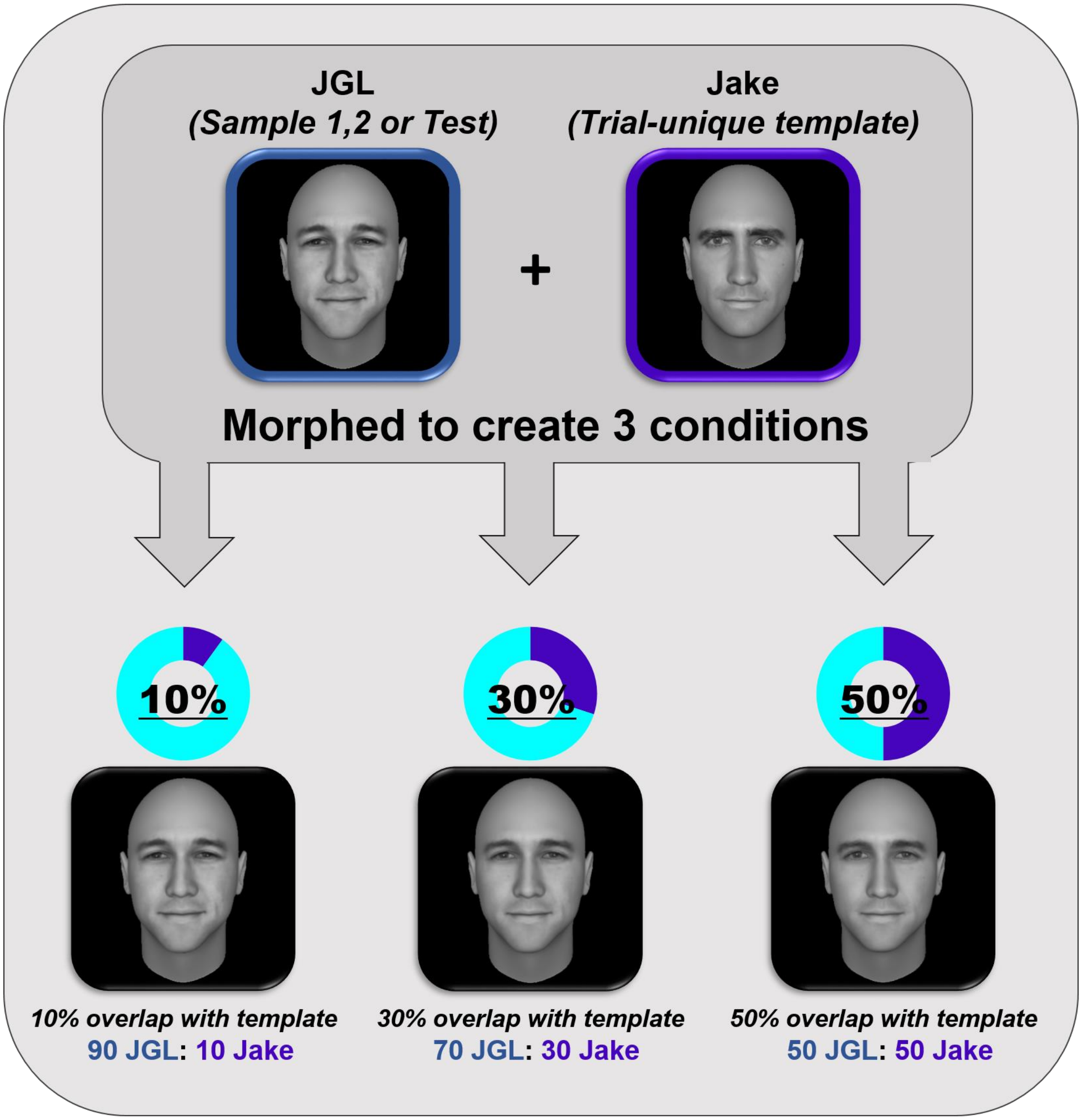


Figure 2. New faces created by morphing different proportion of the initial faces. Images were made using the FaceGen software.

ANALYSIS

Basic Statistics

Basic statistics were calculated using IBM SPSS Statistics 20. Means of the exercise and resistance groups were used to evaluate if the two groups differed between one another at baseline. VO_2 max was converted into a percentile based on the participants age and sex using the ASCM norms (Thompson, Gordon and Pescatello 2010). The conversion was done to normalize the age and sex difference between participants.

MRI Data Pre-processing & Analysis

The bulk of the output data consisted of evaluating structural MRI images and behavioral task performance for both pre and post intervention phases. The Freesurfer software (stable v5.3.0) was used as the main analytical tool for the study. Cortical thickness was evaluated by creating surface maps of the cortex, each MRI slice in the image is applied a vertex on the edge of the white matter and the edge of the grey matter creating a triangle mesh of vertices on two surfaces (Fischl, Salat, et al. 2004). A threshold is used to define these surfaces by voxel-by-voxel analysis (Figure 3). Cortical thickness is measured by subtracting the pial surface of the grey matter with the white matter surface (Figure 4). The software also uses voxel based properties to measure volume of the cortex as well as the volume of subcortical regions like the hippocampus (Fischl, Salat, et al. 2004). Using previously designed atlases and manually traced regions of interest (ROI) (Fischl, et al. 2004; Desikan, et al. 2006), the software can measure volume and thickness based on individual defined cortices.

The software is Linux based and is run through command prompt. The recon-all command of Freesurfer is used as the cortical reconstruction pipeline which includes Talairach transformation, skull stripping, surface smoothing and cortical and subcortical parcelation. A detailed diagram displaying the steps of the recon-all function can be found on Figure 15 in the appendix. As a part of the recon-all process, each participant's T1-weighted structural MR volume is normalized to a coordinate space called fsaverage. This in turn is used for group analysis in the study. There are two atlases as part of the output to the recon-all command, the Destrieux Atlas and the Desikan- Killiany Atlas (Fischl, et al. 2004; Desikan, et al. 2006). For the purposes of this study, I decided to use the Desikan-Killiany Atlas results because the atlas includes the entorhinal cortex as an ROI.

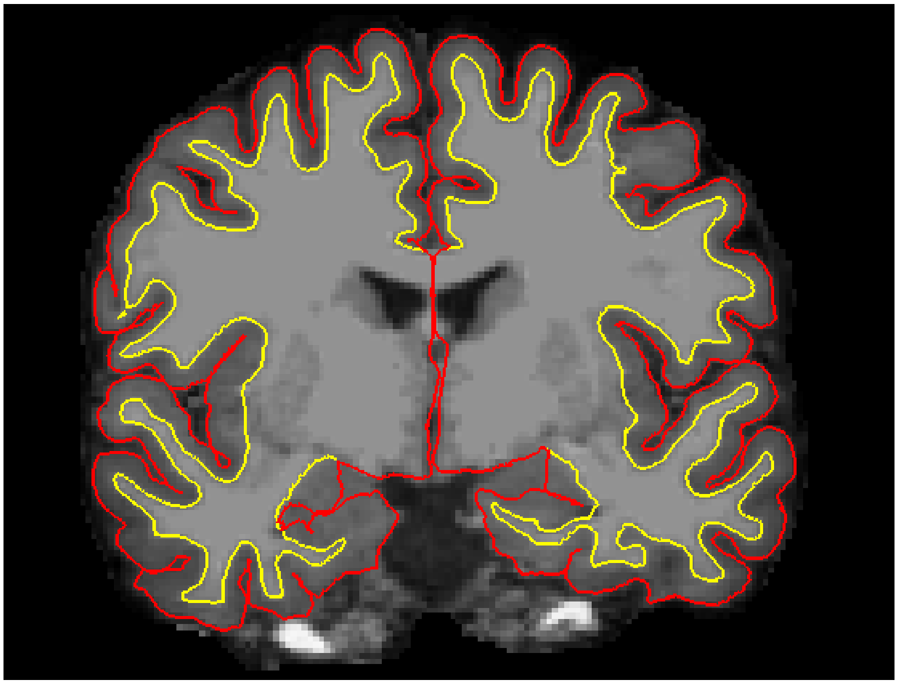


Figure 3. Cortical pial and white matter outlined red and yellow respectively

Figure 4. Cortical thickness measured by subtracting the pial surface (red) and the white matter surface (yellow).

