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Exercise, Cognition, and Cannabis Use in Adolescents

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EXERCISE, COGNITION, AND CANNABIS USE IN ADOLESCENTS

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by

Ileana Pacheco-Colón

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To: Dean Michael R. Heithaus
College of Arts, Sciences and Education

This dissertation, written by Ileana Pacheco-Colón, and entitled Exercise, Cognition, and Cannabis Use in Adolescents, having been approved in respect to style and intellectual content, is referred to you for judgement.

We have read this dissertation and recommend that it be approved.

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Date of Defense: May 24, 2021

The dissertation of Ileana Pacheco-Colón is approved.

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Florida International University, 2022

DEDICATION

I dedicate this dissertation to my parents, family, and life partner. Although they may never fully understand what I do, their love for me and support of my endeavors have always been unwavering.

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This dissertation culminates six years of intellectual growth, professional development, and hard work, which would not have been possible without the help and unconditional support of numerous people. First, I wish to thank Raul Gonzalez, who has been my mentor and fierce advocate throughout my graduate training. I also thank the members of my dissertation committee for helping me develop this project, from grant submission to dissertation proposal to execution and interpretation of analyses. In addition, I'd like to thank several members of the SUN lab who have meaningfully contributed to my journey, especially Samuel W. Hawes, Catalina Lopez-Quintero, Jackie Duperrouzel, Dayana Paula, Karen Granja, and María J. Salamanca.

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ABSTRACT OF THE DISSERTATION

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Heavy and/or chronic cannabis use has been associated with neurocognitive impairment and decline, often in domains such as memory and executive functioning. On the other hand, exercise has been linked to positive effects on brain and cognitive health across the lifespan, as well as to better substance use outcomes. Despite this, little is known about the ways in which exercise could help prevent or ameliorate adverse cannabis-related outcomes among adolescents.

Through three separate studies, the current dissertation examines interrelations among exercise, cognition, and cannabis use in children and adolescents in an effort to determine whether exercise can prevent or ameliorate cannabis-related cognitive decline and other adverse outcomes. The first study examined whether exercise ameliorates cannabis-related declines in episodic memory in a sample of 401 adolescents. Results from multivariate latent growth curve models replicated findings that greater frequency of cannabis use is associated with declines in episodic memory. However, neither initial levels nor change in exercise moderated these associations. The second study examined associations between exercise and cannabis-related outcomes (e.g., cannabis use frequency, cannabis use disorder, cannabis-related problems) after a 6-month period, and

tested the mediating role of exercise effects on decision-making in a sample of 387 adolescents. Results from prospective mediation analyses revealed that more exercise predicted greater cannabis use frequency, but not cannabis use disorder or problems. There was no evidence of a mediating role for decision-making in the associations between exercise and cannabis-related outcomes, and positive effects of exercise on decision-making were better accounted for by demographics. The third study examined cross-sectional associations between exercise, task-related brain activation, and executive functioning in a sample of 7,733 preadolescent children. Results from cross-sectional mediation analyses indicated that the association between exercise and executive functioning was largely accounted for by sociodemographic factors, and did not support a mediating role for task-related activation of frontoparietal and salience networks. Together, findings suggest that effects of exercise on neurocognitive functioning in pediatric populations are small, may be more readily observed within the domain of executive functioning, and may be better explained by sociodemographic characteristics.

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ACRONYMS AND ABBREVIATIONS

Adolescent Brain and Cognitive Development	ABCD
California Verbal Learning Test—2nd Edition	CVLT-II
Cannabinoid type 1	CB_1
Child Behavior Checklist	CBCL
Comparative Fit Index	CFI
Data Analysis and Informatics Center	DAIC
Default-mode network	DMN
Delta-9-tetrahydrocannabinol	THC
Drug Use History Questionnaire	DUHQ
Full information maximum likelihood	FIML
Functional magnetic resonance imaging	fMRI
Game of Dice Task	GDT
General linear model	GLM
Intellectual quotient	IQ
Iowa Gambling Task	IGT
Latent growth curve modeling	LGCM
Marijuana Problems Scale	MPS
Region of interest	ROI
Root mean square error of approximation	RMSEA
Sports and Activity Involvement Questionnaire	SAIQ
Standard deviation	SD
Standardized root mean square residual	SRMR
Structured Clinical Interview for DSM-IV	SCID-IV

Wechsler Memory Scale—Fourth Edition	WMS-IV
Wide Range Achievement Test Fourth Edition	WRAT-4

I. INTRODUCTION TO THE RESEARCH

Over the course of my graduate training, I have built a program of research examining the effects of lifestyle factors, particularly cannabis use, on neurocognitive, psychological, and physical health. Leveraging my personal enthusiasm for the benefits of physical activity, my recent independent research has focused on exploring the interactions between exercise, cannabis use, and cognition among adolescents. Despite high prevalence of cannabis use and knowledge of its adverse effects, little has been done to identify potential methods through which these negative effects could be prevented or ameliorated. Exercise is one such avenue which has received limited attention in the context of cannabis use. Further, although effects of both cannabis use and exercise on cognition have been extensively documented among adults, they remain relatively understudied among children and adolescents (Donnelly et al., 2016; Gonzalez, Pacheco-Colón, Duperrouzel, & Hawes, 2017; Herting & Chu, 2017). This is an important gap in the literature, as adolescence represents a unique developmental stage characterized by rapid neurodevelopment which simultaneously results in increased risk-taking and increased vulnerability to adverse effects (Casey & Jones, 2010a; Lisdahl, Gilbart, Wright, & Shollenbarger, 2013a).

My dissertation leverages data collected through two larger longitudinal studies for secondary data analyses examining associations between exercise, neurocognition, and cannabis use among adolescents and children through three separate studies. The first two studies utilize data acquired through a longitudinal study examining the effects of adolescent cannabis use on neurocognition, particularly in the domains of episodic memory and decision-making (R01 DA031176, PI: Gonzalez). The first manuscript

focuses on longitudinal associations between cannabis use and episodic memory among adolescents, and examines whether engagement in exercise mediates this association (Chapter II). Portions of Chapter II have been accepted for publication in *Addiction*. The second manuscript examines prospective associations between exercise and cannabis-related outcomes among adolescents, and explores whether exercise-related effects on the domain of decision-making may mediate these associations (Chapter III). Chapter III has been accepted for publication in *Substance Use & Misuse.* Finally, the third study uses data from a large national sample of children from the Adolescent Brain and Cognitive Development (ABCD) study (U01 DA041156). It examines cross-sectional associations between exercise and executive functioning, and tests a mediating role for *N*-back task-related activation of the frontoparietal and salience networks (Chapter IV). Because the majority of the children in the ABCD sample were substance-naïve at the baseline assessment (as well as at initial follow-ups), the third study did not explore associations between exercise and cannabis use. Nevertheless, these analyses lay the groundwork for future exploration of these questions once substance use levels in this sample increase.

To the best of my knowledge, my dissertation represents one of the first attempts at elucidating cross-sectional and longitudinal associations between exercise, neurocognition, and cannabis use among children and adolescents. Combining neurocognitive with neuroimaging data obtained from cannabis-using adolescents and/or substance-naïve children will contribute to a more integrated understanding of these relationships. Together, findings from these studies will begin to answer whether, how, and which exercise-related cognitive gains can be leveraged in the prevention and treatment of problematic cannabis use.

II.

EXERCISE AS A MODERATOR OF THE ASSOCIATION BETWEEN CANNABIS USE AND MEMORY

Portions of this chapter are part of a manuscript that has been accepted for publication in Addiction.

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Introduction

Cannabis use is prevalent among Americans, with approximately 16% of individuals over the age of 12 years reporting at least some cannabis use in the past year (Substance Abuse and Mental Health Services Administration (SAMHSA), 2019a). Nearly a fifth of these users reported daily or near daily cannabis use (SAMHSA, 2019b). Both of these estimates represent increases relative to estimates from prior years, suggesting that prevalence of cannabis use may be on the rise (SAMHSA, 2019b). Although these increases were primarily driven by use among adults, cannabis use is also common among adolescents, with 12.5% of teens reporting past year use, and about 8% of these reporting near daily use (SAMHSA, 2019a, 2019b).

Concurrently, public opinion toward cannabis legalization has become more permissive. Whereas only 12% of Americans supported cannabis legalization in 1969, more recent surveys indicate that over 50% support legalization of cannabis (Felson, Adamczyk, & Thomas, 2019; Pew Research Center, 2016). Consistent with these trends, 34 U.S. states have passed medical marijuana laws and 16 (and the District of Columbia) have legalized recreational use for adults over the age of 21. This recent proliferation of more permissive cannabis laws has been accompanied by lower perceived risk of use among adolescents (Hughes, Lipari, & Williams, 2016; Johnston, Miech, Bachman, & Schulenberg, 2014), a population that may be particularly vulnerable to adverse effects of cannabis use.

Indeed, several important large-scale neuromaturational changes take place during adolescence. Although limbic regions associated with reward processing (e.g., amygdala, nucleus accumbens) reach full maturation by adolescence, frontal regions associated with

impulse control and executive functioning (e.g., prefrontal cortex) show a protracted pattern of development into adulthood (Casey, Jones, & Hare, 2008). As posited by the dual systems model of adolescent risk-taking, neurocognitive constructs of reward-seeking and impulse control develop in parallel to their underlying brain structures, such that reward-seeking peaks during adolescence while impulse control increases steadily from childhood into adulthood (Steinberg, 2010). As a result of this developmental imbalance, adolescents are likely to engage in risky behaviors, such as use of substances like cannabis (Casey & Jones, 2010; Steinberg, 2010). Importantly, a growing body of work suggests that these changes may also make adolescents more vulnerable to the neurotoxic effects of substances (Casey & Jones, 2010; Lisdahl, Gilbart, Wright, & Shollenbarger, 2013; Witt, 2010). Thus, developing a more complete understanding of the effects of cannabis use on adolescent brain and cognitive health is both necessary and urgent, and would serve to inform policy, prevention, and intervention efforts.

Heavy and/or chronic cannabis use has been associated with poorer functioning across several neurocognitive domains, including intellectual quotient (IQ), learning and memory, psychomotor performance, processing speed, and aspects of executive functioning (Broyd, Hell, Beale, Yücel, & Solowij, 2016). Three meta-analyses have synthesized findings from studies examining associations between cannabis use and various aspects of neuropsychological functioning, focusing on non-acute effects (i.e., effects that persist beyond acute intoxication). Results from these studies suggest that frequent or heavy cannabis use is associated with small, negative effects on overall cognition, as well as specific domains, particularly learning and episodic memory (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003; Schreiner & Dunn, 2012; Scott et al.,

2018), which is here defined as memory for personally experienced events with their spatiotemporal context and respective perceptual details (Tulving & Markowitsch, 1998; Tulving, 2002). Accumulating evidence also suggests that initiation of heavy and/or chronic cannabis use during adolescence may be associated with increased risk of harmful consequences, including higher risk of addiction (Volkow, Baler, Compton, & Weiss, 2014), lower academic achievement and educational attainment (Pacheco-Colón, Ramirez, & Gonzalez, 2019), and steeper declines in neurocognitive functioning, most commonly in the domains of IQ and episodic memory (Gonzalez et al., 2017).

Adverse effects of cannabis use on learning and memory functioning are perhaps not surprising, considering the neurobiological mechanisms of action that underlie the drug's effects. Delta-9-tetrahydrocannabinol (THC)—the primary psychoactive constituent in cannabis—exerts its effects through cannabinoid receptors type 1 (CB_1 receptors), which are densely concentrated in regions relevant to memory function, such as the hippocampus (Glass, Faull, & Dragunow, 1997). Findings from preclinical studies have shown that THC activity at hippocampal CB_1 receptors inhibits the release of the neurotransmitter GABA, which results in learning and memory impairments (Laaris, Good, & Lupica, 2010). More recent neuroimaging work with human subjects suggests that chronic cannabis use results in the downregulation of CB_1 receptors throughout the cortex, which may be associated with long-term cognitive impairment (Hirvonen et al., 2012). This downregulation is greatest, and shows the least improvement with abstinence, in the hippocampus (Hirvonen et al., 2012; Villares, 2007), thus lending further support to neurocognitive findings.

In contrast, both physical activity and chronic exercise have been linked to a variety of positive effects on cognitive function spanning multiple domains across the lifespan. Physical activity is here defined as bodily movement produced by skeletal muscles that results in the expenditure of energy (Caspersen, Powell, & Christenson, 1985). It is often (though not exclusively) accomplished through exercise, which refers to planned, structured, and repetitive physical activity aimed at improving or maintaining physical fitness (Caspersen et al., 1985). Cognitive benefits of regular exercise can be observed after two- to three-month periods (Best, 2010; Davis et al., 2011; Tomporowski, Davis, Miller, & Naglieri, 2008), and may be a result of multiple underlying mechanisms, including changes in growth factors (e.g., brain derived neurotrophic factor; Cotman, Berchtold, & Christie, 2007), decreased inflammatory response and oxidative stress (Sakurai et al., 2009), increased activity of CB_1 receptors in areas such as the hippocampus (Ferreira-Vieira, Bastos, Pereira, Moreira, & Massensini, 2014), and increased levels of circulating endocannabinoids (Koltyn, Brellenthin, Cook, Sehgal, & Hillard, 2014). Given well-documented health benefits, the American College of Sports Medicine and the Center for Disease Control recommend that adults ages 18-65 engage in at least 150 minutes of moderate-to-vigorous physical activity per week, and two days per week of muscle-strengthening activities (Piercy et al., 2018). The guidelines for children and adolescents ages 6-17 are significantly higher, recommending at least 60 minutes of moderate-to-vigorous physical activity *per day* and three days per week of muscle strengthening activities (Piercy et al., 2018).

In spite of these guidelines, available research suggests that there is a significant decline in physical activity levels from childhood into adolescence (Cairney, Veldhuizen,

Kwan, Hay, & Faught, 2014; Dumith, Gigante, Domingues, & Kohl, 2011; Nader, Bradley, Houts, McRitchie, & O'Brien, 2008; Troiano et al., 2008). This age-related decline has been observed in studies using both objective (e.g., accelerometer), and subjective (e.g., self-report questionnaires) measures of physical activity and exercise (Nader et al., 2008; Troiano et al., 2008). One longitudinal study of children ages 9 to 15 found that physical activity levels decreased by approximately 37 minutes per year (Nader et al., 2008). Indeed, recent estimates suggest that only 24% of children 6 to 17 years of age (and 26% of high school students) participated in the recommended 60 minutes of daily physical activity (Kann, 2018; The Child and Adolescent Health Measurement Initiative, 2016). These estimates are concerning, as physical activity during adolescence is predictive of lifestyle behaviors, physical health, and psychological well-being in adulthood (Malina, 2001; Sacker & Cable, 2006).

Among school-age children and adolescents, exercise has been positively associated with various school-related metrics, including grade-point averages, academic readiness and achievement, reading and mathematical skills, intellectual functioning, and perceptual skills (Donnelly et al., 2016; Esteban-Cornejo, Tejero-Gonzalez, Sallis, & Veiga, 2015; Herting & Chu, 2017; Sibley & Etnier, 2003; Tomporowski et al., 2008). It has also been linked to improvements in specific neurocognitive domains, such as memory (Donnelly et al., 2016; Herting & Chu, 2017; Sibley & Etnier, 2003; Tomporowski et al., 2008). Children and adolescents engaging in regular exercise and/or demonstrating higher fitness levels have shown improvements in verbal working memory (Reynolds & Nicolson, 2007), associative memory (Chaddock, Erickson, Prakash, Kim, et al., 2010), and visuospatial learning and memory (Herting & Nagel, 2012; Lee et al.,

2014; Raine et al., 2013; Ross, Yau, & Convit, 2015; Whiteman, Young, Budson, Stern, & Schon, 2016). Concordantly, studies have documented effects of exercise and fitness on the structure and function of memory-related brain regions in these populations. For instance, studies have found larger entorhinal and hippocampal volumes in more aerobically fit adolescents and emerging adults (Herting & Nagel, 2012; Whiteman et al., 2016), as well as preadolescent children (Chaddock, Erickson, Prakash, Kim, et al., 2010) relative to their less fit counterparts.

