THE ASSOCIATION OF AEROBIC FITNESS WITH RESTING STATE FUNCTIONAL CONNECTIVITY AND VERBAL LEARNING AND MEMORY IN HEALTHY YOUNG ADULTS

by

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ABSTRACT

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The beneficial effects of exercise and cardiopulmonary fitness on general health, quality of life, and reduction of mortality are well known in older adults. There is evidence to support the positive effects of exercise and aerobic fitness on psychiatric and neurocognitive function in children, adults, and older adults. Indeed, many studies have explored the positive effects of aerobic fitness on slowing cognitive decline associated with normal and pathological aging. However, comparatively fewer empirical studies in the literature exist to support and understand the effects of aerobic fitness on the developing brain, particularly during adolescence and young adulthood, especially as it relates to resting state functional connectivity during this dynamic stage of development. The current study investigated the association of aerobic fitness on functional connectivity with the left hippocampus in healthy young adults and the degree to which differential resting state functional connectivity is associated with verbal learning and memory. The sample was comprised of healthy young adults with varying degrees of aerobic fitness as part of a larger study of the effects of cardiorespiratory health on neurocognitive performance, brain structure and function. Results of the study indicated that better aerobic fitness is associated with increased functional connectivity to the left

parahippocampal gyrus, a region known for its role in working memory and encoding. Results from this study contribute to a better understanding of the factors that may underlie the beneficial effects of exercise on brain health and neurocognition and further offer insights into the value of early preventive health behaviors to reduce the risk of later of cognitive decline and impairment.

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INTRODUCTION

1.1 Statement of the Problem

Given the growing evidence of metabolic disorder risk and sedentary behavior in a large percentages of individuals in the United States (Barlow et al., 2016), understanding the link between aerobic fitness and neurocognitive health is of great interest. There is a growing consensus among healthcare professionals that the rise of obesity in the United States presents many serious public health challenges (Masters et al., 2013) including increased rates of type-2 diabetes, hypertension, heart disease, and cancer (NIH, 2013). The prevalence of obesity has been on the rise in the United States since the 1980s but has plateaued in the last 20 years in both youth (Ogden et al, 2016) and adults (Flegal et al., 2016), with 16.8% of youth and 18.5% of adults having a Body Mass Index >30 in 2016 (Hales et al., 2018). Sedentary behavior impacts a large percentage of youth such that 8% of adolescents and 42% of children do not engage in the amount of physical exercise recommended by the American Heart Association (Troiano et al., 2008) and there is evidence that poor physical health or aerobic fitness may negatively impact neurocognition (Voss et al., 2014).

1.2 Background

The hippocampus is a site of known neuroplasticity throughout the lifespan and appears to be particularly sensitive to the positive effects of aerobic exercise (Cotman et al., 2007; Erikson et al, 2011). Preclinical animal studies have found that both acute and sustained aerobic exercise are associated with larger hippocampi (van Praag et al., 2005), hippocampal neurogenesis, prevention of age-related volume loss, and better spatial memory performance in hippocampal mediated tasks (e.g. Morris Water Maze) in young, middle aged, and older aged rodents (van Praag, 2008). For example, age-related declines in hippocampal neurogenesis and cognitive function can be prevented with prolonged running intervention (Kronenber et al., 2006) and rescued with as little as one month of running intervention, even after prolonged sedentary behavior (van Praag et al., 2005). The mechanisms that underlie the effects of aerobic exercise on neuroplasticity and neurogenesis in the hippocampus may be related to changes in various neurotrophic factors (Calof, 1995; Fischer et al., 1994; Kang and Schuman, 1995; Neeper et al, 1995; Molteni et al., 2002; Berchtold et al., 2010), such as brain-derived neurotrophic factor (BDNF; Widenfalk et al, 1999; Lipsky & Marini, 2007; Cowansage et al., 2010; Ding et al., 2011), insulin-like growth factor 1 (IGF-1; Carro et al., 2000; Tang et al., 2010) and vascular endothelial growth factor (VEGF; Trejo et al., 2001) which support new neural growth, synaptic plasticity, and angiogenesis in animal models and human samples. Increases in BDNF expression is associated with faster learning acquisition and better memory in rodents after exercise relative to sedentary controls (Vaynman et al., 2004; Trejo et al., 2001), while increased levels of VEGF are associated with angiogenesis in the hippocampus and subsequent new neurogenesis near new cells (Krum et al., 2002;

Lopez-Lopez et al., 2004; Swain et al., 2003; van Praag et al., 2005). As such, there is clear evidence for the effects of aerobic fitness on brain regions critically associated with learning and memory.

Consistent with pre-clinical animal findings, the literature in older adult human populations shows a link between aerobic fitness and neurocognition, especially in the area of memory. For example, older adults that have been active throughout their lifespan are at a significantly lower risk of developing dementia relative to their low activity and sedentary peers (Griffin et al., 2011). Structured aerobic exercise improves memory in depressed older adults (Khatri et al., 2001), while prolonged exercise slows cognitive decline in cognitively normal older adults and those at risk for neurodegenerative disease (Colcombe & Kramer, 2003) and is associated with larger left hippocampal volume (Firth et al., 2018). Similarly, investigations into the effects of aerobic fitness on brain morphology and functional connectivity in older adult clinical samples have been conducted in an effort to understand the pathophysiology of age-associated neurocognitive disorders (Colcombe & Kramer, 2003; Kramer et al., 1999). Verbal memory is of particular interest, as several disorders impact verbal memory, including many manifestations of dementia, traumatic brain injury, anoxia, drug exposure, and psychiatric disorders (APA, 2013).

However, conclusions made from studies of older adults likely do not generalize to adolescents and young adults, as this population is typically in better physical health, have fewer comorbid medical conditions such as hypertension, hyperlipidemia, and diabetes (CDC, 2017), and are still in a dynamic stage of neurodevelopment that is distinct from both childhood and older adulthood which may moderate the effects of aerobic

fitness interventions on cognitive function. overall brain health and function (Ernst et al, 2006; Casey et al, 2008). During childhood and the transition into adolescence, the brain has an abundance of often-redundant synaptic connections that are pruned away, with those connections that are functionally dormant eliminated (Zehr et al., 2006). This results in reductions in gray matter volume through adolescence and into young adulthood, especially in the prefrontal and parietal regions (Giedd et al., 2012; Gogtay et al., 2004; Sowell, et al., 2004; Lenroot et al., 2007). Frontal gray matter volume peaks by around age 12 followed by reduction in gray matter volume into adolescence while temporal gray matter volume peaks by around age 17 (Giedd et al., 1999). Similar to gray matter, white matter development occurs in sensory and motor pathways earlier followed by higher association cortices later (Giedd et al., 1999), however white matter volumes continue to increase in a mostly linear pattern well into the early 30s without subsequent decreases during and beyond adolescence (Giedd et al., 1999; Jernigan & Gamst, 2005) with the rate of white matter volume maturation roughly equivalent between major subdivisions of the cortex (Thompson et al., 2000). Subcortical regions also display significant changes during adolescence, with some volume differences related to sex-associated hormone changes (Giedd et al., 1996). The interconnectivity of functional networks in the adolescent brain also changes through adolescence into adulthood (Fair et al., 2008; Stevens et al., 2007). Functional connectivity within cortical-subcortical networks follows a similar developmental trajectory to gray and white matter where inefficient connectivity between networks is eliminated as greater connectivity within each network is established (Dosenbach et al, 2010). Increased connectivity within the default mode and other networks may correspond to better cognitive function, including better cognitive flexibility

(Stevens, Pearlson & Calhoun, 2009). The default mode network has connectivity with the hippocampal formation, with the posterior parietal cortex implicated in successful uncued memory recall (Vincent et al., 2006). To date, there have been no neurocognitive investigations of verbal memory network connectivity with the hippocampus in young adults.

Investigations into the effects of aerobic fitness on brain morphology and functional connectivity in preadolescent children have been conducted (Chaddock et al, 2011; Hillman et al, 2009; Hillman, Castelli, & Buck, 2005); however, comparatively few studies have focused on older adolescents or young adults. To date, studies have found that acute exercise is associated with increased verbal learning speed immediately following acute, high impact running in young adult males (Winter et al., 2007), and improved performance on a visual memory and recognition tasks in young adult cyclists (Grego et al., 2008). However, excessive prolonged exercise (generally greater than 60 minutes in one bout) may compromise processing speed and memory performance (Tomporowski, 2003), and may be differentially impacted by type of intervention employed (Lambourne & Tomporowski, 2010). Sedentary young adults who participated in a prolonged aerobic exercise program performed better on a complex pattern separation task along with improvements in maximal oxygen consumption measured via VO_2 Max (Dery et al., 2013).

To our knowledge, there are two studies that examine chronic exercise effects on verbal memory in young adults. High frequency aerobic exercise was associated with improved verbal learning and memory and increased cerebral blood volume in the dentate gyrus of young adults (Pereira et al., 2007), which is consistent with studies coupling neurogenesis with angiogenesis (Louissant et al., 2002; van Praag et al., 2005; Lin et al.,

2002). One exercise intervention study found that aerobic exercise training uniquely impacted relational memory compared to other forms of memory, as it is heavily subserved by the hippocampus, which may be associated with the known neurogenesis that occurs in this region throughout the lifespan (Voss et al., 2013).

Functional connectivity is one way to examine neuronal networks that subserve verbal learning and memory function. The verbal memory network at rest is understood to encompass components of the default mode network and vary based on the nature of the memory task demand. Functional co-activation of neocortical-hippocampal circuits are critical to memory consolidation, while cortico-cortical connectivity is associated with encoding of later successfully recalled verbal information (Albert et al., 2009). Activation in the left medial prefrontal cortex is associated with successful verbal memory encoding (Maillet & Rajah, 2014) and activation of the posterior cingulate cortex is associated with unsuccessful encoding. Further, deactivation of the medial prefrontal cortex is associated with successful memory retrieval (Sestieri et al., 2011) and differential activation of verbal memory network nodes within the default mode network in response to different learning and recall trials (Huo et al., 2018).

To date, only one study has specifically examined the association between aerobic fitness and functional connectivity during a verbal memory task. Herting & Nagel (2013) found no difference between self-reported high and low fitness 15-18-year-old male adolescents in verbal recognition memory performance. However, there was a difference in memory-related default mode network regions during encoding of word pairs that were later successfully recalled, where less aerobically fit adolescents had greater activation in bilateral hippocampi and right superior frontal gyrus, indicating a deficit in deactivation

of the default mode network and switching to task-associated brain networks. The higher aerobic fitness group had greater activation of the hippocampus and concurrent deactivation of the default mode network for remembered words compared to the low fit group, a consistent finding with previous work showing negative activation of the hippocampus and default mode network is associated with better memory retrieval performance (Daselaar et al., 2004; Kim et al., 2011; Vannini et al., 2011). Similarly, in an overlapping sample, Herting & Nagel did not find a significant association between aerobic fitness and verbal list learning and memory but did find a significant effect for spatial learning (Herting & Nagel, 2012). It is notable that these studies utilized a self-reported estimate of aerobic fitness and did not include any females.

Further, given that the few studies that have focused on adolescent and young adult changes in functional networks have targeted males, there is a limited understanding and generalizability of the current literature to females. Indeed, sex differences in hippocampal development, neurotrophic factor regulation, and hormone expression may be negatively correlated with aerobic exercise and cognitive development in females. Sisk & Zehr (2005) report that variations in sex-specific hormones over the course of adolescence and young adulthood may alter the trajectory of cognitive and neurologic development and inform the extent to which aerobic exercise and fitness influences connectivity in developing brains. Further, there are known gender differences in brain structural volume (Persson et al., 2014), functional connectivity (Conrin et al., 2018), and hemispheric asymmetries in memory and language (Hamilton, 2008) that may confer different effects of aerobic intervention on functional and structural organization in the brain. As such, this

study will explore gender differences in the effects of aerobic fitness on resting state functional connectivity and verbal learning and memory.

1.3 Aims of Study

This study will add to the literature by measuring the association between objectively measured aerobic fitness and resting state functional connectivity between the left hippocampus and the rest of the brain in healthy young adults. Further, we examined the degree to which gender moderates these effects. This study offers a unique opportunity to better understand the association of aerobic fitness and neurocognitive function in a gender-balanced sample of healthy young adults. Results from this study may aid in elucidating the extent to which aerobic fitness impacts functional connectivity in the developing brain and how such differential connectivity may serve as protective for subsequent cognitive decline with age. The following aims were proposed:

1.3.1 *Primary Aim:* Assess the Association Between Resting State Functional Connectivity and Aerobic Fitness and the Moderating Influence of Gender.

- Hypothesis 1: Better aerobic fitness will associate with greater connectivity between the left hippocampus and medical prefrontal cortex.
- Hypothesis 2: Better aerobic fitness will associate with a negative association between the left hippocampus and the posterior cingulate cortex.
- Hypothesis 3: There will be a difference in associated connectivity by gender.

1.3.2 *Secondary Aim*: Assess the Association Between Resting State Functional Connectivity and Verbal Learning and Memory in regions that differ by level of aerobic fitness.

- Hypothesis 1: Greater connectivity between the left hippocampus and medial prefrontal cortex will associate with better encoding performance (Trial 1 & Trial 1-5 Total) on the CVLT-II.
- Hypothesis 2: Greater negative correlation between the left hippocampus and posterior cingulate cortex will be associated with better delayed recall on the CVLT-II.

