THE ASSOCIATION BETWEEN AEROBIC FITNESS AND NETWORK CONNECTIVITY IN THE DEFAULT MODE NETWORK IN HEALTHY ADOLESCENTS AND YOUNG ADULTS

by

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ABSTRACT

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Under the Supervision of Professor Krista M. Lisdahl

The beneficial effects of aerobic fitness on psychiatric and cognitive function in older adults have been well demonstrated in existing literature. However, less remains known about the relationship between aerobic fitness and neurocognitive health in emerging adults, who are less likely to suffer from underlying metabolic conditions. Further, few have examined potential sex differences. The transition from adolescence to young adulthood is associated with a reduction in physical activity and accumulating evidence suggests that poor aerobic fitness negatively impacts neurocognition. Therefore, it is crucial to better understand the relationship between aerobic fitness and neurocognitive health during adolescence and young adulthood when interventions may be pivotal. The current study aimed to better characterize the relationships between objectively measured aerobic fitness (VO_2 max testing), resting-state functional connectivity in the default mode network (DMN), and neuropsychological performance in healthy emerging adults; sex differences were also examined. Results of the study showed that better aerobic fitness was associated with increased connectivity between the right PCC and left anterior cingulate. The VO_2 max*sex interaction was significantly associated with increased connectivity between the right PCC and left precuneus (males displayed a more robust relationship) and increased connectivity between the left PCC and right middle temporal gyrus (females displayed a more robust relationship). Co-activation of the right PCC and left anterior cingulate associated with better aerobic fitness was negatively associated with verbal memory recall for the whole group. Further analysis separated by sex revealed males displayed a negative association between these regions and both verbal learning and memory, while females did not have a significant relationship. Co-activation of the left PCC and right middle temporal gyrus associated with better aerobic fitness was positively associated with verbal memory, with females showing a slightly greater benefit, though no significant sex differences were observed. Lastly, co-activation of the left PCC and right middle temporal gyrus was associated with better inhibition in males. Overall, results from this study contribute to a better understanding of the extent to which aerobic fitness impacts functional connectivity in the DMN of the developing brain and its relationship to neuropsychological performance in a sex-balanced, emerging adult sample. Findings may offer insights into the value of early preventive health behaviors aimed at improving neurocognitive health in youth prior to potential onset of psychiatric or neurologic disorders susceptible to disruptions in DMN connectivity.

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Introduction

Globally, approximately one in three adults and four in five adolescents are not meeting the minimum recommended physical activity levels (Guthold et al., 2019; Hallal et al., 2012). The transition from adolescence to young adulthood has been associated with a reduction in physical activity and increase in sedentary behavior (Corder et al., 2019; Hayes et al., 2019). Indeed, existing data suggests a decrease of approximately 5.2 to 7.4 minutes of moderate-to-vigorous activity per day during this transition (Corder et al., 2019). Sedentary behavior and decreased physical activity have been linked to increased body weight and obesity rates, and, ultimately, poorer fitness and increased rates of comorbid health challenges, such as increased rates of hypertension, hyperlipidemia, diabetes, atherosclerosis, heart disease, and cancer, into adulthood (Hruby & Hu, 2016; Hancox et al., 2004). There is accumulating evidence that poor physical fitness and health may negatively impact neurocognition. Aerobic exercise, which promotes increased flow of oxygenated blood and is known to improve aerobic fitness, has been suggested as a means of improving neurocognition. Therefore, it is crucial to better understand the link between aerobic fitness and neurocognitive health, especially during adolescence and young adulthood when interventions may be pivotal.

Preclinical animal studies have found a strong relationship between exercise, brain structure, and brain function (Mandolesi et al., 2018; Swain et al., 2012; Voss et al., 2013). For example, moderate intensity aerobic exercise has been found to increase neurogenesis in animals (Leasure & Jones, 2008; Nokia et al., 2016; Wang & Holsinger, 2018) and this relationship has also been proposed in humans (Basso & Suzuki, 2017; Perini et al., 2016). Preclinical evidence has long suggested that the mechanisms underlying the positive effects aerobic exercise has on brain health is related to neurotrophic factors (Neeper et al., 1995) that support new neural growth, angiogenesis, and synaptic plasticity, including brain-derived neurotrophic factor (BDNF; Cotman & Berchtold, 2002; Vaynman et al., 2004; Wang & Holsinger, 2018), vascular endothelial growth factor (VEGF; Fabel et al., 2003; Karakilic et al., 2021), and insulin-like growth factor 1 (IGF-1; Cetinkaya et al., 2013; Trejo et al., 2001). Indeed, BDNF, VEGF, and IGF-1 have been shown to increase in response to aerobic exercise and improved aerobic fitness level (Basso & Suzuki, 2017). Adult rodent investigations have largely examined the effect of aerobic exercise on the hippocampus (HC), a brain region important for learning and memory, and found benefits such as hippocampal and dentate gyrus neurogenesis, precluding age-related HC volume loss, and improved performance on HC-dependent memory tasks (Mu et al., 2022; van Praag et al., 2005; van Praag, 2008). A few studies have also suggested aerobic exercise exhibits similar positive effects on the medial prefrontal cortex (mPFC) of adult rats, as evidenced by dendritic spine and synaptic growth (Brockett et al., 2015), astrocyte and oligodendrocyte proliferation (Mandyam et al., 2007; Brockett et al., 2015; Tomlinson et al., 2016) and improved mPFC-mediated cognitive functions such as cognitive flexibility and set-shifting (Brockett et al., 2015). Overall, this suggests that aerobic exercise induces upregulation of neurotrophic factors that promote neuroplasticity in areas important for memory recall and consolidation, as well as higher-order cognitive functioning.

In humans, aerobic fitness is commonly measured through self-report and/or objective measures (e.g., VO_2 maximum testing). VO_2 maximum (i.e., VO_2 max) is the maximum capacity of the body to take in and utilize oxygen during exercise (i.e., maximal oxygen consumption) and is a measurement of cardiorespiratory fitness. The literature examining the effects of aerobic fitness in humans has primarily focused on older adults. Thus far, evidence suggests that prolonged exercise or an active lifestyle has proven beneficial in slowing cognitive decline in cognitively normal older adults and those at risk for neurodegenerative disease (Buchman et al., 2012; Colcombe & Kramer, 2003) and is linked to slower disease progression in older adults with dementia (Scarmeas et al., 2011). Structured aerobic exercise has also been found to improve memory in older adults with depression (Khatri et al., 2011) and to increase hippocampal volumes in elderly adults (Erickson et al., 2011) and individuals with schizophrenia (Pajonk et al., 2010). Overall, there is growing evidence that greater physical activity and aerobic fitness levels are associated with larger gray matter volumes within temporal lobes, cingulate cortex, and prefrontal cortex of older adults (Erickson et al., 2014; Floel et al., 2010), specific brain regions sensitive to the effects of aging.

While more is known about the effects of aerobic fitness on neurocognition in older adults, less is known about its effect in adolescents and young adults, who are undergoing ongoing neurodevelopment. As children transition to adolescence and young adulthood, synaptic pruning occurs resulting in reduction of gray matter (Giedd et al., 2015; Tierney & Nelson, 2009), particularly in prefrontal and parietal regions (Giedd et al., 2012; Giedd et al., 2015; Lenroot et al., 2007; Sowell et al., 2004). At the same time, white matter microstructure is shown to improve and increase linearly in adolescence and throughout young adulthood (i.e., into early 30s; Giedd et al., 1999; Giedd et al., 2015; Jernigan & Gamst, 2005), which is characterized by peak cognitive performance. Functional connectivity continues to develop and mature throughout the lifespan. Local connectivity (i.e., connectivity to nearby regions) is strongest during childhood and adolescence though tends to weaken into young adulthood when connectivity with more distant regions strengthens as higher cognitive functions become more efficient (Betzel et al., 2014; Power et al., 2010). Further, adolescents and young adults typically embody better physical health and have fewer comorbid cardiovascular or metabolic medical conditions (e.g., hypertension, hyperlipidemia, diabetes) than older adults. Therefore, conclusions made linking aerobic fitness with brain health in older adults are not entirely generalizable to adolescents and young adults.

To date, there is some evidence linking aerobic fitness and brain health in youth. For example, greater aerobic fitness has been shown to relate to superior white matter quality (measured by greater fractional anisotropy [FA]) in the corpus callosum, superior corona radiata, and superior longitudinal fasciculus (Chaddock-Heyman et al., 2014; Ruotsalainen et al., 2020). Though other studies investigating aerobic fitness and white matter integrity have not found a relationship between FA and aerobic fitness (Herting et al., 2014), which may be due to methodological differences. Structurally, past work has found that superior aerobic fitness in adolescence and young adulthood is related to larger volumes in subcortical and frontal regions (Chaddock et al., 2010; Herting et al., 2012; Herting et al., 2016; Sullivan et al., 2021; Wade et al., 2020; Whiteman et al., 2016) and thinner cortices across the cortex (Chaddock-Heyman et al., 2015; Wade et al., 2020; Williams et al., 2017). Taken together, these studies demonstrate a link between aerobic fitness and brain structure (as measured by gray and white matter quality) in young, physically healthy teens and young adults. However, fewer studies have examined the impact of aerobic fitness on functional brain activation or connectivity patterns.