To answer the first aim of whether aerobic fitness at baseline correlates with morphological brain measures, functions present in Freesurfer's group analysis pipeline were used. Several functions preprocessed the data and these modified images were fed into the general linear model function mri_glmfit. This analysis was used to correlate the subject's pre-intervention VO_2 max percentile with various morphological brain measures including cortical volume and thickness. As an output, inflated heat maps of the cortical surface were created for each hemisphere with a threshold of significance set at $\alpha = 0.05$. Covariates in the general linear model included age, sex and intracranial volume (ICV). Intracranial volume is calculated as a part of recon-all function and is measured by using the correlation between ICV and the transform matrix used to align an image with an atlas (Buckner, et al. 2004).

In addition, Freesurfer supplied raw output of averaged thickness and volume measures for cortical and subcortical ROI. This data was used to validate the inflated cortex maps, evaluate the volume of subcortical regions and used to analyze the effects of MTL structure to performance on the pattern separation task. The Freesurfer output includes the averaged thickness and volume across an individual ROI. IBM SPSS Statistics 20 was used for the analysis and multiple regression models with respect to aerobic fitness were created for left and right entorhinal cortex, both for thickness and volume as well as right and left hippocampal volume. The ROI data was also used to create multiple regression models between morphological data (thickness and volume) and the performance on the pattern separation task similarly for the entorhinal cortex and the hippocampus on both hemispheres. Like the inflated cortical maps, I used age, gender and intracranial volume as covariates for the ROI analysis.

Pattern Separation Analysis

Memory performance was quantified by using the results of the pattern separation task. Like mentioned before, the task is graded by difficulty 10%, 30% and 50% of face a and the equivalent of face b to round up to 100%. The nature of the task gives rise to an array of results with regards to what the participant responded to a particular trial, Table 1 shows the types of answers available for the task. If the participant were correct in identifying that the test face was indeed either face 1 or face 2, or in other words “old”, the response is considered a “hit.” If the participant answers correctly for a test face that is “new” and not either face 1 or face 2 then the response is considered a “correct rejection.” For incorrect answers, if the participant answers incorrectly when the test face is old but believes it to be a new face is considered a “miss” while responding to a new face as an old one (either face 1 or face 2) results in a “false alarm.” In the interest of looking at the corrected accuracy in terms of successful pattern separation, the “false alarm” responses must be subtracted from the “hits” to give a more accurate representation of pattern separation.

Table 1. Possible responses to pattern separation task

		Participant Response	
		“Old”	**“New”**
Correct Response	**“Old”**	Hit	Miss
	“New	False Alarm	Correct Rejection

The second aim focuses on the observed change in morphological brain measures of cortical volume, thickness and memory performance after the 12-week exercise intervention. Repeated measures ANOVAs using the ROI data output were run using SPSS to compare the pre-intervention measures with the post-intervention measures of entorhinal cortical thickness, volume of the entorhinal cortex and the volume of the hippocampus, and if the exercise training group differed from the resistance training group. Similarly, repeated measures ANOVAs were used to look at the change in VO_2 max and memory performance over the intervention period and differences between training groups. Age, sex and intracranial volume (for the structural analysis only) were used as covariates for all of the ANOVAs. Intracranial volume was measured twice, both pre and post, and needs to be corrected for to be included in the analysis as it might change across time. For the volume analysis, the entorhinal cortex volume and hippocampal volume measurements were converted into a fraction of intracranial volume, creating a volume ratio. This ratio was created separately for booth left and right hemispheres and for both pre and post phases, then it was used as the dependent variable in the analysis. For thickness analysis, a change in intracranial volume, or the intracranial volume at post-intervention phase minus the pre-intervention phase, was used as a covariate in the analysis.

RESULTS

Descriptive Statistics

A total of 29 participants (mean age 26.7 ± 3.7 years) successfully finished the study and were included in the analysis. Table 2 shows how the experimental exercise training and control resistance group compare to each other using the pre-intervention data gather in the first visits. Using a two-sided t-test for each category except for education (non-parametric independent sample test), the two groups do not differ significantly with respect to age, education, % of female, intracranial volume or aerobic fitness (VO_2 max).

Table 2. Descriptive statistics, ET- exercise training group, RT- resistance training group, p-value result of two sided t-test between ET & RT. *Education was not normally distributed and a non-parametric independent sample test was used.

	Total	**ET**	**RT**	**p-value**
N	29	11	18	
Age	26.1 ± 3.69	24.7 ± 2.53	26.9 ± 4.10	0.128
Education (years)	16.8 ± 1.42	16.4 ± 1.43	17.1 ± 1.39	0.188*
Intracranial Volume (mm^3, pre)	1.38E+06 ± 1.80E+05	1.37E+06 ± 2.28E+05	1.38E+06 ± 1.52E+05	0.994
VO_2 max percentile (pre)	40.4 ± 29.1	35.5 ± 22.6	43.5 ± 32.7	0.358

Aim #1: Multiple Regressions Models to predict Cortical/Subcortical MTL Structure

Figure 5 below shows the entorhinal cortex on the left and right hemisphere respectively outlined in red. The inflated heat maps display a positively significant correlation between aerobic fitness and thickness across a clear majority of the entorhinal cortex vertices on the left hemisphere. In the right hemisphere we did not see a significant correlation between aerobic fitness and thickness for the entorhinal cortex. Outside of our ROIs, on both hemispheres, the fusiform cortex shows a significant correlation across 1/3 of its length for thickness on the left hemisphere and smaller significant region on the right hemisphere. Looking at the volume data on Figure 6, there was no significant correlation between aerobic fitness and entorhinal volume on either of the hemispheres. Once again, we see portions of the fusiform cortex to be significant, similarly to the thickness results. These results are complementary to the results found in Whitman et al. 2016 that show a correlation with volume of the entorhinal cortex on the right hemisphere.

Figure 7 shows the collected multiple regression models using the averaged ROI data for the entorhinal cortex and the hippocampus versus aerobic fitness on both hemispheres. There is a significant positive correlation between aerobic fitness and the overall entorhinal cortex on the left hemisphere ($p = 0.003$, $R^2 = 0.271$, $df = 28$), this confirms the finding that can be seen on Figure 5. With regards to the entorhinal cortex on the right hemisphere, there is no significant correlation overall with fitness ($p = 0.1$, R^2

= 0.097, df = 28). Similarly, VO_2 max percentile scores do not correlate with the volume of the entorhinal cortex on either the left or right hemisphere respectively (p = 0.782, R^2 = 0.01; p = 0.759, R^2 = 0.002, df = 28). Overall hippocampal volume was not correlated with aerobic fitness on either the left or right hemisphere (p = 0.382, R^2 = 0.029 df = 28; p = 0.146, R^2 = 0.072, df = 28). This finding is in contrast with previous studies showing a correlation between hippocampal volume and aerobic fitness. (Erickson, et al. 2009).

Aim #1: Multiple Regression Models to predict Pattern Separation Performance

Multiple regression plots between fitness and performance on the pattern separation task are displayed in Figures 8. Initially, there was no significant correlation between memory performance and aerobic fitness for all levels of difficulty (10%: p = 0.220, R^2 = -.035, 30%: p = 0.732 R^2 = 0.136, 50%: p = 0.283, R^2 = 0.039, all df = 28, Figure 8). There is a trend of the 10% similarity condition getting easier for higher fits individuals but more difficult trials being harder for higher fit individuals but the correlations are not significant and cannot be concluded upon. Table 3 shows the statistics from the multiple regression models run to observe if corrected accuracy on the pattern separation task correlates with multiple morphological measures in the MTL. The plots are shown on Figure 9 for EC thickness, Figure 10 for EC volume and Figure 11 for hippocampal volume. According to the analysis, corrected accuracy on the 50% condition is negatively correlated with EC thickness on both hemispheres. Corrected accuracy on the 30% condition is negatively correlated with EC volume on the right hemisphere. Finally, Corrected accuracy on the 10% condition is negatively correlated with hippocampal volume on each hemisphere. A trend can be seen that all significant values present are negatively correlated which implies that higher fitness correlates with lower corrected accuracy on the pattern separation task.