Importantly, findings from the above-described literature suggest that cannabis use and exercise may have opposite effects on brain and cognitive function through their activity at CB_1 receptors. Whereas cannabis use downregulates CB_1 receptors in brain regions relevant to cognition (Hirvonen et al., 2012), exercise up-regulates these receptors (Ferreira-Vieira et al., 2014). In addition, exercise results in an increase in circulating concentrations of endocannabinoids (Koltyn et al., 2014), which may help to restore concentrations among chronic cannabis users, for whom these may be depleted (Hirvonen et al., 2012). These opposite effects could potentially result in the prevention or amelioration of cannabis-related cognitive impairment. To support this hypothesis, one recent study found that aerobic fitness moderated the association between cannabis use and neurocognition among adolescents and young adults, such that higher-fit cannabis users showed less impairment in visual memory, executive functioning, and psychomotor speed than their lower-fit counterparts (Wade, Wallace, Swartz, & Lisdahl, 2019). Thus, engagement in exercise may prove an efficacious and cost-effective way to ameliorate cannabis-related cognitive impairment.

The current study aims to examine associations between exercise, cannabis use, and episodic memory among adolescents over time (**Aim 1**), leveraging data collected through a longitudinal study examining the effects of adolescent cannabis use on neurocognition, particularly in the domains of episodic memory and decision-making (R01 DA031176, PI: Gonzalez). On the basis of the above-described body of work, we hypothesized that a) escalation in cannabis use would be associated with declines in episodic memory, and b) this association would be moderated by exercise, such that both higher initial levels of and increases in exercise over time would be associated with lesser cannabis-related memory decline. Findings from these analyses represent the first attempt at examining these relationships longitudinally, and in a sample consisting primarily of adolescent cannabis users.

Method

Subjects and Setting

Participants were 401 adolescents ages 14 to 17 at baseline who were part a larger study examining longitudinal associations between adolescent cannabis use and neurocognition (R01 DA031176, PI: Gonzalez). Participants were recruited from Miami-Dade County middle and high schools, as well as through flyers posted throughout the community and word-of-mouth referrals. Eligibility for the parent study was ascertained via phone screen. Inclusion criteria included ages 14 to 17 years at baseline, and ability to read and write English. In order to recruit a sample that was at risk for escalation in cannabis use, use of alcohol, cigarettes, or cannabis, even if minimal, was also an inclusion criterion. However, by design, approximately 10% of the sample was allowed to have no history of substance use, in order to avoid inadvertently identifying our

participants as substance users and to have some representation of non-users in the sample (who may still have initiated and escalated use during the study). Exclusion criteria included reports of any of the following at the time of screening: lack of proficiency in English, birth complications, in utero drug exposure, developmental disorders, neurological disorders, history of formal diagnosis or treatment for a mental health disorder (excluding ADHD and conduct disorders given high comorbidity with adolescent substance use), history of a traumatic brain injury or loss of consciousness for more than 10 minutes, and use of psychotropic medications with known neurocognitive effects (with the exception of stimulant medications for ADHD). To avoid recruiting adolescents who were already at ceiling levels of use that could obfuscate escalation, participants were also excluded if their screening responses indicated *heavy* use of alcohol (defined as >13 drinks in a week, or >6-7 drinks in a day, on more than three lifetime occasions) or cannabis (defined as using multiple times per day, every day, for >12 weeks) or an alcohol or cannabis use disorder based on responses to items from the Substance Dependence Severity Scale (Miele et al., 2000). In addition, with the exception of alcohol, nicotine, and cannabis, participants were excluded if they reported prior use of any drug more than 10 times, any drug use in the two weeks prior to screening, or use of any drug to a greater extent than cannabis. It is important to note that, although participants were excluded based on these criteria at the time of screening, they were not excluded if they met criteria for mental health and/or substance use disorders as assessed by structured clinical interviews during any of the study assessments, or if they were formally diagnosed with a disorder over the course of the study. Our sample's detailed

demographic, substance use, and mental health characteristics at each assessment wave are shown in Table 1.

Parental consent and participant assent were obtained for all participants prior to the baseline assessment. Participant consents were also obtained for adolescents who became of legal age during the course of the study. The Institutional Review Board at Florida International University approved all procedures for the parent study (IRB-13-0065), as well as the current study's secondary data analyses (IRB-19-0117).

The study involved five assessments conducted at 6-month intervals over a two-year period. The baseline assessment (T1), one-year follow-up (T3), and two-year follow-up (T5) were conducted in person, and consisted of an extensive battery which included toxicology testing, paper-and-pencil neuropsychological tests, structured and semi-structured clinical interviews assessing substance use and mental health, and self-report questionnaires assessing various other constructs. The 6-month follow-up (T2) and 18-month follow-up (T4) were conducted over the phone, and consisted of an abbreviated battery which included semi-structured interviews assessing substance use, and self-report questionnaires assessing mental health and other topics. The current study involves substance use data collected at all five timepoints, as well as neuropsychological memory performance data collected at in-person assessments (T1, T3, T5). Additionally, an exercise questionnaire was added to the study after study onset, and was administered at the three final timepoints (T3, T4, T5).

Measures

Substance use history. The Drug Use History Questionnaire (DUHQ) is a detailed semi-structured interview used to assess frequency and amount of use of 16

different drug classes (i.e., alcohol, nicotine, cannabis, K2/spice/synthetic cannabinoids, cocaine, methamphetamine, other stimulants, heroin, other opiates, benzodiazepine, barbiturates, ecstasy, hallucinogens, other club drugs, PCP, and inhalants) during a participant's lifetime (only at baseline), the past 6 months, and the past 30 days (Duperrouzel et al., 2019; Rippeth et al., 2004). For follow-up assessments, examiners queried participants' typical frequency (in days) and amount of use for each month in the 6-month assessment interval. Cumulative lifetime frequency of cannabis use was calculated at each timepoint by adding the lifetime frequency at baseline, and the relevant 6-month follow-up frequencies, and was used as our primary measure of cannabis use in the current study. Cumulative lifetime frequencies of alcohol and nicotine use were also included as covariates in our analyses.

Toxicology testing. During in-person assessments, we collected saliva samples with the Intercept® Oral Fluid Drug Test (OraSure Technologies, Inc.: Bethlehem, PA), which were sent for laboratory testing to Forensic Fluids Laboratories (Kalamazoo, MI) to determine recent use (limit of detection for THC: 1ng/ml). Of note, participants were instructed to abstain from using any drugs for at least 24 hours prior to their in-person assessments. In addition, any participants who were deemed to be acutely intoxicated by examiner observation were asked to return at a later date and did not undergo further testing. However, because the toxicology tests were analyzed by an external laboratory, we could not exclude participants with positive results at the time of the assessment. Thus, we used positive THC test results as a covariate to account for the impact subacute intoxication on cognitive performance.

Exercise. The Sports and Activity Involvement Questionnaire (SAIQ) is a questionnaire originally developed for use in the ABCD study (Barch et al., 2018). It was adapted as a self-report questionnaire for use with participants in the current study. The SAIQ collects detailed information regarding participants' involvement in sports, exercise, and other types of activities over the past 6 months and past 30 days. Participants indicated the number of months, weeks per month, days per week, and minutes per day that they spent on each endorsed activity. Using the total number of minutes spent on sports and exercise, we calculated the average number of hours per week spent on sports and exercise over the past 6 months, which was used as our primary measure of exercise. A full list of the activities included in this questionnaire (and in our measure) can be found in the Table 2. Because the SAIQ was added to our protocol after parent study onset, it was only administered at T3, T4, and T5. It was completed by 60 participants at T3, 138 participants at T4, and 198 participants at T5 (n = 199 for analyses including only the exercise variable).

Episodic memory. Episodic memory performance was assessed via performance-based measures administered at in-person assessments (T1, T3, and T5). The California Verbal Learning Test—2nd Edition (CVLT-II) is a valid, reliable, and commonly used instrument used to assess verbal learning and memory (Woods, Delis, Scott, Kramer, & Holdnack, 2006). Participants were orally presented with a 16-item word list that was repeated across 5 trials, and they were asked to recall as many words as possible after each trial (Immediate Free Recall). Participants were then presented with a new list of words, and were asked to recall them. After this, they were asked to once again recall the words from the first list, both freely and with semantic cues. Finally, after a 20-minute

delay, participants were asked to recall the words from the first list both freely (Long Delay Free Recall) and with semantic cues.

The Wechsler Memory Scale—Fourth Edition (WMS-IV) is another memory assessment tool with well-established validity and reliability (Wechsler, 2009). Participants completed the Logical Memory and Designs subtests, which assess memory for verbal and visual information, respectively. During the Logical Memory subtest, participants are orally presented with two structured narratives, and asked to recall as much information as they can remember from these stories both immediately (Logical Memory Immediate Recall) and following a 20- to 30-minute delay (Logical Memory Delayed Recall). The Designs subtest involved the brief (10-second) presentation of a visual array consisting of abstract designs on a spatial grid over four trials. After each array was removed, participants were asked to select the correct designs from a set of cards including target and distractor designs, and to place them in their correct locations on the grid both immediately (Designs Immediate Recall) and after a 20- to 30-minute delay (Designs Delayed Recall).

For our primary measures of immediate memory and delayed memory, we transformed the raw scores for these trials into T-scores (mean = 50, SD = 10) using the mean and standard deviation of each measure at the baseline assessment, and computed their average. For our immediate memory index, we averaged the T-scores from the Total Immediate Recall across all trials of the CVLT-II, and the Logical Memory I and Designs I immediate recall trials. For our index of delayed memory, we averaged T-scores from the Long Delay Free Recall of the CVLT-II, and Logical Memory II and Designs II delayed recall trials.

Estimated IQ. The Wide Range Achievement Test 4 – Word Reading Subtest (WRAT-4 Reading) requires participants to correctly read words out loud and is often used as a proxy of general intelligence (Wilkinson & Robertson, 2006). We used this index to estimate participants' IQs at baseline, including it as a covariate in our analyses.

Analytic Plan

We used latent growth curve modeling (LGCM) to characterize patterns of cannabis use and memory performance over the two-year study period, as well as patterns of self-reported exercise over the last year of the study. We first ran four separate unconditional linear growth models for cannabis use, immediate memory, delayed memory, and exercise.

Next, to examine main effects of cannabis use on memory performance, we ran two separate parallel process LGCMs, each of which simultaneously estimated the growth curve of cannabis use and one of the memory variables (immediate and delayed memory, separately). The following parameters were specified for each parallel process model: 1) the cannabis use intercept was correlated with the relevant memory intercept, 2) the cannabis use slope was regressed on the memory intercept, 3) the memory slope was regressed on the cannabis use intercept, and 4) the memory slope was regressed on the cannabis use slope (Figures 1 and 2). We then ran two additional parallel process LGCMs to examine main effects of exercise on immediate and delayed memory performance (Figures 3 and 4).

To address the study hypotheses, we then conducted a series of latent interaction models examining the impact of the interaction between cannabis use and exercise on memory performance. These models included a) the simultaneously estimated growth

curves of cannabis use, exercise, and memory; b) the same parameters as the parallel process models described above; and c) an interaction term. First, we examined whether initial levels of exercise prevented cannabis-related memory decline by regressing the memory slope on the interaction between the exercise intercept and cannabis use slope (Figures 5 and 6). Second, we examined whether *change* in exercise over time prevented cannabis-related memory decline by regressing the memory slope on the interaction between the exercise and cannabis use slopes. Separate models were run for immediate and delayed memory as outcomes, for a total of four latent interaction models (Figures 7 and 8).

Finally, we identified theoretically relevant covariates which may influence associations between cannabis use and neurocognition, which included sex (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013), estimated IQ, baseline age, use of other substances, such as alcohol and nicotine (Jacobus & Tapert, 2013; Schuster, Crane, Mermelstein, & Gonzalez, 2015), and toxicology results suggesting sub-acute THC intoxication at each available timepoint (Broyd et al., 2016). We re-tested all models and compared findings after accounting for these covariates. Importantly, due to power limitations and the high number of parameters included in the interaction models, these models only retained covariates shown to have significant effects in previous steps.

All analyses were conducted using M*plus* 8 (Muthén & Muthén, 1998). All models were specified using maximum likelihood estimation with standard errors and a chi-squared statistic that are robust to non-normality (MLR). Model fit was assessed using absolute fit indices, such as the Comparative Fit Index (CFI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR).

CFI values of .95 or greater were used to indicate excellent fit, and values between .90 and .94 were used to indicate acceptable fit (McDonald & Ho, 2002); RMSEA values less than .05 were used to indicate excellent fit, whereas values between .05 and .10 were used to indicate acceptable fit (McDonald & Ho, 2002); and SRMR values below .08 were considered to indicate good fit (Hu & Bentler, 1999). Of note, these indices are not available for the latent interaction models (Muthén & Muthén, 1998).

Missing data. Of the 401 participants that completed the baseline assessment, 391 completed the six-month follow-up assessment (98%), 383 completed the one-year follow-up assessment (96%), 380 completed the 18-month follow-up assessment (95%), and 387 completed the two-year follow-up assessment (96.5%). Thus, there were low rates of missingness in the cannabis use and memory variables in our sample. We found no differences on any of the variables used in the current study when comparing participants with complete data and those who missed entire assessments. However, because collection of exercise data began after parent study onset, approximately half of our participants completed exercise measure at least once (n = 199 for analyses involving only the exercise variable).

We used full information maximum likelihood (FIML) to handle missing data. The FIML method can be applied to an incomplete dataset to produce parameter estimates that accurately describe the entire sample. FIML uses information from all available data points to construct parameter estimates under the assumption that the data are missing at random, as in the current study.

Results

Pattern of Cannabis Use over Time

The unconditional LGCM of cannabis use showed acceptable fit, as shown in Table 3. On average, lifetime frequency of cannabis use increased significantly over the two-year -period ($p < .001$). With every assessment, lifetime cannabis use frequency increased by an average of 42.22 days, which represented an effect approximately ¾ of a standard deviation (SD) in magnitude. However, there was significant variability in the slope of cannabis use, suggesting that individual participants varied substantially in their patterns of change over time. The correlation between the cannabis use intercept and slope was also large and significant ($p < .001$), indicating that participants with more frequent cannabis use at baseline demonstrated greater escalation in cannabis use over the course of the study.

Pattern of Exercise over Time

The unconditional LGCM of exercise showed acceptable fit (Table 3). Of note, we obtained a negative, non-significant variance for the slope of exercise, which led us to rerun the model setting the slope variance to zero (Dillon, Kumar, & Mulani, 1987). On average, participants' self-reported amount of exercise remained stable over the course of the study ($p = .081$).

Patterns of Episodic Memory over Time

For both immediate and delayed memory, the unconditional linear growth models showed excellent fit (Table 3). On average, participants' immediate and delayed memory performance increased significantly over time (ps <.001). With every assessment, participants' immediate memory performance increased by an average of 1.01 points,

whereas delayed memory performance increased by an average of 1.16 points. These represented large effects (~2 SD for immediate memory, and ~2.5 SD for delayed memory). The slope variances were not significant, indicating that participants' memory performance improved uniformly among participants across study visits. The correlations between intercepts and slopes were not significant for either immediate (p = .436) or delayed memory (p = .494).

Cannabis Use and Immediate Memory

Table 4 lists estimates for the unadjusted parallel process model of cannabis use and immediate memory. The intercepts were significantly and negatively correlated (p = .005). This indicated that a greater number of lifetime days of cannabis use reported at baseline was associated with worse immediate recall at baseline. In addition, the cannabis use slope predicted the immediate memory slope (p = .023). Participants with greater escalation in cannabis use showed lesser gains in memory performance during the two-year study period, consistent with our hypotheses. Specifically, for every 10-day increase in cannabis use, participants' immediate memory performance improved by .04 fewer points; this was a small effect (less than ¼ SD). The immediate memory intercept significantly predicted the cannabis use slope (p = .039); however, as illustrated in Figure 1, this effect became nonsignificant after controlling for covariates. No significant associations were observed between the cannabis use intercept and immediate memory slopes (p = .963). Detailed results from covariate-adjusted models are presented in Table 5.

Cannabis Use and Delayed Memory

As shown in Table 4, the correlation between the cannabis use intercept and the delayed memory intercept was negative and significant (p = .001), consistent with hypotheses that participants with greater cannabis use at baseline also demonstrated worse performance on delayed recall trials at baseline. Surprisingly, the delayed memory intercept was negatively and significantly associated with the cannabis use slope (p = .001), such that better performance on delayed recall trials predicted lesser escalation in cannabis use over the course of the study. Specifically, a one-point increase in delayed memory performance predicted 1.5 fewer days of increase in cannabis use frequency. This effect was small in magnitude (less than ¼ SD), but remained significant even after controlling for estimated IQ, as illustrated in Figure 2. Associations between the cannabis use intercept and delayed memory slope, and between the cannabis use and delayed memory slopes were not significant (ps = .680 and .351, respectively), suggesting that neither baseline nor change in cannabis use predicted changes in delayed memory performance. Detailed results from the covariate-adjusted model of cannabis use and delayed memory can be found in Table 6.