Functional MRI (fMRI) is a neuroimaging technique that measures connectivity within and between different brain regions. Brain connectivity can be measured as the temporal correlation between measurements, or the changes of oxygen levels in the brains blood supply (BOLD responses), in separate parts of the brain. Brain connectivity can be examined during task engagement (i.e., paradigm or task-based) or when at rest (i.e., when not engaging in a task), coined resting state functional connectivity (RSFC). During both resting-state and task-based fMRI, certain brain regions are shown to be activated (i.e., display an increase in BOLD signal) while others are deactivated (i.e., display a decrease in BOLD signal); the default mode network (DMN) has been found to exhibit high levels of activity during rest and lower levels of activity when there is an increase in external processing demands (Greicius et al., 2003). The DMN is a functional brain network that extensively matures throughout childhood and adolescence. The DMN has been discovered as early as infancy, as evidenced by a "proto-default-mode network" shown to comprise of the precuneus and bilateral parietal cortex (Fransson et al., 2007). In late adolescence, when the DMN is almost fully developed (Bluhm et al., 2008), it is comprised of various regions including the posterior cingulate cortex (PCC), hippocampal formation, lateral temporal cortex, medial and lateral parietal cortex, precuneus, and medial prefrontal cortex (Buckner et al., 2008; Fox et al., 2005; Greicius et al., 2003; Raichle et al., 2001). Moreover, while the regions that compose the DMN appear to be similar between childhood and adulthood, the connectivity between regions is notably weaker in childhood and strengthens across adolescence and adulthood (Fair et. al., 2008; Fan et al., 2021), though inconsistency has been noted across studies (Power et al., 2010).

Behaviorally, the DMN is well associated with aspects of internally focused thoughts and processes (Immordino-Yang et al., 2012). It has shown to be active during stimulus-independent thought (i.e., mind wandering; Mason et al., 2007), self-referential thought (Gusnard et al., 2001; Harrison et al., 2008), attention and inhibitory control (Fair et al., 2008; Whitfield & Ford, 2012), social cognition (Iacoboni et al., 2004; Li et al., 2014), and episodic memory (Huo et al., 2018). While the PCC, a major node of the DMN, has been associated with internally directed thought processes, it has also been suggested to be involved in attention and monitoring of environmental changes that might require altered behavior (Leech et al., 2012). Activation of the DMN is known to be anticorrelated with activation within the task-positive network (Fox et al., 2005; Fransson, 2005). Despite this typical anticorrelation, poorer deactivation of the DMN may intrude upon the task-positive network and result in attentional lapses (Weissman et al., 2006) and reaction time variability (Whelan et al., 2012). Indeed, failure to deactivate the DMN has been associated with poorer cognitive efficiency and has been implicated in both psychiatric and neurological disorders such as attention deficit/hyperactivity disorder (ADHD), schizophrenia, anxiety, depression, and dementia, among others (Broyd et al., 2009). In contrast, stronger connectivity within the DMN has been associated with increased working memory performance (Sala-Llonch et al., 2012; Sambataro et al., 2010).

Studies investigating the relationship between aerobic fitness and DMN connectivity in older adults have generally found that greater aerobic fitness predicts greater connectivity (Voss et al., 2016; Voss, Erickson, et al., 2010; Voss, Prakash, et al., 2010) and improved executive function performance (Voss et al., 2010). In clinically healthy young adults (ages 18-30; *N* = 242), aerobic fitness (as measured by VO_2 max) has been shown to contribute to individual differences in functional connectivity between multiple RSFC networks (as measured by Multivariate Distance-Based Matrix Regression) related to attention and learning (i.e., dorsal and ventral attention networks), executive function (i.e., frontoparietal network), and memory (i.e., default mode network) (Talukdar et al., 2018). In a smaller study (*N* = 26), Kronman et al. (2020) suggested that aerobic fitness (as measured by VO_2 max) is associated with greater resting-state connectivity between the HC and the ventromedial prefrontal cortex, PCC, lateral temporal cortex, and dorsomedial prefrontal cortex in healthy young adults (ages 18-35), further suggesting a relationship between aerobic fitness and broad cognitive domains including, but not limited to, memory. Furthermore, our group (Jennette et al., under review) found that better aerobic fitness was related to increased connectivity between the left HC and left parahippocampal gyrus, which was correlated with better auditory attention, verbal working memory, and verbal learning in healthy young adults (ages 18-25). One study to date has found a link between aerobic fitness and DMN connectivity in younger adolescent males while examining brain activity in hippocampal regions during a verbal associative memory task (Herting & Nagel, 2013). They found that high-fit adolescent males (ages 15-18) displayed more robust deactivation (i.e., decrease in BOLD signal) within certain DMN regions (i.e., the ventral medial prefrontal cortex and PCC) during a verbal encoding memory task in comparison to low-fit adolescent males. This suggests aerobic fitness may not only impact brain structure during adolescence but may also influence brain function and network connectivity. However, it should be noted that Herting & Nagel (2013) utilized a self-report assessment of aerobic fitness, and the sample did not include females; thus, these findings need to be replicated utilizing objective aerobic fitness measurement in both males and females.

As outlined above, the majority of studies investigating the effects of aerobic fitness on functional connectivity in the DMN in adolescents and young adults have included predominantly male samples (Herting & Nagel, 2013) or did not investigate potential sex differences (Kronman et al., 2019; Talukdar et al., 2018). Therefore, there remains a limited understanding of sex differences and ability to generalize existing literature to young females. Notably, past literature has documented sex-at-birth differences between male and females in brain connectivity of the DMN, generally suggesting females exhibit subtly greater connectivity (Alcaron et al., 2018; Bluhm et al., 2008; Filippi et al., 2013; Hjelmervik et al., 2014). For example, Alarcon and colleagues (2018) found adolescent females displayed stronger functional connectivity between the medial PFC and right posterior cerebellum in comparison to males.

Moreover, adult females have been found to display higher functional connectivity in various parts of the DMN including the right precuneus and dorsal ACC (Filippi et al., 2013), the anterior fronto-parietal network (Hjelmervik et al., 2014), and between the PCC/precuneus and bilateral medial frontal cortex (Bluhm et al., 2008). Notably, DMN connectivity does not vary with menstrual cycle phase (Hjelmervik et al., 2014). Past work has also documented sex differences between males and females in aerobic fitness, suggesting that females tend to exhibit lower VO_2 max in comparison to males in both adolescence (Fomin et al., 2012) and adulthood (Sparling, 1980). To the best of our knowledge, no study to date has examined potential sex differences in the effect of aerobic fitness on RSFC in the DMN in healthy emerging adults. However, prior work in our group utilizing a similar sample (Jennette et al., under review) found that males displayed a more robust relationship between aerobic fitness and network connectivity in a verbal learning network, suggesting males may benefit more from exercise effects. Therefore, the current study aimed to explore the extent to which sex moderates the effects of aerobic fitness on RSFC in the DMN and related neuropsychological functioning.

Study Aims

Aim 1: Examine the association between aerobic fitness and resting state functional connectivity in the DMN using a bilateral PCC seed, and to examine if sex moderates any findings.

Hypothesis 1: Better aerobic fitness would be associated with stronger connectivity between the right and left PCC and other DMN nodes.

Hypothesis 2: There would be a difference in associated connectivity by sex. Males would demonstrate a more robust relationship between aerobic fitness and connectivity in the DMN (Jennette et al., under review).

Aim 2: Examine the association between DMN regions linked with aerobic fitness and neuropsychological functioning.

Hypothesis 1: Stronger connectivity in DMN regions (i.e., the right and left PCC and other DMN nodes [intra-DMN connectivity]) that are linked with aerobic fitness would be associated with better performance on measures of selective and sustained attention, working memory, inhibition, and verbal memory. Alternatively, stronger connectivity with areas typically anti-correlated with the DMN (e.g., the task-positive network) would be associated with poorer performance on neuropsychological measures.

Method

Participants

Participants in the present study included 61 healthy, young adults (30 female, 31 male) ages 16-25 (see Table 1 for descriptive statistics) drawn from a larger parent neuroimaging study (PI: Lisdahl, R01 DA030354) that investigated the effects of cannabis use and aerobic fitness on neuropsychological outcomes in adolescents and young adults. Participants were recruited from the community via advertisements and flyers. Participants were included in the parent study if they were between the ages of 16-25, right-handed, spoke English, and were willing to abstain from substance use over a three-week period prior to their study participation. Participants were excluded from the parent study based on the following criteria: (1) reported prenatal exposure to alcohol (>6 drinks/week or >4 drinks/day) or nicotine; (2) birth complications or premature birth (<33 weeks gestation); (3) history of neurologic disorders or head trauma with >2-minute loss of consciousness; (4) vision or hearing impairments; (5) major medical conditions including metabolic disease (e.g., hyperlipidemia, hypertension, diabetes); (6) inability to safely complete VO_2 Max testing as indicated by elevated Physical Activity Readiness Questionnaire (PAR-Q) scores; (7) Independent DSM-IV Axis I (mood, anxiety, psychotic, or attention) disorder; (8) history of a learning and/or intellectual disability; (9) use of psychoactive medication; (10) contraindication to MRI. The current study also excluded participants if they had used cannabis >104 times in the past year or had significant illicit substance use (>30 lifetimes uses).

Procedures

After receiving verbal consent from participants (or verbal assent from the participant and verbal consent from their parent if under 18), those who were interested were screened by phone for the eligibility criteria. Participants who were still eligible after this screening were mailed a written consent form (or, if under 18, parent consent and participant assent form) prior to a more detailed phone screening. The detailed phone screening comprehensively assessed for lifetime substance use, psychiatric history, extent of physical activity, and physical ability to safely engage in VO_2 max testing.

All participants in the parent neuroimaging study were requested to maintain abstinence from drugs and alcohol (with the exception of nicotine use) three weeks prior to their participation and across study sessions. Adherence was monitored by urine toxicology and/or continuous sweat patch toxicology testing. Participants were also balanced during screening for active versus sedentary physical activity based upon their IPAQ score. All protocols were approved and carried out in accordance with guidelines set by the Institutional Review Boards at the University of Wisconsin-Milwaukee and the Medical College of Wisconsin.

Eligible participants came in for five study sessions over the course of three weeks to partake in study procedures. Sessions one through three occurred one week apart from each other and included a brief neuropsychological and mood battery (see Wallace et al., 2020) and toxicology testing. Sessions four and five occurred at minimum one week after session three was completed. Session four included toxicology testing, a longer neuropsychological battery, mood questionnaires, and aerobic fitness VO_2 maximum (VO_2 max) testing. Session five occurred within 24-48 hours of session four; participants underwent toxicology testing, a brain MRI scan, and completed questionnaires. Participants were paid for their participation in the parent study.