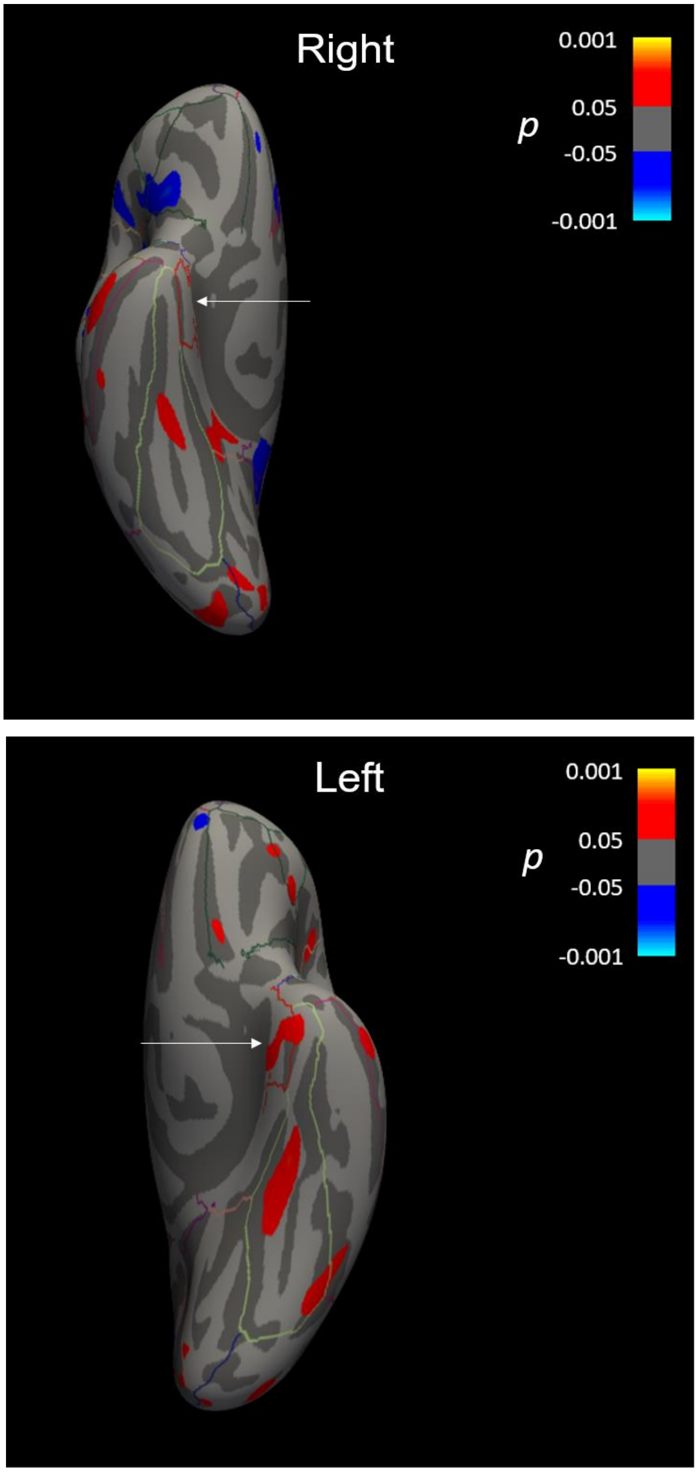


Figure 5. Cortical significance maps of the correlation between VO_2 max percentile and cortical thickness for the left and right hemispheres. Images are looking at the brain ventrally.

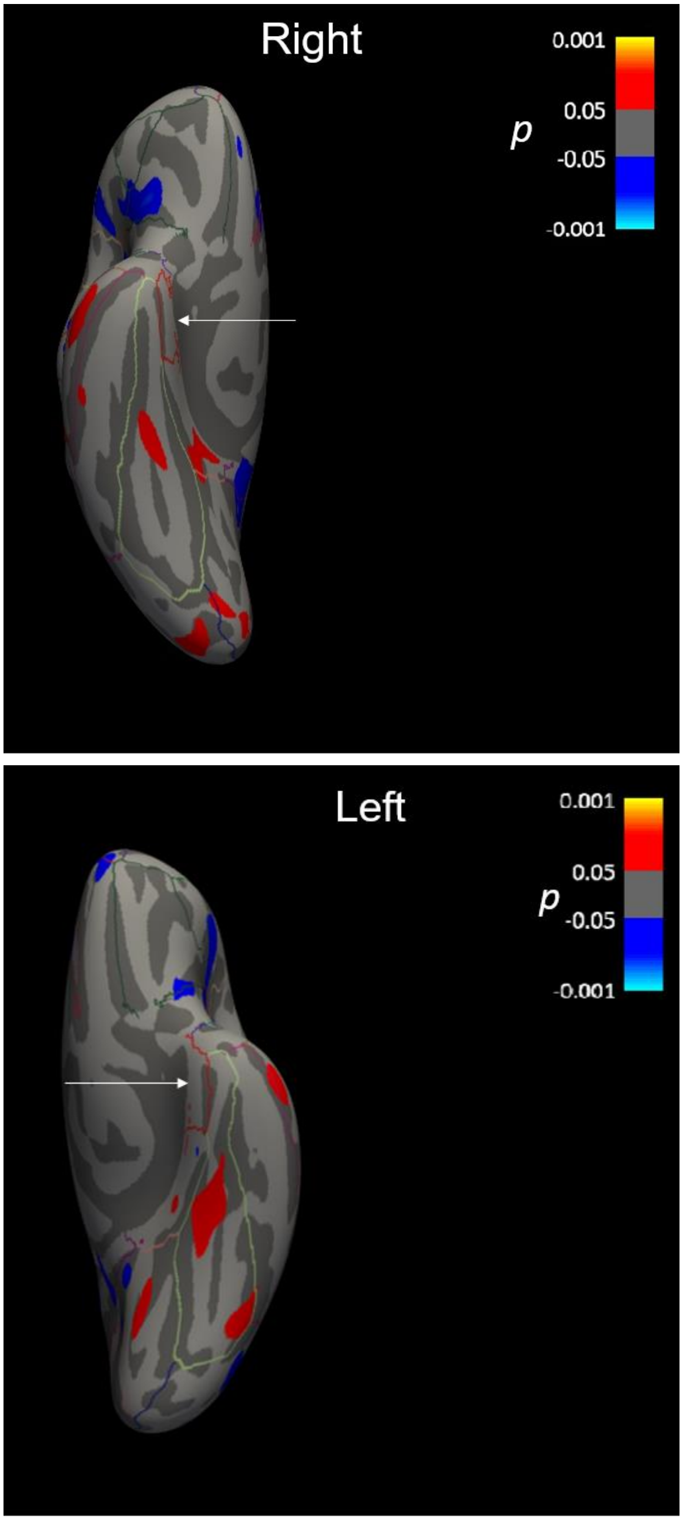


Figure 6. Cortical significance maps of the correlation between VO_2 max percentile and cortical volume for the left and right hemispheres. Images are looking at the brain ventrally.