Exercise and Immediate Memory

As shown in Table 7, associations between exercise and immediate memory were not significant. Contrary to expectation, the association between the slopes was non-significant, suggesting that change in exercise did not impact change in immediate memory. Results were similar even after controlling for covariates, as detailed in Table 8 and illustrated in Figure 3.

Exercise and Delayed Memory

Results from unadjusted parallel process model of cannabis use and exercise are presented in Table 7. The delayed memory and exercise intercepts were negatively and significantly correlated (p = .038), suggesting that better memory performance at baseline was associated with lower self-reported exercise at T3. However, this correlation was non-significant after controlling for relevant covariates (Table 9). These findings are further illustrated in Figure 4.

Interaction between Exercise Intercept and Cannabis Use Slope

The interactive effect of the exercise intercept and cannabis use slope on the immediate memory slope was not significant (b = -.010, SE = .012, p = .404). Results were similar for delayed memory performance (b = -.008, SE = .043, p = .843), and remained unchanged after controlling for covariates, as shown in Tables 10 and 11. This suggests that initial levels of exercise did not moderate the negative association between cannabis use and memory slopes. In other words, individuals who reported higher initial levels of exercise showed similar cannabis-related memory decline as those who reported lower initial levels of exercise. These models are illustrated in Figures 5 and 6 (not all paths are shown).

Interaction between Exercise Slope and Cannabis Use Slope

The interaction between the exercise and cannabis use slopes did not significantly impact the immediate memory slope (b = .012, SE = .025, p = .640), or the delayed memory slope (b = .010, SE = .206, p = .837). Similar results were obtained after controlling for covariates, as shown in Tables 12 and 13. Thus, change in exercise did not moderate the negative association between cannabis use and memory slopes. Contrary to

hypotheses, cannabis-related effects on memory were similar across participants with varying levels of change in exercise. These models are depicted in Figures 7 and 8 (not all paths are shown).

Discussion

The current study examined longitudinal associations between cannabis use and episodic memory, and explored whether exercise moderated these associations. Consistent with our hypotheses and with the extant literature, greater lifetime cannabis use was associated with poorer episodic memory at baseline, and greater escalation in cannabis use predicted lesser gains in immediate episodic memory over time. On the other hand, exercise did not predict improvements in episodic memory. Contrary to study hypotheses, neither higher levels of nor change in exercise moderated the association between escalation in cannabis use and change in memory performance over time. These findings remained unchanged after controlling for important confounds, such as age, sex, estimated IQ, concurrent use of alcohol and nicotine, and sub-acute THC intoxication. Thus, in our sample of adolescent cannabis users, there was no evidence that exercise could help ameliorate cannabis effects on memory.

Even after controlling for effects of sub-acute intoxication via oral fluids testing for THC, adolescents reporting more lifetime days of cannabis use showed worse immediate memory at baseline, and those with greater escalation in their use showed lesser improvements in immediate memory performance over time. Delayed memory, on the other hand, was impacted cross-sectionally at baseline, but not longitudinally. This is consistent with other studies finding adverse effects of cannabis on the learning of new information, rather than with forgetting previously learned information (Bossong et al.,

2012; Schoeler & Bhattacharyya, 2013). Nonetheless, this does not rule out the possibility that delayed recall may also be affected with continued escalation. Overall, our results are consistent with evidence that cannabis use results in the downregulation of CB_1 receptors, which are found in high density in hippocampal regions (Hirvonen et al., 2012). This study also replicates findings from a large body of work suggesting that cannabis use results in small adverse effects on episodic memory (Grant et al., 2003; Schreiner & Dunn, 2012; Scott et al., 2018) even in a young adolescent sample with a more limited history of cannabis use.

Surprisingly, poorer delayed memory performance at baseline predicted greater escalation in cannabis use in our sample, even after accounting for global cognitive ability. This suggests that poorer delayed memory could be a neurocognitive risk factor for problematic cannabis use. This is consistent with the idea that substance misuse can both result from and lead to aberrant learning and memory (Hyman, 2005; Torregrossa, Corlett, & Taylor, 2011), although these studies have typically focused on memory processes as they relate to reward. Alternatively, several studies suggest that executive functioning skills can impact free recall in episodic memory tasks (Dickerson et al., 2007; Noël et al., 2012; Parks et al., 2011). Although we were not able to test this in the current study, it is possible that the association between baseline delayed memory and cannabis use escalation could be better explained by poorer executive functioning, which is a more commonly reported neurocognitive risk factor for problematic substance use (Kim-Spoon et al., 2017). Nevertheless, this finding warrants replication and further exploration with a more diverse sample.

Contrary to hypotheses, the current study did not find evidence of either a main effect or a moderating role of exercise in the association between cannabis use and episodic memory. Our results are thus consistent with those of several previous studies that have found no effect of chronic exercise and adolescent cognition (Herting & Nagel, 2013; Pindus et al., 2015; Tarp et al., 2016; Verburgh, Königs, Scherder, & Oosterlaan, 2013; Zervas, Danis, & Klissouras, 1991). There are several possible explanations for these results. First, adolescents are considered to be approaching peak cognitive health in young adulthood (Salthouse & Davis, 2006), which may leave little room for exercise-related improvement in cognition during adolescence (Hillman, Erickson, & Kramer, 2008). Indeed, memory performance in our sample was largely within the average range at the baseline assessment (Duperrouzel et al., 2019), and improved over time, which could be the result of both neuromaturation and practice effects. However, although this could explain the absence of a main effect of exercise, it does not preclude the possibility of a moderating role of exercise in the association between cannabis use and cognition. Second, the average levels of exercise reported by participants in our sample fall below the recommended physical activity guidelines for adolescents (Piercy et al., 2018). Although evidence suggests that even smaller amounts of exercise and physical activity can be associated with cognitive benefits (Piercy et al., 2018), it is possible that higher levels of exercise may be needed to combat the effects of escalating cannabis use, particularly given the downregulation of CB_1 receptors associated with chronic patterns of use (Hirvonen et al., 2012). Third, of the studies examining associations between exercise and memory, many studies focused on visuospatial learning and memory (Herting & Nagel, 2012; Lee et al., 2014; Raine et al., 2013; Ross et al., 2015; Wade et

al., 2019; Whiteman et al., 2016), whereas the current study relied on a composite measure including two indices of verbal episodic memory and one index of visual memory. Thus, it is possible that effects of exercise may be more readily observed in the domain of visuospatial learning and memory, or in executive domains not assessed in the current study, such as inhibitory control. Finally, it should be considered that exercise could have an impact on neurocognition even in the absence of effects on task performance. For instance, Herting et al. (2013) found that higher-fit adolescents showed lower hippocampal activation during the encoding portion of an associative memory task, but had equivalent task performance as their lower-fit counterparts, which the authors interpreted as evidence of greater neural "efficiency."

One previous cross-sectional study found support for a moderating role for aerobic fitness in the association cannabis use and neurocognition among adolescents and young adults (Wade et al., 2019). Small moderating effects were reported in the domains of visual memory, executive functioning, and psychomotor speed, but not verbal memory (Wade et al., 2019). Our study differed from theirs in several notable ways. First, whereas the current study focused on reported hours/week of exercise, Wade et al. (2019) tested participants' aerobic fitness, i.e., the ability to deliver oxygen to the muscles and utilize it to generate energy to support muscle activity during exercise (Armstrong, Tomkinson, & Ekelund, 2011). Although greater involvement in exercise is thought to lead to improved aerobic fitness among youth (Armstrong et al., 2011), these are nevertheless distinct constructs. Indeed, other studies have found effects of fitness, but not reported exercise or physical activity, on cognitive performance among children and adolescents (Oliveira et al., 2017; Ruotsalainen et al., 2019). In addition, the SAIQ employed in the current study

was a self-report measure. Self-report questionnaires have been shown to have low to moderate correlations with objectively measured physical activity (Prince et al., 2008). Also, because this measure did not assess the intensity of reported activities, our index of exercise may have included both light and moderate-to-vigorous intensities, whereas many studies documenting positive effects on cognition focus only on the latter. Finally, Wade et al. (2019) conducted cross-sectional group-based comparisons between cannabis users and nonusers, whereas the current longitudinal study examined associations between cumulative lifetime frequency of cannabis use and neurocognition in a sample of adolescents at varying levels of use. It is possible that more positive or ameliorating effects of exercise on memory may be more readily observed among more regular, chronic users for whom memory performance may be below expectancy.

The current study has several notable strengths, including the relatively large sample of young adolescents, the use of longitudinal LGCMs to examine bidirectional associations over time, the exploration of two different aspects of episodic memory, and the inclusion of several theoretically important confounding variables as covariates. Nevertheless, our findings should be interpreted in light of several limitations. First, our measure of exercise relied on participant self-report which, in addition to the above-described limitations, is likely subject to social desirability and memory biases. Future studies should examine these associations using more objective measures of exercise and fitness. Second, because the exercise measure was added after parent study onset, there was a large proportion of missing data for this variable. Relatedly, this measure was only administered at the final three timepoints. Thus, while associations between cannabis use and memory were examined over a two-year period, effects of exercise were only

examined over a one-year period, as we did not have data regarding participants' engagement in exercise during the first two timepoints. It is possible that effects of exercise on change in memory performance would have become apparent if we had examined them concurrently at each timepoint. Assessing exercise at additional timepoints would also have helped to better characterize the growth curve of the exercise variable, as the current study was limited to fitting a linear model given the three available timepoints. In addition, the current study relied on composite measures of immediate and delayed episodic memory, each of which included two indices of verbal memory and one index of visual memory. This method did not allow for more fine-grained examination of specific sub-domains (e.g., verbal narrative memory, verbal list learning, visual spatial memory), but it is less likely to result in Type-I error. Finally, several characteristics of our sample may limit the generalizability of our findings. For instance, as shown in Table 1, our sample was predominantly White (77%) and of Hispanic/Latino ethnicity (90%). Although this is consistent with the demographic makeup of the greater Miami metropolitan area, it may limit generalizability to other racial, ethnic, and cultural groups. However, we have no evidence to hypothesize that associations between cannabis use and neurocognition may vary across common U.S. ethnic groups. In addition, despite observed escalation in cannabis use, the majority of participants in the sample had limited histories of cannabis use because of their young age, and did not report heavy, daily cannabis use. Additional work is needed to determine whether these results would differ in older samples with more chronic histories of heavy cannabis use. Lastly, although participants were asked to abstain from drugs for 24 hours prior to each assessment and assessments were not completed if participants appeared

intoxicated, a subset of the sample tested positive for THC in oral fluids at in-person assessments (see Table 1). Although we covaried for positive toxicology results for THC, given limits of detection for oral fluids testing, it is possible that some participants may have experienced sub-acute effects at the time of testing and therefore exacerbated the magnitude of observed effects on memory performance in the current study.

In conclusion, the current study replicates prior findings that poorer immediate episodic memory is a consequence of escalating cannabis use and extends this to a young adolescent sample at relatively early stages of use using a longitudinal LGCM design. Poorer memory among adolescent cannabis users may explain associations between cannabis use and poorer academic outcomes (Lynskey & Hall, 2000; Pacheco-Colón, Ramirez, et al., 2019), and further supports the contention that cannabis use is not benign among adolescent users. However, our results do not support a role for exercise in the amelioration of cannabis-related memory decline, as neither higher levels of nor change in exercise moderated the association between escalation in cannabis use and change in memory performance over time. Examination of these associations using more objective measures of exercise and fitness may help to clarify for whom and under what circumstances exercise may help support adolescent cognitive and brain function.

III.

EXERCISE, CANNABIS-RELATED OUTCOMES, & THE MEDIATING ROLE OF DECISION-MAKING

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Introduction

Participation in sports and exercise has been consistently linked to increased alcohol use and lower cigarette use (Kwan, Bobko, Faulkner, Donnelly, & Cairney, 2014; Terry-McElrath, O'Malley, & Johnston, 2011). Associations with cannabis use, on the other hand, are less clear, as studies have often lumped cannabis in with other illicit substances (Kwan et al., 2014; Lisha & Sussman, 2010; Terry-McElrath et al., 2011). Some studies have found that adolescents and young adults who report greater engagement in sports and exercise are less likely to use cannabis (Barber, Eccles, & Stone, 2001; Darling, 2005; Dawkins, Williams, & Guilbault, 2006; Dever et al., 2012; Henchoz et al., 2014; King, Merianos, Vidourek, & Oluwoye, 2016; Terry-McElrath et al., 2011), whereas others have found no relationship (Aaron et al., 1995; Eccles & Barber, 1999; Mahoney & Vest, 2012; Wichstrøm & Wichstrøm, 2009), or suggested moderation by factors such as age, sex, exercise intensity, and team involvement (Boyes, O'Sullivan, Linden, McIsaac, & Pickett, 2017; Kwan et al., 2014). There is some evidence that exercise and team involvement work synergistically to predict lower cannabis use, although this association may also vary with specific sports (Ford, 2007; Lisha & Sussman, 2010; Terry-McElrath et al., 2011). Exercise interventions have also been linked to increased abstinence rates in the treatment of substance use disorders (Wang, Wang, Wang, Li, & Zhou, 2014; Zschucke, Heinz, & Ströhle, 2012), including one specifically targeted to cannabis use disorders (Buchowski et al., 2011). Several factors have been identified as potential mediators of the association between exercise and positive substance use outcomes, including decreases in internalizing symptoms, decreased stress reactivity, increased social support, development of adaptive coping

strategies, and increased self-efficacy (Wang et al., 2014; Zschucke et al., 2012). However, the potential mediating role of exercise-related effects on cognition has not yet been examined.

Indeed, exercise has been linked to a variety of positive effects on cognitive function spanning multiple domains, including intellectual functioning, perceptual skills, memory, and executive functioning (Hillman et al., 2008; Sibley & Etnier, 2003), which can often be observed within two to three month periods (Best, 2010; Tomporowski et al., 2008). Within the domain of executive functioning, higher levels of exercise have been associated with improvements in attention, reasoning, set-shifting, processing speed, inhibitory control, error monitoring, cognitive flexibility, and working memory (Best, 2010; Guiney & Machado, 2013; Hillman et al., 2014; Kamijo & Takeda, 2010; Kelly et al., 2014). All of these aforementioned executive processes are involved in decision-making, i.e., the ability to make optimal choices that maximize reward in the presence of risk (Bechara & Damasio, 2002; Pacheco-Colón, Hawes, Duperrouzel, Lopez-Quintero, & Gonzalez, 2019). Despite this, effects of exercise on decision-making have rarely been studied. One recent study found that a 3-month exercise program resulted in reduced effort-discounting, but had no impact on risky decision-making (Bernacer et al., 2019). In other words, participants were more willing to expend physical effort to obtain monetary rewards post-intervention, whereas their valuing of monetary rewards based on explicit risk probabilities remained unchanged. Thus, there is some evidence that exercise may impact certain aspects of decision-making, which could potentially affect substance use and other risky behaviors.

Poor decision-making has been identified as a potential risk factor for problematic substance use, placing certain individuals at greater risk for escalation in use and subsequent addiction. It has been linked to earlier age of onset of substance use disorders (Tarter et al., 2003), faster transition to drug co-use (Lopez-Quintero et al., 2018), and relapse across various substances (Bowden-Jones, McPhillips, Rogers, Hutton, & Joyce, 2005; Nejtek, Kaiser, Zhang, & Djokovic, 2013; Passetti, Clark, Mehta, Joyce, & King, 2008; Paulus, Tapert, & Schuckit, 2005; Verdejo-Garcia et al., 2014). Specifically with regards to cannabis use, Gonzalez et al. (2012) found that, despite no differences in decision-making performance between young adult cannabis users and non-users, poor decision-making was associated with a higher number of cannabis use disorder symptoms among cannabis users. Greater cannabis use also predicted a higher number of cannabis-related problems, but only among those with poor decision-making (Gonzalez, Schuster, Mermelstein, & Diviak, 2015). Thus, there is some evidence that poor decision-making may represent a neurocognitive risk factor for adverse cannabis-related outcomes.

The current prospective study examines associations between exercise, decision-making, and cannabis use among adolescents over six months (**Aim 2**). Based on the aforementioned findings, we hypothesize that more exercise will be associated with positive cannabis-related outcomes, including lower cannabis use frequency, lower odds of having a cannabis use disorder, and lower severity of cannabis-related problems six months later. In addition, we predict that these effects will be mediated by exercise-related effects on decision-making, such that higher levels of exercise will be associated with better decision-making performance, which will in turn predict better cannabis use outcomes. Findings from these analyses will begin to answer whether exercise-related

cognitive gains can be leveraged in the prevention of cannabis addiction among adolescents.