Measures

Psychiatric Disorder Screening

Psychiatric history was assessed at baseline utilizing the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and/or MINI-Kid (Sheehan et al., 2010),

Physical Activity Screening

Participants were screened with the Physical Activity Readiness Questionnaire (PAR-Q; Thomas et al., 1992) to determine their physical ability to safely engage in VO_2 max testing. The International Physical Activity Questionnaire (IPAQ; Fogelholm et al., 2006) was administered to measure self-reported physical activity levels.

Toxicology & Pregnancy Testing

Participants provided a urine sample at each study visit to test for adulterants (Specimen Validity Test; DrugTestStrips, Greenville, SC), cotinine level (a nicotine metabolite; NicAlert strips, Nymox Pharmaceutical Corporation, Hasbrouck Heights, NJ), and recent drug use (One Step Drug Screen Test Dip Card Panel; Innovacon, Inc., San Diego, CA). Participants were also administered a breath alcohol test (Alco-Sensor IV; Inoximeters Inc., St. Louis, MO). All female participants completed a urine pregnancy test (HGC Pregnancy Test Card; DrugTestStrips, Greenville, SC). During the study, and beginning at session one, participants wore a PharmCheck sweat patch to monitor substance use between visits that may not appear in the urinalysis; the sweat patch was changed at each weekly visit. Participants that presented to sessions two or three with positive toxicology results were asked to reschedule and return after one week of abstinence. At their subsequent sessions, participants were required to test negative on their toxicology screens.

Substance Use

Past year substance use was assessed using a modified version of the Timeline Follow Back (TLFB; Sobell et al., 1992). The TLFB was administered to examine participants' substance use patterns week-by-week within the last year. Research assistants utilized a calendar and memory cues (e.g., holidays, personal events) to assist with recall. All substances were measured using standard units (e.g., alcohol in standard drinks; nicotine in number of cigarettes and hits of chew, snuff, pipe, cigar, hookah; cannabis in joints; etc.). Lifetime substance use was measured with the Customary Drinking and Drug Use Record (CDDR; Brown et al., 1998; Stewart & Brown, 1995) at baseline.

Body Fat Percentage

The Tanita SC-331S Body Composition Monitor (Tanita, Arlington Heights, IL), an electrical bioimpedance analysis system, was utilized to measure body fat percentage in proportion to body weight. Anthropometric measures were assessed in light clothing and without shoes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

VO_2 Testing

Participants' aerobic fitness was assessed using the gold-standard objective measure VO_2 max testing and quantified as a VO_2 max score, the maximum intake of oxygen during intense exercise (i.e., aerobic capacity). Participants were requested to refrain from food and caffeine for four hours prior to aerobic fitness testing. Prior to each session, the metabolic measurement system ParvoMedics TrueOne 2400 (ParvoMedics, Salt Lake City, UT) was calibrated according to manufacturer instructions 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 three-liter syringe for the pneumotachometer. Participants were fitted with the rubber mouthpiece connected to a Hans Rudolf 2700 series two-way nonrebreathing valve (Kansas City, MO), nose clip, and heart rate strap (Polar Wearlink 31, Finland) for collection of expired gases and heart rate measurement. Participants completed maximal incremental exercise testing on a treadmill (Full Vision Inc., TMX425C Trackmaster, Newton, KS) following the Bruce protocol, a well-known standardized approach, until volitional fatigue. Expired gases were measured continuously using the ParvoMedics TrueOne 2400 metabolic measurement system (ParvoMedics, Salt Lake City, UT). Participants were informed of exercise testing procedures and the known minimal risks. They were requested to complete as much of the exercise testing as possible and informed they could discontinue testing at any time. Participants were instructed to begin exercise testing by walking or running at a comfortable speed. Speed and grade were systematically increased at each stage of the Bruce protocol. Criteria for determination of attainment of VO_2 max were based on those previously recommended (Howley et al., 1995).

Neuropsychological Assessments

Estimated premorbid intelligence was assessed for group comparison using the Wide Range Achievement Test-4th Edition (WRAT-4; Wilkinson, 2006) Reading subtest age-adjusted score. Participants underwent a larger neuropsychological battery as part of the parent neuroimaging study (Wade et al., 2019). Four neuropsychological tests were utilized in the present study. The Ruff 2 & 7 Total Speed and Total Accuracy raw scores were used to measure selective and sustained attention (Ruff & Allen, 1996). The Paced Auditory Serial Addition Test

(PASAT; Gronwall, 1977) total correct score was utilized to assess working memory and sustained attention. The Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) Color-Word Interference Test Condition 3 (Inhibition) total completion time was used to assess inhibitory control. The California Verbal Learning Test, 2nd Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) Trial 1, Total Learning (Trials 1-5), and Long Delay Free Recall (LDFR) raw scores were utilized to assess verbal learning and memory.

Neuroimaging Acquisition

MRI data acquisition was conducted at the Medical College of Wisconsin on a 3T Signa LX MRI scanner (GE Healthcare, Waukesha, WI) with a 32-channel quadrature transmit/receive head coil. High-resolution, 3-dimensional, T1-weighted anatomical images were obtained using a spoiled gradient-recalled at steady-state (SPGR) pulse sequence (parameters: TR = 8.2s, TE = 3.4s, TI = 450ms, flip angle = 12°, field of view [FOV] = 240mm, resolution = 256x256mm, slice thickness = 1mm, 150 sagittal slices). Participants also underwent an 8-minute resting state fMRI scan in which they were instructed to lie awake with their eyes closed (parameters: TR = 2s, TE = 25ms, flip angle = 77°, FOV = 240mm, matrix = 64x64, slice thickness = 3.7mm, 40 sagittal slices, 240 repetitions).

Neuroimaging Processing

Neuroimaging processing steps have been described in detail previously (see Ritchay et al., 2021). Raw functional images were pre-processed using 1000 Functional Connectomes Project (Fcon1000; Biswal et al., 2010) and Analysis of Functional Neuroimages (AFNI) software (Cox, 1996). Pre-processing steps included dropping the first four time points of each acquisition (TRs; 3dcalc: Cox, 2021), deobliquing (3drefit: Cox, 2009), reorientation (3dresample: Reynolds, 2014), motion correction (3dTstat: Hammett & Cox, 2021; 3dvolreg:

"AFNI program: 3dvolreg," 2021), skull stripping (3dAutomask: "AFNI program: 3dAutomask," 2021; 3dcalc: Cox, 2021), registration within each subject (3dcalc: Cox, 2021), registration to the anatomical image and to MNI space (flirt: Greve & Fischl, 2009; Jenkinson et al., 2002; Jenkinson & Smith, 2001), spatial smoothing with a 6mm full width half maximum (FWHM) Gaussian kernel (fslmaths: Woolrich et al., 2001), grand-mean scaling (fslmaths: Woolrich et al., 2001), band-pass filtering (high pass cutoff = 0.005Hz, low pass cutoff = 0.1 Hz; 3dFourier: Ross & Heimerl, 1999), linear and quadratic detrending (3dcalc: Cox, 2021; 3dTstat: Hammett & Cox, 2021; 3dDetrend: "AFNI program: 3dDetrend," 2021), and regression of nuisance variables (including white matter, CSF, and six motion parameters; 3dmaskave: "AFNI program: 3dmaskave," 2021; 3dTstat: Hammett & Cox, 2020; 3dcalc: Cox, 2021; flirt: Greve & Fischl, 2009).

Data Analysis

One-way analysis of variances (ANOVAs) were conducted in SPSS v.25 to examine potential differences on demographic variables in relation to sex and aerobic fitness. A voxel-wise seed-based correlation analysis was conducted using a bilateral PCC seed, ascertained using automated gyral-based neuroanatomical labelling atlas (Desikan et al., 2006) in AFNI. This specific region was selected to remain consistent with prior studies as it is considered the major hub of the DMN (Ernst et al., 2019, Fox et al., 2005; Pujol et al., 2014; Ritchay et al., 2021). The BOLD timeseries was then extracted from the left and right PCC for each subject using 3dROIstats ("AFNI program: 3dROIstats," 2020). The resultant seed timeseries values were correlated with each voxel of the brain using 3dfim+ (Ward, 2020). These correlations were transformed to Z-scores. The seed-based connectivity maps extracted for each subject were used in GLMs. We corrected for multiple comparisons using 10,000 Monte Carlo simulations with individual voxels considered significant at $p < .001$ and corrected for Family-Wise Error (FEW) at cluster thresholds of $p < .05$; such thresholds have been found to adequately control false-positive rates (Cox et al., 2017). This assisted in determining the minimum cluster size to meet these thresholds. Finally, AFNI's 3dMVM (Chen et al., 2014) was used to 1) identify clusters significantly correlated with VO_2 max performance and 2) to assess VO_2 max by sex interaction. Resultant Fischer Z-scores that demonstrated the strength of the relationship between the PCC and clusters significantly associated with VO_2 max or VO_2 max*sex interactions were extracted and correlated (using SPSS) with select neuropsychological measures (i.e., Ruff 2 & 7, PASAT, D-KEFS Color-Word Interference Test, CVLT-II) to assess the potential relationship between connectivity pattern and neuropsychological performance in brain regions linked with aerobic fitness.

Results

Sample Descriptive Statistics

Sample descriptive statistics were separated by sex (Table 2) and VO_2 max median split (Table 3). In terms of sex, there was a significant difference in raw VO_2 max performance, body fat percentage, and moderate to vigorous intensity activity minutes per day. Males had a higher average VO_2 max score ($F = 19.014$, $p < .001$) and engaged in more moderate to vigorous intensity activity minutes per day ($F = 4.646$, $p = .036$) compared to females. Males also had a lower average percentage of body fat compared to females ($F = 41.719$, $p < .001$). When the sample was divided by median VO_2 max (median = 42.4 mL/kg/min), there was a significant difference in body fat percentage and raw VO_2 max performance, as expected. The low VO_2 max group had a higher average percentage of body fat ($F = 7.211$, $p = .009$) and lower average VO_2 max score ($F = 81.742$, $p < .001$) compared to the high VO_2 max group.