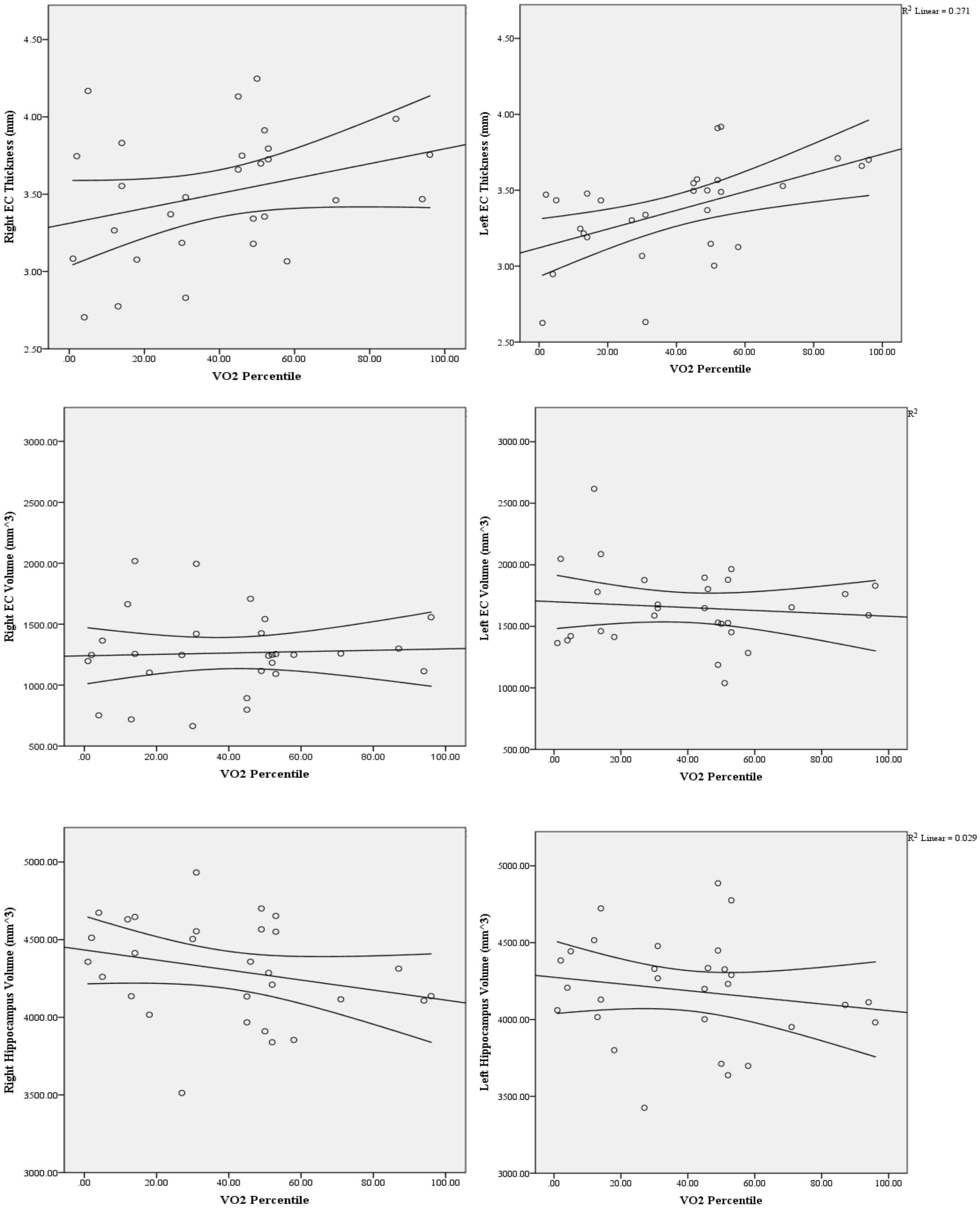


Figure 7. Multiple regression plots for the right and left hemispheres. First row is cortical thickness, the second row is cortical volume and the last row hippocampal volume all plotted against VO$_2$ max percentile.

Table 3. Statistical analysis using multiple regression models on corrected accuracy trials 10%, 30% and 50% and MTL morphology. Asterisk identify significant results.

	Trial	**Statistical measure**	**EC Thickness**		**EC Volume**		**Hippocampal Volume**	
			Left	**Right**	**Left**	**Right**	**Left**	**Right**
Corrected Accuracy	**10%**	**t**	-0.355	-0.535	0.173	-0.625	-2.778*	-2.941*
		p	0.725	0.598	0.480	0.538	0.010*	0.007*
		R^2	-0.140	-0.133	-0.122	-0.128	0.133*	0.158*
	30%	**t**	1.011	0.381	1.054	-2.160*	-0.188	-0.800
		p	0.322	0.706	0.302	0.041*	0.853	0.432
		R^2	0.141	0.110	0.144	0.251*	0.106	0.128
	50%	**t**	-2.330*	-2.668*	-1.484	-1.638	-0.160	0.850
		p	0.029*	0.013*	0.151	0.114	0.874	0.404
		R^2	0.154*	0.199*	0.049	0.066	-0.037	-0.008

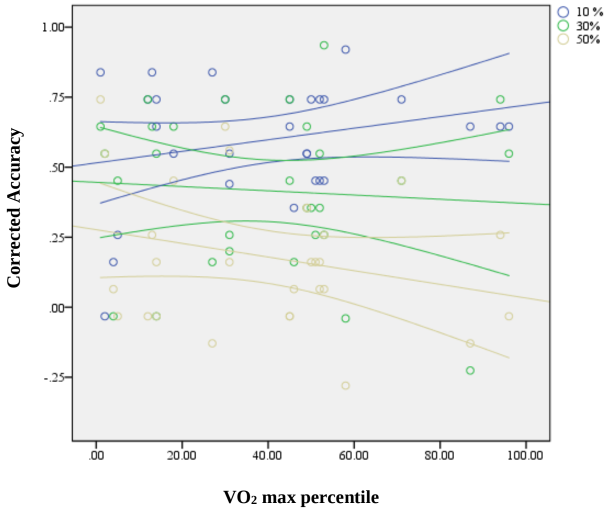


Figure 8. Memory performance correlated with aerobic fitness. Corrected accuracy: correct answers - false alarms. Difficulty divided into similarity levels of 10%, 30% and 50%

Aim #2: Repeated Measures ANOVAs on Fitness

Overall changes in VO_2 max between the pre-intervention and post-intervention periods were not observed to be significant (Time: F = 0.394, p = 0.536 df = 25; Group: F = 0.669, p = 0.421 df = 25; Figure 12). Further analysis was done to measure the impact higher fitness (50-100% VO_2 max percentile) has on the overall model compared to lower fitness (0-50% VO_2 max percentile). Figure 13 shows the results of a repeated measures ANOVA looking at the difference between higher fit and lower fit individuals after the exercise intervention. Results show that there is a significant between-subjects main effect of fitness group (F = 29.3, p < 0.01, df =25) and a positive time*fitness group interaction (F = 5.09, p = 0.03, df = 25). Looking at the interaction effect of time*fitness group a simple effect test shows that fitness groups differ both at pre-intervention and post intervention time points respectively ($F = 41.8$, $p < 0.01$, $df = 25$; $F = 26.28$, $p < 0.01$, $df = 25$).

Aim #2: Repeated Measures ANOVAs on MTL Cortical/Subcortical Structure

The graphs of the repeated measures ANOVA for morphological measures can be found in Figure 14 and statistics in Table 4. There is no significant change in entorhinal cortex thickness with respect to time or group on either hemisphere. There is a group difference in entorhinal cortical volume on the right hemisphere but no significant change with respect to time. Cortical volume of the EC is not significantly different between pre and post and groups on the left hemisphere. With regards to hippocampal volume, there were no observed changes between pre and post or between groups on either hemisphere.

Aim #2: Repeated Measures ANOVAs on Pattern Separation Performance

Results for the repeated measures ANOVA memory performance can be seen in Figure 16. There was a significant change in corrected accuracy for the 10% condition with respect to time ($F = 4.50$, $p = 0.04$, $df = 25$) and no significant difference between groups ($F = 0.06$, $p = 0.81$, $d = 25$). Other condition s of the pattern separation task were not significant with respect to time or group respectively (30% condition: $F = 0.97$, $p = 0.34$; $F = 1.70$, $p = 0.20$. 50% condition: $F = 0.57$, $p = 0.46$; $F = 1.15$, $p = 0.46$, all $df = 25$).