METHODS

2.1 Procedures

Data were drawn from participants from a larger parent study assessing the effects of cannabis use and aerobic fitness on neuropsychological outcomes in adolescents and young adults (PI Lisdahl; R01 DA030354). All aspects of the study protocol were approved by the University of Wisconsin-Milwaukee Institutional Review Board (Study # PRO00016025). There was a two-part screening process. Prior to the initial phone screen, oral consent was received from parents and youth participants who were 18 and older; oral parent permission and assent was received for youth who were minors. On initial screen, interested participants and one parent were interviewed over the phone for demographic information (including age, gender, race/ethnicity, and years of education) and basic eligibility requirements. If determined to be eligible, written consent was obtained from participants aged 18 or older and parents; written parental permission and assent was obtained for participants under age 18. Parents and youth were screened using the Mini Psychiatric Interview (MINI; Sheehan et al, 1998) or the MINI-Kid (Sheehan et al, 1998) to rule out independent life and past-year DSM-IV Axis I disorders other than substance use disorder. The Customary Drinking and Drug Use Record (CDDR; Brown

et al, 1998) was used at baseline to assess the frequency and age of onset of use if applicable for cannabis, alcohol, nicotine and other drug use.

The detailed screen also included the International Physical Activity Questionnaire (IPAQ), a questionnaire of typical physical activity (Fogelholm et al, 2006), and the Physical Activity Readiness Questionnaire (PAR-Q), a questionnaire to assess ability to engage in VO_2 maximum testing (Thomas et al, 1992). Eligible youth participants then came in for five study sessions over the course of 3.5 weeks. The first three sessions occurred weekly and included a brief neuropsychological battery, drug patch and urine toxicology testing. Sessions four and five occurred at least one week after session three and included measures of anthropometrics, aerobic fitness via VO_2 maximum testing, detailed neuropsychological testing, and a brain MRI occurring within 24 to 48 hours of each other and not occurring on the same day. During enrollment in the study, participants were instructed to abstain from alcohol, cannabis, and other drug use, with the exception of tobacco use. Adherence was confirmed through urine, breath, and sweat toxicology assay. Participants who used tobacco were asked to abstain from use at least one hour prior to their MRI session.

2.2 Sample

2.2.1 Participants

A total of 57 healthy young adult participants (see *Sample Descriptive Statistics* table) were recruited from a larger parent study (PI Lisdahl; R01 DA030354). Participants were recruited from the community via media advertisements and flyers posted around universities and local businesses.

Table 1: Sample Descriptive Statistics		
	Mean or Percentage (SD)	***Range***
Age	21.6 (2.18)	18-25
Education (years)	14.8 (1.91)	12-21
WRAT-4 Reading (SS)	105.6 (10.4)	87-133
VO_2 Max (mL/kg/min)	41.4 (8.9)	24.5-62.9
Body Fat (%)	22 (9.7)	6.7-47.2
Race (% Caucasian)	68.40%	
Gender (% Female)	50.90%	

2.2.2 Inclusion/Exclusion Criteria

Inclusion Criteria: Participants were included in the current study if they were English speakers, right-handed, between the ages of 18-25, and had useable resting state functional magnetic resonance imaging (rs-fMRI) data.

Exclusion criteria: Exclusion criteria for the current study included: parent or youth reported prenatal exposure to alcohol (>6 drinks per week or >4 drinks per day) or nicotine, birth complications, premature birth (<33 weeks gestation), history of neurologic disorder, head trauma with >2-minute loss of consciousness, vision or hearing impairments, major health problems (hyperlipidemia, hypertension, diabetes), ability to safely complete VO_2 Max testing, independent DSM-IV Axis I diagnoses, learning and/or intellectual disability, use of psychoactive medication, presence of non-removable metal in body (or other MRI safety and quality contraindications), past year use of cannabis > 104 times, and significant illicit substance use (>30 lifetime uses). Individuals in the parent study were expected to remain abstinent from substances for three weeks prior to their participation, with adherence monitored by urine toxicology and/or continuous sweat patch toxicology testing.

2.3 Measures

2.3.1 Screening and Eligibility

The Mini International Psychiatric Interview (MINI) and the Mini International Psychiatric Interview for Children and Adolescents (MINI-KID) are structured diagnostic interviews developed for use in the United States and Europe designed to be a brief assessment of Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) and International Classification of Diseases (ICD) 10th revision psychiatric disorders (Sheehan et al, 1998). Both have been found to be valid and reliable assessments of Axis I psychopathology (Sheehan et al, 2010).

The Customary Drinking and Drug Use Record (CDDR) is in an interviewer-administered questionnaire that provides past 3 months and lifetime measures of alcohol and drug-related use characteristics, including level of involvement, withdrawal characteristics, symptoms of psychological and behavioral dependence, and negative consequences of use. The CDDR has been found to be a reliable and valid assessment of substance use patterns in both clinical and research settings (Brown et al, 1998).

A modified version of the Timeline Follow-Back (TFLB; Sobell & Sobell, 1992) was used to assess patterns of substance use over the course of the past year by providing memory cues anchored to personal events and holidays (Lisdahl & Price, 2012). Quantity of substance use was measured by standard units: alcohol (standard drinks), nicotine (number of cigarettes and hits of chew/snuff/pipe/cigar/hookah), cannabis (all methods converted to joints or milligrams in concentrates), ecstasy (number of tablets), sedatives (number of pills or hits of GHB), stimulants (cocaine and methamphetamine use converted to milligrams and number of amphetamine pills),

hallucinogens (number of hits or occasions of ketamine/salvia/shrooms/other hallucinogens), opioids (number of hits of heroin/opium), and inhalants (number of hits).

2.3.2 Neuropsychological Assessment

Verbal Learning and Memory: Participants were administered a comprehensive battery of neuropsychological tests as part of the parent study. Of relevance to the proposed study, the California Verbal Learning Test – 2nd Edition (CVLT-II; Delis et al., 2000) was used as measure of unstructured verbal learning and memory. The CVLT-II involves the auditory presentation of 16 words that conform to four semantic categories. The word list is presented five times with a free recall prompt after each trial. Participants are then administered a distractor list of 16 words that conform to the same four semantic categories. There is then an immediate free recall prompt where the participant is instructed to recall as many words as they can from the first list that was presented five times, followed by a cued recall where they are instructed to recall words that belong to each semantic category in turn. There is then an unprompted 20-30-minute delay period before the participant is asked to both free recall and cued recall the list, followed by a forced choice recognition trial.

2.3.3 Anthropometrics

Anthropometric measures included height and weight measured in light clothes and without shoes, with Body Mass Index (BMI) calculated as participant weight divided by height squared ($kg*m_2$). Body fat percentage was measured by electrical bioimpedance analysis system [The Tanita Body Composition Analyzer, TBF-300 (Tanita Corporation, Tokyo, Japan)].

2.3.4 Physical Activity and Aerobic Fitness

Participants' aerobic fitness level was measured as a function of maximal aerobic capacity and quantified as a VO_2 maximum (VO_2 Max) score. Participants were instructed to refrain from food and caffeine for 4 hours prior to VO_2 Max testing. Prior to each participant session, the metabolic measurement system [ParvoMedics TrueOne 2400 (ParvoMedics, Salt Lake City, UT)] was calibrated using a two-point calibration for the gas analyzers (room air and certified gas: 4.008% CO_2, 15.98% O_2, balance N_2) and a 3L syringe for the pneumotachometer. Participants were fitted with the rubber mouthpiece connected to a two-way non-rebreathing valve [Hans Rudolf 2700 series (Kansas City, MO)], nose clip, and heart rate strap (Polar Wearlink 31, Finland) for heart rate measurement and collection of expired gases. Maximal aerobic capacity is the point at which oxygen consumption reaches a plateau during sustained aerobic activity and is considered the gold standard for measuring cardiorespiratory capacity during exercise (Myers et al, 2002), and is understood to be a stable measure of aerobic fitness despite short term changes in levels of physical activity. VO_2 Max was measured using a treadmill (Full Vision Inc., TMX425C Trackmaster, Newton, KS) following the Bruce protocol for graded exercise testing, a widely used, reliable, standardized approach appropriate for use in young adult samples (ACSM, 2006). Participants were provided with procedures, explanation of known minimal risks, and instructed to complete as much work as possible but they could stop the assessment at any time they wished. They were then instructed to begin by walking or running at a comfortable speed. The speed and/or grade were then systematically increased at each Bruce protocol stage. Heart rate expired respiratory

gases, and subjective rating of exertion by each participant were collected at each stage. The assessment was ended when the participant reached their individual max or reached grade VI of the Bruce protocol.

2.3.5 MRI Acquisition and Processing

Acquisition: MRI scan data were collected using a 3T Signa LX MRI scanner (GE Healthcare, Waukesha, WI) using a 32-channel quadrature transmit/receive head coil. High-resolution anatomical images were acquired using a T1-weighted spoiled gradient-recalled at steady-state (SPGR) pulse sequence (TR = 8.2 ms, TE = 3.4 s, TI = 450 and flip angle of 12°). The in-plane resolution of the anatomical images was 256x256 with a square field of view (FOV) of 240 mm. One hundred fifty slices were acquired at 1 mm thickness. Functional resting-state MRI scans were acquired with gradient-echo echo planar imaging (EPI) pulse sequences in the sagittal orientation (TR = 2 sec, TE = 25 ms and flip angle = 90°). The in-plane resolution was 64x64 with a FOV of 240 mm with 40 contiguous 3.7 mm slices. Participants were instructed to lie awake with their eyes closed for the six-minute resting scan.

MRI Preprocessing: Resting-state fMRI scan data were preprocessed and analyzed using AFNI software (Cox, 1996). The first four time points of each acquisition were removed due to T1 stabilization effects. Motion was corrected for by rigidly aligning each volume to the mean image volume of the sample. The data were despiked and linear and quadratic detrended. Functional data was smoothed in-plane using a 6 mm full width half maximum Gaussian kernel and then temporally filtered ($0.005 < f < 0.1$). The SPGR was normalized to a standard dataset (MNI152) and the resulting registration matrix was

applied to the resting-state scan. Nuisance signals, including white matter and CSF signals, and six motion parameters were regressed from the data using 3DDeconvolve (Fox et al., 2005; Gusnard, Raichle, & Raichle, 2001).

2.4 Data Analysis

2.4.1 Primary Aim: Resting State Functional Connectivity and Aerobic Fitness Analysis

To assess functional connectivity between the left hippocampus and the rest of the brain, seed-based whole brain resting state functional connectivity analyses were performed using a 4-millimeter radius sphere centered in the left hippocampus (MNI coordinates: -20, -30, -8), consistent with previous literature assessing whole hippocampus connectivity (Holmes et al., 2014). The correlation between time series activation in the left hippocampus and whole brain was calculated to identify regions of correlated and anti-correlated activation. Correlation coefficients were transformed to Fischer Z-scores in AFNI software (Cox, 1996). Changes in hippocampal functional connectivity associated with VO_2 Max performance was first analyzed using a general linear model via 3Dttest++ in AFNI. A second GLM of a VO_2 Max*Gender interaction predicting hippocampal connectivity was then conducted to assess the moderating effect to gender. A family-wise error (FWE) threshold of $p_{FWE} < 0.05$ (individual voxel level ($p < 0.001$) was used via a cluster-threshold method to correct for multiple comparisons at the whole group level, and $p_{FWE} < 0.10$ (individual voxel level ($p < 0.001$) at the subgroup level using 10,000 Monte Carlo simulations via 3DClustSim within AFNI. These threshold cutoffs have shown to reduce false-positive rates (Cox, Chen, Glen, Reynolds, & Taylor, 2017; Slotnick, 2017).

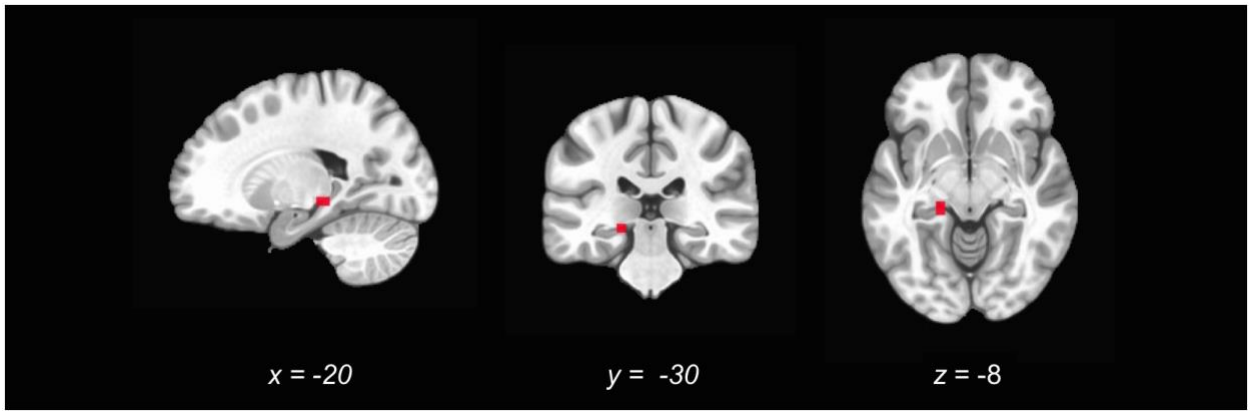

Figure 1: Location of 4mm seed in left hippocampus (MNI: -20, -30, -8).