DMN Seed Validity Check

The left and right PCC seeds recognized the main nodes of the DMN, including the PCC, precuneus, mPFC, lateral temporal cortex/temporal gyrus, parahippocampal gyrus, and parietal cortex/angular gyrus (see Figure 1).

Main Effect of VO_2 Max

Results of the association between VO_2 max and RSFC pattern between the left or right PCC and the whole brain revealed one statistically significant cluster. Greater VO_2 max was related to increased connectivity between the right PCC and left anterior cingulate (X = 12, Y = -30, Z = -3; $F = 25.93775$, $p < 0.001$; cluster size: 25 voxels; see Figure 2), with males displaying a more robust relationship (see Figure 3).

VO_2 Max by Sex Interaction

The VO_2 max*sex interaction was significantly associated with connectivity between the right PCC and left precuneus (X = 15, Y = 69, Z = 48; $F = 18.47617$, $p = < 0.001$; cluster size: 42 voxels; see Figure 4) and connectivity between the left PCC and right middle temporal gyrus (X = -51, Y = 72, Z = 15; $F = 22.51731$, $p = < 0.001$; cluster size: 22 voxels; see Figure 5). Results showed that while both males and females displayed a link between increased VO_2 max and increased connectivity from the right PCC to the left precuneus, males had a more robust relationship (see Figure 6). In contrast, females displayed a more robust relationship between the increased VO_2 max and increased left PCC and right middle temporal gyrus connectivity (see Figure 7).

Brain-Behavior Relationships

Fischer z-scores from the significant clusters of activation in the left anterior cingulate, left precuneus, and right middle temporal gyrus were correlated with previously selected indices from the PASAT, Ruff 2 & 7, CVLT-II, and D-KEFS. Brain-behavior relationships for the whole sample are displayed in Table 4. Brain-behavior relationships separated by sex are displayed in Table 5 (females) and Table 6 (males). Co-activation of the right PCC and left anterior cingulate (ACC) that associated with better aerobic fitness was negatively associated with verbal memory recall for the whole group (CVLT-II LDFR; $r = -.278$, $p = .031$; see Figure 8). Further analysis separated by sex revealed males displayed a negative association between these regions and both verbal learning (CVLT-II Total Learning; $r = -.464$, $p = .009$; see Figure 9) and verbal memory ($r = -.497$, $p = .005$; see Figure 8), while females did not have a significant relationship between these regions and neuropsychological performance. Co-activation of the left PCC and right middle temporal gyrus that was positively associated with aerobic fitness was positively associated with verbal memory recall for the whole group (CVLT-II LDFR; $r = .259$, $p = .045$; see Figure 10), with females showing a slightly greater benefit ($p = .08$); though, no significant differences were observed when separated by sex. Co-activation of the left PCC and right middle temporal gyrus was further associated with faster completion time on D-KEFS Inhibition for males ($r = -.357$, $p = .049$; see Figure 11). There were no significant findings between co-activation of the right PCC and left precuneus with neuropsychological performance, although a marginal relationship was observed in the males with improved CVLT-II Trial 1 performance ($p = .09$).

Discussion

The current study aimed to explore the effects of aerobic fitness on RSFC in the DMN and related neuropsychological functioning, as well as the extent to which sex may be a moderating factor, in healthy emerging adults. Greater VO_2 max was positively associated with connectivity between the right PCC and left ACC. The aerobic fitness-by-sex interaction was significantly associated with increased connectivity between the right PCC and left precuneus, with males displaying a more robust positive relationship between the increased VO_2 max and increased right PCC to left precuneus connectivity. The sex-by-aerobic fitness interaction was also significantly associated with connectivity between the left PCC and right middle temporal gyrus, with females showing a more robust positive relationship between increased VO_2 max and increased left PCC and right middle temporal gyrus connectivity.

The significant association between superior aerobic fitness and increased connectivity between the right PCC and left precuneus is consistent with known functional neuroanatomy of the DMN. The precuneus is adjacent to and interconnected with the PCC and this combined hub is crucial for efficient communication between the DMN and other areas important for memory retrieval (Alvarez & Squire, 1994; Cavanna & Trimble, 2006). Additionally, the precuneus has been implicated in visuospatial imagery (Cavanna & Trimble, 2006). The adult precuneus has generally been found to display decreased activation during externally oriented tasks (Raichle et al., 2001; Fransson, 2005) and increased activation when at rest or during tasks of episodic and autobiographical memory (Maddock et al., 2001; Lundstrom et al., 2005). The precuneus has also been found to display increased and broader connectivity to the frontoparietal networks during cognitively- and attention-demanding tasks in both childhood and young adulthood (ages 8-26; Li et al., 2019), though studies have found this relationship to become increasingly anticorrelated as youth age into young adulthood (Chai et al., 2014, DeSerisy et al., 2021), suggesting modification of connectivity may strengthen across development. Notably, the current study found a significant sex-by-aerobic fitness interaction such that males displayed a more robust relationship than females between better aerobic fitness and increased connectivity between the right PCC and left precuneus. Interestingly, prior work has found that adult females tend to exhibit stronger resting-state DMN connectivity (Ritchie et al., 2018; Weis et al., 2020) and PCC connectivity (Biswal et al., 2010; Weis et al., 2020) than adult males. However, aerobic fitness and sex may play important contributory roles in the current findings. Indeed, prior work has found increased grey matter volume and cortical thickness following aerobic exercise in young adults, including the left precuneus (Zhu et al., 2021). The current findings may extend prior volumetric findings that found greater self-reported aerobic fitness level was associated with increased grey matter surface area of the left precuneus in a male adolescent sample (n=34; ages 15-18) in comparison to low-fit adolescent males (Herting et al., 2016). In that context, it is possible that females have stronger baseline connectivity within these regions and the beneficial effects of exercise may be more pronounced in males. Further, males in our sample demonstrated a marginally significant link between this increased connectivity and superior performance on a verbal working memory task. Thus, our intra-DMN connectivity findings are promising and suggest aerobic exercise positively impacts functional connectivity of major nodes within the DMN that may be moderated by sex. Additional investigation is warranted to better understand implications for possible downstream cognitive effects.

We also found a significant main effect of aerobic fitness such that greater aerobic fitness was related to increased connectivity between the right PCC and left ACC, which was mainly driven by males in the present sample. The ACC is known to integrate emotional and cognitive functioning, as well as pain and motor processing (Stevens et al., 2011). For example, the ACC is important for monitoring conflicts between different sources of information or response options, and aids in adjusting behavior to optimize one’s performance (Stevens et al., 2011). Further, the ACC plays a role in processing emotional information and is recruited in the evaluation of emotionally salient information (Stevens et al., 2011). Prior work has found that greater aerobic exercise and/or physical activity induces structural changes in the ACC, which has been associated with improved emotional and executive functioning in young adults (Bento-Torres et al., 2019). Behaviorally, we found co-activation of the right PCC and left ACC that associated with better aerobic fitness was negatively associated with verbal memory recall for the whole group. Further analysis indicated males displayed a significant negative association between these regions and performance on both verbal learning and verbal memory, while females did not have a significant relationship, indicating increased connectivity was related to poorer performance in males. As predicted, greater connectivity between the DMN and a component of an attentional network was related to worse neuropsychological performance, suggesting a behavioral disadvantage. There are a few hypotheses that may explain the decreased performance. First, this finding may reflect a general lapse in attention and engagement in stimulus-independent mentation that activated the DMN, while simultaneous activation of the ACC was related to monitoring alterations in attentional control. Second, it is possible that males who exercise regularly do so as a coping mechanism for affective regulation. Notably, in this sample aerobic fitness was unexpectedly unrelated to current mood symptoms (Wade et al., 2021). While acute improvement in mood may be anticipated following exercise, this may not be entirely effective and result in a behavioral disadvantage of active engagement with emotionally salient thought processes or increased emotional response which may lead to introspective reflection that activates the DMN. Indeed, prior work has found a positive relationship between greater negative emotions and increased connectivity between the DMN and attentional networks (Weathersby et al., 2019).

Lastly, the sex-by-aerobic fitness interaction was positively associated with connectivity between the left PCC and right middle temporal gyrus, with females showing a more robust positive relationship. The middle temporal gyrus, one of three lateral surface gyri of the temporal lobe, has been implicated in language processing and semantic memory retrieval and consolidation, and has been associated with the DMN (Buckner et al., 2008). Behaviorally, we found that co-activation of the left PCC and right middle temporal gyrus that associated with better aerobic fitness was positively correlated with better verbal memory for the whole group, with females showing a greater benefit, though no significant differences were observed by sex. It is well documented in the literature that females tend to perform better than males on verbal memory tasks across the lifespan (Kramer et al., 1997; Kramer et al., 1988; Lewin et al., 2001; Pauls et al., 2013) which may explain the visually inspected and marginally significant behavioral advantage. Nonetheless, this suggests that the relationship between aerobic fitness and connectivity between the left PCC and right middle temporal gyrus is beneficial for verbal memory. Co-activation of the left PCC and right middle temporal gyrus was also associated with better inhibition in males (i.e., faster completion time on an inhibition task). Prior work investigating the relationship between VO_2 max and functional connectivity between multiple RSFC networks found that while the right middle temporal gyrus associated with the DMN, it also had functional connections with other networks including ventral attention and frontoparietal networks (Talukdar et al., 2018), which supports the role of this region in attentional and executive processes.