Method

Participants

Participants were 387 adolescents ages 15 to 18 who were primarily cannabis users and were predominantly Hispanic/Latino (90%) and White (77%). Participants were recruited from Miami-Dade County middle and high schools, as well as through word-of-mouth referrals as part of a larger study examining the effects of different adolescent cannabis use trajectories on episodic memory and decision-making (R01 DA031176; N = 401). This parent study recruited a sample of adolescents who were at risk for escalation in cannabis use; inclusion and exclusion criteria for the parent study were described in detail in Chapter II.

Procedure

Parental consent and participant assent were obtained for all participants prior to the baseline assessment of the parent study. Participant consents were also obtained for youths who became of legal age during the course of the study. All study procedures were approved by the Institutional Review Board at Florida International University (IRB-13-0065 for parent study; IRB-19-0117 for current study).

As described in Chapter II, the parent study involved five assessments conducted at 6-month intervals over a two-year period. However, the current study only includes data collected at the fourth and fifth assessments of the parent study. The fourth assessment of the parent study is referred to as “baseline” for this study, as it was the first measurement wave at which a large number of participants completed the exercise

measure, whereas the fifth assessment of the parent study is here referred to as the "6-month follow-up." Participants from the parent study were included in the current study if they completed at least one of these two measurement waves (N = 387).

Measures

Exercise. As described in Chapter II, the current study used the number of hours per week spent on sports and exercise over the past six months, as measured by the SAIQ as our measure of exercise (Barch et al., 2018). Participants also indicated whether they engaged in each activity as part of a team; they were coded as being involved in teams if they reported team involvement for *most* of the activities endorsed. Because the SAIQ was added to our protocol after parent study onset, it was completed by 138 participants (~36% of the sample) at the current study's baseline assessment.

Substance use. We assessed three cannabis-related outcomes at the 6-month follow-up through the following three questionnaires. The DUHQ, which was also described in Chapter II, yielded past 6-month frequency (in days) of cannabis use at the 6-month follow-up, which we used as one of our cannabis outcome measures (Duperrouzel et al., 2019; Rippeth et al., 2004). To account for the influence of other substance use on cannabis outcomes, we covaried for past 6-month frequency of alcohol and nicotine use.

We also used the substance use modules of the Structured Clinical Interview for DSM-IV (SCID-IV; First, Spitzer, Gibbon, & Williams, 1994)) to diagnose the presence of alcohol and other substance use disorders at the 6-month follow-up. We used a dichotomous variable indicating presence of a cannabis use disorder (abuse or dependence) in the past 6 months as one of our cannabis outcomes.

Finally, participants who reported a history of cannabis use also completed the Marijuana Problems Scale (MPS), a 35-item self-report questionnaire with adequate validity and reliability (Buckner, Ecker, & Cohen, 2010; Stephens, Roffman, & Curtin, 2000). This instrument assesses negative social, personal, occupational, and physical consequences experienced as a result of cannabis use over the past 6 months. We used the total MPS score at the 6-month follow-up as one of our cannabis outcomes.

Decision-Making. Decision-making was assessed through three computerized tasks at the 6-month follow-up. The Cups Task measures decision-making under conditions of specified risk for both gain and loss domains (Levin & Hart, 2003). In this task, participants were shown a display of 2, 3, or 5 cups on each side of the screen, and were instructed to choose a cup from one of the two sides for a total of 54 trials. One side always yielded a definite reward or a smaller loss, while the other side provided a chance for a greater reward. We used the number of total risky choices from the gain and loss domains as our indices of decision-making for this task.

Participants also completed the Game of Dice Task (GDT), which assesses decision-making under explicit risk conditions (Brand et al., 2005). Participants were asked to guess the result of a die throw by selecting combinations of one, two, three, or four numbers for a total of 18 trials. Low-risk choices (i.e., combinations of three or four numbers) are associated with greater probability of smaller gains, whereas high-risk choices (i.e., combinations of one or two numbers) are associated with lower probability of higher gains. The total number of risky choices was used as our index of decision-making for the GDT.

Finally, participants completed the Iowa Gambling Task (IGT), which measures decision-making under conditions of ambiguous risk (Bechara, Damasio, Damasio, & Anderson, 1994). Across 100 trials, participants were instructed to select from four card decks, which included two "good" decks (Decks C and D), and two "bad" decks (Decks A and B), while trying to earn as much money as possible. We used the reverse-scored IGT Net Score (i.e. choices from good decks minus choices from bad decks) as our index of DM for this task (Bechara, 2007).

We then used the following four indices—total risky choices in the gain domain from the Cups and total risky choices in the loss domain from the Cups Task, total risky choices from the GDT, and reverse-scored Net Score from the IGT—to derive a latent construct of decision-making, the properties of which have been described in detail elsewhere (Pacheco-Colón, Hawes, et al., 2019), for use in our analyses. This variable served as our primary measure of decision-making across all analyses. Utilizing latent variables reduces measurement error and results in increased power and less biased estimates (Little, Bovaird, & Widaman, 2006). This is particularly important for mediation analyses, as measurement error associated with a mediator can severely impact parameter estimates (Muthén & Asparouhov, 2015). Of note, higher scores in our latent construct of decision-making indicate higher risk-taking, and thus, worse decision-making performance.

Estimated IQ. As in Chapter II, the WRAT-4 Word Reading subtest was used to estimate participants' IQs at the baseline assessment of the parent study (Wilkinson & Robertson, 2006), and covary for effects of global cognitive function on decision-making performance.

Demographics. Participants' sex and age at the baseline assessment were also used as covariates in our analyses.

Analytic Plan

First, we examined the independent direct effects of the predictor on later outcomes. Specifically, we conducted three separate regression models examining the effect of baseline exercise on each of our three cannabis use outcomes at the 6-month follow-up (Path c; Figures 9, 10, and 11).

In order to evaluate decision-making as a mediator of the relationship between exercise and cannabis use outcomes, we then ran prospective mediation models which included three paths: the effect of past 6-month exercise at baseline on decision-making performance at 6-month follow-up (Path a), the effect of decision-making performance at 6-month follow-up on cannabis outcomes at the 6-month follow-up (Path b), and the direct effect of past 6-month exercise at baseline on cannabis outcomes at the 6-month follow-up after controlling for the mediating influence of decision-making (Path c'). We ran a total of three such models, using past 6-month cannabis use frequency, past 6-month presence of a cannabis use disorder, and total MPS score at the follow-up as outcomes, respectively. The first two models (cannabis use frequency and disorder as outcomes) included the full sample (N = 387). However, participants with no history of cannabis use (n = 66) were excluded from analyses involving the MPS score, as this questionnaire examines problems experienced as a result of cannabis use and was therefore not administered to non-users. Finally, analyses were repeated, controlling for theoretically relevant covariates. Covariate-adjusted models controlled for the influence

of sex, baseline age, and IQ on decision-making, as well as for the influence of sex, baseline age, and concurrent use of alcohol and nicotine on cannabis use outcomes.

All analyses were conducted using M*plus* 8. We used the M*plus* INDIRECT command to assess the significance of the indirect effect (Path a*b). To account for nonnormality in our data and avoid assumptions regarding the distribution of the indirect effect, we estimated standard errors and confidence intervals of model path coefficients using nonparametric bootstrap sampling (20,000 samples).

Missing data. There were low rates of missingness in the cannabis use and decision-making variables. However, because collection of exercise data began after parent study onset, the SAIQ was completed by 138 participants at the current study's baseline assessment (~36% of the sample). Missingness in the exercise questionnaire was related to cannabis use, such that users with missing exercise data also reported more cannabis use. To ensure that data were missing at random, we examined the effect of exercise on cannabis-related outcomes using only those participants with complete exercise data; results were unchanged. We used FIML to handle missing data in this and all other study variables. This method can be applied to an incomplete dataset to produce parameter estimates that more accurately describe the entire sample. FIML uses information from all available data points to construct parameter estimates under the assumption that the data are missing at random, as in the current study. FIML has been shown to outperform other methods for handling missing data even with large proportions of missing data (Xiao & Bulut, 2020).

Results

Participant Characteristics

Demographics and substance use characteristics of our sample are presented in Table 14. Use of drugs other than alcohol, nicotine, and cannabis was low. Most commonly endorsed drugs were hallucinogens (n = 51), benzodiazepines (n = 38), and cocaine (n = 37), with most of these participants endorsing use ≤ 2 days over the past 6 months.

Cannabis Use Frequency

The direct effect of past 6-month exercise at baseline on past 6-month cannabis use frequency at the 6-month follow-up was significant (path c: b = 3.02., SE = .89, p = .001, 95% CI [1.28, 4.78]). This association was contrary to our hypotheses, such that for every additional hour/week of exercise reported at baseline, there was a 3.02-day increase in past 6-month cannabis use frequency at the follow-up. This represented a small effect (less than ¼ SD).

Our hypothesized mediation model revealed a marginally significant path from exercise at baseline to decision-making at the follow-up (path a: b = -.04, SE = .02, p = .059, 95% CI [-.08, -.004]), such that more exercise predicted less risk-raking or better decision-making. The path from decision-making to past 6-month cannabis use frequency at the 6-month follow-up was not significant (path b: b = 1.26 1, SE = 5.46, p = .818, 95% CI [-9.41, 9.74]). After controlling for the role of decision-making, the direct effect of exercise on cannabis use frequency was largely unchanged (path c': b = 2.99, SE = .94, p = .002, 95% CI [1.05, 4.78]). However, the indirect effect of exercise on cannabis use

frequency via decision-making was not significant (path a*b: b = -.04, SE = .22, p = .841, 95% CI [-.61, .30]).

As shown in Figure 9, after controlling for effects of sex, age, and IQ, the effect of exercise on decision-making (Path a) was not significant. On the other hand, the direct effect of exercise on cannabis use frequency (Path c') remained significant even after controlling for covariates.

Cannabis Use Disorder

The direct effect of past 6-month exercise at baseline on past 6-month cannabis use disorder assessed at the 6-month follow-up was not significant (path c: b = .02, SE = .02, p = .197, 95% CI [-.02, .06]).

The subsequent mediation model showed a significant association between past 6-month exercise at baseline and decision-making performance at the 6-month follow-up (path a: b = -.04, SE = .02, p = .035, 95% CI [-.07, -.01]), such that more exercise predicted less risk-taking. However, decision-making did not predict past 6-month cannabis use disorder at the 6-month follow-up (path b: b = -.003, SE = .09, p = .979, 95% CI [-.18, .19]). After controlling for the mediating role of decision-making, the direct effect of baseline exercise on cannabis use disorder at follow-up remained unchanged (path c': b = .02, SE = .02, p = .224, 95% CI [-.02, .06]). The indirect path from exercise to cannabis use disorder via decision-making was also not significant (path a*b: b = .00, SE = .00, p = .982, 95% CI [-.01, .01]).

As shown in Figure 10, the effect of exercise on decision-making (Path a) became nonsignificant after controlling for covariates. All other findings remained unchanged.

Cannabis-Related Problems

Among cannabis users in our sample, the effect of past 6-month exercise at baseline on cannabis-related problems reported at the 6-month follow-up was not significant (path c: b = .03, SE = .08, p = .704, 95% CI [-.12, .21]). Similar to previous models, our hypothesized mediation model revealed a significant association between baseline exercise and decision-making at the 6-month follow-up (path a: b = -.05, SE = .02, p = .026, 95% CI [-.10, -.01]), as well as a nonsignificant association between decision-making and cannabis-related problems at the follow-up (path b: b = .06, SE = .52, p = .906, 95% CI [-.87, 1.16]). The direct effect of exercise on cannabis-related problems remained nonsignificant after accounting for the role of decision-making (path c': b = .55, SE = .34, p = .106, 95% CI [-.10, 1.22]). The indirect effect via decision-making was also not significant (path a*b: b = -.03, SE = .02 p = .276, 95% CI [-.11, .001]).

As illustrated in Figure 11, after controlling for other covariates, the direct effect of exercise on decision-making became nonsignificant, whereas all other findings remained unchanged.

Post-Hoc Exploratory Moderation Analyses

In an effort to better understand our unexpected finding, we conducted a series of post-hoc analyses to further explore the association between baseline exercise and cannabis use frequency at the 6-month follow-up. Because these variables have previously been identified as moderators, we conducted separate regression models to determine whether a) sex and b) involvement in team sports moderated this relationship.

Results revealed a significant interaction between sex and exercise, (b = -3.02, SE = 1.47, p = .039, 95% CI [-5.61, .23]). Probing of this interaction revealed that the association between exercise and cannabis use was primarily driven by males (b = 3.07, SE = 1.11, p = .006, 95% CI [.88, 5.25]), rather than females (b = .05, SE = 1.17, p = .435, 95% CI [-2.02, 5.90]). This interaction is illustrated in Figure 12. The interactive effect of exercise and involvement in team sports was not significant (b = 2.55, SE = 2.11, p = .226, 95% CI [-1.86, 6.55]).

Discussion

The current study examined associations between engagement in exercise and various cannabis-related outcomes among adolescents, and whether decision-making performance mediated these relationships. Our results suggest that, although participation in exercise did not predict later presence of a cannabis use disorder or cannabis-related problems, there was a significant association between self-reported exercise at baseline and greater cannabis use frequency at the 6-month follow-up, even after controlling for covariates. Contrary to our hypotheses, none of these associations were mediated by exercise-related effects on decision-making. Across models, more exercise at baseline predicted better decision-making performance at the follow-up, but this association became nonsignificant after controlling for covariates. Decision-making, on the other hand, did not predict any of the cannabis-related outcomes explored in this study.

Unexpectedly, we found that adolescents who reported more hours/week of exercise at baseline also reported greater past 6-month frequency of cannabis use at the follow-up assessment. This effect remained significant even after controlling for the effects of age, sex, and concurrent use of alcohol and nicotine on cannabis use. Post-hoc

exploratory analyses also revealed that this effect was driven by males, as males in our sample reported higher levels of both exercise and cannabis use. These findings are inconsistent with those of several studies documenting protective effects of exercise and sports participation against cannabis use (Barber et al., 2001; Darling, 2005; Dawkins et al., 2006; Dever et al., 2012; King et al., 2016; Terry-McElrath et al., 2011). These discrepancies may be explained, at least in part, by the characteristics of our sample. First, in contrast to previous studies, our study examined these effects in a predominantly Hispanic/Latino sample (90%). In addition, our participants were part of a larger study, the inclusion/exclusion criteria of which were successfully applied to recruit a sample of adolescents at risk for escalation in cannabis use (Duperrouzel et al., 2019; Hawes, Trucco, Duperrouzel, Coxe, & Gonzalez, 2018). Thus, by design, our participants may have had certain characteristics (e.g., personality traits, lower perceived risk of substance use) that made them more likely to use cannabis and other substances, and may not be representative of all adolescents. In addition, associations between exercise and cannabis use may have been influenced by other variables not assessed by the current study, including but not limited to parental monitoring and peer deviance (Dever et al., 2012; King et al., 2016). It is possible that participants in our sample may have had lower parental monitoring and thus more unsupervised time with peers, which may have placed them at greater risk for experimentation with substances and subsequent escalation. Finally, many of the studies examining the associations between sports participation and later cannabis use utilize data that were collected over a decade ago. The recent proliferation of recreational and medical cannabis laws has been accompanied by increased acceptance of cannabis use and decreases in perceptions of risk (Hughes et al.,

2016; Pew Research Center, 2016). Thus, it is possible that associations between exercise and cannabis use may be different now than they previously were.

It should also be noted that there is significant cross-study variability in the assessment and operationalization of participation in sports and exercise. For instance, some studies have employed binary variables to measure participation in sports (Darling, 2005), with others using Likert scales to indicate extent of involvement in sports and exercise (Darling, 2005; Dever et al., 2012; King et al., 2016; Terry-McElrath et al., 2011), or continuous variables to represent time or years spent in these activities (Dawkins et al., 2006). Because we were interested in the cognitive benefits of exercise, we opted for the latter, as minutes per week has been described as the most predictive index of total health benefits (Piercy et al., 2018). Furthermore, although the terms "sports and exercise," and "physical activity" are sometimes used interchangeably, they are not equivalent (Khan et al., 2012). Sports and exercise are subsets of physical activity, but physical activity can also include activities performed through work, chores, at home, and while traveling. Effects on health-related behaviors, such as substance use, may be different for sports and exercise versus physical activity. Indeed, after adjusting for mutual influences, Henchoz et al. (2014) found that participation in sports and exercise was protective against later cannabis use, but higher levels of physical activity were positively associated with later at-risk cannabis use. Of note, the measure used in the current study primarily assessed sports and exercise, although it may also have captured some non-exercise components of physical activity (e.g., active transport through bike riding or skateboarding). Future studies should assess participation in sports and exercise,

as well as overall levels of physical activity in order to determine which of these can be protective in the context of substance use, and for whom.