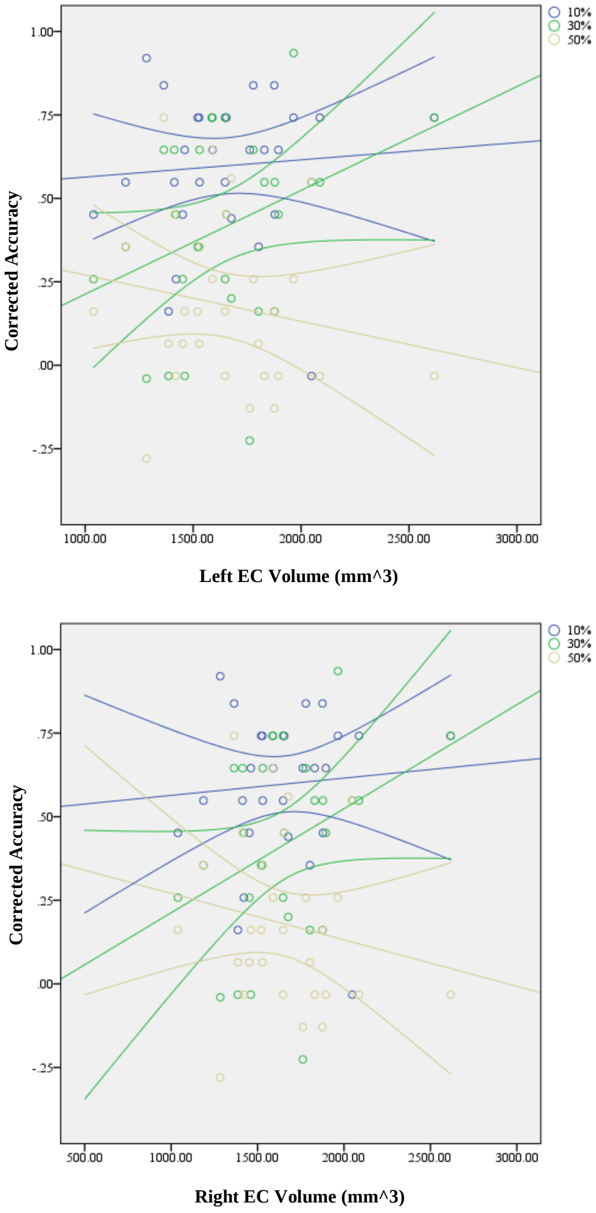


Figure 9. Memory performance correlated with volume of the EC. Corrected accuracy is: correct answers - false alarms. Difficulty divided into similarity levels of 10%, 30% and 50%

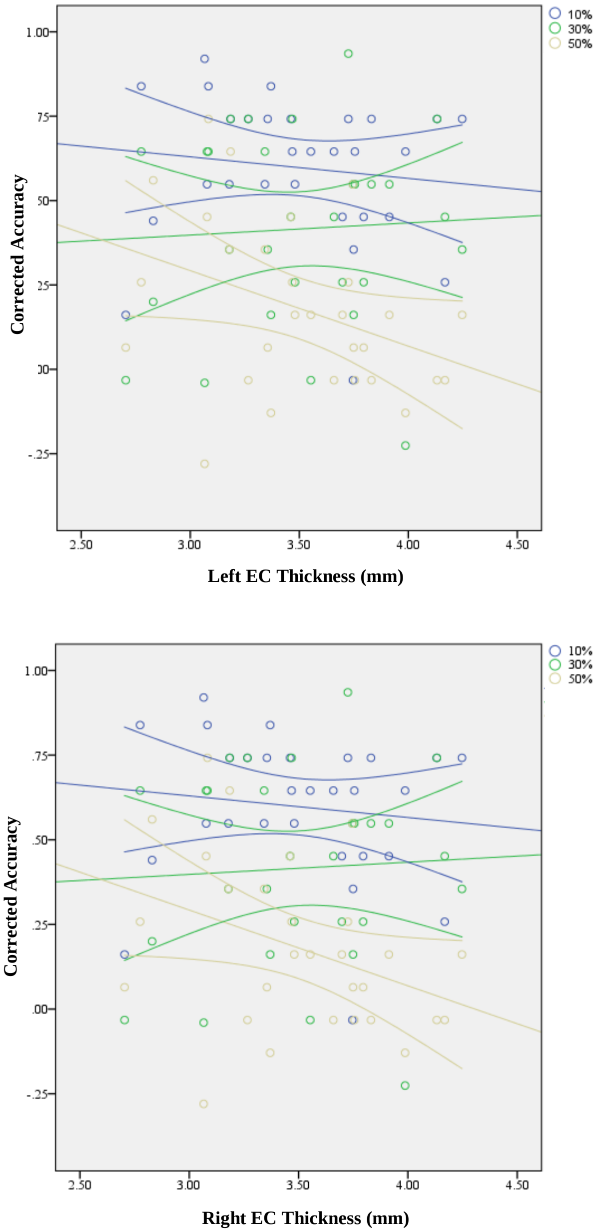


Figure 10. Memory performance correlated with thickness of the EC. Corrected accuracy is: correct answers - false alarms. Difficulty divided into similarity levels of 10%, 30% and 50%

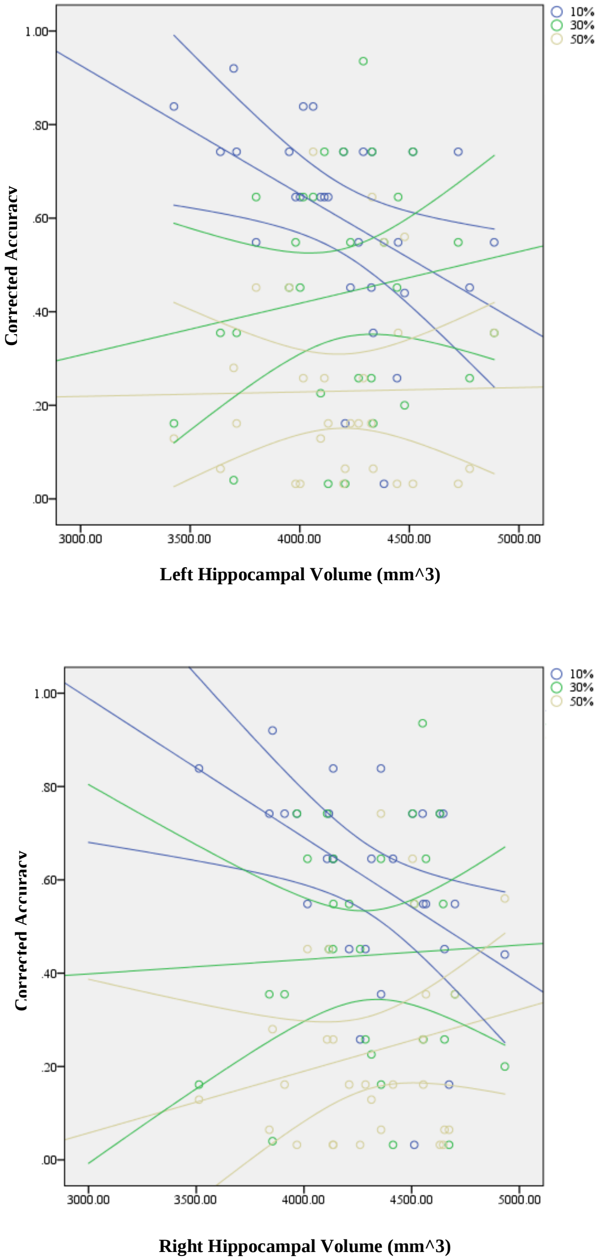


Figure 11. Memory performance correlated with volume of the Hippocampus. Corrected accuracy is: correct answers - false alarms. Difficulty divided into similarity levels of 10%, 30% and 50%

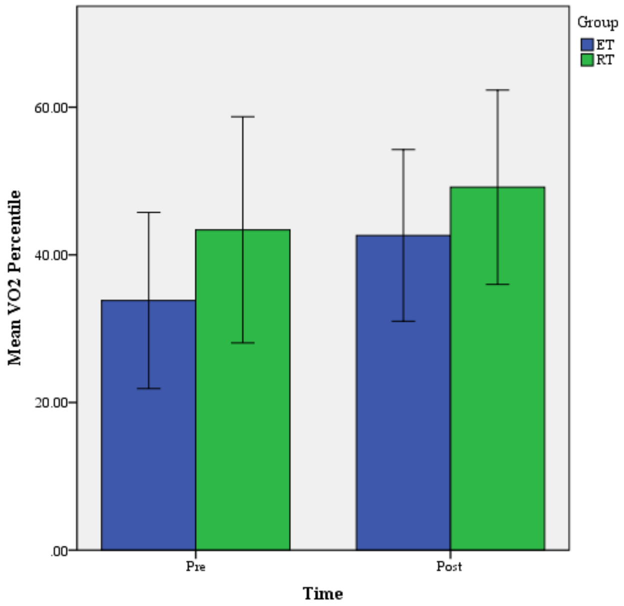


Figure 12. VO$_2$ max changes between pre-intervention and post-intervention phases as well as group differences between exercise and resistance groups.