Overall, findings from the present study suggest sex is an important moderator when considering aerobic fitness and its impact on brain connectivity within the DMN. As noted previously, females have generally been shown to have stronger resting-state DMN and PCC connectivity than males (Biswal et al., 2010; Ritchie et al., 2018; Weis et al., 2020). However, males are known to have greater aerobic capacity and fitness than females in both adolescence and adulthood (Fomin et al., 2012; Sparling, 1980). Aerobic fitness has been linked to increased endorphins, endocannabinoid release, growth factors (e.g., BDNF, VEGF, IGF-1) that support angiogenesis and neurogenesis, decreased neuroinflammation (Barrientos et al., 2011), and improved catecholaminergic function (Zouhal et al., 2008), all of which may support enhanced brain health and function (Basso & Suzuki, 2017). Notably, it has been suggested that sex may moderate the impact aerobic exercise has on increasing levels of BDNF, as factors such as epigenetic regulation of gene expression, age, and menstrual cycle influence overall BDNF expression (Barha & Liu-Ambrose, 2018). However, it is possible that young male brains may benefit more from these underlying neural mechanisms given their greater aerobic capacity that likely leads to increased oxygen intake, blood flow, and related greater release of neurotrophic factors. Indeed, males in the present sample had a higher average VO_2 max score and engaged in more moderate to vigorous intensity activity minutes per day compared to females. This may indicate that there is a minimum VO_2 max threshold or exercise dose intensity to be reached before there is a significant effect on functional connectivity. It is possible that a mix of these explanations contributed to the sex-by-aerobic fitness interactions found in the present study, though additional investigation is warranted to better understand the relationship between sex, aerobic fitness, and underlying neural mechanisms.

From a public health standpoint, the findings from the current study suggest that aerobic exercise has generally beneficial effects on brain connectivity within the DMN and related cognition, particularly for verbal memory and aspects of executive functioning (e.g., inhibition), in healthy emerging adults, with one exception. It is noted that a behavioral disadvantage was observed in males in the present sample; males displayed increased right PCC and left ACC co-activation that associated with better aerobic fitness which was behaviorally related to poorer verbal learning and memory. This may suggest that aerobic exercise is not entirely effective for affective regulation, at least for the males in the present sample. Nonetheless, the present study found multiple beneficial effects which further highlights the importance of promoting aerobic exercise in adolescence and young adulthood and focusing on maintaining this advantageous health behavior throughout adulthood. One such avenue may be through incorporating aerobic or physical activity into the academic curriculum to decrease sedentary behavior, as youth and emerging adults typically spend most of their time in this setting. After-school programs and community-based organizations may also have great potential to promote engagement in physical activity. Additionally, college campuses should work to establish free or low-cost gym access and incorporate general courses that provide psychoeducation regarding the link between exercise and brain health, as well as behavior change strategies to initiate and maintain an active lifestyle. Ensuring college campuses and towns are pedestrian and bicycle friendly may be an additional means to increase physical activity. Furthermore, medical professionals at routine health visits should inquire as to how often youth and young adults are engaging in physical activity and offer psychoeducation on the established positive effects to provide recommendations and encourage engagement. For youth, parent involvement in psychoeducation will be beneficial to help increase accessibility to such opportunities. It is also recommended that both sexes are encouraged to engage in aerobic exercise. The present study found males and females displayed their own unique beneficial effects, and even in instances where one sex did not display a significant positive relationship the results were typically trending in a visually positive direction. Ultimately, aerobic exercise may be a viable low-cost intervention with a high return that can improve brain health in both nonclinical and clinical samples.

While the present study has numerous strengths including a sex-balanced sample and use of an objective measure of aerobic fitness (VO_2 max testing), there are potential weaknesses to note in the current study. First, causality cannot be determined given the cross-sectional nature of the present study. Second, fMRI scans were obtained approximately 24 hours after both aerobic fitness and neuropsychological testing. While acute neurocognitive benefits are anticipated, our participants did not engage in neuropsychological testing while undergoing fMRI, potentially reducing our ability to measure brain-behavior relationships. Third, the present sample is relatively small and comprised of cognitively healthy young adults without psychiatric, metabolic, or other significant medical comorbidities, which may limit the ability to detect significant functional and neuropsychological changes. However, it is noted that despite this we did find significant associations, some of which are advantageous for neurocognitive health, which lends evidence to support a link between recent exercise and DMN connectivity. It is possible that additional DMN findings would appear in an older sample or sample with metabolic conditions. Fourth, the present sample was predominantly white which limits generalizability. Future studies should further investigate the relationship between aerobic fitness and DMN connectivity in more diverse samples to better understand these relationships in a nationally representative sample. It will also be important to investigate access to exercise-related interventions and resources across diverse populations during development to ensure such public health initiatives are equitable. Fifth, it is important to note the high correlation between VO_2 max and body fat percentage that could not be controlled for in the present study due to multicollinearity. These limitations highlight the importance of prospective, longitudinal studies such as the Adolescent Brain Cognitive Development (ABCD) Study that can more adequately assess the relationship between physical activity, body fat, and brain development in a large sample of youth as they age.

In summary, the present study contributes to the rapidly growing body of literature that shows a generally positive relationship between aerobic fitness and brain health. From a public health standpoint, the current findings are promising and suggest that such benefits are observed even in physically healthy emerging adults. Additionally, sex was found to be an important moderator in the present study and should be considered in future investigations. Additional factors such as body fat and hormonal and genetic variations (e.g., BDNF) should also be considered as they may further moderate the relationship between aerobic fitness and brain health. Furthermore, it is noteworthy that the present study found multiple inter-hemispheric connectivity connections which may reflect a unique impact of VO_2 max on connectivity, which may or may not be further modulated by sex and warrants further investigation in this unique developmental period. Overall, these findings lend support to the importance of initiatives that promote physical activity and aerobic exercise in adolescents and emerging adults and focus on maintenance of these advantageous health behaviors through adulthood when physical activity levels tend to decline. Ultimately, aerobic exercise may be a viable low-cost intervention with a high return that can improve brain health in both nonclinical and clinical samples. Future studies should also investigate the utility of aerobic exercise interventions in neuropsychological and psychiatric clinical populations across the lifespan such as ADHD, substance use, traumatic brain injury, and other acquired brain conditions.

Figures

Figure 1. The left (A) and right (B) PCC seeds recognized the main nodes of the DMN.

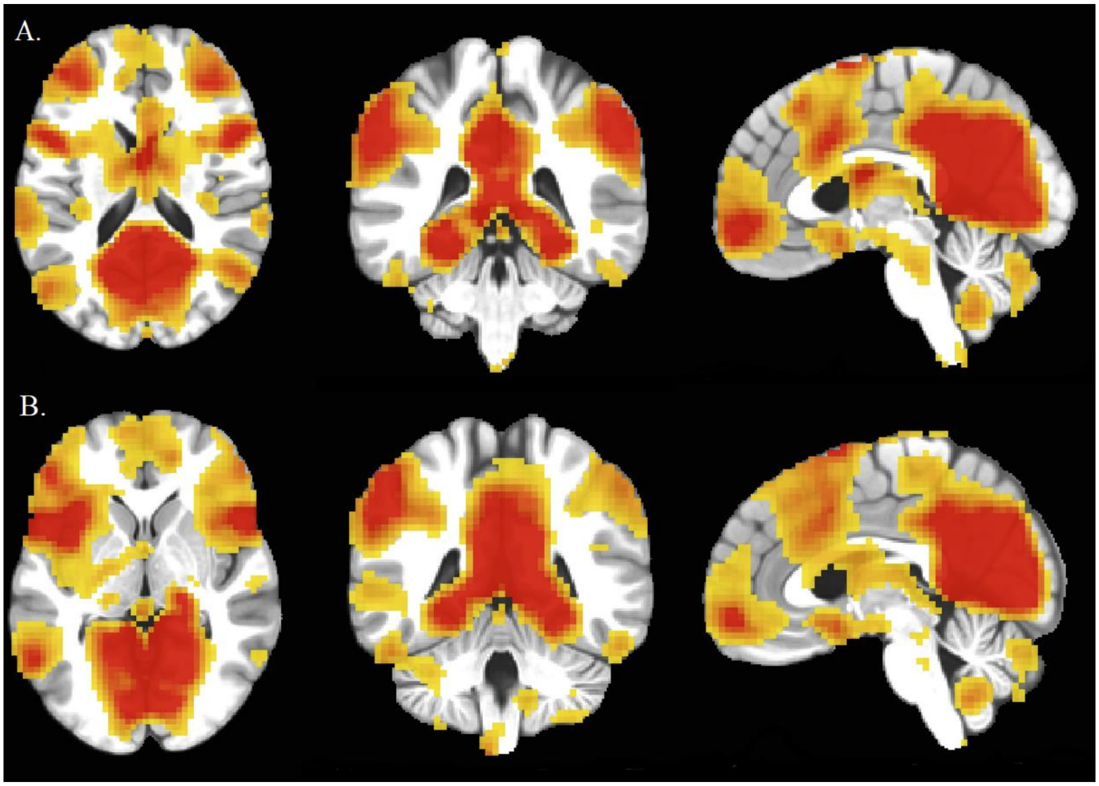


Figure 2. Greater VO_2 max was associated with increased connectivity (in red) between the right PCC and left anterior cingulate.

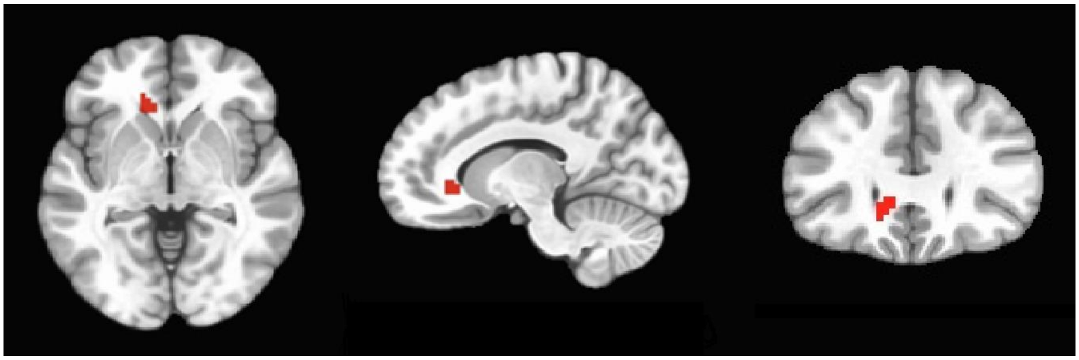


Figure 3. Bivariate scatterplot demonstrating association between extent of connectivity between right PCC and left anterior cingulate associated with VO_2 max score, parsed by sex.