Nonetheless, several previous studies have found positive associations between sports participation and cannabis use. For instance, Ewing (1998) found that sports participation predicted greater cannabis use among high school males, whereas Peretti-Watel (2002) described a "U-curve" such that cannabis use was highest for males at both the lowest and highest levels of physical activity. Further, Ford (2007) found that this association varied with both sex and specific sport, such that female soccer players and male hockey players reported the highest levels of cannabis use, with runners reporting the lowest. It is thus possible that engagement in sports and exercise may be a protective factor for some and a risk factor for others. More recently, a cross-sectional study found that adults who endorsed using cannabis concurrently with exercise were more likely to be male, and reported more minutes of exercise (both aerobic and anaerobic) per week as well as greater enjoyment of and motivation to exercise (YorkWilliams et al., 2019). This is in line with our findings, as well as with athletes' subjective reports that cannabis use enhances their athletic performance (Nguyen, 2019), and evidence of lower body-mass index among cannabis users (Ross, Pacheco-Colón, Hawes, & Gonzalez, 2020). It is therefore possible that increased enjoyment of exercise while under acute cannabis intoxication may have contributed to greater cannabis use frequency, as observed in the current study. Large scale longitudinal studies would allow for more fine-grained analyses in order to develop a nuanced understanding of the association between exercise and cannabis use, and its directionality.

In line with our hypotheses, we found a significant association between baseline exercise and risky decision-making at the 6-month follow-up, such that more hours/week of self-reported exercise predicted less risk-taking, or better decision-making. However, this effect appeared to be better explained by effects of age, sex, and IQ on decision-making. Decision-making encompasses many higher-order cognitive functions (e.g., working memory, response activation and inhibition, performance monitoring, reward learning). Previous work suggests that exercise effects on executive aspects of cognition are most often observed in the domains of inhibitory control and cognitive flexibility among pediatric populations. It is possible that the tasks employed in the current study do not sufficiently tap into these domains, which are more readily assessed through cognitive tasks, such as stop signal and flanker tasks (Erickson, Hillman, & Kramer, 2015; Hillman et al., 2014; Westfall et al., 2018). Future work should examine whether exercise effects on these cognitive domains may mediate associations between exercise and substance use.

In addition, we found no association between decision-making and cannabis use outcomes, including frequency of cannabis use, presence of a cannabis use disorder, and problems resulting from cannabis use. These findings contribute to a mixed body of work examining associations between cannabis use and decision-making (Broyd et al., 2016; Crean, Crane, & Mason, 2011; Gonzalez et al., 2012, 2015). Importantly, despite the wide range of cannabis use in our sample, most of our adolescents reported relatively low levels of cannabis use, with only about a third reporting chronic, near daily use and most reporting low severity of cannabis-related problems (as illustrated by the narrow interquartile range of MPS scores shown in Table 14). It is thus possible that participants

may not have been using cannabis at high levels *long enough* for more adverse cannabis-related outcomes to manifest. More longitudinal work is needed to explore associations between decision-making and cannabis use over longer periods of time.

Findings from the current study must be interpreted in light of several limitations. First, as mentioned in Chapter II, our measure of exercise relied on participant self-report, which has been shown to have low to moderate correlations with objectively measured physical activity (Prince et al., 2008). Second, cannabis use is very complex, with increasingly varied methods of use and potencies. Our study relied on days of use as our index of cannabis use, as frequency indices have been shown to be slightly more reliable than reported amounts of use for adolescents completing timeline follow-back interviews (Levy et al., 2014). However, we were not able to examine the impact of other factors, such as route of administration, product type, and potency. Third, because the exercise measure was added after parent study onset, there was a large proportion of missing data in this variable. However, we used FIML to handle missing data in all study variables. FIML has been shown to produce more accurate parameter estimates than other methods, even when data are sparse (Xiao & Bulut, 2020). Also due to limitations regarding the exercise measure and parent study design, our study covers a 6-month time window, with decision-making and CU outcomes assessed at the same time-point. Although exercise effects can be observed over short periods of time (Best, 2010; Tomporowski et al., 2008), future studies should explore the impact of both exercise and decision-making on later cannabis-related outcomes over longer periods of time, as this would also help to clarify the temporality of these associations. Finally, as previously mentioned, our sample

was predominantly Hispanic/Latino, which may limit generalizability to more diverse samples.

In sum, higher levels of exercise at baseline predicted greater cannabis use frequency at the 6-month follow-up, but did not predict the presence of a cannabis use disorder, or cannabis-related problems. Baseline exercise predicted better decision-making at the follow-up, although this path was marginally significant in one of our models. However, this effect was better accounted for by the effects of sex, age, and IQ on decision-making. Decision-making did not predict cannabis-related outcomes. The indirect effects of decision-making were also not significant, and thus did not support a mediating role of decision-making in associations between exercise and cannabis-related outcomes among adolescents. To the best of our knowledge, ours is the first study to examine associations between exercise, cannabis use, and risky decision-making. Future studies should continue to examine the effects of exercise on cognition using objective measures of exercise and/or fitness to determine whether exercise-related cognitive gains can be utilized in prevention and treatment efforts aimed at substance-using adolescents.

IV.

EXERCISE, EXECUTIVE FUNCTIONING, & THE MEDIATING ROLE OF TASK-RELATED BRAIN ACTIVATION

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Introduction

Positive effects of exercise on executive functioning have been extensively documented among older adults (Chen et al., 2020; Colcombe & Kramer, 2003). Although there has been increased interest in recent decades, these effects have been relatively understudied among children and adolescents (Donnelly et al., 2016). In pediatric populations, chronic exercise, physical activity, and/or fitness have been linked to improvements in executive functioning performance. These effects have been documented in both observational and intervention studies, and span several sub-domains, including cognitive and/or inhibitory control (Chaddock, Erickson, et al., 2012a; Crova et al., 2014; Hillman et al., 2014; Khan et al., 2015; Pontifex et al., 2011; Scudder et al., 2014; Wu et al., 2011), abstract reasoning (Ardoy et al., 2014), planning (Davis & Cooper, 2011; Davis et al., 2007), working memory (Drollette et al., 2016; Scudder et al., 2014), and fluid intelligence (Reed, Maslow, Long, & Hughey, 2013). Across most studies, positive effects of exercise remained significant even after controlling for important confounders, which have commonly included age, sex, socioeconomic status, and IQ (Donnelly et al., 2016).

Similarly, studies have also found exercise-related alterations in the structure and function of several brain regions involved in executive functioning processes among children and adolescents. For instance, structural magnetic resonance imaging (MRI) studies have found larger gray matter volumes in areas such as the medial prefrontal cortex (Herting, Keenan, & Nagel, 2016), orbitofrontal cortex (Ross et al., 2015), and basal ganglia (Chaddock, Erickson, Prakash, VanPatter, et al., 2010; Chaddock, Hillman, et al., 2012) in aerobically fit children. Additionally, a handful of functional MRI (fMRI)

studies have examined the effects of chronic exercise and/or fitness on brain function among healthy, typically developing children (Chaddock, Erickson, et al., 2012b; Chaddock-Heyman et al., 2013; Voss et al., 2011), as well as overweight children (Davis & Cooper, 2011; Krafft et al., 2014). Most of these studies have examined cognitive and/or inhibitory control using variations of the Eriksen flanker task. Although there has been significant cross-study variability with regards to the specific brain regions affected, effects of exercise and fitness have been commonly reported in frontal regions, such as the anterior cingulate cortex, medial frontal gyrus, and prefrontal cortex (Chaddock, Erickson, et al., 2012b; Chaddock-Heyman et al., 2013; Davis et al., 2011; Krafft et al., 2014; Voss et al., 2011). The directionality of the findings has also varied across studies. Some have found that exercise and fitness resulted in decreased task-related activation (Chaddock-Heyman et al., 2013; Krafft et al., 2014), which is typically interpreted as a sign of "increased efficiency," whereas others have found increased activation (Chaddock, Erickson, et al., 2012b; Davis et al., 2011; Voss et al., 2011).

Importantly, several studies documenting effects of exercise on brain and cognition among children have either failed to find, or failed to examine associations between these two constructs (Davis et al., 2011; Krafft et al., 2014; Voss et al., 2011). For instance, Krafft et al. (2014) found both improvements in cognition and decreases in task-related brain activation during an antisaccade task among children who completed an exercise intervention; however, associations between changes in brain activation and changes in cognitive performance were not significant. In addition, an exercise intervention by Davis et al. (2011) found dose-response improvements in executive function (i.e., planning) and math, as well as evidence of increased bilateral prefrontal

activation and decreased posterior parietal activation during an anti-saccade task. However, they did not describe the association between fMRI activation and cognitive performance. Further, in contrast to adult studies (Broadhouse et al., 2020; Liu, Wu, Li, & Guo, 2018; Peven et al., 2019; Voss et al., 2010; Wong et al., 2015), studies on pediatric populations have not formally tested a mediating role for these neural changes in the association between exercise and cognitive performance. For this reason, it is not yet clear whether exercise effects on children's cognition can be explained by effects on underlying brain structure and/or function.

Another limitation of the literature examining the impact of exercise on pediatric brain and cognitive functioning is its heavy emphasis on flanker tasks, whereas less is known about the effects of exercise on other commonly used executive tasks, such as the *N*-back task. The *N*-back task is typically used to assess working memory (i.e., the ability to mentally hold or manipulate information for a brief period of time), as it requires participants to indicate whether each stimulus is the same as the one presented *N* trials ago (Jaeggi, Buschkuehl, Perrig, & Meier, 2010), and has been shown to predict performance in other cognitive domains, particularly fluid intelligence (Jaeggi et al., 2010). This task has been shown to elicit concordant activation of parietal cortices, insula, claustrum, and cerebellum across both children and adults, whereas activation of specific frontal regions varies by age group (Yaple, Stevens, & Arsalidou, 2019). Two behavioral studies have found positive associations between fitness and *N*-back task performance (Drollette et al., 2016; Scudder et al., 2014), but these studies did not involve neuroimaging. One fMRI study of preadolescent children found that acute bouts of aerobic exercise resulted in improved *N*-back task performance, as well as increased

activation of parietal cortices, hippocampus, and cerebellum (Chen, Zhu, Yan, & Yin, 2016). However, less is known about the effects of chronic exercise on brain activation during this task.

The current study examines cross-sectional associations between exercise and executive functioning, and explores a potential mediating role for task-related brain function in relevant neural networks among children (**Aim 3**) utilizing data from the landmark ABCD study (U01 DA041156). These analyses focus on brain activation during an *N*-back task in the frontoparietal and salience networks due to their involvement in cognitive control and executive functioning (Marek & Dosenbach, 2018; Seeley, 2019; Seeley et al., 2007). We hypothesized that a) more exercise would be associated with better executive functioning, and b) this association would be mediated by exercise effects on task-related activation of the frontoparietal and salience networks, such that more exercise would predict greater mean-level network activation, which would in turn be associated with better executive functioning. In a more exploratory way, we also examined the role of the default-mode network (DMN), a network involved in self-referential processes and thought to be deactivated during cognitive tasks (Buckner, Andrews-Hanna, & Schacter, 2008), but which may also play a role in working memory processes (Bluhm et al., 2011; Esposito et al., 2009). Because the majority of the children in this sample were substance-naïve at the baseline assessment (as well as at the one-year follow-up), we did not explore associations between exercise and cannabis use in the current study. Nevertheless, these analyses will lay the groundwork for later exploration of these questions once substance use levels in this sample increase.

Method

Participants and Setting

Data for the current study were obtained from the annual 3.0 data release of the ABCD study. The ABCD study recruited 11,878 children aged 9 to 10 years old at the baseline assessment to be followed for a period of 10 years into early adulthood. A total of 9,553 children completed the *N*-back task while in the MRI scanner at baseline. Of these, 1,820 participants were excluded due to poor data quality (e.g., poor quality of structural image, <60% accuracy in task performance), as recommended by the ABCD 3.0 Release Notes. Thus, the current study utilized data from 7,733 children with quality *N*-back fMRI data the baseline assessment. Participants were recruited across 21 study sites through public and private elementary schools with methods intended to yield a final sample that approximated national sociodemographic characteristics (Garavan et al., 2018). Participants and their legal guardian provided assent and consent, respectively, to participate. All study procedures were approved by institutional review boards at participating institutes.

Measures

Exercise. In the current study, exercise was assessed through the SAIQ, which was completed by parents at baseline. A full list of the activities included in this questionnaire is included in Table 2. For each endorsed activity, parents indicated the number of years, months per year, and days per week that their child engaged in each endorsed activity. They also indicated the number of minutes spent in each session through a Likert scale (1 = less than 30 minutes; 2 = 30 minutes; 3 = 45 minutes; 4 = 60 minutes; 5 = 90 minutes; 6 = 1 hour; 7 = 2.5 hours; 8 = 3 hours; 9 = greater than 3 hours).

Multiplying these variables, we calculated the total time spent on each activity, and added these totals (excluding non-sports activities) to obtain lifetime amount of time spent on sports for each participant, which was used as our measure of exercise. Of note, although this variable does not have meaningful time units due to the Likert scale nature of the "minutes per session" ratings, higher values on this variable indicate more time spent in exercise.

Executive functioning. ABCD study participants completed the NIH Toolbox® cognition measures. This battery consists of seven tasks and provides several composites, which have shown good validity and reliability among both children and adults (Akshoomoff et al., 2013; Heaton et al., 2014). The current study used the uncorrected Fluid Intelligence Composite as our cognitive outcome measure, as it assesses multiple aspects of executive functioning, including attention, cognitive control, working memory, and processing speed. Specifically, this composite includes scores from five tests—the Toolbox Pattern Comparison Processing Speed Test® (Carlozzi, Beaumont, Tulsky, & Gershon, 2015), the Toolbox List Sorting Working Memory Test® (Tulsky et al., 2014), the Toolbox Picture Sequence Memory Test® (Bauer et al., 2013), the Toolbox Flanker Task®, and the Toolbox Dimensional Change Card Sort Task® (Zelazo et al., 2013).

***N*-back task.** Participants completed two runs of an emotional *N*-Back task in the scanner, which assesses working memory as well as emotional processing (Barch et al., 2013; Casey et al., 2018). Each run consisted of eight blocks, half of which involved the 2-back condition and half of which were 0-back. Stimuli consisted of happy, neutral, and fearful faces, as well as places. In the 2-back condition, participants had to press a button to indicate whether each picture matched the one they saw two trials back. In the 0-back

condition, they indicated whether each picture matched the target. Each block included 10 trials, and began with a colored fixation (500ms) to signal a switch in task condition, by cue indicating the condition (2.5s; e.g., “2-back”). Each stimulus was then presented (2s) and followed by a fixation cross (500ms). To assess working memory, the current study focused on the 2-back versus 0-back contrast.

Image preprocessing and calculation of ROI data. Leveraging validated methods used in other studies, the ABCD Data Analysis and Informatics Center (DAIC) performed centralized processing and analysis of MRI data (Casey et al., 2018; Hagler et al., 2019). To summarize, parcellated cortical regions used in study analyses were derived from cortical surface reconstruction performed using FreeSurfer v5.3.0 (Fischl, 2012). Estimates of canonical task-related activation were computed at the participant level using a general linear model (GLM) through AFNI's 3dDeconvolve program and were released as contrast beta weights (Cox, 1996). For the 2-back versus 0-back contrast used in the current study, average beta coefficients were computed during each of two runs and then averaged across runs (Casey et al., 2018; Hagler et al., 2019). Outliers were winsorized at ± 3SD, and did not exceed 5% for any brain region.

Selection of ROIs. We identified ROIs belonging to each network of interest as defined by the Gordon parcellation using the nearest Destrieux parcel (Hagler et al., 2019). We tested 11 ROIs as part of the frontoparietal network: frontomarginal gyrus and sulcus, transverse frontopolar gyrus and sulcus, middle frontal gyrus, middle frontal sulcus, superior frontal gyrus, intraparietal sulcus and transverse parietal sulci, inferior frontal sulcus, supramarginal gyrus, the inferior part of the precentral sulcus, inferior temporal sulcus, and orbital gyrus. The salience network consisted of two ROIs: the

anterior segment of the circular sulcus of the insula (anterior insula), and anterior cingulate gyrus and sulcus. Finally, the default-mode network (DMN) consisted of 13 ROIs: frontomarginal gyrus and sulcus, middle frontal gyrus, superior frontal gyrus, superior frontal sulcus, anterior cingulate gyrus and sulcus, middle to posterior cingulate gyrus and sulcus, angular gyrus, precuneus, lateral superior temporal gyrus, superior temporal sulcus, middle temporal gyrus, subparietal sulcus, and gyrus rectus.