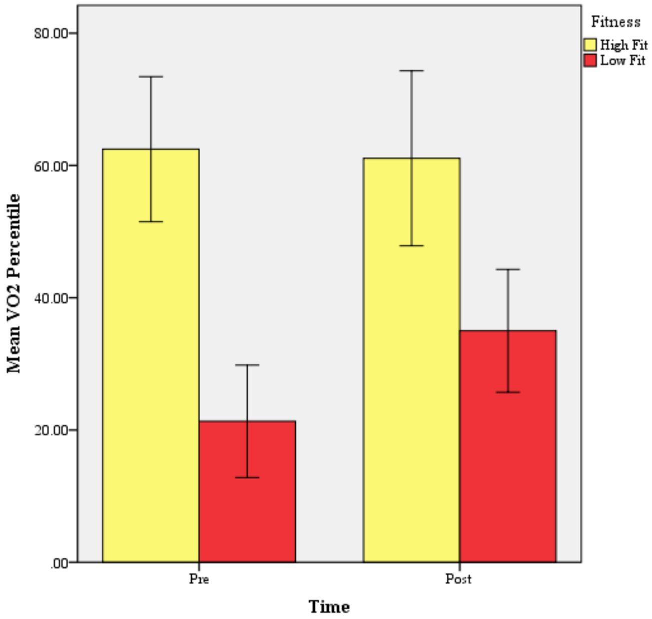


Figure 13. VO$_2$ max changes between pre-intervention and post-intervention phases. Group differences between higher fit (50-100% VO$_2$ max percentile) and lower fit (0-50% VO$_2$ max percentile) individuals.

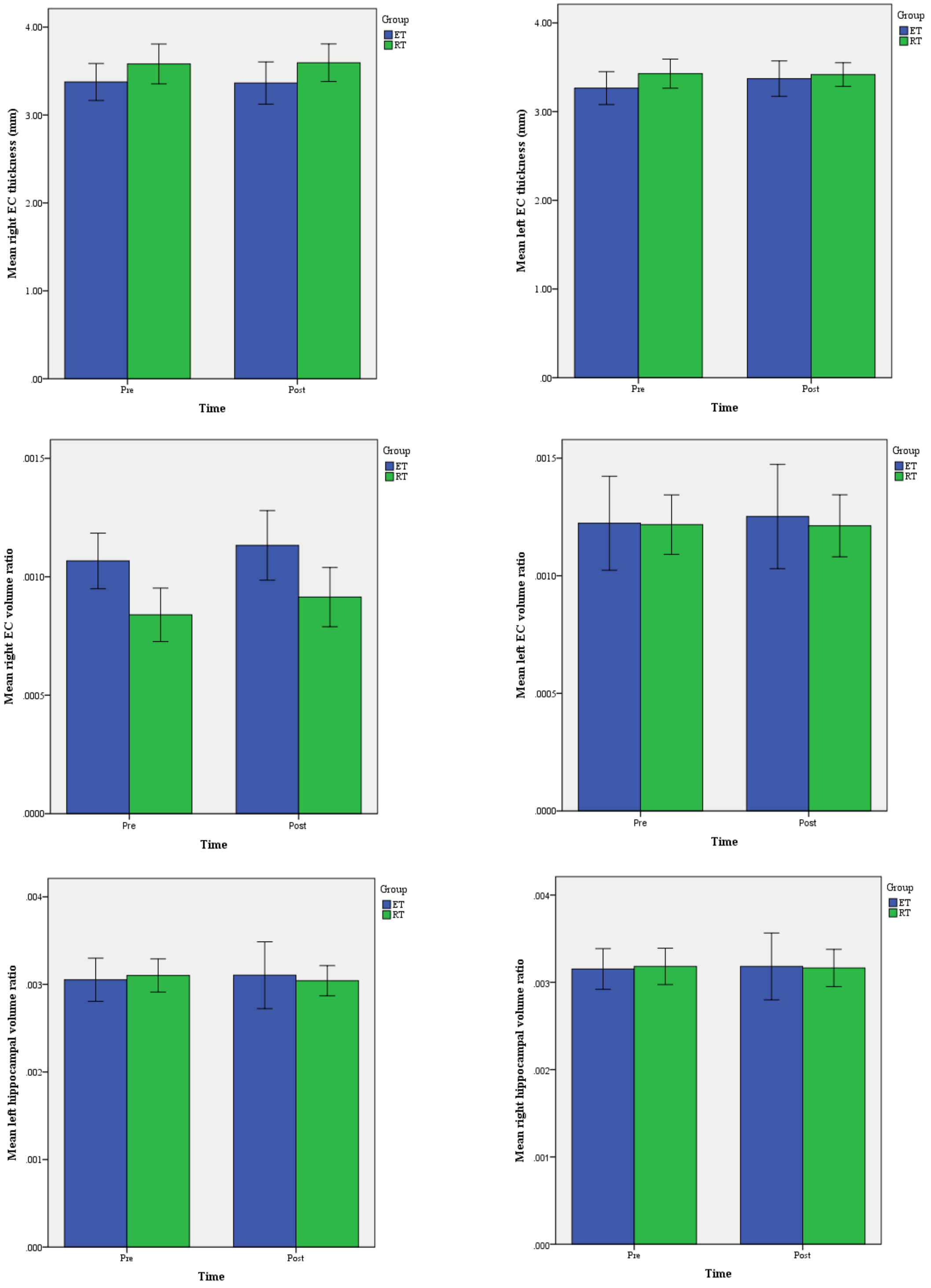
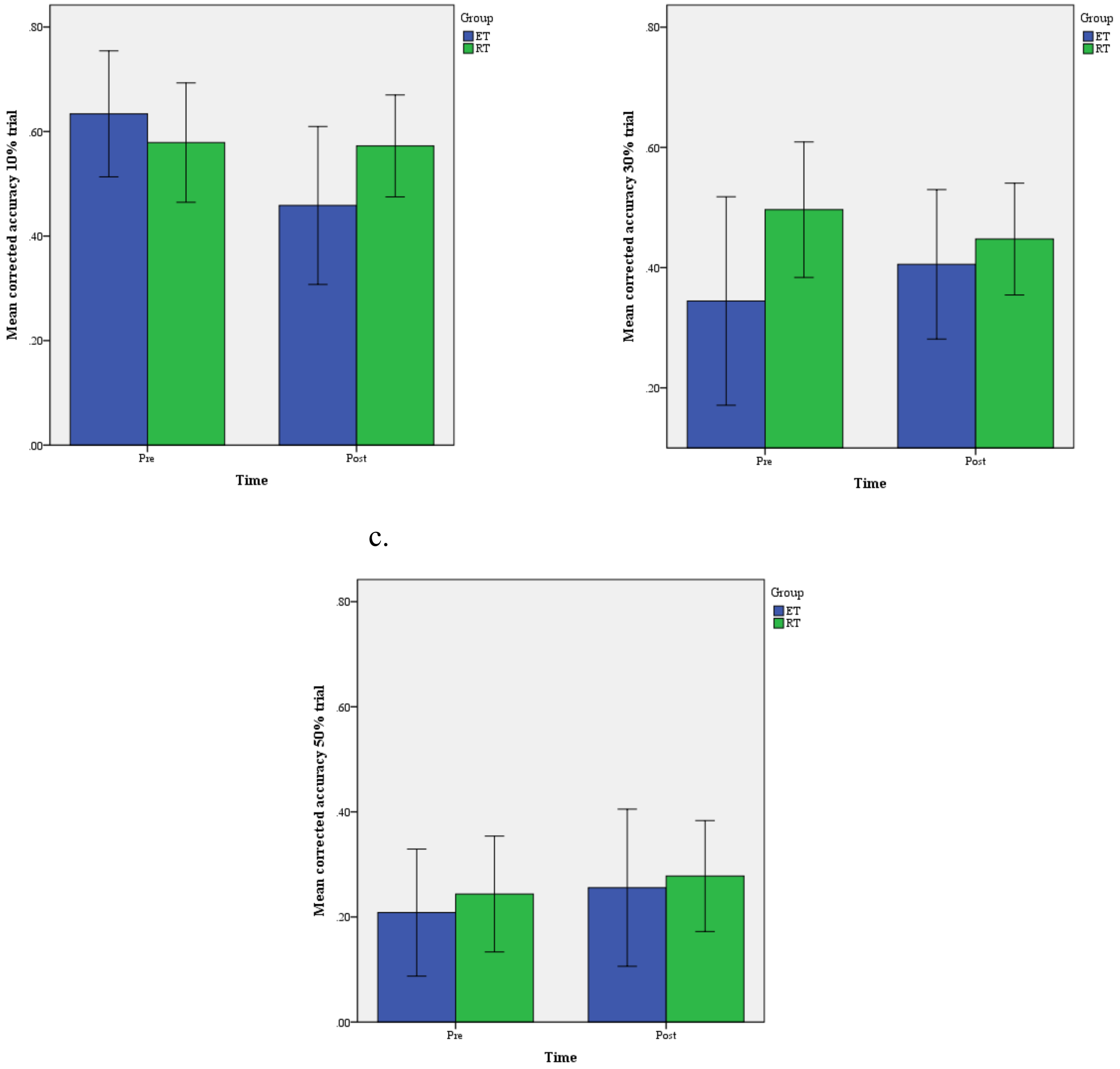