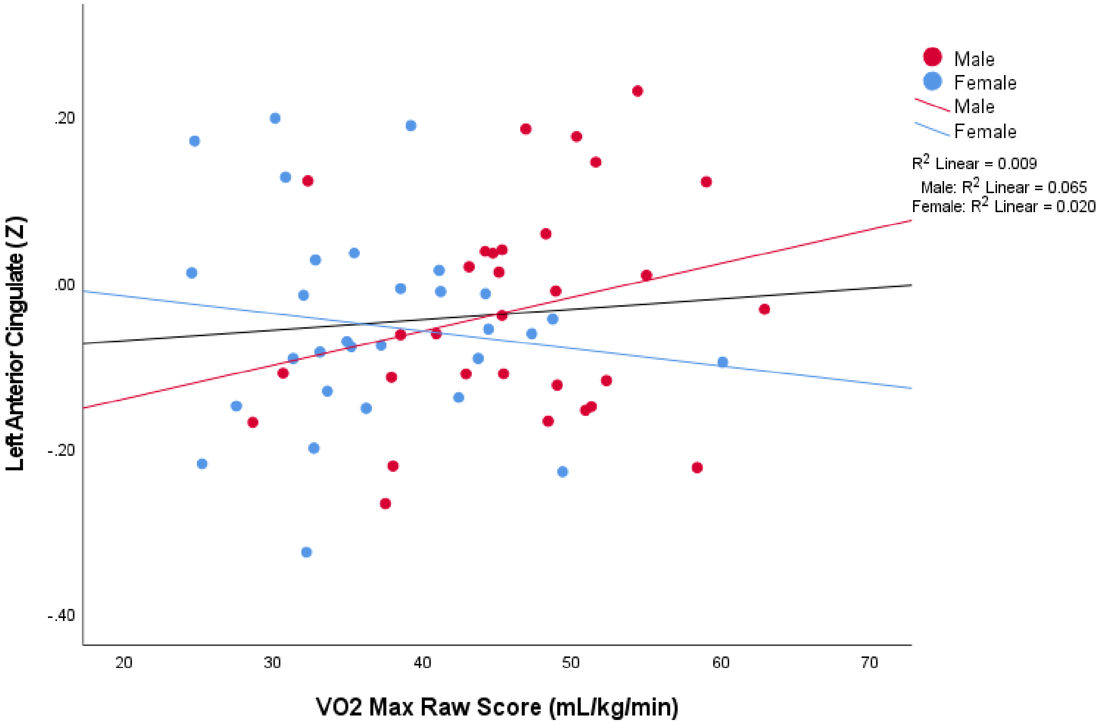


Figure 4. The VO_2 max*sex interaction was significantly associated with increased connectivity (in red) between the right PCC and left precuneus.

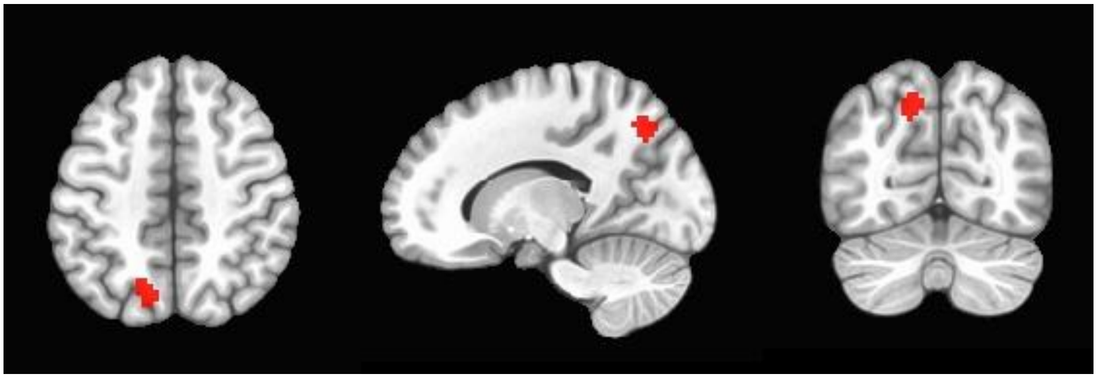


Figure 5. The VO_2 max*sex interaction was significantly associated with increased connectivity (in red) between the left PCC and right middle temporal gyrus.

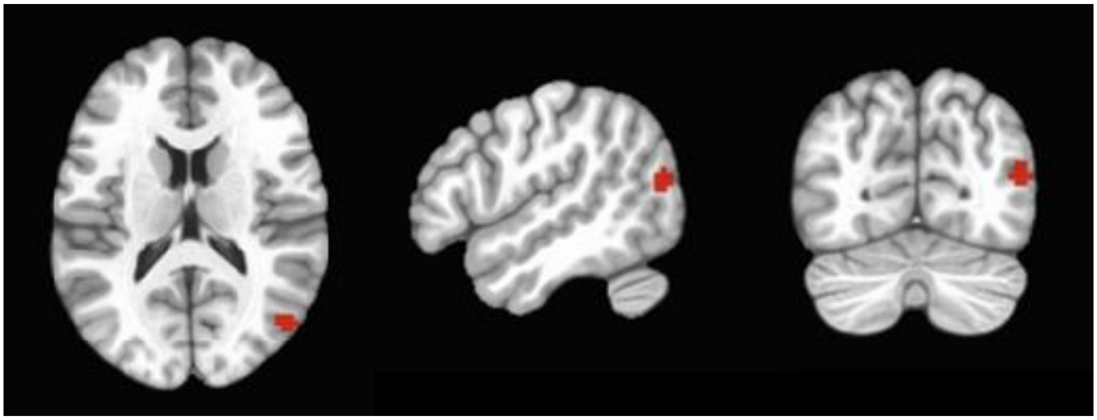


Figure 6. Bivariate scatterplot demonstrating extent of connectivity between right PCC and left precuneus associated with VO_2 max*sex interaction, parsed by sex.

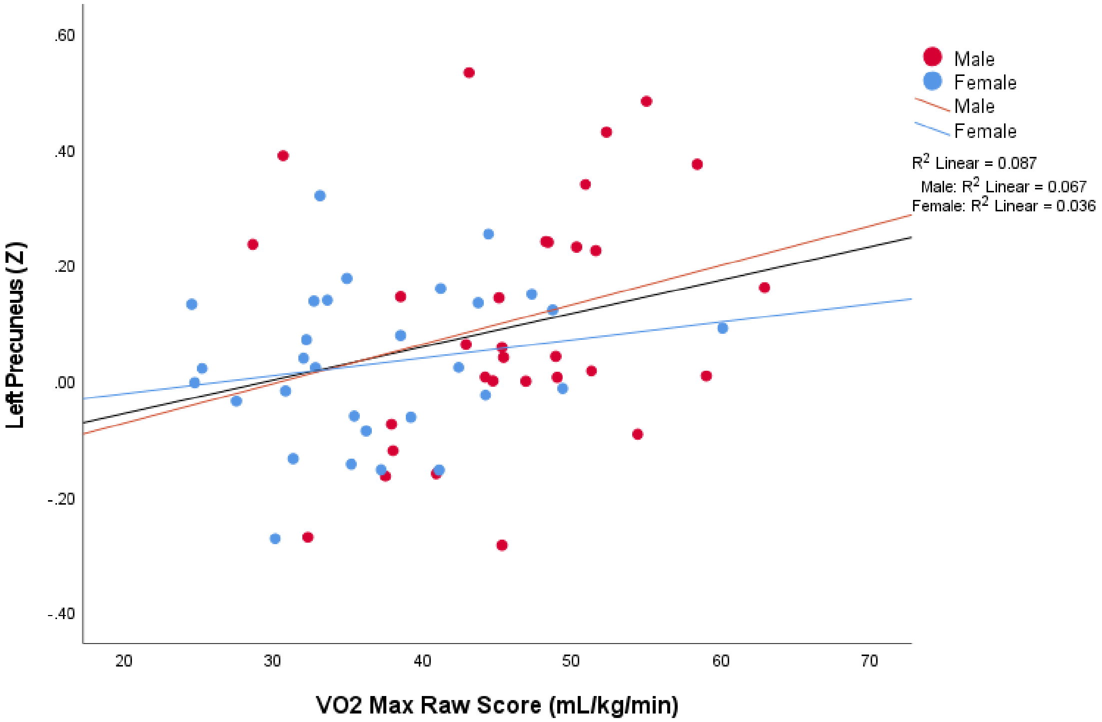


Figure 7. Bivariate scatterplot demonstrating extent of connectivity between left PCC and right middle temporal gyrus associated with VO_2 max*sex interaction, parsed by sex.