2.4.2. Secondary Aim: Resting State Functional Connectivity and Verbal Learning and Memory Analysis

Fischer Z-scores demonstrating the strength of relationship between the seed region (left hippocampus) and clusters that were significantly associated with VO_2 Max or gender interactions were extracted and correlated with CVLT-II learning and memory scores to assess the degree to which differential connectivity associates with out of scanner verbal learning and memory performance. SPSS software (Microsoft, version 24) was used to calculate the Pearson's correlation coefficient between the mean Z-score of each significant resting state functional connectivity region and scores of the CVLT-II (specifically Trial 1, Trial 1-5 Total Score, Short Delay Free Recall, and Long Delay Free Recall).

RESULTS

3.1 Sample Descriptive Statistics

Descriptive statistics of the sample separated by gender (Table 2) and VO_2 Max median split (Table 3) are reported below. In terms of gender, there was a significant difference in raw VO_2 Max performance, where males had a higher average VO_2 Max score compared to females ($t = 4.883$, $p < 0.05$). There was also a difference in racial identification by gender, where females had a higher percentage of Caucasians relative to the males ($\chi_2 = 12.09$, $p < 0.05$).

Table 2: Descriptive Statistics by Gender

	Female (n=29)	Male (n=28)		
	Mean (SD) [range]		*t-stat or χ2*	*p-value*
Age	21.7 (1.9) [18-25]	21.5 (1.9) [18-25]	-0.387	0.70
Education (years)	14.7 (1.7) [12-19]	14.9 (1.7) [12-21]	0.399	0.69
WRAT-4 Reading (SS)	104.5 (10.1) [90-133]	106.7 (10.7) [87-133]	0.809	0.42
Body Fat (%)	28.3 (7.1) [16.3-47.2]	16.1 (8.0) [6.7-41.7]	**-6.078**	**<0.001**
VO_2 Max (mL/kg/min)	36.7 (7.1) [28.6-62.9]	46.4 (7.9) [24.5-49.4]	**4.883**	**< 0.05**
Race (% Caucasian)	75.9%	58.6%	**12.09**	**< 0.05**
Gender (%Female)	0.51	0.49	0.018	0.90

When the sample was divided by median VO_2 Max (median = 42.4 mL/kg/min), as expected there was a significant difference in percentage body fat, where the lower VO_2 Max group had a higher average percentage body fat compared to high VO_2 Max group ($t = 4.782$, $p = 0.00001$). There was also a difference observed gender percentage by VO_2 Max group, where there was a higher than statistically expected representation of females in the low VO_2 Max group and lower representation in the high VO_2 Max group ($\chi_2 = 12.81$, $p = 0.001$).

Table 3: Descriptive Statistics by VO_2 Max				
	VO_2 Max Low (n=28)	**VO_2 Max High (n=29)**		
	Mean (SD) [range]		***t-stat or χ2***	***p-value***
VO_2 Max Median Split	34.0 (4.9) [24.5-41.2]	48.6 (5.1) [42.4-62.9]		
Age	21.8 (2.1) 18-25]	21.4 (2.3) [18-25]	0.701	0.49
Education (years)	15.0 (2.0) [12-21]	14.6 (1.8) [12-19]	0.958	0.34
Body Fat (%)	27.7 (8.9) [8.7-47.2]	17.2 (7.5) [6.7-31.8]	**4.782**	**0.00001**
Race (% Caucasian)	57.1%	79.3%	3.24	0.064
Gender (% Female)	75%	27.6%	**12.81**	**0.001**

3.2 Primary Aim: Whole Brain Resting State Functional Connectivity and VO_2 Max Analysis

VO_2 Max: Results of association between VO_2 Max level and resting state functional connectivity pattern between the left hippocampus and the whole brain revealed one statistically significant cluster of co-activation in the left parahippocampal gyrus (cluster size: 112 voxels; center of mass (20.6, 17.1, -9.7); peak (24, 18, -12) after correction for multiple comparisons (cluster $p_{FWE} < 0.05$, voxel $p < 0.001$).

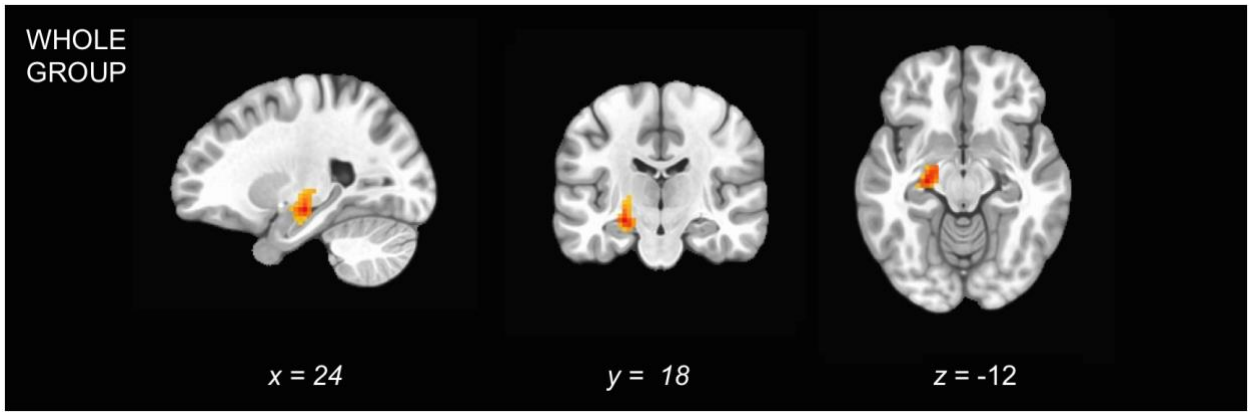

Figure 2: Functional connectivity between the left hippocampus and left parahippocampal gyrus associated with aerobic fitness level

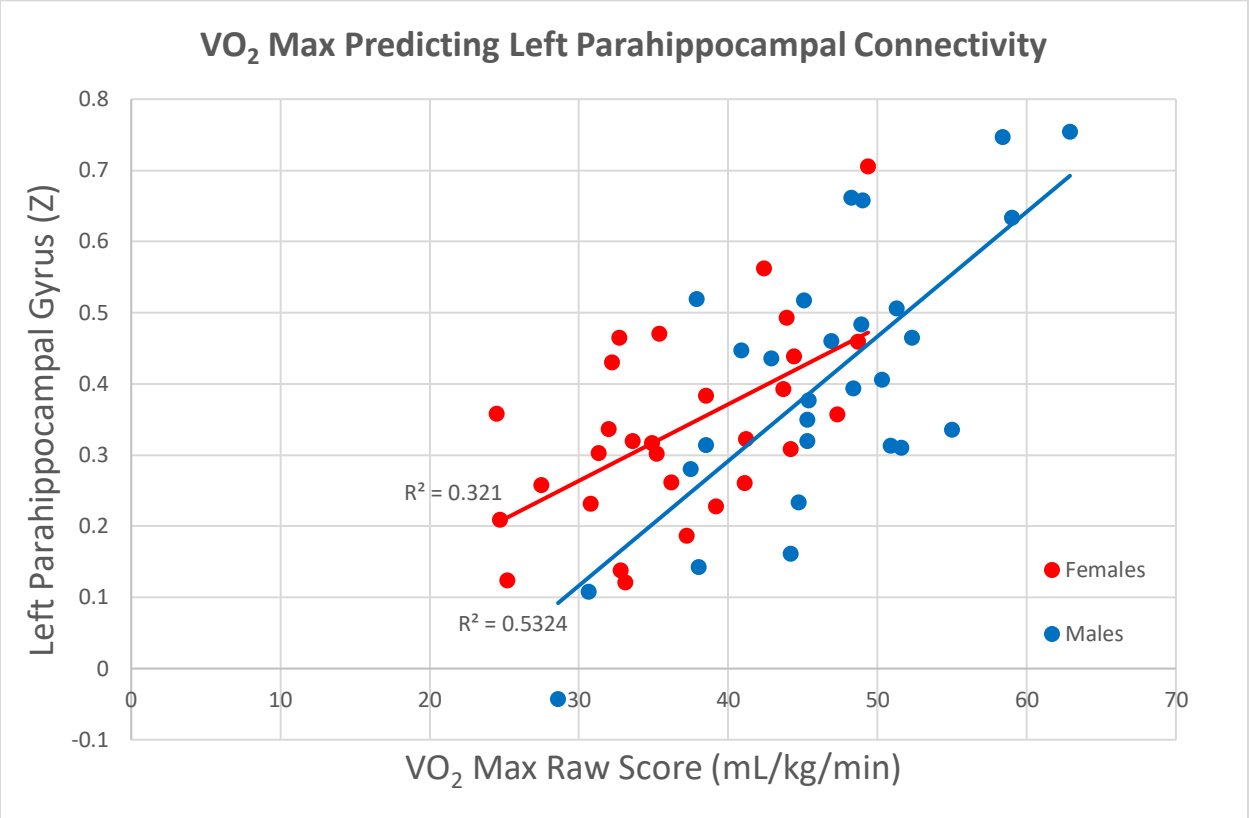

Figure 3: Bivariate scatterplot demonstrating association between extent of connectivity between left parahippocampal gyrus and left hippocampus associated with VO_2 Max score, parsed by gender.

VO_2 Max*Gender: Results of VO_2 Max*Gender association with left hippocampal functional connectivity yielded one cluster of anti-correlation with the right parahippocampal gyrus, which did not survive correction for multiple comparisons (cluster size: 30 voxels; center of mass (-27.7, 4.1, -16.4); peak (-24, 3, -15).

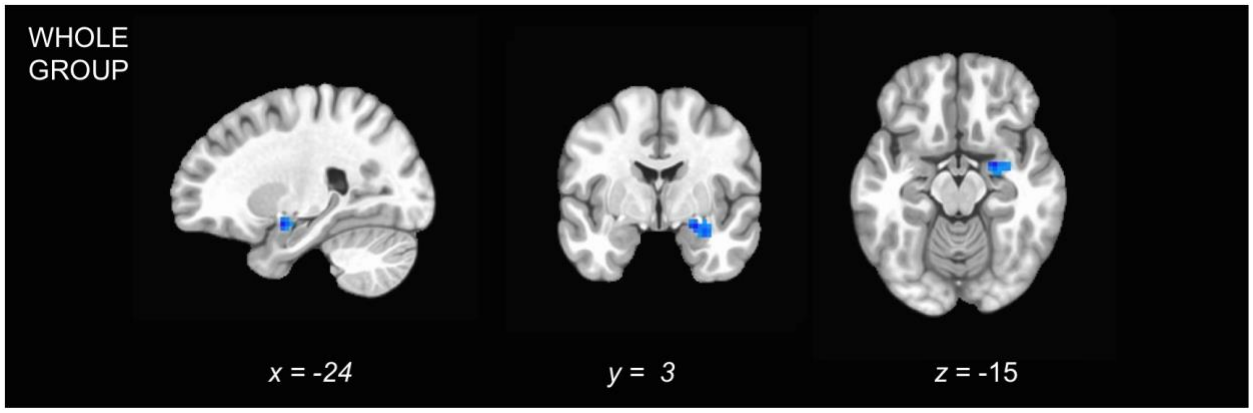

Figure 4: Functional connectivity between left hippocampus and right parahippocampal gyrus marginally associated with aerobic fitness.

Exploratory Post-Hoc Whole Brain Connectivity: VO_2 Max Separately by Gender

Males: Results of VO_2 Max level associated with resting state functional connectivity to the left hippocampus in the male group yielded one statistically significant cluster of co-activation in the left parahippocampal gyrus (cluster size: 57 voxels; center of mass (21.2, 13.1, -14.2); peak (18, 9, -19) that survived correction for multiple comparisons ($p_{FWE} < 0.10$ (individual voxel level $p < 0.001$) and one cluster of co-activation in the right parahippocampal gyrus (cluster size: 39 voxels; center of mass (-25.9, 6.1, -16.2); peak (-24, 6, -15) that did not survive correction for multiple comparisons.

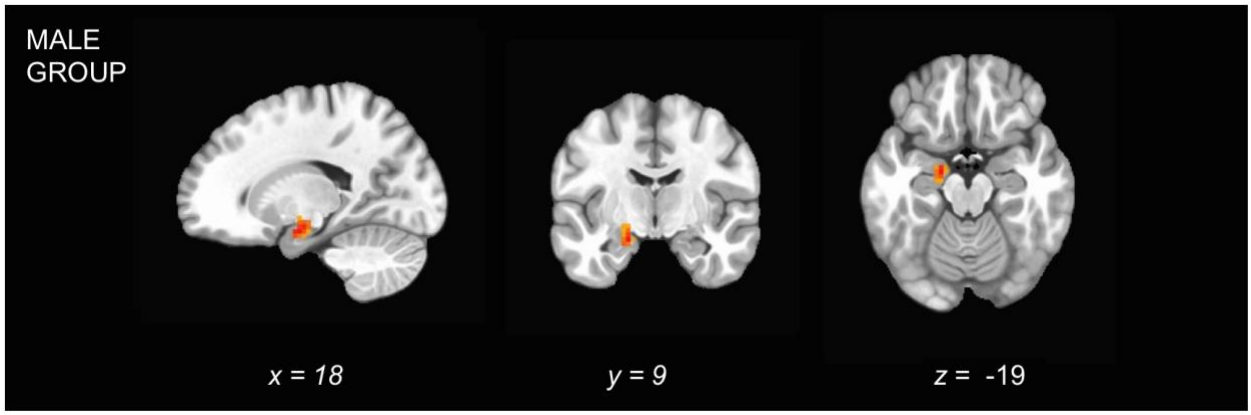

Figure 5: Functional connectivity between left hippocampus and left parahippocampal gyrus associated with aerobic fitness in males.