Figure 14. Morphological measure changes between pre-intervention and post-intervention phases and group differences between exercise (ET) and resistance (RT) groups. First row: EC thickness, second row: EC volume ratio, third row: HP volume ratio


a.

b.

c.

Figure 15. Memory performance changes between pre-intervention and post-intervention phases and group differences between exercise (ET) and resistance (RT) groups. a. 10% similarity trial, b. 30% similarity trial, c. 50% similarity trial.

Table 4. Repeated measures ANOVA results for morphology of the MTL including the entorhinal cortex (EC) thickness, volume and hippocampal volume.

Variable	Statistical Measure	EC Thickness		EC Volume		Hippocampal Volume	
		Left	Right	Left	Right	Left	Right
Time	F	0.036	0.000	1.271	0.109	1.162	1.298
	P	0.851	0.998	0.270	0.744	0.291	0.283
Time* Group	F	0.328	0.145	0.971	0.004	2.203	0.765
	P	0.572	0.707	0.334	0.948	0.150	0.390
Between-subject Group	F	0.124	1.169	0.122	5.913*	0.094	0.038
	P	0.727	0.290	0.730	0.023*	0.761	0.847

DISCUSSION

In the current study, I examined the relationship between aerobic fitness and exercise, cortical morphological measures of the MTL and memory performance before and after a 12-week exercise intervention. The results suggest a positive correlation between aerobic fitness and thickness of the EC on the left hemisphere and negative correlations between corrected accuracy and various MTL structures. Additionally, there is a significant group difference in right entorhinal volume after the exercise intervention but no significant difference with respect to time. These observations both confirm and contrast previous work in our laboratory but show indications that change in the MTL can be observed due to aerobic exercise in sedentary young adult participants.

Aim #1: Cross-Sectional Analysis

The cross-sectional results from the pre-intervention phase suggest a positive correlation between aerobic fitness and cortical thickness of the entorhinal cortex on the left hemisphere. These results supplement previous results from our lab that found gray matter volume of the entorhinal cortex on the right hemisphere was correlated with fitness (Whiteman, Young and Budson, et al. 2016). Fitness can alter gray matter volume in adults and this is supported by various studies (Erickson, Leckie and Weinstein 2014). Higher levels of physical activity are associated with higher levels of neurotrophin granulocyte colony stimulating factor (C-CSF), another neurotrophin present in neurogenesis, and increased cerebral volume in older adults (Floel, et al. 2010). This connection might serve as the link between exercise and MTL changes seen in this study. Other results suggest that there is no correlation between aerobic fitness and the volume of the hippocampus on either side. This is in contrast with previous results that show correlations between hippocampal volume, fitness and virtual Morris Water task performance in adolescents (Herting, et al. 2012). Studies looking at environmental enrichment models in mice show low to no change in hippocampal volume outside the dentate gyrus (Diamond 1988). The confinement of adult hippocampal neurogenesis to the granular cell layer of the dentate gyrus subregion might explain why whole hippocampal volume did not change in our young adult population. The Freesurfer analysis used in this study did not allow examination of specific subregions within the hippocampus but the current release of Freesurfer 6.0 includes hippocampal subfield segmentation. This analysis could be used to further delineate the presence of neurogenesis in the dentate gyrus correlated with fitness.

Memory performance was negatively correlated with structural change in entorhinal cortex and the hippocampus. This finding is in contrast with previous research in our lab that indicates a positive correlation between memory performance on natural images, aerobic fitness and entorhinal volume bilaterally (Whiteman, Young and Budson, et al. 2016). A study shows that even a single bout of exercise can increase memory performance in young adults (Weinberg, et al. 2014). This study might be benefiting with the effects of retesting effect and the participant's similarity with the task. The study described here is much longer and it can be assumed there is little retesting effect. The negative correlations must be investigated further in order to elucidate its meaning since it's not supported by the literature.

Aim #2: Longitudinal Analysis

Overall, VO_2 max percentile was not significantly changed after the exercise intervention and there was no difference between groups. This result is not consistent with literature that show even a 6-week exercise intervention is enough to exhibit changes in VO_2 max (Stroth, et al. 2009). Further analysis was done to elucidate if higher fit individuals with VO_2 max percentiles of 50% and above are masking lower fit individuals with VO_2 max percentiles less than 50% who might be significantly changing in VO_2. As can be seen from Figure 13, there is a significant difference in how higher fit individuals are changing in VO_2 percentile compared to lower fit individuals. In other words, initially lower fit participants improved in VO_2 max, whereas initially higher fit participants did not. Additional analysis shows that the lower fit individuals are significantly increasing in VO_2 max percentile over the exercise intervention. This result illuminates the difficulty of recruiting similarly fit individuals or in other words, successfully recruiting sedentary individuals.

The longitudinal approach shows evidence for a between-subjects group difference for entorhinal cortex volume ratio after the intervention. This observation is challenged by the non-significance of time in the model and this result does not prove to be a significant factor in explaining changes in structure of the MTL due to aerobic exercise. Since there was no significant change in time, the between-subjects group difference that we see is just an indication of the group difference found at the beginning of the study between randomly created groups. Literature has shown that as far as longitudinal analysis are concerned, changes in entorhinal cortex are not associated with exercise interventions but lateral temporal, cingulate and prefrontal cortices in older adults are (Colcombe, et al. 2006, Erickson, et al. 2011).

Similarly, entorhinal cortex volume on the left hemisphere as well as entorhinal thickness and hippocampal volume on each hemisphere show no significant change between group and time points. These results are in contrast with literature results showing an increase in grey matter volume in the hippocampus after a 9-year interval in older adults (Erickson, et al. 2010). Although this study uses older adults and a longer time period, the exercise measurement was a simple questionnaire asking how many blocks the participants walks per week. This was sensitive enough to elucidate a difference and looking at VO_2 in this population for an extensive amount of time could further solidify the relationship of fitness and hippocampal volume. The non-significance of morphologic changes in the MTL might be contributed to the size of the ROIs involved and the lack of using higher resolution scans. The hippocampus and especially the entorhinal cortex are small in comparison to neighboring cortices like the fusiform cortex. Measuring change in these regions might require higher resolution scans like T2-weighted MRI images with high in-plane resolution. Freesurfer has the capability to analyze T2-weighted images and it is a step that should be made to ensure change can be captured in these regions longitudinally.

Changes in memory performance after the exercise intervention were significant on the 10% condition with respect to time but not any of the more difficult trials. The difficulty of the task might be contributing to the non-significance of the more difficult trials. Although a significant change in the performance of the easiest condition might indicate the start of memory performance improvement.