Covariates. To control for the influence of demographic factors, we included participant age, sex, race/ethnicity, combined household income, and parental education as covariates (Zhang, Lee, White, & Qiu, 2020). To control for the influence of mental health factors on cognition, we included the internalizing and externalizing problem subscales from the Child Behavior Checklist (CBCL) as covariates (Achenbach & Ruffle, 2000; Thompson et al., 2019). In addition, we controlled for the influence of other social and environmental factors that have been shown to influence both cognition and sports participation among children (Sangawi, Adams, & Reissland, 2021; Zhang et al., 2020). These included parental monitoring, as assessed by the Parental Monitoring questionnaire, as well as school involvement and environment, as assessed by the School Risk and Protective Factors inventory (Zucker et al., 2018).

Analytic Plan

We used latent variable modeling to determine whether each network's ROIs showed significant co-activation, i.e., whether each ROI loaded significantly onto a broader network factor. For each network, we specified a second-order factor model in which a) each lateralized ROI loaded onto a right or left hemisphere network factor (first-order); and b) these lateralized factors loaded onto an overarching network factor

(second-order). We also modeled the correlations between the residuals of homologous ROI pairs (e.g., the left precuneus with the right precuneus). This modeling approach has been previously applied to neuroimaging data (Bolt et al., 2018; Hawes et al., 2020), as latent variables are known to reduce measurement error and result in increased power (Little et al., 2006). In addition, this modeling approach allows us to explore associations between exercise and mean levels of activation in several higher-order network factors, rather than individual ROIs, which results in a lower number of comparisons.

To address study hypotheses, we first examined the independent direct effects of lifetime exercise on the fluid intelligence composite through a linear regression model (Path c). In order to evaluate network-level task-based activation as a mediator of the relationship between exercise and fluid intelligence, we then ran cross-sectional mediation models which included three paths: the effect of lifetime exercise on network-level activation during an executive task (Path a), the effect of network-level task-based activation on fluid intelligence (Path b), and the direct effect of lifetime exercise on fluid intelligence after controlling for the mediating influence of network-level activation (Path c'). We ran a total of three such models to examine the potential mediating roles of the frontoparietal, salience, and default-mode networks, respectively. Models were retested after accounting for the influence of age, sex, parental education, income, race/ethnicity, internalizing and externalizing problems, parental monitoring, and school engagement and involvement on both mean network activation and fluid intelligence.

All analyses were conducted using M*plus* 8 using maximum likelihood estimation with standard errors (MLR) that are robust to non-normality. Complex sampling and recruitment procedures for the ABCD study were accounted for using CLUSTER

correction (for sibling pairs) and stratification sampling (for study site) procedures (Muthén & Muthén, 1998). For our three mediation models, we used the M*plus* INDIRECT command to assess the significance of the indirect effect (Path a*b). Missing data were handled using FIML.

Results

Second-Order Network Factors

The frontoparietal network factor model showed acceptable fit (CFI = .895, RMSEA = .057, SRMR = .085). As shown in Table 16, all final ROIs loaded significantly onto the frontoparietal network factor. Of note, two ROIs—orbital gyrus and inferior temporal sulcus—were excluded from the model because they did not load highly onto the network factor and resulted in poorer model fit. Thus, the final frontoparietal network factor consisted of nine ROIs, as shown in Figure 13.

The salience network factor model showed good fit (CFI = 1.000, RMSEA = .008, SRMR = .005). As shown in Table 17, all ROIs loaded significantly onto the salience network factor, which is further illustrated in Figure 15.

Finally, the DMN factor model showed good fit (CFI = .895, RMSEA = .049, SRMR = .060). Due to low factor loading and poorer model fit, the gyrus rectus was excluded from the final model. Thus, the final DMN model consisted of 12 ROIs, as shown in Figure 16. Factor loadings for the DMN model are found in Table 18.

Associations between Exercise and Executive Functioning

Lifetime exercise was significantly associated with executive functioning, such that participants with greater reported involvement in exercise had higher fluid intelligence scores at the baseline assessment (Path c: $\beta = .108$, $SE = .014$, $p < .001$, 95%

CI [.080, .135]). After controlling for the influence of theoretically relevant covariates, this association was attenuated but remained statistically significant (Path c: β = .030, *SE* = .012, *p* = .016, 95% *CI* [.005, .054]). This suggests that the association between lifetime exercise and executive functioning can be in large part accounted for by other variables, including demographics, parental monitoring, and school-related factors.

Mediating Role of Frontoparietal Network

Our hypothesized mediation model showed a significant path from lifetime exercise to the frontoparietal network factor (Path a: β = .026, *SE* = .012, *p* = .034, 95% *CI* [.002, .050]), suggesting that more lifetime exercise was associated with higher mean-level frontoparietal network activation in the 2-back versus 0-back condition. The frontoparietal factor predicted executive functioning (Path b: β = .109, *SE* = .013, *p* < .001, 95% *CI* [.084, .134]), such that higher mean-level network activation predicted higher fluid intelligence scores. After accounting for the potential mediating role of frontoparietal network activation, the direct effect of exercise on fluid intelligence remained significant (Path c': β = .105, *SE* = .014, *p* < .001, 95% *CI* [.078, .132]). The indirect effect of exercise on executive function via frontoparietal network activation was very small and marginally significant (Path a*b: β = .003, *SE* = .001, *p* = .040, 95% *CI* [.000, .006]).

As shown in Figure 16, after controlling for covariates, the association between lifetime exercise and the frontoparietal network factor attenuated to non-significance (Path a). The paths from frontoparietal network factor to executive function, as well as the direct effect of lifetime exercise on executive function (Paths b and c') remained significant. However, the mediated effect of frontoparietal network activation was not

significant (Path a*b). Detailed estimates for this covariate-adjusted mediation model can be found in Table 19.

Mediating Role of Salience Network

Our hypothesized mediation model showed a nonsignificant path from lifetime exercise to the salience network factor (Path a: β = .019, *SE* = .014, *p* = .160, 95% *CI* [-.008, .046]), suggesting no effect of exercise on mean-level activation of the salience network. The salience network factor was associated with executive function (Path b: β = .059, *SE* = .014, *p* < .001, 95% *CI* [.031, .087]), such that higher mean salience network activation predicted higher fluid intelligence scores. After accounting for the mediating role of salience network activation, the direct effect of exercise on executive function remained unchanged, (Path c': β = .107, *SE* = .014, *p* < .001, 95% *CI* [.079, .134]). The indirect effect was also not significant (Path a*b: β = .001, *SE* = .001, *p* = .182, 95% *CI* [-.001, .003]), indicating that salience network activation did not mediate the relationship between exercise and cognitive performance.

As previously described, the direct effect of exercise on executive functioning was attenuated after controlling for theoretically relevant covariates. Findings remained otherwise unchanged, as illustrated in Figure 17. Detailed estimates from this covariate-adjusted mediation model are presented in Table 20.

Mediating Role of DMN

Our mediation model revealed a non-significant path from lifetime exercise to the DMN factor (Path a: β = .019, *SE* = .012, *p* = .121, 95% *CI* [-.005, .039]), indicating that exercise did not predict DMN activation. The association between the DMN factor and executive functioning was significant (Path b: β = .078, *SE* = .013, *p* < .001, 95% *CI*

[.053, .103]), such that greater mean-level activation predicted higher fluid intelligence scores. Accounting for the potential role of the DMN as a mediator, the effect of exercise on executive function remained unchanged, (Path c': β = .106, *SE* = .014, $p < .001$, 95% *CI* [.079, .129]), and the indirect effect was non-significant (Path a*b: β = .001, *SE* = .001, $p = .135$, 95% *CI* [.000, .003]). Thus, results did not support a mediating role for DMN activation.

As shown in Figure 18, model results remained mostly unchanged after controlling for covariate effects. As in other models, the direct effect of exercise on executive functioning was attenuated, but remained statistically significant. Estimates for this covariate-adjusted model are detailed in Table 21.

Discussion

The current study examined associations between exercise and executive functioning in a large sample of children from the ABCD study, and explored the mediating role of frontoparietal, salience, and default-mode network activation during an *N*-back task. In line with hypotheses, there was a small but significant association between exercise and executive functioning, such that more lifetime exercise was associated with higher fluid intelligence scores. However, this association was attenuated (while remaining statistically significant) after controlling for the effect of demographic, mental health, and school-related factors. Greater activation of frontoparietal, salience, and default-mode networks during a working memory task (i.e., 2-back vs. 0-back contrast) was associated with better executive functioning. However, contrary to expectation, exercise did not predict activation in any of the networks examined, and

results did not support a mediating role for task-related network activation in the association between exercise and executive functioning.

Parent-reported lifetime involvement in exercise was associated with better executive functioning at the baseline assessment of the ABCD study. However, this association was attenuated after controlling for covariates. With regards to demographics, older participant age, male sex, higher household income, and higher levels of parental education predicted higher fluid intelligence scores. Of the social factors included as covariates, fluid intelligence scores were positively impacted by higher levels of parental monitoring, as well as participants' school environment, and level of involvement in school. Finally, lower levels of externalizing problems were associated with higher fluid intelligence scores. Of note, with the exception of male sex, these variables were also associated with a greater lifetime involvement in exercise. Thus, our results suggest that observed associations between exercise and executive functioning in our sample may be better explained by sociodemographic factors that influence both cognition and the extent to which children participate in sports and exercise. It should also be noted that, although this association remained statistically significant, it was a very small effect and is not likely to be clinically meaningful. These results stand in contrast to those of several other cross-sectional studies suggesting positive effects of exercise and fitness on executive functioning among children, even after controlling for effects of potential confounders (Chaddock, Erickson, et al., 2012a; Davis & Cooper, 2011; Donnelly et al., 2016; Drollette et al., 2016; Jacob et al., 2011; Scudder et al., 2014; Syväoja, Tammelin, Ahonen, Kankaanpää, & Kantomaa, 2014).

There are several possible explanations for this discrepancy. First, the primary variable of interest in many of these studies was aerobic fitness or utilized objective assessments of exercise and physical activity, while the current study examined parent-reported participation in sports and exercise. The limitations associated with self-report measures of exercise have been described in great detail in Chapters II and III. In brief, self-report assessments of exercise show low to moderate correlations with objective assessments, and may be biased in several respects (Prince et al., 2008). Indeed, of the studies examining effects of exercise on cognition among children, one study found that although objectively measured moderate-to-vigorous physical activity (via accelerometer) predicted cognitive performance, self-reported physical activity did not (Syväoja et al., 2014). It is thus possible that our results could differ if we used a more objective assessment of exercise. In addition, our measure of exercise assessed involvement in sports and exercise over the child's lifetime, which could have obscured effects of more recent activity levels. Future studies should focus on a shorter period of the child's life that is more proximal to the cognitive assessment (e.g., past year). Second, although most of the aforementioned studies included demographics and physical health factors as covariates, they rarely accounted for important social and mental health variables that could impact associations between exercise and cognition. Future studies should examine whether these factors may moderate effects of exercise, such that exercise effects are greater among individuals who do not already have these protective factors. Finally, our study utilized a very large sample with characteristics that approximated national demographics which was well powered to detect small effects. On the other hand, most extant studies, including a prior meta-analysis (Sibley & Etnier,

2003), relied on smaller samples. It is thus possible that previously reported effects of exercise on pediatric cognitive and brain function may have been overestimated, as overestimation of effect sizes has been shown to occur with smaller samples (Button et al., 2013; Ioannidis, 2008).

Contrary to our hypotheses, the current study did not find support for a mediating role of task-related network activation in the association between exercise and executive functioning. Given observed covariate effects, it is possible that the effects of exercise on cognition may be driven by social, demographic, and mental health variables, rather than by causal effects on underlying neurocircuitry. However, associations between exercise-related constructs and brain activation have previously been described among children and adolescents (Chaddock, Erickson, et al., 2012b; Chaddock-Heyman et al., 2013; Davis & Cooper, 2011; Krafft et al., 2014). Many of these studies have employed cognitive control tasks (e.g., flanker tasks), whereas we focused on a working memory task (e.g., *N*-back task). Like executive functioning, cognitive control is an umbrella term which encompasses several more specific domains, including inhibitory control (i.e., the ability to ignore distracting information), cognitive flexibility (i.e., the ability to shift attention or strategies to meet changing task demands), and working memory. Although it is often said that exercise and fitness are associated with better cognitive control, broadly, it is possible they may have stronger effects on certain subcomponents of this domain (e.g., inhibitory control) than others (e.g., working memory). To obtain a better understanding of global and specific effects on cognition, future studies should examine the effects of exercise on brain activation during different commonly used fMRI tasks

that assess various aspects of executive function (e.g., flanker, *N*-back, Go-NoGo, Stroop).

The frontoparietal, salience, and default-mode network factors predicted better executive functioning, such that greater mean-level activation of all three networks was associated with higher fluid intelligence scores. This association was strongest for the frontoparietal network factor. This is not surprising, as this network is thought to be given its key role in executive functioning and previously documented associations with fluid intelligence (Cole, Ito, & Braver, 2015; Marek & Dosenbach, 2018; Ptak, Schnider, & Fellrath, 2017). The salience network (particularly, the insula) has also been previously implicated in *N*-back task performance among children (Yaple et al., 2019). In addition, greater activation in the DMN factor during the *N*-back task was associated with better cognitive performance. This was somewhat unexpected, as the DMN is thought to be most active during rest, and deactivated during active task performance (Buckner et al., 2008). It should be noted that our DMN factor had several overlapping ROIs with the frontoparietal network factor (e.g., frontomarginal gyrus and sulcus, middle and superior frontal gyri), which may have influenced our results. However, this overlap is supported by evidence that regions of the frontoparietal network are connected to the DMN and are involved in the regulation of introspective processes (Dixon et al., 2018). Finally, some studies suggest that DMN regions may play important roles in working memory, which may explain activation during a working memory task (Bluhm et al., 2011; Esposito et al., 2009).

The current study has several notable strengths, including the large sample of children that are close in age, the application of latent variable modeling to ROI data to

examine overarching brain networks, and the examination of the mediating role of task-related activation as a mediator of the association between exercise and executive function. Nonetheless, these findings should be interpreted in light of several limitations. First, in addition to the aforementioned limitations associated with self-report (see Chapters II and III), the SAIQ used in the current study did not assess for some physical activities that are commonly performed by school-age children (e.g., biking). Second, mediation examines causal processes that are inherently longitudinal because they unfold over time. Cross-sectional mediation models like the one used in the current study may at times over- or underestimate these effects (Maxwell & Cole, 2007). Thus, future studies should apply longitudinal mediation analyses, as these will also allow us to better isolate the effects of exercise and physical activity. Nevertheless, the current analyses lay the groundwork for exploration of associations between exercise, brain function, and neurocognition in this sample across later timepoints. Third, although the current study focused on task-based fMRI, it is possible that exercise could have effects on brain structure and/or function that were not assessed or included in our analyses. For instance, Chaddock et al. (2012b) found that more aerobically fit children showed increased prefrontal and parietal recruitment during the early blocks but reduced activation in the later blocks of a flanker task. This suggests that exercise and fitness may impact how children adapt to cognitive tasks. Because of our use of average beta weights, we were not able to examine variability in network activation throughout the task. In addition, several adult studies suggest that exercise results in changes to functional connectivity, i.e., the extent to which multiple spatially-distinct brain regions or networks are engaged simultaneously in a task (Bernacer et al., 2019; Flodin, Jonasson, Riklund, Nyberg, &

Boraxbekk, 2017; Liu et al., 2018; Peven et al., 2019; Rogers, Morgan, Newton, & Gore, 2007; Tao et al., 2017). However, this has not yet been examined among children. One fMRI study found that high-fit adolescents showed greater deactivation of regions typically associated with the DMN during a memory task than their low-fit counterparts. Although this was not directly assessed, the authors posited that higher aerobic fitness may lead to changes in functional connectivity, such that task-relevant networks and the DMN are more strongly anticorrelated. Future studies should explore the effects of exercise on both resting-state and task-based functional connectivity, particularly in light of evidence that the frontoparietal network interacts with other networks (e.g., DMN), to coordinate goal-directed behaviors (Marek & Dosenbach, 2018). Fourth, we selected ROIs for our network factors based on the Gordon parcellation using the nearest Destrieux parcel (Hagler et al., 2019). The Gordon parcellation is based on an adult sample; it is possible that these networks may differ among children. Future studies should conduct independent component analyses to identify and compare neural networks observed in our sample of children. Finally, it should be noted that although our sample approximates national sociodemographic characteristics, it overrepresents children from higher socioeconomic strata (Table 13), which may limit generalizability to other samples. Nevertheless, our sample includes representation from lower socioecomonic groups, and we statistically controlled for the influence of related factors, such as parental education and combined household income.