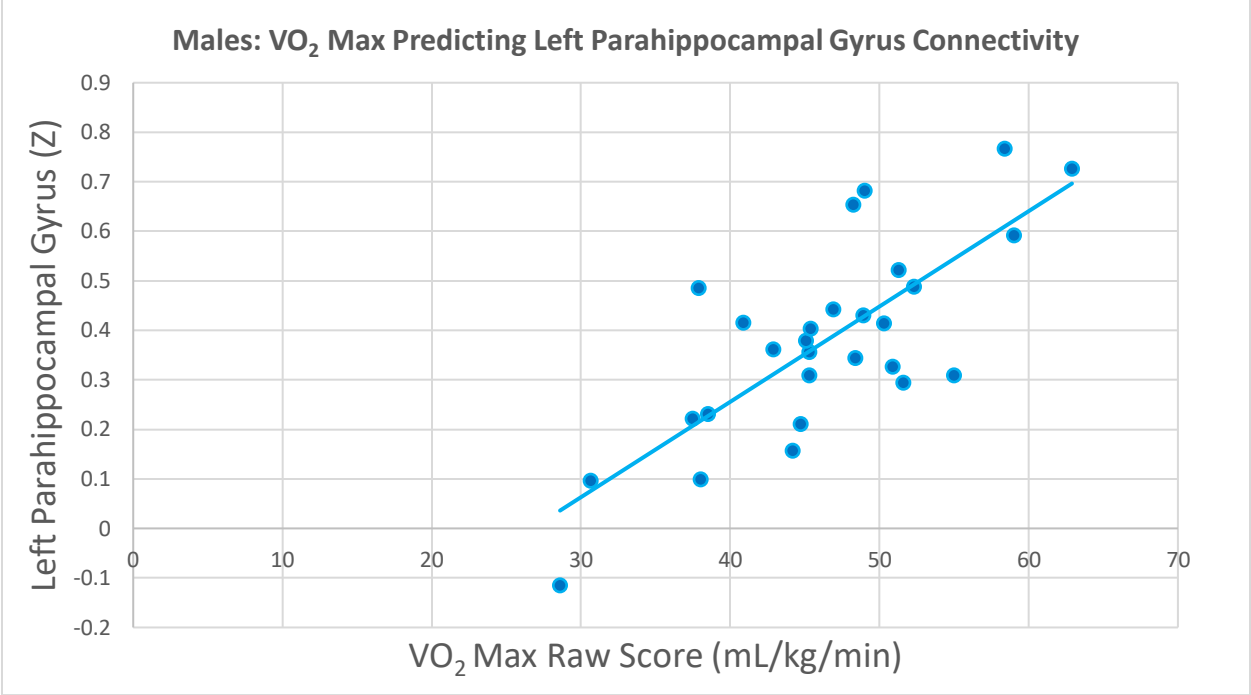

Figure 6: Bivariate scatterplot demonstrating association between extent of connectivity between left parahippocampal gyrus and left hippocampus associated with VO2 Max score in males.

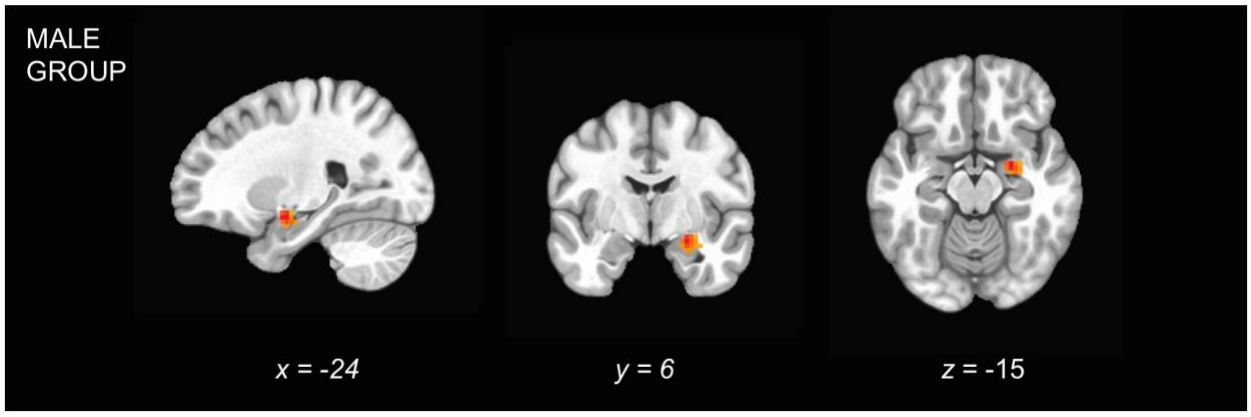

Figure 7: Functional connectivity between left hippocampus and right parahippocampal gyrus marginally associated with aerobic fitness in males.

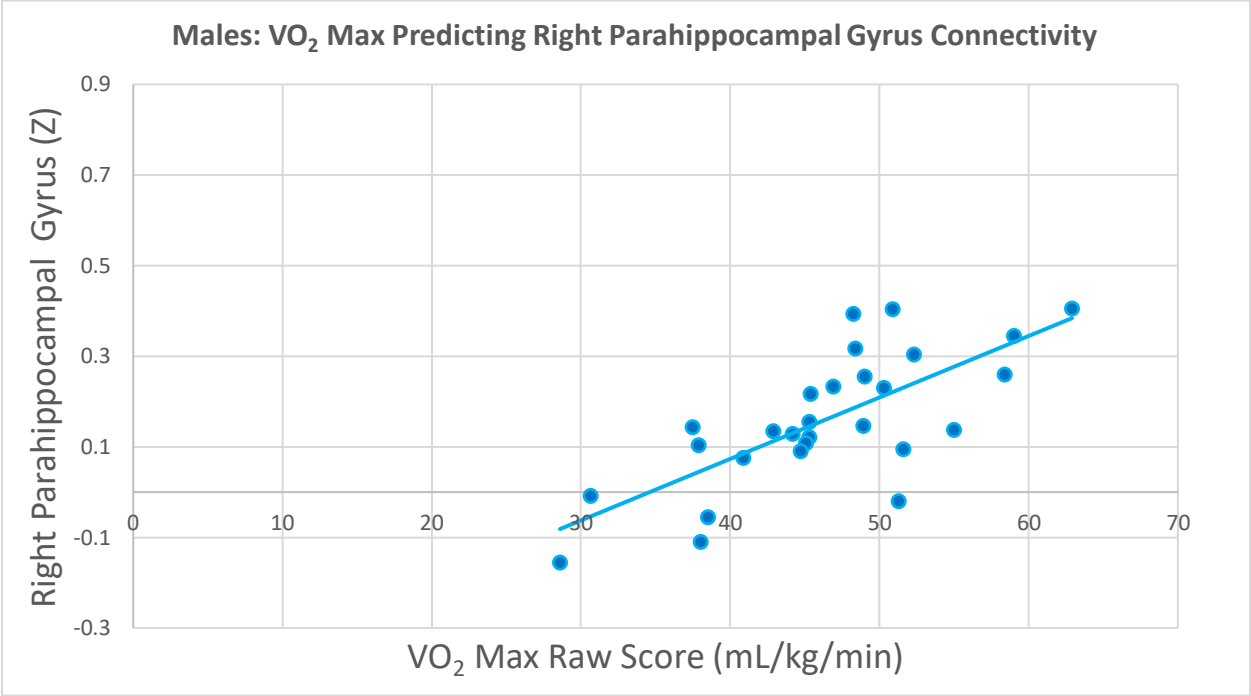

Figure 8: Bivariate scatterplot demonstrating marginal association between extent of connectivity between right parahippocampal gyrus and left hippocampus associated with VO2 Max score in males.

Females: Results of VO_2 Max level predicting resting state functional connectivity to the left hippocampus in the female group did not yield statistically significant clusters

that survived correction for multiple comparisons. Two clusters were observed before correction: co-activation in the left cingulate gyrus (cluster size: 29 voxels; center of mass (20.4, 35.1, 36.2); peak (24, 36, 39) and anti-correlation in the right inferior temporal gyrus (cluster size: 23 voxels; center of mass (-53.7, 59.7, -4.9); peak (-57, 66, -3).

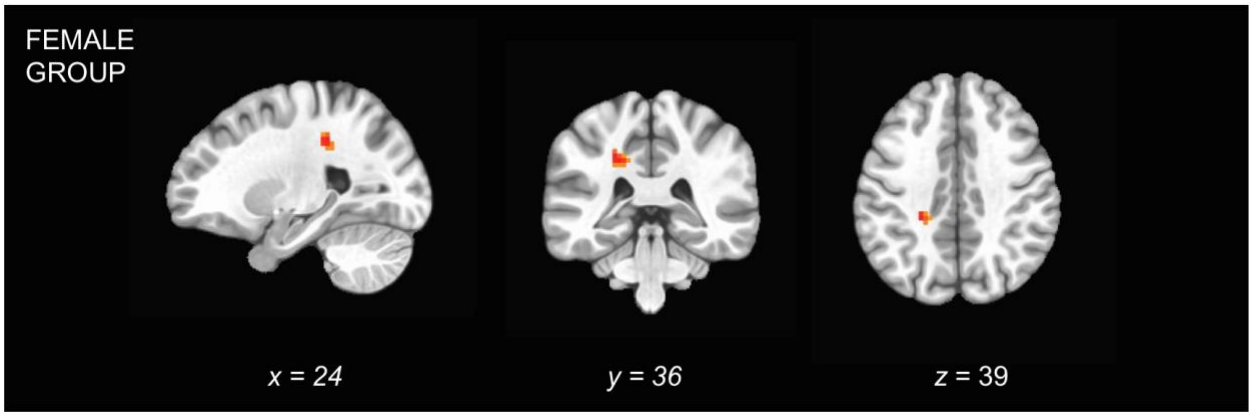

Figure 9: Functional connectivity between left hippocampus and left cingulate gyrus marginally associated with aerobic fitness in females.

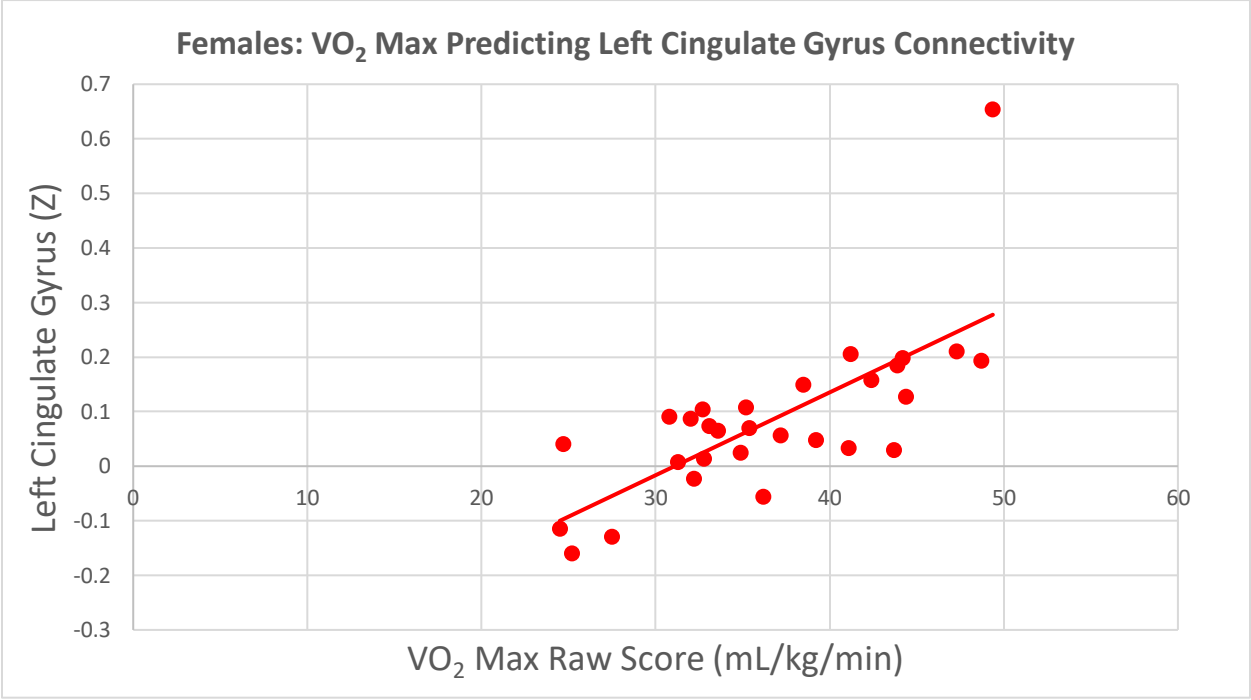

Figure 10: Bivariate scatterplot demonstrating non-significant association between extent of connectivity between left cingulate gyrus and left hippocampus associated with VO_2 Max scores in females.