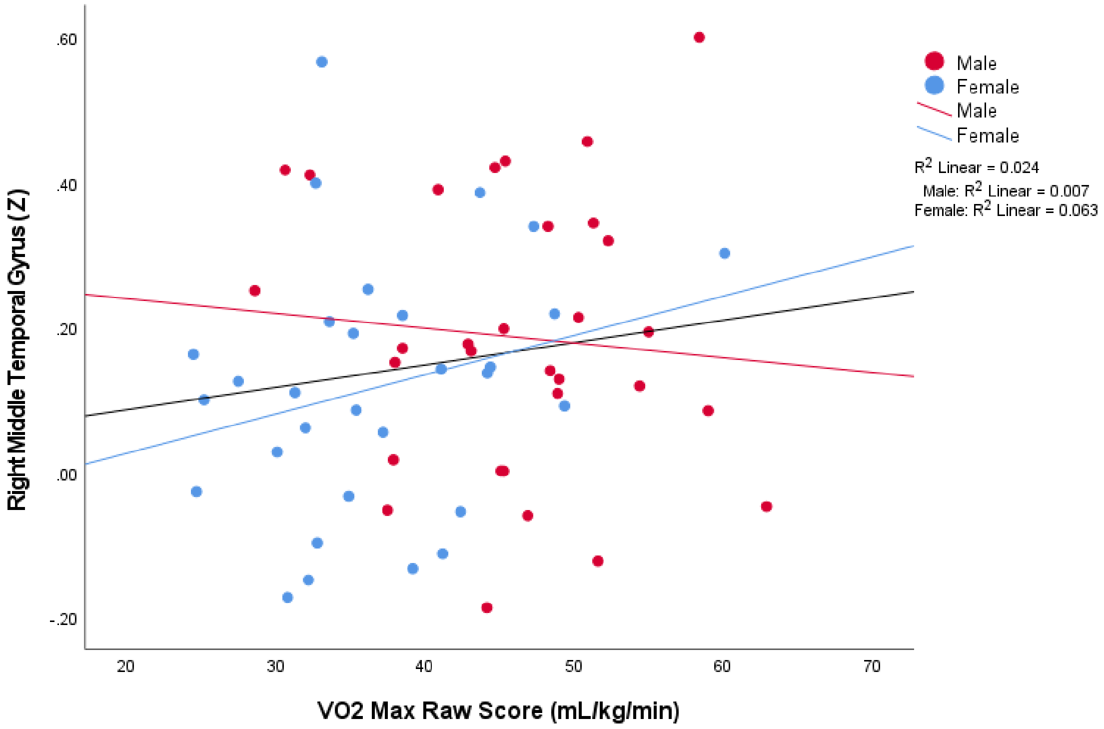


Figure 8. Bivariate scatterplot demonstrating association between co-activation of the right PCC and left ACC with CVLT-II Long Delay Free Recall Raw Score, parsed by sex.

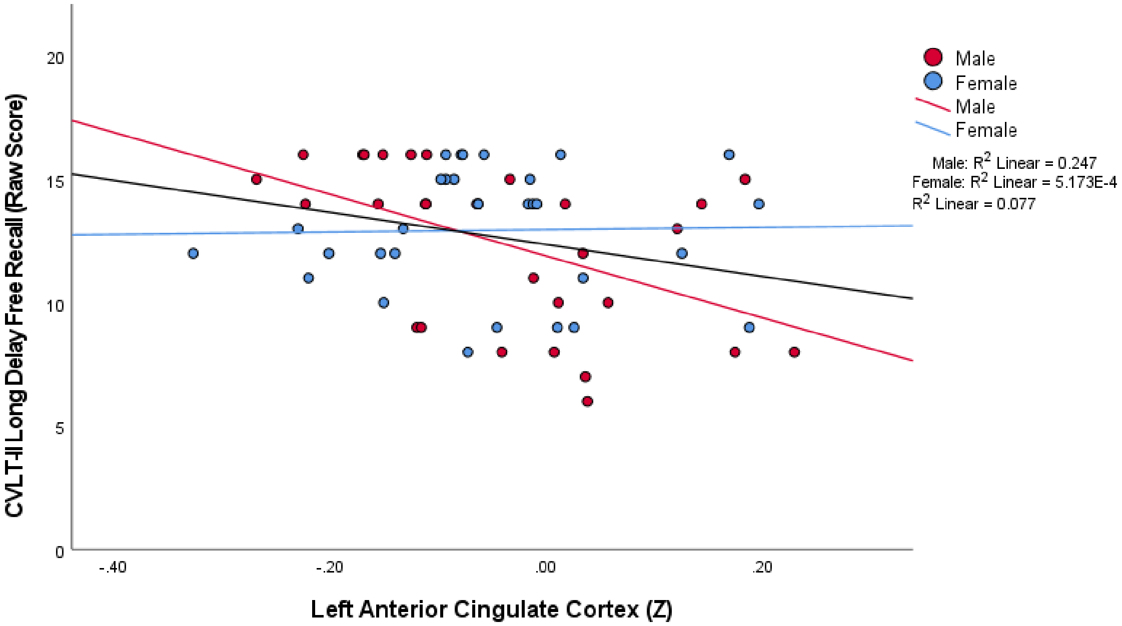


Figure 9. Bivariate scatterplot demonstrating association between co-activation of the right PCC and left ACC with CVLT-II Total Correct (Trials 1-5) Raw Score in males.

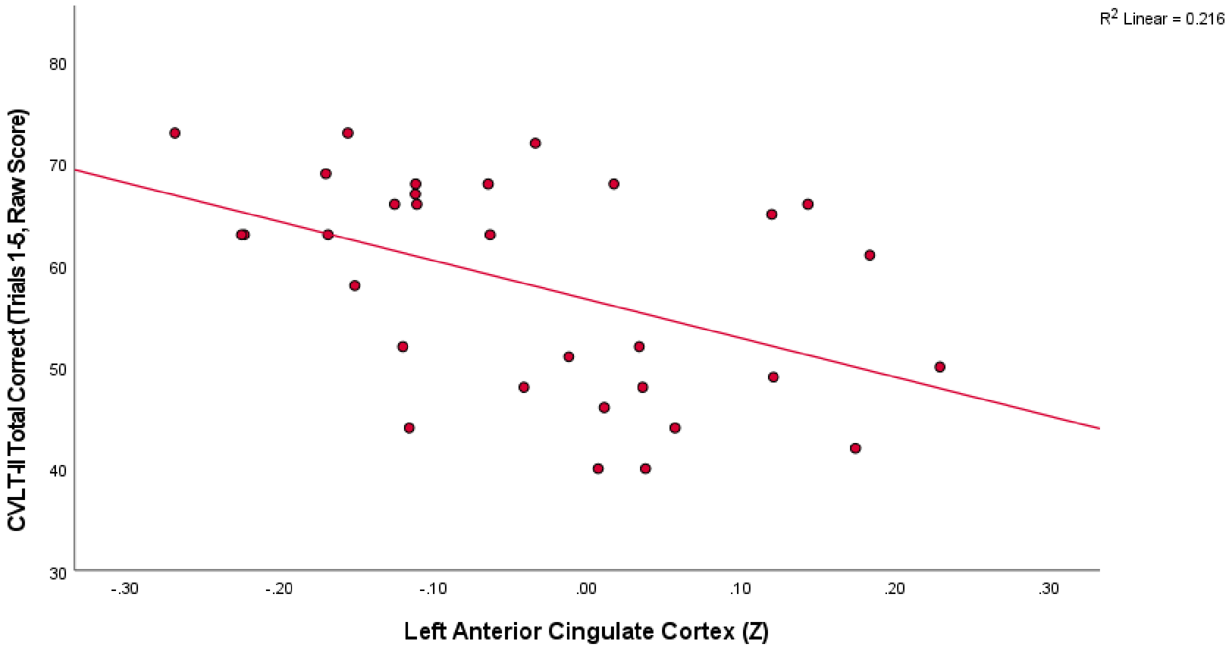


Figure 10. Bivariate scatterplot demonstrating association between co-activation of the left PCC and right MTG with CVLT-II Long Delay Free Recall Raw Score, parsed by sex.

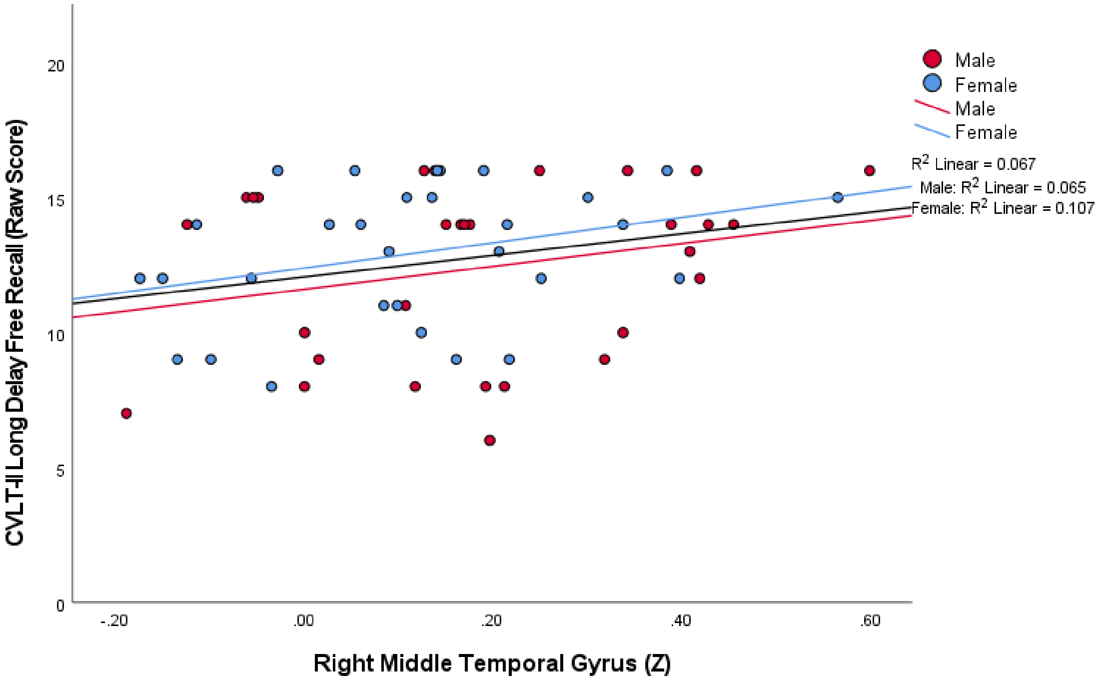
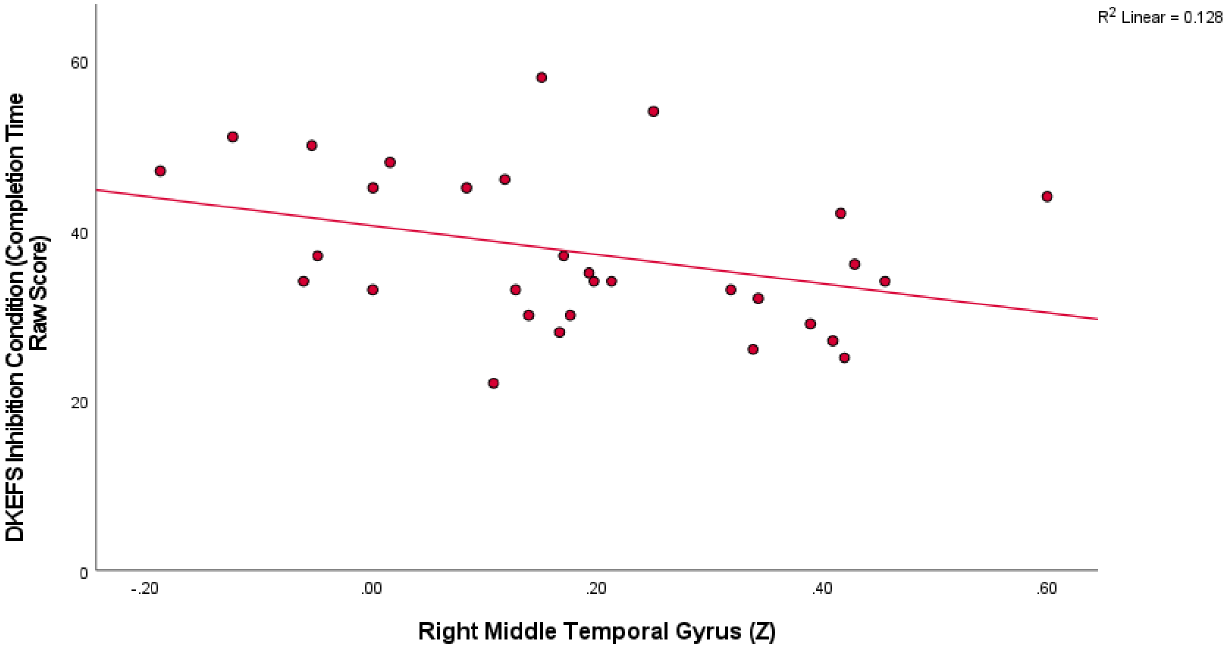