In conclusion, greater lifetime exercise cross-sectionally predicted higher fluid intelligence. However, this association was significantly attenuated after controlling for important sociodemographic and mental health factors, including participant age and sex,

parental education, household income, parental monitoring, school environment and involvement, and externalizing problems. Although this association remained statistically significant, it was very small and likely not clinically meaningful. This suggests that positive effects of parent-reported exercise on executive functioning may be better explained by other factors. Although lifetime exercise did not predict activation of frontoparietal, salience, or default-mode networks, greater activation in all three networks predicted higher fluid intelligence, with this association being strongest for the frontoparietal network. However, the indirect effects of network activation were not significant, and thus did not support a mediating role of task-related brain activation in the association between exercise and executive functioning. Future studies should continue to examine the effects of exercise on cognition among children longitudinally using objective measures of exercise, as well as different neuroimaging analyses techniques (e.g., structural imaging, functional connectivity).

V. DISCUSSION

The studies that comprise this dissertation yielded mixed findings that were at times contrary to study hypotheses. The first study replicated previous work that cannabis use results in episodic memory declines, but found that exercise did not ameliorate this decline among adolescents. The second and third studies found positive effects of exercise on executive function among children and adolescents. However, across studies, these effects were attenuated after accounting for the influence of several sociodemographic variables. These effects were also not mediated by task-related activation of cognitive networks during a working memory task. Finally, the second study documented a small but significant association between greater engagement in exercise and greater cannabis use frequency among adolescents, suggesting that engagement in exercise may represent a risk factor for problematic cannabis use. Potential implications of these findings are discussed in greater detail below.

Does Exercise Improve Neurocognition among Children and Adolescents?

Prior research suggests that exercise is associated with small to moderate positive effects on cognition among children and adolescents (Donnelly et al., 2016; Herting & Chu, 2017; Sibley & Etnier, 2003). Although the current project did not find exercise-related effects on immediate or delayed episodic memory among adolescents, there was evidence of small positive effects on aspects of executive function, namely fluid intelligence and risky decision-making, among children and adolescents, respectively. This is consistent with previous work suggesting that effects of exercise and fitness may be more readily observed in certain cognitive domains, such as executive functioning, in pediatric populations (Best, 2010; Donnelly et al., 2016). At first glance, this is also

consistent with the idea that exercise can help support adolescent brain function, as it suggests improved functioning of frontal regions underlying executive functioning, which are still maturing during this stage (Casey et al., 2008).

However, in both our child and adolescent samples, these associations were attenuated after controlling for the confounding effects of third variables. These variables included participant sex and age, as well as parental education, household income, school environment and involvement, parental monitoring, and externalizing problems; many of these factors predicted both greater engagement in exercise and better executive performance. Effects of exercise on children's executive functioning were also not mediated by effects on neural activation during an executive task. Thus, our results suggest that sociodemographic factors may be driving the association between exercise and cognitive function. Although these findings contrast with those of several other studies that controlled for demographics and other biological characteristics (Donnelly et al., 2016), prior work has rarely accounted for important social factors, such as parental monitoring, opportunities available within the school environment, and engagement in school activities. In addition, effects of exercise on cognition have typically been studied in samples smaller than the ones included in the current project, which may have previously resulted in overestimation of effect sizes (Ioannidis, 2008).

Can Exercise Prevent or Ameliorate Cannabis-Related Cognitive Decline among Adolescents?

Our findings suggest that exercise does not lessen cannabis-related declines in episodic memory among adolescents. Although one prior cross-sectional study suggests that aerobic fitness moderates the association between cannabis use and neurocognition,

effects reported by this team were small, and would not have survived correction for multiple comparisons (Wade et al., 2019). Our results are thus not wholly inconsistent with previous findings.

However, several considerations hamper the definitiveness of our conclusion. For instance, the current study was observational and did not involve any interventions to promote exercise or physical activity. Indeed, observed levels of exercise in our sample of adolescent cannabis users were lower than recommended by national health guidelines, which is not uncommon among adolescents (Kann, 2018; Nader et al., 2008; Piercy et al., 2018). It is therefore possible that higher levels of exercise, as promoted by an exercise intervention, would be better able to combat cannabis-related decline. In addition, observed effects of cannabis use on memory in our sample were small (i.e., less than ¼ SD), and memory performance fell largely within the average range even among cannabis users (Duperrouzel et al., 2019). Positive effects of exercise on memory performance may be more readily observed among populations with more room for improvement (Kelly et al., 2014; Reynolds & Nicolson, 2007).

Does Exercise Promote Better Cannabis-Related Outcomes among Adolescents?

Contrary to our hypotheses and in contrast to previous work, more exercise was predictive of greater cannabis use frequency among adolescents, an effect that was driven primarily by males and was not influenced by team involvement. Although exercise did not predict the development of a use disorder or cannabis-related problems, this suggests that greater engagement in exercise may be a risk factor for problematic cannabis use among adolescents. This is concerning, given that adolescent cannabis use has been linked to poorer educational outcomes, including higher rates of school dropout, lower

academic achievement, and lower educational attainment, in addition to neurocognitive decline (Fergusson & Boden, 2008; Gonzalez et al., 2017; Lynskey & Hall, 2000; Pacheco-Colón, Ramirez, et al., 2019).

Our findings contrast with those of an older body of work suggesting that increased engagement in sports and exercise was protective against cannabis use (Barber et al., 2001; Darling, 2005; Dawkins et al., 2006; Dever et al., 2012; King et al., 2016; Terry-McElrath et al., 2011). However, they are consistent with more recent reports of concurrent use of cannabis with exercise among adults (Nguyen, 2019; YorkWilliams et al., 2019). Recently reported associations between exercise and cannabis use should be interpreted in the context of increasingly permissive cannabis legislation, and lowered perceptions of risk of use among both adolescents and adults (Hughes et al., 2016; Pew Research Center, 2016). Considering these shifts in public perception, it is entirely plausible that associations between exercise and cannabis use may have changed over the past few decades.

Although these findings warrant replication in more diverse samples, they suggest some caution when recommending involvement in exercise and sports to youth. Further exploration is necessary to identify for whom and under what circumstances exercise may represent a protective versus a risk factor in the context of cannabis and other substance use, and what factors can serve to buffer potential risk. For instance, it will be important to further examine the role of demographic factors (e.g., age, sex), and to explore the role of peer influences, parental monitoring, and sports-specific factors, such as team culture, and level of involvement (e.g., competitive versus recreational). This work would help to

maximize the benefits associated with physical activity, while minimizing potentially detrimental effects.

Conclusions, Limitations, and Future Directions

In summary, findings from this dissertation suggest that associations between exercise and neurocognition among children and adolescents are small, not likely to be clinically meaningful, not attributable to effects on task-related brain activation, and better explained by sociodemographic factors. Further, greater involvement in exercise did not ameliorate cannabis-related memory decline, and may instead represent a risk factor for problematic cannabis use among adolescents (particularly males).

Despite mostly null effects of exercise on neurocognition, there is evidence that exercise, physical activity, and fitness contribute to positive outcomes among youth in several other ways. For instance, they benefit multiple aspects of physical health (e.g., lower adiposity, lower blood pressure), as well as mental health (e.g., lower depression, improved self-esteem; Biddle & Asare, 2011; Janssen & LeBlanc, 2010). Physical activity in youth is also predictive of lifestyle behaviors, physical health, and psychological well-being well into adulthood (Malina, 2001; Sacker & Cable, 2006). Thus, exercise should still be promoted among pediatric populations, even if not for its benefits to cognition. These recommendations can then be tailored as more evidence becomes available regarding the role of sports and exercise in the context of adolescent substance use.

This dissertation has several strengths, including the use of large samples of children and adolescents, high internal validity to examine neurocognitive correlates of adolescent cannabis use, the use of multiple indices of neurocognitive function, and the

combination of neurocognitive and neuroimaging data. The specific limitations associated with each study have been described in detail in each individual chapter. It should be noted that although many of the limitations associated with the first two studies (Chapters II and III) are not addressable, limitations associated with the third study (Chapter IV) should instead be viewed as future directions, as the ABCD study is still ongoing. For instance, one limitation common across studies was the use of a subjective questionnaire (self- or parent-report) of engagement in sports and exercise, as this type of measure typically shows low to moderate correlations with objective measures of exercise (Prince et al., 2008). The ABCD study began collecting accelerometer (i.e., Fitbit) data for a subset of participants at the one-year follow-up. Thus, as the study progresses, future projects will be able to examine correlations between accelerometer and questionnaire data over specific time intervals (Bagot et al., 2018). Scientists will also be able to determine whether objectively measured physical activity has a more significant impact on cognitive and brain function, as previously reported by some studies (Syväoja et al., 2014). As data from additional follow-up timepoints continue to become available, more complex longitudinal analyses will allow for the examination of bidirectional influences between these constructs over time (e.g., multivariate LGCM), and for the exploration of longitudinal mediation processes (i.e., the mediating role of *change* in a particular variable). Finally, some studies suggest that aerobic fitness has a stronger influence on cognitive and brain function than physical activity (Ruotsalainen et al., 2019; Voss et al., 2016). Although greater involvement in physical activity is thought to lead to improved aerobic fitness (Armstrong et al., 2011), the latter is also heavily influenced by other factors, such as genetics (Bouchard et al., 1999, 2010). Thus,

although the ABCD study does not directly assess aerobic fitness, its large sample size and wealth of data have positioned it well to disentangle the contributions of genetics and exercise to brain and cognitive function among children and adolescents.

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TABLES

Table 1. Participant demographics, substance use, mental health, and neuropsychological performance by assessment wave.

	Assessment Wave				
	T1 (N = 401)	**T2 (N = 391)**	**T3 (N = 383)**	**T4 (N = 380)**	**T5 (N = 387)**
Demographics (M, SD)					
Age	15.40 (.72)	15.96 (.81)	16.38 (.71)	16.92 (.78)	17.39 (.75)
Sex (% Male)	54.1	53.7	54.0	53.9	54.0
Race (% White)	76.8	76.7	76.2	76.8	77.0
Ethnicity (% Hispanic/Latino)	89.8	89.5	89.3	89.7	89.7
Years of Education	9.11 (.84)	9.74 (.90)	10.08 (.85)	10.73 (.88)	11.07 (.84)
Years of Maternal Education	14.23 (2.49)				
WRAT-4 Reading Standard Score	108.31 (14.73)				
Substance Use Characteristics (Md, [IQR])					
Lifetime Cannabis Use (Days)	21.00 [1.00, 144.50]	36.00 [2.00, 186.00]	62.00 [3.00, 266.00]	82.00 [4.00, 350.00]	108.00 [8.50, 483.00]
Lifetime Alcohol Use (Days)	5.00 [1.00, 19.50]	8.00 [1.00,31.00]	13.00 [3.00, 38.00]	17.00 [5.00, 56.50]	24.00 [7.50, 72.00]
Lifetime Nicotine Use (Days)	.00 [.00, 3.00]	.00 [.00, 6.00]	1.00 [.00, 9.25]	1.00 [.00, 12.75]	2.00 [.00, 21.00]
Current CUD (%)	13.2	11.5	19.6	17.6	23.3
Lifetime CUD (%)	22.2	29.4	37.8	42.4	47.8
THC+ Oral Fluids Toxicology (%)	3.5	-	9.5	-	20.7
Mental Health					
Current Internalizing Disorder (%)	5.5	-	4.7	-	4.9
Current Externalizing Disorder (%)	11.0	-	8.1	-	5.9
Lifetime Internalizing Disorder (%)	16.2	-	21.7	-	26.5
Lifetime Externalizing Disorder (%)	12.2	-	17.2	-	19.1
Neuropsychological Performance (M, SD)[a]					
Cups Task, Risky Choices Gain Domain*	50.00 (10.00)	-	50.04 (9.30)	-	50.31 (9.84)
Cups Task, Risky Choices Loss Domain*	50.00 (10.01)	-	49.64 (9.88)	-	49.85 (9.79)
GDT, Risky Choices*	50.00 (9.99)	-	46.13 (9.16)	-	45.28 (9.13)
IGT Net Score (reverse-scored)*	50.00 (10.00)	-	46.91 (11.90)	-	44.90 (12.78)
CVLT-II Total Immediate Recall	50.00 (10.00)	-	52.50 (10.01)	-	54.78 (10.54)
WMS-IV Logical Memory I	50.00 (10.00)	-	51.52 (9.98)	-	54.03 (9.89)
WMS-IV Designs I	50.00 (10.00)	-	52.75 (10.29)	-	53.73 (10.60)

CVLT-II Long Delay Free Recall	49.99 (10.01)	-	52.70 (9.66)	-	55.18 (9.89)
WMS-IV Logical Memory II	50.00 (10.00)	-	52.11 (9.72)	-	56.12 (10.20)
WMS-IV Designs II	50.00 (10.00)	-	51.38 (10.92)	-	53.01 (11.08)
Self-Reported Exercise (Md, [IQR])			n = 60	n = 138	n = 198
Past 6-mont Hours per Week	-	-	3.50 [.78, 7.73]	2.71 [.55, 8.14]	1.50 [.11, 4.69]
Number of Sports Endorsed			2.00 [1.00, 2.50]	2.00 [1.00, 3.00]	1.00 [1.00, 2.00]
% Reporting Team Involvement			51.7	35.8	31.3

Note: [a]T-scores were calculated using the T1 mean and standard deviation. *Higher scores for these tests denote worse performance. M = mean; SD = Standard Deviation; Md = Median; IQR = interquartile range. Mental Health was assessed through the Diagnostic Interview Schedule for Children using DSM-IV criteria. Participants were coded as being involved in teams if they reported team involvement for *most* of the activities endorsed.

Table 2. List of activities queried in the SAIQ and included in our exercise measure.

Activities Queried in SAIQ	Included in Calculation of Past 6-month Exercise for Chapters II and III (X)	Included in Calculation of Lifetime Exercise for Chapter IV (X)
Aerobics classes (e.g., Zumba)	X	N/A
Ballet or dance	X	X
Baseball or softball	X	X
Basketball	X	X
Biking	X	N/A
Cardio machine exercise (e.g., treadmill, elliptical)	X	N/A
Climbing	X	X
Competitive games like chess, cards, or darts		
Crafts like knitting or building model cars or airplanes		
Drama, theatre, acting, or film		
Drawing, painting, graphic art, photography, pottery, or sculpting		
Field hockey	X	X
Football	X	X
Gymnastics	X	X
Ice hockey	X	X
Horseback riding or polo	X	X
Ice or inline skating	X	X
Lacrosse	X	X
Martial arts	X	X
Music (playing musical instruments like piano, drums, violin, flute, or guitar, singing, choir, orchestra, band, rock band)		
Hobbies like collecting stamps or coins		
Rugby	X	X
Skateboarding or longboarding	X	X
Skiing or snowboarding	X	X
Soccer	X	X
Surfing	X	X
Swimming or water polo	X	X
Tennis	X	X
Track, running, or cross-country	X	X
Weightlifting or CrossFit	X	N/A
Wrestling or mixed martial arts	X	X
Volleyball	X	X
Yoga or tai chi	X	X
Video Games		N/A
Other	*	N/A

*Other responses were included in the calculation if they referred to physical activity. N/A denotes activities that were not queried by the original version of the SAIQ employed in the ABCD study; these activities were added to the adapted self-report version of the SAIQ used in Studies 1 and 2, as these are often endorsed among adolescents.

Table 3. Fit indices and estimates for unconditional linear growth models of cannabis use, exercise, and memory.

Variable	χ^2	*df*	CFI	RMSEA	SRMR	Intercept $\overline{x}$	Slope $\overline{x}$	Intercept σ^2	Slope σ^2	Cov (I/S)
Cannabis use	166.37**	10	.95	.20	.02	10.72**	4.22**	397.67**	28.41**	56.91**
Exercise	2.47	3	1.00	.00	.12	5.74**	-.68	18.68**	.00	-
Immediate memory	.00	1	1.00	.00	.00	50.00**	1.01**	38.43**	.30	.86
Delayed memory	3.37	1	1.00	.08	.02	49.83**	1.16**	39.56 **	.20	.74

**$p < .001$, *$p < .05$. All estimates represent unstandardized values.

Note: df = degrees of freedom; CFI = Comparative Fit Index; RMSEA = Root Mean Square Error of Approximation; SRMR = Standardized Root Mean Square Residual; Cov (I/S) = Covariance between intercept and slope.