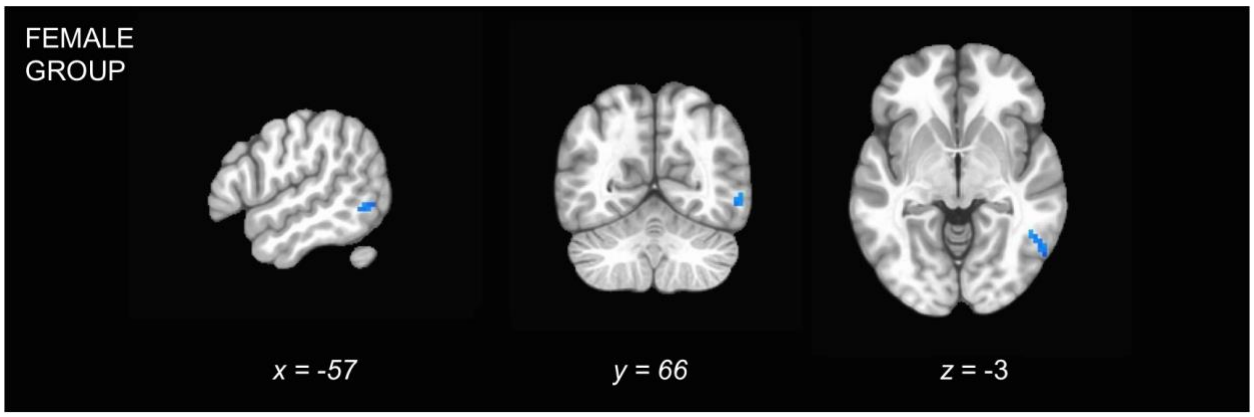

Figure 11: Functional connectivity between left hippocampus and right inferior temporal gyrus marginally associated with aerobic fitness in females.

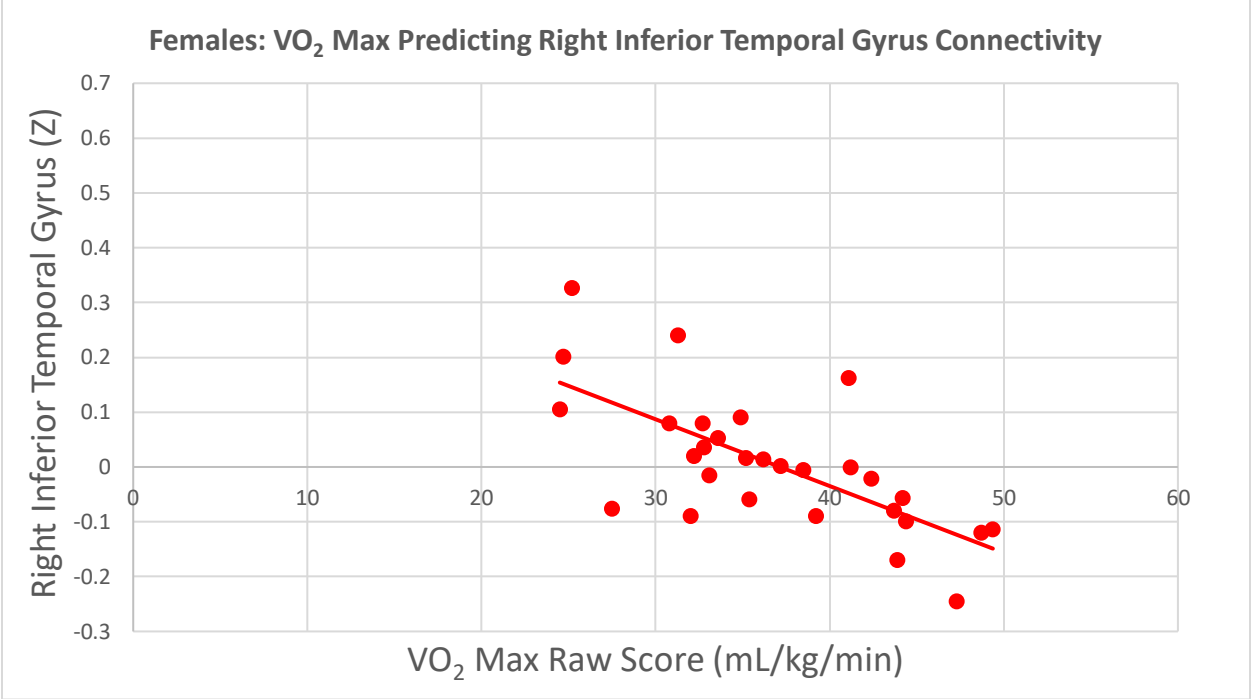

Figure 12: Bivariate scatterplot demonstrating non-significant right inferior temporal gyrus anti-correlation with left hippocampus associated with VO2 Max scores in females.

3.3 Secondary Aim: Brain-Behavior Relationships: Resting State Functional Connectivity ROIs and Verbal Learning and Memory Analysis

Fisher Z-scores from the significant cluster of co-activation in the left parahippocampal gyrus were correlated with CVLT-II indices. There was a significant

negative correlation between connectivity to the left parahippocampal gyrus and total intrusions (r = -0.265, p = 0.047). Marginally significant correlations were observed for trial 1 (r = 0.235, p = 0.079) and trial B (r = 0.213, p = 0.111). No significant correlations were observed for trial 1-5 total score (p = 0.816), short delay (p = 0.703), or long delay (p = 0.582) free recall memory.

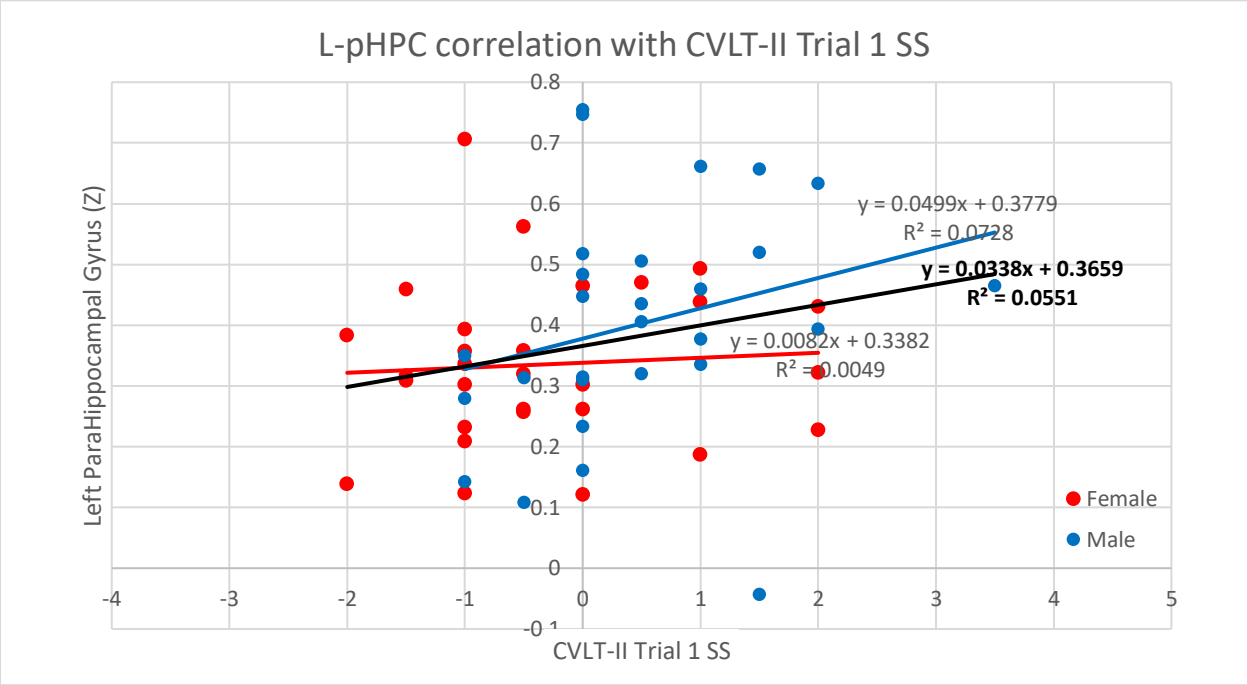

Figure 13: Bivariate scatterplot demonstrating marginal association between extent of connectivity to the left parahippocampal gyrus with CVLT-II Trial 1 standard score.

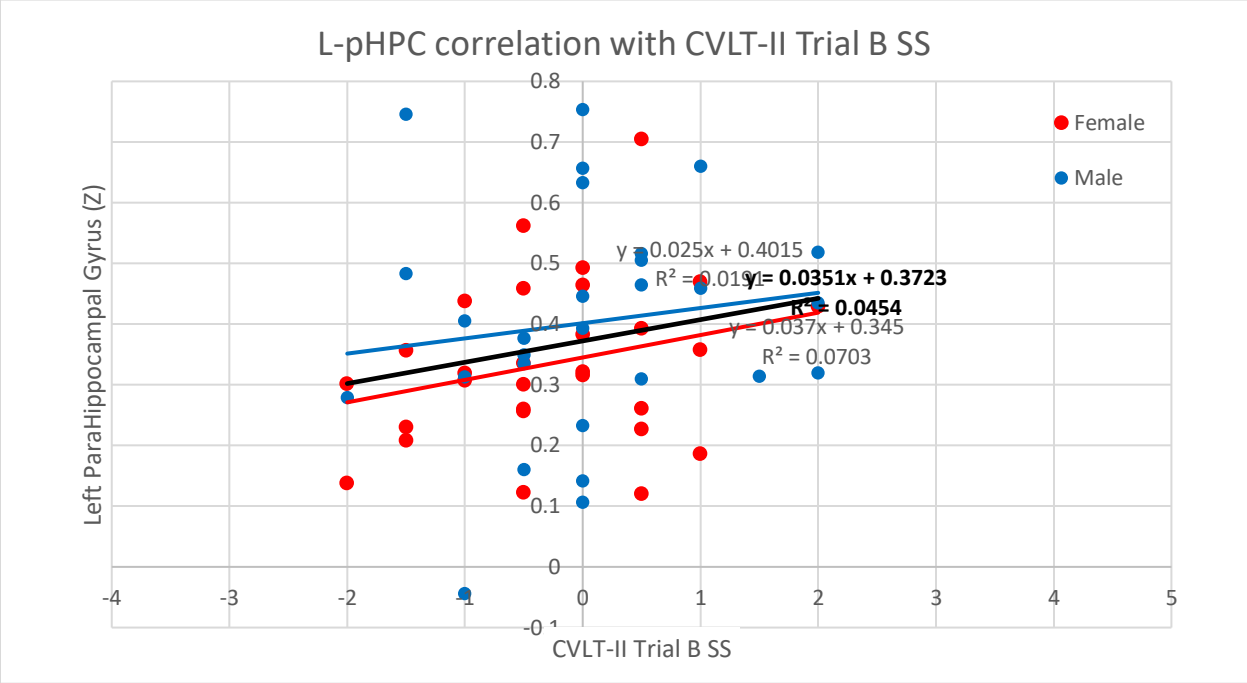

Figure 14: Bivariate scatterplot demonstrating marginal association between extent of connectivity to the left parahippocampal gyrus with CVLT-II Trial B standard score.

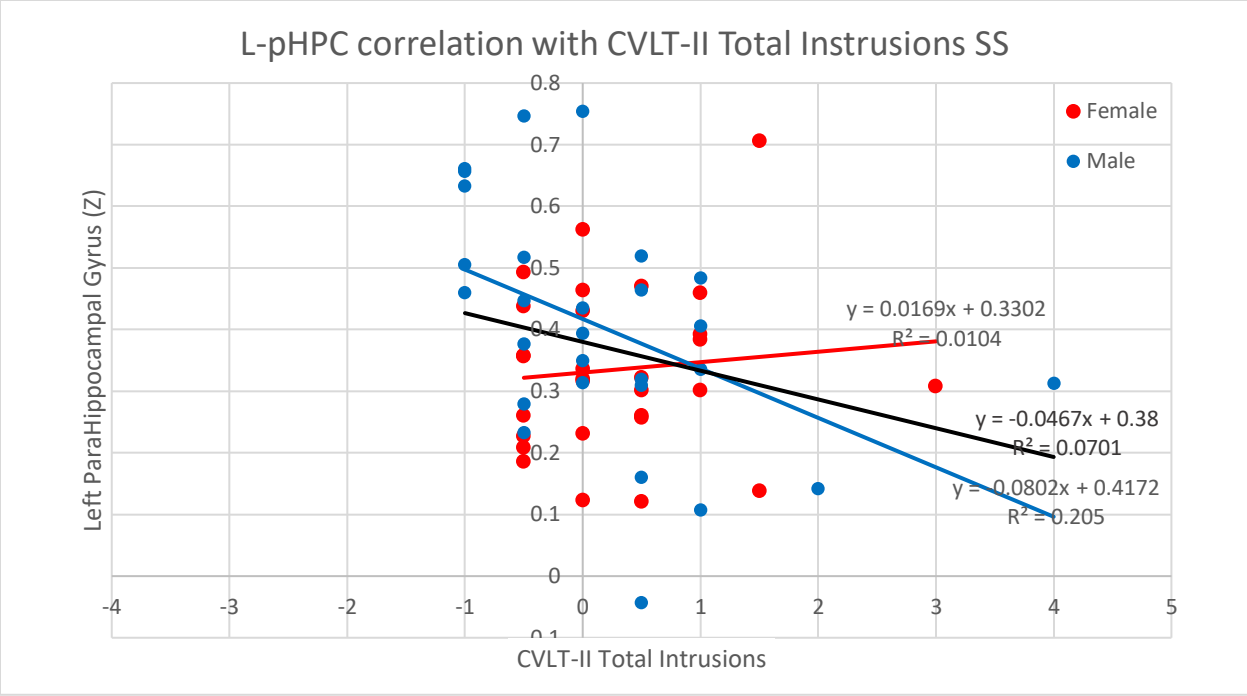

Figure 15: Bivariate scatterplot demonstrating significant association between extent of connectivity to the left parahippocampal gyrus with CVLT-II Total Intrusions standard score.