Limitations & Forward Progress

Limitations of this study include a small population size of 29 participants. The current study is ongoing and additional young adults will be finishing the intervention to add to this total. Supplementary, there is an additional older adult population that is part of the same study and offers the chance to look at differences in aerobic fitness and morphology of the MTL in different age populations.

Other limitations include the close monitoring of participants during the exercise trials and their sedentary status. As mentioned before, sedentary status is measured using a questionnaire so there is no empirical data that might suggest a participant is truly sedentary. A submaximal test like the one used in the fitness visits could be implemented at the screening stage to exclude non sedentary individuals. External physical activity of the participants during the study is also a cause for concern especially if they are exercising outside of the training sessions. A diary is used to encourage the participants to inform our laboratory if they have exercised or not and how extraneous the exercise is. Examination of the exercise diaries is important to further validate the impact of a 12-week intervention versus shorter ones.

Moving forward, the current study is looking to finish all data collection and a more comprehensive look at aerobic fitness and its impact on brain structure can be elucidated with a bigger population. Blood draws collected during the study will be analyzed and measurements of BDNF levels can be used to examine the relationship between peripheral neurotrophic levels and structural changes in the MTL after exercise training. The release of Freesurfer 6.0 will also allow the closer examinations of hippocampal subfields and the relationship between subfield changes with VO_2 max and memory performance.

Outside of the ongoing study, future studies should focus on looking more closely at what specific areas in the entorhinal cortex are correlated with aerobic fitness. In rodent models there is evidence that the posterior part of the entorhinal cortex is correlated with environmental enrichment. Additionally, medial entorhinal cortex is more closely associated with spatial information processing, while lateral entorhinal cortex is not (Hargreaves, et al. 2005). Targeting more specifically the regions that are associated with fitness will require the use of higher resolution MRI images and more sensitive analytical tools. Combining these results with fMRI data on memory tasks will further explore the connection of structure change to memory function. Additionally, looking at networks rather than individual ROI's might shed some light on what effect the exercise has on the MTL as a whole as well as other areas of the brain implemented in memory including the pre-frontal cortex (PFC) and the posterior cingulate cortex (PCC).

Finally, changes in entorhinal cortex might have interesting implication with regarding spatial cognition due to the growing evidence of specific cells that code for place, head direction in the entorhinal cortex. The MTL is also responsible for spatial cognition and looking at performance on spatial navigation tasks is another important direction in confirming change in MTL structure due to exercise is functionally relevant.

CONCLUSION

The current study shows evidence for a correlation between MTL structure and aerobic fitness. This is consistent with the previous results in our lab that changes in MTL structure might be due to aerobic after a 12-week exercise intervention. Exercise-induced adult hippocampal neurogenesis may impact entorhinal structure and function through the direct anatomical connection between EC and DG, the neurogenic zone of the hippocampus. In the future, our data was important in understanding what the full impact exercise has on the human brain and might also be later translated into preventative measures to combat the progression of degenerative diseases like Alzheimer’s disease. Looking ahead, studies that include the neurotrophin BDNF analysis with entorhinal structure and exploring spatial cognition performance are various venues that studies in the future can continue to unravel the importance of cardiovascular fitness in mental health.

APPENDIX

Table 5. Visit #1 Questionnaires and neuropsychological testing

Screening Questionnaires and Tools:

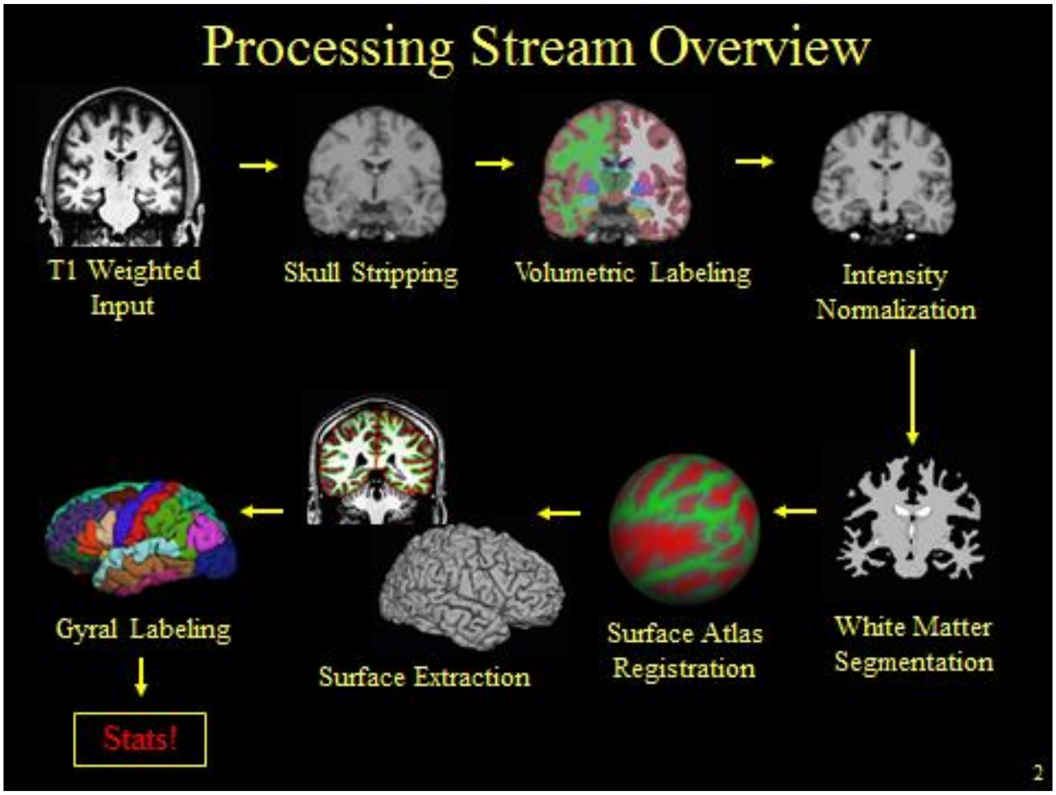
1. General health screening
2. Exercise readiness (BU FitRec guidelines)
3. Exercise habits (Baecke physical activity questionnaire, Baecke 1982)
4. MR compatibility (BU 3T safety screening)
5. Eating disorders (EDE Q 6.0, Fairburn and Beglin 1994)
6. Drug abuse
7. Alcohol misuse (Alcohol Use Questionnaire AUDIT, Saunders, et al. 1993)
8. Compulsive exercising (EAI, Terry, Szabo and Griffiths 2004)
9. Edinburg Handedness Inventory (Oldfield 1971)
10. Perceived Stress Scale (Cohen, Kamarck and Mermelstein 1983)
11. Anthropometric Measures and Vital Signs
12. Rabin Subjective Memory Test (Rabin, et al. 2009)
13. Squire Memory Self Rating Scale (Squire, Wetzel and Slater 1979)
14. Depression: Beck Depression Inventory II (Beck, Steer and Brown, Beck Depression Inventory-II 1996)
15. Anxiety: Beck Anxiety Inventory (Beck and Steer, 1990)

Neuropsychological Testing:

1. Trail Making Test Versions A and B (Strauss, Sherman and Spreen 2006)
2. Stroop Test, Victoria version (Strauss, Sherman and Spreen 2006)
3. The North American Adult Reading Test, NAART (Blair and Spreen 1989; Nelson 1982)
4. Grip Strength Test using the Smedley Dynamometer (Strauss, Sherman and Spreen 2006)

Table 6. Post-Scanning Cognitive tasks

1. Delayed match to sample recall section
2. WAIS-IV subtests- Digit Span Forward, Backward, and Sequencing
3. WAIS-IV subtest Symbol Search
4. WAIS-IV subtest Coding (Wechsler 2008)
5. Perspective Taking/Spatial Orientation Test
6. Road Map Test
7. Santa Barbara Sense-Of-Direction Scale



Processing Stream Overview

T1 Weighted Input

Skull Stripping

Volumetric Labeling

Intensity Normalization

White Matter Segmentation

Surface Atlas Registration

Surface Extraction

Gyral Labeling

Stats!

Figure 16: Recon-all processing stream steps for Freesurfer MRI analysis (Kaufman 2016)

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CURRICULUM VITAE

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