Figure 11. Bivariate scatterplot demonstrating association between co-activation of the left PCC and right MTG with DKEFS Inhibition Condition Completion Time Raw Score in males.



Tables

Table 1. Sample Descriptive Statistics

	Mean (SD)	**Range**
Age	21.16 (2.49)	16-25
Education (Years)	14.47 (2.20)	9-21
WRAT-4 Reading (SS)	105.67 (10.39)	87-133
VO_2 Max (mL/kg/min)	41.59 (9.26)	24.5-62.9
Body Fat (%)	22.33 (10.06)	6.4-47.2
Sex (% Female)	49%	
Race (% Caucasian)	72%	
Ethnicity (% Not Hispanic)	90%	

Table 2. Descriptive Statistics by Sex

	Female (*n*=30)	**Male (*n*=31)**		
	Mean (SD) [Range]		**F**	***p***
Age	21.4 (2.56) [16-25]	20.93 (2.44) [16-25]	.523	.472
Education (years)	14.56 (2.17) [11-21]	14.38 (2.26) [9-19]	.100	.753
WRAT-4 Reading (SS)	104.2 (10.22) [87-133]	107.09 (10.52) [90-133]	1.187	.280
VO_2 Max (mL/kg/min)	36.98 (8.15) [24.5-60.1]	46.06 (8.09) [28.6-62.9]	**19.014**	**<.001**
Body Fat (%)	28.78 (7.33) [16.3-47.2]	15.87 (8.12) [6.4-41.7]	**41.719**	**<.001**
Moderate to Vigorous Physical Activity (Mins/Day)	31.83 (19.65) [6.5-85.85]	43.5 (20.4) [13.85-110.33]	**4.646**	**.036**
Sedentary Behavior (Mins/Day)	670.65 (192) [315-1030.4]	648.8 (175.36) [302.5-982.1]	.195	.661

Table 3. Descriptive Statistics by VO_2 Max

	VO_2 Max Low (*n*=36)	**VO_2 Max High (*n*=25)**		
	Mean (SD) [Range]		**F**	***p***
Age	21.33 (2.61) [16-25]	20.92 (2.34) [16-25]	.400	.530
Education (years)	14.61 (2.36) [9-21]	14.28 (1.96) [10-17]	.330	.568
WRAT-4 Reading (SS)	105.83 (10.75) [87-133]	105.44 (10.07) [90-126]	.021	.886
VO_2 Max (mL/kg/min)	35.76 (6.18) [24.5-45.4]	50 (5.84) [41.1-62.9]	**81.742**	**<.001**
Body Fat (%)	25.03 (10.39) [6.4-47.2]	18.26 (8.15) [6.7-31.8]	**7.211**	**.009**
Moderate to Vigorous Physical Activity (Mins/Day)	34.35 (21.81) [6.5-110.3]	43.04 (18.37) [13.9-85.9]	2.414	.126
Sedentary Behavior (Mins/Day)	683.65 (190.21) [315-1030.4]	625 (168.1) [302.5-947]	1.399	.242
Sex (% Female)	55%	40%	--	--

Table 4. Correlations Between Significant Clusters and Performance on Selected Neuropsychological Measures in Whole Sample (*N*=61)

		Left ACC	**Left Precuneus**	**Right MTG**
PASAT Total Correct Raw Score	Pearson Correlation	-.036	.083	.095
	Sig. (2-tailed)	.782	.526	.466
Ruff 2 & 7 Total Speed Raw Score	Pearson Correlation	.004	-.007	.043
	Sig. (2-tailed)	.974	.956	.745
Ruff 2 & 7 Total Accuracy Raw Score	Pearson Correlation	-.080	-.049	-.047
	Sig. (2-tailed)	.538	.708	.719
CVLT-II Trial 1 Raw Score	Pearson Correlation	-.028	.176	-.064
	Sig. (2-tailed)	.831	.175	.627
CVLT-II Total Correct (Trials 1-5) Raw Score	Pearson Correlation	-.218	.014	.175
	Sig. (2-tailed)	.092	.912	.177
CVLT-II Long Delay Free Recall Raw Score[a]	Pearson Correlation	**-.278***	.007	**.259***
	Sig. (2-tailed)	**.031**	.960	**.045**
DKEFS Color-Word Interference Inhibition Condition Completion Time Raw Score	Pearson Correlation	-.087	-.066	-.204
	Sig. (2-tailed)	.505	.611	.115

*. Correlation is significant at the .05 level (2-tailed)

[a] *n*=60; one male participant was identified as an outlier and dropped from this correlation

Abbreviations: ACC = Anterior Cingulate Cortex, MTG = Middle Temporal Gyrus.

Table 5. Correlations Between Significant Clusters and Performance on Selected Neuropsychological Measures in Females (*n*=30)

		Left ACC	**Left Precuneus**	**Right MTG**
PASAT Total Correct Raw Score	Pearson Correlation	-.084	.198	-.162
	Sig. (2-tailed)	.661	.294	.394
Ruff 2 & 7 Total Speed Raw Score	Pearson Correlation	-.042	.139	.102
	Sig. (2-tailed)	.825	.463	.590
Ruff 2 & 7 Total Accuracy Raw Score	Pearson Correlation	-.089	.036	-.111
	Sig. (2-tailed)	.641	.851	.560
CVLT-II Trial 1 Raw Score	Pearson Correlation	.002	-.115	-.197
	Sig. (2-tailed)	.992	.545	.298
CVLT-II Total Correct (Trials 1-5) Raw Score	Pearson Correlation	.062	-.192	.286
	Sig. (2-tailed)	.745	.309	.125
CVLT-II Long Delay Free Recall Raw Score	Pearson Correlation	.023	-.121	.326
	Sig. (2-tailed)	.905	.604	.078
DKEFS Color-Word Interference Inhibition Condition Completion Time Raw Score	Pearson Correlation	.044	-.066	-.026
	Sig. (2-tailed)	.819	.730	.891

*. Correlation is significant at the .05 level (2-tailed)

Abbreviations: ACC = Anterior Cingulate Cortex, MTG = Middle Temporal Gyrus.

Table 6. Correlations Between Significant Clusters and Performance on Selected Neuropsychological Measures in Males (*n*=31)

		Left ACC	**Left Precuneus**	**Right MTG**
PASAT Total Correct Raw Score	Pearson Correlation	-.046	-.080	.201
	Sig. (2-tailed)	.807	.668	.277
Ruff 2 & 7 Total Speed Raw Score	Pearson Correlation	.035	-.088	.001
	Sig. (2-tailed)	.850	.640	.997
Ruff 2 & 7 Total Accuracy Raw Score	Pearson Correlation	-.071	-.126	.038
	Sig. (2-tailed)	.702	.501	.838
CVLT-II Trial 1 Raw Score	Pearson Correlation	.026	.309	-.017
	Sig. (2-tailed)	.892	.090	.926
CVLT-II Total Correct (Trials 1-5) Raw Score	Pearson Correlation	**-.464****	.110	.068
	Sig. (2-tailed)	**.009**	.555	.717
CVLT-II Long Delay Free Recall Raw Score[a]	Pearson Correlation	**-.497****	.099	.255
	Sig. (2-tailed)	**.005**	.604	.174
DKEFS Color-Word Interference Inhibition Condition Completion Time Raw Score	Pearson Correlation	-.196	-.074	**-.357***
	Sig. (2-tailed)	.290	.691	**.049**

*. Correlation is significant at the .05 level (2-tailed)

**. Correlation is significant at the .01 level (2-tailed)

[a] *n*=30; one male participant was identified as an outlier and dropped from this correlation

Abbreviations: ACC = Anterior Cingulate Cortex, MTG = Middle Temporal Gyrus.

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