DISCUSSION

The current study set out to understand the relationship between objective measures of aerobic fitness and resting state functional connectivity between the left hippocampus, a region critically involved in verbal learning and memory, and the whole brain. Superior aerobic fitness was positively associated with connectivity between the left hippocampus and the left parahippocampal gyrus, a region known for its role in encoding and memory (Strange et al., 2002). Co-activation of the left hippocampus and left parahippocampal gyrus that associated with better aerobic fitness was also correlated with superior verbal working memory, auditory attention, and single-trial learning in this sample of healthy adolescents and young adults. There was no significant gender-by-aerobic fitness interactions, however exploratory analyses suggest this is an area that requires additional research with a larger sample.

The significant association of superior aerobic-fitness and increased connectivity between the left hippocampus and parahippocampal gyrus is consistent with known functional neuroanatomy of the hippocampal complex and mesial temporal lobe structures. The hippocampus is physically connected to parahippocampal gyrus via the subiculum, with the anterior aspect of the parahippocampal gyrus comprised of the entorhinal cortex, a region that serves as a node for input and output between association cortex and the hippocampal formation (Blumenthal, 2010). Further inputs to the hippocampal formation via the entorhinal cortex rise from the posterior two thirds of the parahippocampal gyrus, comprised of the perirhinal cortex and parahippocampal cortex. Functional connectivity between the left hippocampus and parahippocampal gyrus associated with aerobic fitness is likely due to aerobic effects on neuroplasticity in

the greater hippocampal complex, especially the dentate gyrus (Toda et al., 2019). This plasticity is likely to be mediated by the various neurotrophic (e.g. BDNF) and angiogenic (e.g. VEGF and IGF-1) factors known the be released and associated with acute and sustained aerobic exercise (Pereira et al., 2007; Louissant et al., 2002; van Praag et al., 2005; Lin et al., 2002; Voss et al., 2013).

In this connectivity network associated with aerobic fitness, we found that positive functional connectivity was correlated with superior performance on single trial learning, auditory attention, and verbal working memory, which are essential components of successful encoding and subsequent retrieval (Delis et al, 2000). Consistent with these findings, several functional studies have shown that activation in the parahippocampal gyrus is associated with better encoding, retrieval, and recognition of both verbal (Fernandez & Tendolkar, 2002) and visual information *(*Brewer et al 1998; Wagner et al., 1997; Kirchoff et al., 2000; Aggelton & Brown, 1999). Activity in parahippocampal gyrus has also been associated with item novelty (Tulving et al, 1996; Stern et al., 1996; Dolan & Fletcher, 1997; Gabrieli et al., 1997) and better performance on single presentation memory tasks (Eichenbaum et al., 2000), which may facilitate better working memory performance. It appears that the benefits of aerobic fitness on functional connectivity with the hippocampus are focal to immediately physically connected and functionally associated mesial temporal regions, thereby conferring more efficient connectivity between the hippocampus and a critical “on ramp” for afferents to the greater hippocampal complex. Further, findings by Strange and colleagues (2002) support the functional integration of perirhinal cortex and hippocampal body in encoding and retrieval and that both regions may independently contribute to verbal encoding.

These results were found in predominantly left-sided perirhinal and hippocampal activation in response to list learning and recall, consistent with the historical and contemporary understanding of the dominance of the left medial temporal lobe in verbal memory (Milner, 1972).

While gender was not found to moderate the relationship between aerobic fitness and hippocampal resting-state connectivity, visual inspection of the scatter plots revealed potential gender differences, such that males appeared to drive the association between higher aerobic fitness and left parahippocampal connectivity. Further, males appeared to drive the correlation between aerobic fitness associated with left parahippocampal gyrus co-activation with CVLT-II Trial 1 and Total Intrusions. Notably, left parahippocampal connectivity separated by gender shows the male group had more individuals with raw VO_2 Max scores >50 mL/kg/min, while no individuals in the female group exceeded 50 mL/kg/min. This finding may indicate that there is a minimum raw VO_2 Max threshold to be reached before there is a robust effect on functional connectivity and may also reflect that males benefit more from increased aerobic fitness in brain regions important for verbal learning and memory. However, these results are considered exploratory due to lowered power to detect small effect sizes for the gender by VO_2 Max interaction (57% power estimated; Erdfelder et al, 1996). Thus, larger studies that include male and female adolescents and young adults with a greater range of VO_2 Max scores would help elucidate the mechanisms at play that confer this potential gender difference. Additional research is also needed to examine whether interventions aimed at improving neurocognitive functioning via aerobic exercise regimens impact the sexes differently.

Several factors may account for the lack of support for the original hypotheses. This study sought to understand the influence of cardiovascular fitness on the hippocampus, a region with known sensitivity to the beneficial effects provided by superior aerobic fitness, including evidence of increased neuroplasticity, neurogenesis, and angiogenesis. Previous studies have found association between aerobic fitness and broader default mode network activation (Herting & Nagel, 2013) during a scanner-based task, which we did not observe. It is possible that there is a selective sensitivity of the greater hippocampal complex and surrounding cortex to aerobic fitness benefits. Indeed, prior studies have shown the dentate gyrus and hippocampal formation to be uniquely impacted by neurotrophic and angiogenic factors (Pereira et al, 2007; Redlila et al, 2006), an effect which may be more nuanced in other parts of the brain. Secondly, our sample was comprised of young, metabolically healthy individuals with no significant cardiovascular or other medical comorbidities; it is possible that more robust relationships between aerobic fitness and hippocampal connectivity would be observed in samples with a greater range of cardiorespiratory fitness and varying degrees of health status. Even so, a subtle relationship between cardiovascular fitness and hippocampal – parahippcampal gyrus connectivity was observed and this was correlated with downstream verbal learning and memory performance. Thus, the present findings support the idea that aerobic fitness is linked with brain health even in a young, healthy sample. This may lay the foundation for protective factors for later onset risk of mood, psychiatric, and cognitive impairments as we age. Additional considerations for future research include using measures of learning and memory to predict verbal memory connectivity networks and how that connectivity is moderated by

level of aerobic fitness. Such an approach may offer unique insights into networks associated with specific domains of neurocognitive function and the role that aerobic fitness may play in moderating the functional connectivity of these specific networks. Further, integration of other covariates of aerobic and metabolic health, such as subjective reports of physical activity type, degree, and quantity as well as measures of visceral and subcutaneous adipose tissue, may further elucidate the relationship between health status and functional activity in the brain.

Limitations to the current study include a relatively small sample size comprised of healthy young adults with no psychiatric or medical comorbidities and without expected learning or memory deficits, thus creating a truncated range of both raw aerobic fitness scores and neurocognitive performance, likely reducing effect size and power especially in detecting gender interactions. Future studies would benefit from a broader range of ages, cognitive status, health and lifestyle factors that may increase variability and thus sensitivity to change. Another important consideration is the high correlation of VO_2 Max with percentage body fat, which could not be controlled for in the analysis due to multicollinearity. Importantly, this study only assessed the correlation between aerobic fitness and functional connectivity in a cross section of time, thereby not allowing for predictive or causal conclusions. For example, it is possible that participants with greater functional connectivity engage in more aerobic exercise. These limitations emphasize the importance and need for prospective, longitudinal studies such as the Adolescent Brain Cognitive Development (ABCD) Study ® (Jernigan et al, 2018) that assess the relationship between physical activity, adiposity, and brain development in a large sample of boys and girls as they age.

In summary, this study contributes to the rapidly growing body of literature that increasingly shows a positive relationship between aerobic fitness and neurocognitive function. From a public health standpoint, these findings suggest that the benefits of aerobic fitness on neurocognitive function may not only be reserved for those that have experienced subjective and objective change in the cognitive function. These cross-sectional findings lend support to the importance of public health initiatives to promote physical activity and aerobic fitness in adolescents and young adults and that maintenance of these positive health behaviors should be sustained through young adulthood when activity levels often begin to decline. This also lends further evidence that aerobic exercise may be a viable low-cost, high-return intervention to improve brain health in clinical samples. Further studies should investigate the use of aerobic exercise interventions in neuropsychological and psychiatric clinical populations across the lifespan such as addiction/substance use, traumatic brain injury, and other acquired brain injuries (Lisdahl et al, 2013).

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CURRICULUM VITAE

Kyle J. Jennette

EDUCATION

Ph.D **Clinical Psychology**, University of Wisconsin-Milwaukee
Graduate Advisor: Krista Lisdahl, Ph.D.
Dissertation: *The Association of Aerobic Fitness with Resting State Functional Connectivity and Verbal Learning and Memory in Young Adults*
2014 –2020

M.A. **Gerontology** (Minor: Clinical Service), University of South Florida
Graduate Advisor: Brent Small, Ph.D.
Thesis: *The Association of Cognitive Endophenotypes and Risky Single Nucleotide Polymorphisms of Alzheimer's Disease within the Alzheimer's Disease Neuroimaging Initiative (ADNI) Database*
2012–2015

B.A. **Psychology** (Minor: Environmental Science), Flagler College
Thesis (Psychology): *The Distinguishing Factors of Dementia: Etiologies, Diagnostics, and Treatments*.
Thesis (Environmental Science): *The Effects of Increased Acidity on Shell Integrity and Body Size of Crassostrea virginica*.
2008-2011

APA-ACCREDITED POSTDOCTORAL FELLOWSHIP

University of Illinois – Chicago – Adult Neuropsychology (2020-2022)
Training Director: Jason Soble, Ph.D. ABPP-CN
Supervisors: Neil Pliskin, Ph.D. ABPP-CN, Jason Soble, Ph.D., ABPP-CN and Woojin Song, Ph.D.

APA-ACCREDITED PREDOCTORAL INTERNSHIP

The University of Chicago Medicine - Adult Neuropsychology Track (2019 – 2020)
Training Director: Shona Vas, Ph.D.

Memory Disorders Clinic (July 2019-December 2019)
Supervisors: Joseph Fink, Ph.D., ABPP-CN and Maureen Lacy, Ph.D.

General Neuropsychology: Administer comprehensive neuropsychological evaluations for variety of predominantly amnestic syndromes. Conduct interviews and feedback sessions. Supervise doctoral externs on rotation. Geriatric Neuropsychology: Administer brief, focused neuropsychological evaluations, with an emphasis on differential diagnosis and treatment recommendations in a fast paced clinic. Assess differential etiologies of primary progressive dementias, vascular dementia, and other amnestic syndromes. Conduct interviews of patients and family. Supervise doctoral student externs on rotation.

Medical Neuropsychology Clinic (July 2019-December 2019)
Supervisors: Joseph Fink, Ph.D., ABPP-CN and Maureen Lacy, Ph.D.

Neuropsychological assessment of adult patients drawn from Neurology, Neurosurgery, Neuropsychiatry, Geriatrics, Oncology, and General Medicine clinics, as well as from private referral sources. Referrals include adult ADHD, aphasia, epilepsy, degenerative disorders, tumors, learning disabilities, and traumatic brain injury. Flexible battery approach based on referral question, typically day long evaluations. Supervise doctoral student externs on rotation.

University of Chicago Neuropsychology Service Satellite Clinic, (January 2020 –June 2020)
St. Mary's Hospital, Hobart, IN
Supervisors: Joseph Fink, Ph.D., ABPP-CN

Neuropsychological assessment of adult patients from community and rural hospital referral sources. Referrals include cognitive impairment secondary to cerebrovascular disease, aphasia, epilepsy, degenerative disorders, electrical injury, and traumatic brain injury. Forensic referrals are also common. Supervise doctoral student externs on rotation.

Conducted teleneuropsychological evaluations and served on select Teleneuropsychology Taskforce to maintain clinical service during COVID-19 pandemic.

Consultation/Liaison Psychiatry Service (January 2020 –June 2020)
Supervisors: Yasmin Asvat, Ph.D. and Marie Tobin, M.D.

Provide bedside supportive care, psychotherapy interventions, and brief neurocognitive assessments for general medical and psychiatric inpatients within the University of Chicago Medical Center hospitals as part of an inpatient psychiatry team. Populations of emphasis include severe mental illness including schizophrenia spectrum disorders, personality disorders, bipolar disorders, and suicidal/homicidal ideation.

Continued service telephonically and by video conference during COVID-19 pandemic.

Behavioral Medicine and Primary Care Consultation Service (January 2020 –June 2020)
Supervisor: Fabiana Souza Araújo, Ph.D.

Provide consult services for primary care clinic patients via focused psychotherapy interventions. Facilitated weekly group therapy for patients with COVID-19 related stress. Served as on-call crisis line clinician for COVID-19 frontline healthcare workers in the UCMC system. Provided group therapy and lectures for individuals with COVID-19 related grief, mood dysfunction, and cognitive compromise.

General Outpatient Psychotherapy Clinic (July 2019-June 2020)
Supervisors: Sarah Keedy, Ph.D. and Daniel Fridberg, Ph.D.

Tiered Clinical Neuropsychology Supervisor:

- Aamir Laique, M.S. (Ph.D. Candidate, Illinois Institute of Technology)
- Richard Keezer, M.A., LPC (Psy.D. Candidate, Wheaton College)
- Amanda Wisinger, M.S. (Psy.D. Candidate, Chicago School of Professional Psychology)
- Bailey Cation, M.S. (Psy.D. Candidate, Roosevelt University)
- Atash Sabet, M.S. (Psy.D. Candidate, Adler University)
- Olivia Beers, M.S. (Psy.D. Candidate, National Louis University)
- Alexis Siple, M.S. (Psy.D. Candidate, Adler University)

CLINICAL TRAINING EXPERIENCES

Advanced Clinical Neuropsychology Extern - Clement J. Zablocki VAMC (2018-2019)
Supervisors: Eric Larson, Ph.D., ABPP-CN, Angel Gleason, Ph.D., ABPP-CN, & Kathleen Paterson, Ph.D., ABPP-CN

Provided neuropsychology consultation services for outpatients, domiciliary residents, and geriatric, rehabilitation, medical-surgical, neurology, cardiac, and psychiatry inpatients. Caseload included recently returning service members to geriatric patients. Common referrals included memory loss, evaluation of dementia, dementia vs. pseudodementia, traumatic brain injury, personality changes, ADHD, learning disabilities, demyelinating diseases, and seizure disorders as well as decisional capacity evaluations.

Advanced Clinical Health/Neuropsychology Extern - Department of Transplant Surgery, Froedtert Hospital and Medical College of Wisconsin (2018-2019)
Supervisors: Jenessa Price, Ph.D. & Stephanie Zanowski, Ph.D.

Provided comprehensive neuropsychological assessment and intervention services for patients with complex medical conditions pre- and post- solid organ transplant (heart, lung, kidney, liver) for adherence and health maintenance. Conduct brief, tailored neuropsychological evaluations to inform individualized treatment interventions. Conduct individual/family sessions to provide feedback and recommendations. Interventions included goal-setting, motivational interviewing, relapse prevention, cognitive-behavioral, and dialectical-behavioral techniques.

Clinical Neuropsychology Extern - Department of Neurology, Froedtert Hospital and Medical College of Wisconsin (2017-2018)
Supervisors: Sara Swanson, Ph.D., ABPP-CN, David Sabsevitz, Ph.D., ABPP-CN, Julie Bobholtz, Ph.D., ABPP-CN & Laura Umfleet, Psy.D.

Provided comprehensive neuropsychological evaluations for young adults through older adults in both inpatient and outpatient settings. Referrals included traumatic brain injury,

epilepsy, memory disorders, movement disorders, and neuro-oncology (including pre-, post-, and peri-radiation/chemotherapy/surgery assessment). Participated in interviews and feedback of results. Attended weekly professional development and didactics.

Graduate Student Therapist - UW-Milwaukee Psychology Clinic (2016-2019)
Supervisors: Shawn Cahill, Ph.D. & Robyn Ridley, Ph.D.

Clinics: Behavioral and Exposure Therapy for Anxiety & CBT for Depression/Anxiety
Provided evidence-based outpatient treatments for depression, anxiety, panic disorder, and post-traumatic stress disorder, including Cognitive-Behavioral Therapy, Behavioral Activation, and Exposure Therapy, with members of the community.

Graduate Student Assessment Clinician - UW-Milwaukee Child Neuropsychology Clinic (2015-2019)
Supervisor: Bonnie Klein-Tasman, Ph.D.

Conducted pediatric learning disability and psychodiagnostic assessments using a range of cognitive, achievement, and neuropsychological measures, as well as symptom and behavioral questionnaires for community pediatric referrals. Completed clinical interviews, reports, and feedback sessions.

Graduate Student Assessment Clinician - UW-Milwaukee Psychology Clinic (2015-2016)
Supervisors: Hanjoo Lee, Ph.D., Kristin Smith, Ph.D. & Dave Osmon, Ph.D, ABPP-CN.

Conducted learning disability and psychodiagnostic assessments using a range of cognitive, achievement, and neuropsychological measures, as well as symptom and behavioral questionnaires. Completed clinical interviews, reports, and feedback sessions.

Clinical Practicums - UW-Milwaukee Psychology Clinic (2014-2016)
Supervisors: Christopher Martell, Ph.D., ABPP & Robyn Ridley, Ph.D.

- 2015-2016: Integrated Behavioral Couples Therapy; Behavioral Activation for Depression
- 2014-2015: Cognitive Behavioral Therapy for Depression/Anxiety; Integrated Behavioral Couples Therapy

Forensic Psychometry Consultant - Comprehensive Clinical & Consulting Services, Milwaukee, WI (2015-2018)
Supervisors: Itzhak Mutasiak, Ph.D. & Pamela Schaefer, Ph.D.

Conducted brief neurocognitive assessments of children and adults on referral from local courts.

Child Psychometry Consultant - Eidex Testing Center, Atlanta, GA (2014-2017)
Supervisor: Rivkah Eidex, Psy.D.

Conducted comprehensive psychodiagnostic evaluations and wrote interpretive reports for children referred primarily for moderate to severe autism spectrum disorder and other neurodevelopmental disorders.

Senior Clinical Psychometrist - Department of Psychiatry & Behavioral Neurosciences; Byrd Alzheimer's Disease Research Center, University of South Florida Morsani College of Medicine (2012-2013)
Supervisors: Michael Schoenberg, Ph.D., ABPP-CN, Michelle Mattingly, Ph.D., ABPP-CN & Eric Rinehardt, Ph.D., ABPP-CN

Supervisor for neuropsychological assessment in outpatient psychiatry clinic and ADRC multidisciplinary care team. On-call psychometrist for pre-surgical evaluations at Tampa General Hospital Neurosurgery Service. Prepared and summarized patient data for multidisciplinary case conferences. Research responsibilities included maintaining neuropsychology research database, participant recruitment, and data analysis for presentation and manuscript presentation.

Junior Clinical Psychometrist - Department of Psychiatry & Behavioral Neurosciences; Byrd Alzheimer's Disease Research Center, University of South Florida Morsani College of Medicine (2011-2012)
Supervisors: Michael Schoenberg, Ph.D., ABPP-CN, Michelle Mattingly, Ph.D., ABPP-CN & Eric Rinehardt, Ph.D., ABPP-CN

Outpatient neuropsychological assessment, office management and maintenance of HIPPA compliance for private health information. Assisted in data entry and management for research projects.

On-Call Clinical Psychometry Consultant - Comprehensive Inpatient Rehabilitation Unit, Florida Hospital, Tampa, FL (2012-2013)
Supervisor: Michael Schoenberg, Ph.D., ABPP-CN

On-call psychometrist for treatment and recovery tracking for inpatient vascular rehabilitation unit. Specifically trained in targeted bedside neuropsychological assessment.

RESEARCH EXPERIENCE

Graduate Research Assistant & Community Outreach Lead - Adolescent Brain and Cognitive Development (ABCD) Study, UW –Milwaukee (2016-2019)
P.I.: Krista Lisdahl, Ph.D. Funding Source: U01 DA041025. National Institute of Health (NIH)/National Institute on Drug Abuse (NIDA).

Served as a research assistant in charge of coordinating community and school-based recruitment of parents and families and hosting community engagement events. Also responsible for conducting interviews and running sessions of parent and youth (psychiatric, substance use, bioassays, MRI, health [adiposity, sleep, physical activity).

Graduate Research Assistant - Integration of Standing Desks in Elementary Schools to Reduce Sedentary Behavior and Improve Neuropsychological Functioning, UW-Milwaukee, Kinesiology & Psychology Departments (2016-2017)
P.I.: Ann Swartz, Ph.D.; Co-I & Neuropsychology Supervisor: Krista M. Lisdahl, Ph.D.

Assisted in a year-long study of in a community elementary school to determine possible outcomes of standing desks compared to sitting desks on executive function, learning, attention, postural stability, and physical activity levels. Conducted cognitive evaluations of grade school aged (3rd-6th grade) participants using the NIH Toolbox at baseline, 4 months, and 8 months.

Graduate Student Program Evaluator - Clinical & Translational Science Institute, Medical College of Wisconsin (2015)

Cleaned, processed, and analyzed longitudinal data for a graduate program tracking system for research scholar funding programs. Prepared report of analysis and findings and created protocol for future analysis and report preparation.

Graduate Research Assistant - Neurobiology of Memory Lab, UW-Milwaukee (2014-2016)
P.I.: Ira Driscoll, Ph.D.

Conducted and analyzed behavioral studies of learning and memory in older adults using fear conditioning and eye tracking methodologies.

Clinical Research Coordinator - Division of Cognitive Neurology & Alzheimer's Disease Research Center, Emory University School of Medicine (2013-2014)
Supervisors: Felicia Goldstein, Ph.D., ABPP-CN, Allan Levey, M.D., Ph.D. & James Lah, M.D., Ph.D.

Lead research coordinator for multisite international Phase-III clinical trial sponsored by Takeda Pharmaceuticals. Conducted study screenings, intakes, neuropsychological testing, phlebotomy, and recruitment through community outreach presentations. Coordinated several other active drug trials. Attended bi-weekly clinical case conference meetings for research and clinical activities. Supervised neuropsychological assessment training.

Clinical Research Scholar - Departments of Psychiatry and Psychology; Neuroscience, Mayo Clinic of Florida (2010-2011)
Supervisors: Otto Pedraza, Ph.D., ABPP-CN & Nilufer Taner, M.D., Ph.D.

Conducted analyses of relationships between single nucleotide polymorphisms associated with risk or protection from Alzheimer's disease and longitudinal neuropsychological test performance via PLINK analyses software. Assisted in conducting assays of genetic samples, and manuscript preparation.

Research Assistant - Guana-Tolomato-Matanzas National Estuarine Research Reserve, Saint Augustine, FL (2011)

Assisted staff scientists with field data collection for two separate studies; one of nutritional composition of hammock soil pre and post controlled burn, and another as assessing the impact of water pH on shell integrity of NE Florida oysters.

Clinical Research Intern - Division of Developmental Pediatrics; Center for Autism and Related Disabilities, University of Florida College of Medicine (2010)
Supervisors: Jacqueline Brown, Ph.D., ABPP-CN & David Childers, M.D.

Assisted with neuropsychological assessment of children with moderate to severe pervasive developmental and rare neurogenetic disorders. Responsible for data entry, management, and summarization for multidisciplinary case conferences. Hosted several community outreach presentations targeted toward providing underserved, low SES communities with information concerning available resources and pro bono evaluations.

Research Assistant - Department of Social-Behavioral Sciences; Natural Sciences, Flagler College (2009-2010)

Responsibilities: Assisted with literature reviews and data management for faculty members in psychology, sociology, and environmental science.

NSF Undergraduate Research Scholar - Departments of Functional Genomics; Neuroscience, University of Florida Whitney Laboratory for Marine Biosciences (2009-2010)
Supervisors: Peter Anderson, Ph.D. & Christelle Bouchard, Ph.D.

Conducted mentored research in evolutionary neuroscience of marine invertebrates, specifically *Cyanea capillata* and *Physalia physalis* to isolate novel genetic markers for neurotransmission in primitive nervous systems and functional neuroscience investigations of cnidocyte behavior and biochemical characteristics.

PEER-REVIEWED PUBLICATIONS

Jennette, K., Wallace, A., Swartz, A., & Lisdahl, K.M. (In preparation). Aerobic fitness and resting state functional connectivity to the left hippocampus associates with attention and working memory performance.

Wallace, A., Hatcher, K., **Jennette, K.**, & Lisdahl, K.M. (under revision). Attention function improves following three-weeks of monitored abstinence in regular cannabis using adolescents and young adults.

Kangiser, M., Kaiver, C., Knecht, B., **Jennette, K.**, & Lisdahl, K.M. (under review). Increased binge drinking is associated with cognition in adolescents and emerging adults.

Jennette, K., Wallace, A.L., Swartz, A.M., & Lisdahl, K.M. (In preparation). Aerobic fitness predicts increased functional connectivity in verbal memory networks in healthy adolescents and young adults.

Jennette, K., Wallace, A.L., Kangiser, M., & Lisdahl, K.M. (In preparation). Semantic organization predicts delayed verbal recall in cannabis-using and non-drug using adolescents and young adults.

Jennette, K., Kangiser, M., Knecht, B., Groth, M., & Lisdahl, K.M. (In preparation). The influence of binge drinking behavior on verbal learning and memory strategy in young adults.

Wallace, A., **Jennette, K.**, Mulligan, D., Lisdahl, K.M. (In preparation) Impact of Three-Weeks of Sustained Abstinence on Cognition in Young Adult Cannabis Users.

Pedraza, O., Allen, M., **Jennette, K.**, Carrasquillo, M., Crook, J., Serie, D….Ertekin-Taner, N. (2014). Evaluation of memory endophenotypes for association with CLU, CR1, and PICALM variants in black and white subjects. *Alzheimer's & Dementia*, 10(2), 205-213.

Rudd, M., **Jennette**, **K.**, Duey, B., Selman, A., & Seron, T. (2013). The effects of increased acidity on the shell integrity and body size of c. virginica: A comparison of oyster populations in northeast florida. *The Journal of Young Investigators*, 25 (2).

Pedraza, O., Allen, M., **Jennette, K.**, Crook, J., Carrasquillo, M., Palusak, R….Ertekin-Taner, N. (2011) Evaluation of Cognitive Endophenotypes for Association with CLU, CR1 and PICALM LOAD Risk Genes. *Alzheimer's & Dementia*, 7(4), S191-S192.

CONFERENCE PRESENTATIONS

Jennette, K. (2020, February) *Aerobic fitness predicts increased functional connectivity in verbal memory networks in healthy adolescents and young adults*. Poster presented at the International Neuropsychological Society (INS) 48th Annual Meeting, Denver, CO.

Wallace, A., **Jennette, K.**, Lisdahl, K (2018, June) *Effects of Continued Cannabis Abstinence on Neuropsychological Performance*. Poster presented at the College of Problem Drug Dependence 80th Annual Scientific Meeting

Lehman, S., **Jennette, K.**, Wallace, A. & Lisdahl, K. (2018, April) *Effects of Early Onset Marijuana Use on Executive Functioning Compared to Late Onset Marijuana Use*. Poster presented at the National Conference on Undergraduate Research, University of Central Oklahoma.

Groth, M., **Jennette, K.** & Lisdahl, K. (2018, April) *Binge Drinking Impact on Verbal Memory Recall in Adolescents and Young Adults*. Poster presented at the National Conference on Undergraduate Research, University of Central Oklahoma.

Jennette, K., Kangiser, M., Lisdahl, K. (2018, February) *The Influence of Binge Drinking Behavior on Verbal Learning and Memory Strategy in Young Adults*. Poster presented at the International Neuropsychological Society (INS) 46th Annual Meeting, Washington, DC.

Jennette, K., Gilbart, E. & Lisdahl, K. (2017, June) *The Association of Learning Strategy and Delayed Recall in Adolescents and Young Adult Marijuana Users and Controls*. Poster presented for the College of Problem Drug Dependence 79th Annual Scientific Meeting, Montreal, Québec, Canada.

Kangiser, M., **Jennette, K.**, Thomas, A. & Lisdahl, K. (2017, June) *Gender Moderates Chronic Nicotine Effects on Cognition in Young Adults*. Poster presented for the College of Problem Drug Dependence 79th Annual Scientific Meeting, Montreal, Québec, Canada.

Jennette, K., Gilbart, E. & Lisdahl, K. (2017, February) *The Relationship Between Marijuana Use, Inhibitory Control, and Learning Strategy in Adolescents and Young Adults*. Poster presented at the International Neuropsychological Society (INS) 45th Annual Meeting, New Orleans, LA.

Blujus, J., Kaiver, C., **Jennette, K.**, Gracian, E., Hannula, D. & Driscoll, I. (2016, November) *Using Eye Movements to Dissociate Memory Performance in Normal and Pathological Aging*. Poster presented at the Society for Neuroscience (SfN) Annual Meeting, San Diego, CA.

Jennete, K., Hopkins, L., Kaiver, C., Helmstetter, F., Driscoll, I. (2015, October) *Contingency Awareness for Delay and Trace Fear Conditioning in Normal Aging*. Poster presented at the Pre-Society for Neuroscience (SfN) UWM Symposium, Milwaukee, WI.

Jennette, K., Gracian, E. & Driscoll, I. (2015, April) *Association of Eye Tracking Relational Memory with Neuropsychological Performance in Middle and Older Age Adults*. Poster presented at the University of Wisconsin - Milwaukee Health Sciences Research Symposium, Milwaukee, WI.

Jennette, K. (2015, February) *The Association of Cognitive Endophenotypes and Risky Single Nucleotide Polymorphisms of Alzheimer's Disease within the Alzheimer's Disease Neuroimaging Initiative (ADNI) Database*. Poster presented at the International Neuropsychological Society (INS) 43rd Annual Meeting, Denver, CO.

Jennette, K., Avenengo, S., Rinehardt, E. & Schoenberg, M. (2013, September) *Relative Influence of Spatial Reasoning vs. Processing Speed on Neurocognitive Performance in Women with*

Multiple Sclerosis. Poster presented at the University of South Florida Health Research Symposium, Tampa, FL.

Jennette, K. (2012, November) *Influence of Depression and Anxiety on Measures of Intelligence in Patients with Multiple Sclerosis*. Poster presented at the National Academy of Neuropsychology (NAN) 32nd Annual Conference, Nashville, TN.

Jennette, K., Kaufman, R. & Rinehardt, E. (2012, September) *The Influence of Depression and Anxiety on Neurocognitive Performance in Patients with Multiple Sclerosis*. Poster presented at the University of South Florida Neuroscience Research Symposium, Tampa, FL.

Pedraza, O., Allen, M., Jennette, K., Crook, J., Carrasquillo, M., Palusak, R….Ertekin-Taner, N. (2011, June) *Evaluation of Cognitive Endophenotypes for Association with CLU, CR1 and PICALM LOAD Risk Genes.* Poster presented at the International Conference on Alzheimer's Disease (ICAD), Paris, France.

INVITED TALKS

Jennette, K. (November, 2015) *The Association of Cognitive Endophenotypes and Risky Single Nucleotide Polymorphisms of Alzheimer's Disease within the Alzheimer's Disease Neuroimaging Initiative (ADNI) Database*. Community lecture presented at the School of Aging Studies, University of South Florida.

Jennette, K. (May, 2014) *What is Normal Aging?* Invited lecture and discussion panel for the City of Decatur Lifelong Community Advisory Board. Awarded honorary key to the city for contributions.

Jennette, K. (2013-2014) *Where Did I Put My Keys? Myths and Misconceptions of Alzheimer's Disease.* Series of over 20 community-based presentations to various underserved communities in the greater Atlanta community on behalf of the Emory University Alzheimer's Disease Research Center.

Jennette, K. (2012, 2013) *Pursuing Graduate Training and a Career in Clinical Neuropsychology*. Panel Discussion for the Psi Chi Honor Society and Social Sciences Club, Flagler College

Jennette, K. (2011) *The Distinguishing Factors of Dementia: Etiologies, Diagnostics, and Treatments*. Senior Thesis in Psychology presented to the Community and Department of Social and Behavioral Sciences, Flagler College

Jennette, K. (2011) *The Effects of Increased Acidity on Shell Integrity and Body Size of Crassostrea virginica*. Senior Thesis in Environmental Science presented to the Community and Department of Natural Sciences, Flagler College

Jennette, K. (2011) *The Hunt for an Epithelial Sodium Channel (ENaC) in Cyanea capillata*. Presented to the Community and Whitney Laboratory for Marine Biosciences, University of Florida as required per NSF REU Grant.

JOURNAL REVIEWING

2019 Ad-Hoc Co-Reviewer *Journal of Neurology, Neurosurgery, and Psychiatry*
2015 Ad-Hoc Co-Reviewer *Alcohol*

TEACHING EXPERIENCE

Teaching Assistant - University of Wisconsin-Milwaukee

- Graduate Clinical Assessment Practicum (2017-2019)
- *Psychological Statistics* (2015-2017)
- Social Psychology (2015)
- Research Methods in Psychology (2014)

Invited Lecturer
The University of Chicago Pritzker School of Medicine

- Psychiatry 305: Human Behavior in Health and Illness course (medical students; 2019).
- Department of Psychiatry and Behavioral Neuroscience:
    - *Cross-Cultural Neuropsychology* (2020, February)
    - *Basal Ganglia* (2019, November)
    - *Laboratory Results for Use in Neuropsychology* (2019, November)
    - *Alzheimer's Disease Genetics and Treatments* (2019, September)
    - *Executive Functioning* (2019, August)
    - *Psychopharmacology* (2019, December)

University of Wisconsin-Milwaukee

- *Cross Cultural Neuropsychology*, (2020) Advanced Neuropsychology Seminar (Graduate)
- *Clinical Use of the WAIS-IV* (2018) First-Year Assessment Practicum (Graduate)
- *Training and Careers in Clinical Neuropsychology* (2018) First-Year Assessment Practicum (Graduate)
- *Normal Aging, MCI, and Cortical Dementias* (2017) Assessment II (Graduate)
- *Alzheimer's Disease and Related Dementias* (2016) Neuropsychology (Undergraduate)

Charles Darwin University, Casuarina, Northern Territory, Australia

- Clinical Neuropsychology: Diagnosis, Prevention, and Treatment of Cognitive Disorders (2020) Clinical Neuroscience for Providers Practicum (Graduate)

Mount Mary University, Milwaukee, WI

- *Introduction to Clinical Neuropsychology and Behavioral Neuroscience* (2017) Introduction to Psychology (Undergraduate)

DEPARTMENTAL & UNIVERSITY SERVICE

University of Chicago Medicine:
Member, Tele-neuropsychology Task Force (2020)
Volunteer, COVID-19 Crisis Line for Frontline Healthcare Workers (2020)

University of Wisconsin-Milwaukee:
Vice President, Association of Graduate Students in Health Psychology (2018-2019)
Secretary, Association of Graduate Students in Neuropsychology (2017-2018)
Volunteer, Eating Disorders Seminar (2017)
Student Representative, Clinical Training Committee, Psychology Department (2014-2015)

University of South Florida:
Thesis Committee Member, (Daniel Lattimore), Undergraduate Honors College (2012)

Flagler College:
Molecular Biology Laboratory Technician, Department of Natural Sciences (2010-2011)
Co-Founder and Vice President, Social Sciences Club (2010-2011)
Resident Advisor, Department of Residence Life (2010-2011)
Elected Member, Leadership Flagler, Office of the President (2010-2011)
Elected Member, Ambassador Leadership Council, Office of Admissions (2010-2011)
Lead Ambassador, Office of Admissions (2008-2011)
Child Psychology Service Learning Mentor, Flagler College and EPIC of Saint Augustine (2009)

NATIONAL & PROFESSIONAL SERVICE

International Neuropsychological Society:
Student Representative, Association for Internship Training in Clinical Psychology (2017-2019)

National Academy of Neuropsychology:
Senior Volunteer Coordinator, 36th Annual Conference, Seattle, Washington (2015-2016)
Member, Program Planning Committee (2015-2016)
Member, Legislative Action and Advocacy Committee (2014-2015)
Junior Volunteer Coordinator, 35th Annual Conference, Austin, Texas (2014-2015)
Incoming Volunteer Coordinator, 34th Annual Conference, Fajardo, Puerto Rico (2013-2014)
Student Volunteer, 33rd Annual Conference, San Diego, CA (2013)

Board of Certified Psychometrists:
Member, Certification Exam Development and Item Approval Committee (2014-2015)
Member, Marketing and Outreach Committee (2014-2015)

PROFESSIONAL MEMBERSHIP AND CERTIFICATIONS

Student Member, Association for Psychological Science (2018-Present)
Member, Association of Neuropsychology Students in Training (2014-Present)
Board Member, Board of Certified Psychometrists (2013-2015)

Student Member, American Academy of Clinical Neuropsychology (2013-2014)
Student Member, International Neuropsychology Society (2013-Present)
Student Member, American Psychological Association (2012-Present)
Division 40 (Society for Clinical Neuropsychology)
Division 22 (Rehabilitation Psychology)
Division 20 (Adult Development and Aging)
Student Member, National Academy of Neuropsychology (2011-Present)

Certifications:

Board Certified Specialist in Psychometry (CSP-0260), *Lapsed in good standing (2011-2014)*

- *Passed exam with distinction (top 5%)*

CPR/BLS Certified (2010-Present)
PADI Certified Open Water SCUBA Diver (2009-Present)

Honor Societies:

Phi Kappa Phi Honor Society
Omicron Delta Kappa Leadership Honor Society
Sigma Phi Omega Honor Society, Upsilon Chapter
Sigma Xi Research Honor Society
Golden Key International Honour Society

PROFESSIONAL TRAININGS

2019	Cultural Competence and Diversity Training, University of Chicago Medicine (18 hours)
2018	Functional Neuroimaging Workshop, University of Wisconsin-Milwaukee, (16 hours)
2016	Introduction to 'R' – Learning by Example Seminar
2016	Clinical Assessment and Treatment of Eating Disorders Seminar, University of Wisconsin – Milwaukee (40 Hours)
2016	Behavioral Activation Therapy Workshop, University of Wisconsin – Milwaukee (8 Hours)
2015	fMRI Safety Training—Medical College of Wisconsin
2014	Analysis of Functional Imaging (AFNI) On-site Training National Institutes of Health, Bethesda, MD, (40 hours)

GRANTS, HONORS, SCHOLARSHIPS & AWARDS

2019	Child Neuropsychology Clinic Travel Award, University of Wisconsin-Milwaukee
2017	Summer Research Fellowship, Department of Psychology, University of Wisconsin-Milwaukee
2015	Featured Alumni in Flagler College Magazine for Research in Alzheimer's Disease
2015	Featured in Flagler College Admissions Publications as Distinguished Alumni
2013	Harold L. Sheppard Endowed Memorial Scholarship, School of Aging Studies, University of South Florida
2012-2015	Dean's List, University of South Florida Graduate School
2011	Clinical Research Internship Scholar Program (CRISP) Award, Mayo Clinic of Florida
2011	Distinguished Scholar Lecture Grant Co-Recipient, Southern Sociological Society
2010	Research for Undergraduates (REU) Student Grant, National Science Foundation
2010	Featured in Flagler College Honor Roll Publication for Academic, Community, & Civic Excellence
2008-2011	Dean's List, Flagler College