Table 4. Fit indices and estimates for unadjusted parallel process models of cannabis use and memory performance.

Parameter	Unstandardized Estimate (Standard Error)	*p*-value	χ^2	*df*	CFI	RMSEA	SRMR
CU and IM			317.40**	28	.94	.16	.02
IM intercept ←→ CU intercept	-22.28 (7.97)	.005*					
CU intercept → IM slope	.00 (.01)	.963					
IM Intercept → CU slope	-.09 (.05)	.039*					
CU slope → IM slope	-.04 (.02)	.023*					
CU intercept ←→ CU slope	58.26 (7.25)	<.001**					
IM intercept ←→ IM slope	-.01 (.67)	.993					
CU and DM			322.13**	28	.94	.16	.02
DM intercept ←→ CU intercept	-24.86 (7.51)	.001**					
CU intercept → DM slope	.002 (.01)	.680					
DM Intercept → CU slope	-.15 (.05)	.001**					
CU slope → DM slope	-.02(.02)	.351					
CU intercept ←→ CU slope	49.86 (7.16)	<.001**					
DM intercept ←→ DM slope	.07 (.62)	.915					

**$p \leq .001$, *$p < .05$.

Note: CU = cannabis use; IM = immediate memory; DM = delayed memory; df = degrees of freedom; CFI = Comparative Fit Index; RMSEA = Root Mean Square Error of Approximation; SRMR = Standardized Root Mean Square Residual. Bidirectional arrows represent correlations and unidirectional arrows represent regression paths.

Table 5. Detailed estimates for covariate-adjusted parallel process model of cannabis use and immediate memory.

Parameter	Unstandardized Estimate (Standard Error)	*p*-value	Lower 95% *CI*	Upper 95% *CI*
IM intercept ←→ CU intercept	-14.838 (7.156)	.038*	-28.864	-.812
CU intercept → IM slope	.001 (.005)	.834	-.010	.012
IM Intercept → CU slope	-.075 (.044)	.088	-.161	.011
CU slope → IM slope	-.051 (.022)	.020*	-.094	-.008
CU intercept ←→ CU slope	44.947 (6.430)	<.001**	32.343	57.551
IM intercept ←→ IM slope	-.011 (.659)	.987	-1.302	1.280
Sex→ CU intercept	-5.410 (1.856)	.004*	-9.047	-1.773
Sex→ CU slope	-2.066 (.516)	<.001**	-3.077	-1.055
Sex→ IM intercept	.608 (.741)	.412	-.845	2.061
Sex→ IM slope	.129 (.173)	.458	-.211	.469
Baseline Age→ CU intercept	3.278 (1.094)	.003*	1.134	5.422
Baseline Age→ CU slope	.672 (.356)	.059	-.025	1.369
Baseline Age→IM intercept	-.074 (.507)	.885	-1.067	.920
Baseline Age→ IM slope	.147 (.117)	.211	-.083	.376
Estimated IQ → IM intercept	.163 (.024)	<.001**	.116	.210
Estimated IQ → IM slope	.005 (.006)	.362	-.006	.017
Lifetime Alcohol T1 → Lifetime CU T1	.737 (.215)	.001**	.317	1.158
Lifetime Alcohol T2 → Lifetime CU T2	.680 (.184)	<.001**	.319	1.040
Lifetime Alcohol T3 → Lifetime CU T3	.694 (.157)	<.001**	.386	1.002
Lifetime Alcohol T4 → Lifetime CU T4	.725 (.161)	<.001**	.408	1.041
Lifetime Alcohol T5 → Lifetime CU T5	.791 (.161)	<.001**	.476	1.107
Lifetime Nicotine T1 → Lifetime CU T1	.203 (.164)	.215	-.118	.525
Lifetime Nicotine T2 → Lifetime CU T2	.172 (.129)	.182	-.081	.426
Lifetime Nicotine T3 → Lifetime CU T3	.178 (.096)	.063	-.010	.366
Lifetime Nicotine T4 → Lifetime CU T4	.193 (.082)	.019*	.032	.354
Lifetime Nicotine T5 → Lifetime CU T5	.214 (.081)	.008**	.055	.373
THC Toxicology T1 → IM T1	-1.183 (1.064)	.266	-3.268	.902
THC Toxicology T3 → IM T3	-.210 (1.067)	.844	-2.301	1.881
THC Toxicology T5 → IM T5	.548 (.749)	.464	-.920	2.016

**$p \leq .001$, *$p < .05$.

Note: IM = immediate memory; CU = cannabis use; CI = Confidence Intervals. Bidirectional arrows represent correlations and unidirectional arrows represent regression paths.

Table 6. Detailed estimates for covariate-adjusted parallel process model of cannabis use and delayed memory.

Parameter	Unstandardized Estimate (Standard Error)	*p*-value	Lower 95% *CI*	Upper 95% *CI*
DM intercept ←→ CU intercept	-16.437 (7.104)	.021*	-30.362	-2.513
CU intercept → DM slope	.004 (.006)	.529	-.008	.016
DM Intercept → CU slope	-.122 (.045)	.006*	-.210	-.034
CU slope → DM slope	-.029 (.023)	.213	-.075	.017
CU intercept ←→ CU slope	43.652 (6.308)	<.001**	31.287	56.016
DM intercept ←→ DM slope	.014 (.613)	.981	-1.187	1.215
Sex→ CU intercept	-5.406 (1.856)	.004*	-9.044	-1.768
Sex→ CU slope	-2.071 (.512)	<.001**	-3.074	-1.068
Sex→ DM intercept	.619 (.739)	.402	-.830	2.068
Sex→ DM slope	.027 (.168)	.871	-.302	.356
Baseline Age→ CU intercept	3.276 (1.095)	.003*	1.130	5.422
Baseline Age→ CU slope	.642 (.354)	.070	-.052	1.336
Baseline Age→ DM intercept	-.039 (.505)	.939	-1.029	.952
Baseline Age→ DM slope	.172 (.109)	.115	-.042	.387
Estimated IQ → DM intercept	.163 (.024)	<.001**	.115	.210
Estimated IQ → DM slope	.001 (.005)	.791	-.009	.012
Lifetime Alcohol T1 → Lifetime CU T1	.737 (.214)	.001**	.318	1.155
Lifetime Alcohol T2 → Lifetime CU T2	.678 (.184)	<.001**	.318	1.039
Lifetime Alcohol T3 → Lifetime CU T3	.692 (.158)	<.001**	.383	1.001
Lifetime Alcohol T4 → Lifetime CU T4	.723 (.162)	<.001**	.404	1.041
Lifetime Alcohol T5 → Lifetime CU T5	.789 (.162)	<.001**	.472	1.107
Lifetime Nicotine T1 → Lifetime CU T1	.207 (.164)	.208	-.115	.528
Lifetime Nicotine T2 → Lifetime CU T2	.175 (.130)	.178	-.080	.430
Lifetime Nicotine T3 → Lifetime CU T3	.181 (.096)	.062	-.009	.369
Lifetime Nicotine T4 → Lifetime CU T4	.195 (.082)	.018*	.034	.356
Lifetime Nicotine T5 → Lifetime CU T5	.216 (.081)	.008*	.056	.375
THC Toxicology T1 → DM T1	-.654 (.926)	.480	-2.469	1.161
THC Toxicology T3 → DM T3	-.440 (.932)	.637	-2.266	1.387
THC Toxicology T5 → DM T5	.144 (.825)	.862	-1.473	1.760

**$p \leq .001$, *$p < .05$.

Note: DM = delayed memory; CU = cannabis use; CI = Confidence Intervals. Bidirectional arrows represent correlations and unidirectional arrows represent regression paths.

Table 7. Fit indices and estimates for unadjusted parallel process models of exercise and memory performance.

Parameter	Unstandardized Estimate (Standard Error)	*p*-value	χ^2	*df*	CFI	RMSEA	SRMR
Exercise and IM			48.071**	11	.93	.09	.17
IM intercept ←→ Exercise intercept	-2.02 (3.48)	.560					
Exercise intercept → IM slope	.19 (.65)	.772					
IM Intercept → Exercise slope	-.01 (.06)	.850					
Exercise slope → IM slope	-.14 (.32)	.668					
Exercise intercept ←→ Exercise slope	6.994 (13.07)	.59					
IM intercept ←→ IM slope	.37 (1.68)	.83					
Exercise and DM			55.69**	11	.93	.11	.17
DM intercept ←→ Exercise intercept	-7.67 (3.70)	.038*					
Exercise intercept → DM slope	.07 (.13)	.575					
DM Intercept → Exercise slope	.07 (.05)	.213					
Exercise slope → DM slope	.004 (.09)	.964					
Exercise intercept ←→ Exercise slope	7.48 (12.87)	.561					
DM intercept ←→ DM slope	.66 (1.27)	.602					

**$p \leq .001$, *$p < .05$.

Note: IM = immediate memory; DM = delayed memory; df = degrees of freedom; CFI = Comparative Fit Index; RMSEA = Root Mean Square Error of Approximation; SRMR = Standardized Root Mean Square Residual. Bidirectional arrows represent correlations and unidirectional arrows represent regression paths.

Table 8. Detailed estimates for covariate-adjusted parallel process model of exercise and immediate memory.

Parameter	Unstandardized Estimate (Standard Error)	*p*-value	Lower 95% *CI*	Upper 95% *CI*
IM intercept ←→ Exercise intercept	.053 (2.98)	.986	-5.786	5.893
Exercise intercept → IM slope	.045 (.151)	.766	-.252	.342
IM Intercept → Exercise slope	-.008 (.074)	.914	-.154	.138
Exercise slope → IM slope	-.045 (.131)	.728	-.301	.210
Exercise intercept ←→ Exercise slope	9.728 (15.156)	.521	-19.977	39.434
IM intercept ←→ IM slope	.089 (.674)	.895	-1.231	1.409
Sex→ Exercise intercept	-2.914 (1.386)	.036*	-5.631	-.197
Sex→ Exercise slope	.406 (.995)	.683	-1.544	2.355
Sex→ IM intercept	.708 (.726)	.329	-.714	2.130
Sex→ IM slope	.309 (.418)	.460	-.510	1.129
Baseline Age→IM intercept	-.015 (.498)	.976	-.990	.960
Baseline Age→ IM slope	.098 (.114)	.391	-.126	.321
Estimated IQ → IM intercept	.165 (.024)	<.001**	.118	.212
Estimated IQ → IM slope	.004 (.006)	.534	-.008	.015
THC Toxicology T1 → IM T1	-1.074 (1.141)	.347	-3.309	1.162
THC Toxicology T3 → IM T3	-.782 (1.041)	.453	-2.822	1.259
THC Toxicology T5 → IM T5	-.559 (.690)	.418	-1.911	.793

**$p \leq .001$, *$p < .05$.

Note: IM = immediate memory; CU = cannabis use; CI = Confidence Intervals. Bidirectional arrows represent correlations and unidirectional arrows represent regression paths.

Table 9. Detailed estimates for covariate-adjusted parallel process model of exercise and delayed memory.

Parameter	Unstandardized Estimate (Standard Error)	*p*-value	Lower 95% *CI*	Upper 95% *CI*
DM intercept ←→ Exercise intercept	-3.854 (2.748)	.161	-9.240	1.531
Exercise intercept → DM slope	.042 (.052)	.416	-.059	.144
DM Intercept → Exercise slope	.054 (.056)	.333	-.056	.165
Exercise slope → DM slope	.041 (.052)	.424	-.060	.143
Exercise intercept ←→ Exercise slope	10.176 (14.536)	.484	-18.314	38.666
DM intercept ←→ DM slope	.215 (.680)	.753	-1.119	1.547
Sex→ Exercise intercept	-2.756 (1.383)	.046*	-5.466	-.046
Sex→ Exercise slope	.220 (1.028)	.831	-1.795	2.234
Sex→ DM intercept	.575 (.724)	.427	-.845	1.994
Sex→ DM slope	.171 (.208)	.411	-.236	.578
Baseline Age→DM intercept	-.025 (.497)	.960	-.999	.950
Baseline Age→ DM slope	.158 (.108)	.144	-.054	.371
Estimated IQ → DM intercept	.155 (.025)	<.001**	.107	.203
Estimated IQ → DM slope	.002 (.005)	.698	-.008	.012
THC Toxicology T1 → DM T1	-.667 (.985)	.498	-2.599	1.264
THC Toxicology T3 → DM T3	-1.164 (.926)	.209	-1.979	.651
THC Toxicology T5 → DM T5	-.585 (.721)	.418	-1.771	.829

**$p \leq .001$, *$p < .05$.

Note: DM = delayed memory; CU = cannabis use; CI = Confidence Intervals. Bidirectional arrows represent correlations and unidirectional arrows represent regression paths.

Table 10. Detailed estimates for covariate-adjusted latent interaction model examining interactive effect of exercise intercept and cannabis slope on immediate memory slope.

Parameter	Unstandardized Estimate (Standard Error)	*p*-value	Lower 95% *CI*	Upper 95% *CI*
IM intercept ←→ CU intercept	-15.547 (7.079)	.028*	-29.422	-1.673
CU intercept → IM slope	.001 (.006)	.837	-.010	.013
IM Intercept → CU slope	-.092 (.043)	.032*	-.177	-.008
CU slope → IM slope	-.041 (.157)	.793	-.348	.266
IM intercept←→ Exercise intercept	-1.232 (3.273)	.707	-7.647	5.183
Exercise intercept→ IM slope	-.045 (.086)	.601	-.213	.123
Exercise slope → IM slope	-.029 (.042)	.479	-.111	.052
CU intercept ←→ Exercise intercept	2.173 (21.477)	.919	-39.923	44.268
CU slope ←→ Exercise slope	.313 (3.467)	.928	-6.482	7.107
Exercise intercept X CU slope→ IM slope	.000 (.026)	.990	-.051	.051
CU intercept ←→ CU slope	44.710 (6.699)	<.001**	31.273	58.215
Exercise intercept ←→ Exercise slope	-4.922 (44.036)	.911	-91.232	81.388
IM intercept ←→ IM slope	-.092 (.691)	.894	-1.340	1.273
Sex→ CU intercept	-5.119 (1.825)	.005*	-8.697	-1.542
Sex→ CU slope	-2.236 (.502)	<.001**	-3.219	-1.252
Sex→ Exercise intercept	-3.013 (.820)	<.001**	-4.620	-1.407
Baseline Age→ CU intercept	2.177 (.920)	.018*	.373	3.981
Estimated IQ → IM intercept	.160 (.021)	<.001**	.120	.201
Lifetime Alcohol T1 → Lifetime CU T1	.758 (.213)	<.001**	.341	1.175
Lifetime Alcohol T2 → Lifetime CU T2	.707 (.178)	<.001**	.357	1.057
Lifetime Alcohol T3 → Lifetime CU T3	.738 (.148)	<.001**	.449	1.027
Lifetime Alcohol T4 → Lifetime CU T4	.768 (.153)	<.001**	.468	1.069
Lifetime Alcohol T5 → Lifetime CU T5	.841 (.151)	<.001**	.545	1.138
Lifetime Nicotine T4 → Lifetime CU T4	.044 (.036)	.213	-.025	.114
Lifetime Nicotine T5 → Lifetime CU T5	.072 (.048)	.134	-.022	.166

**$p \leq .001$, *$p < .05$.

Note: IM = immediate memory; CU = cannabis use; CI = Confidence Intervals. Bidirectional arrows represent correlations and unidirectional arrows represent regression paths.

Table 11. Detailed estimates for covariate-adjusted latent interaction model examining interactive effect of exercise intercept and cannabis slope on delayed memory slope.

Parameter	Unstandardized Estimate (Standard Error)	*p*-value	Lower 95% *CI*	Upper 95% *CI*
DM intercept ←→ CU intercept	-17.578 (6.923)	.011*	-31.147	-4.010
CU intercept → DM slope	.004 (.006)	.527	-.008	.016
DM Intercept → CU slope	-.135 (.044)	.002*	-.221	-.049
CU slope → DM slope	.018 (.079)	.817	-.137	.174
DM intercept←→ Exercise intercept	-3.631 (2.351)	.122	-8.238	.976
Exercise intercept→ DM slope	.011 (.060)	.859	-.106	.127
Exercise slope → DM slope	.030 (.055)	.592	-.078	.137
CU intercept ←→ Exercise intercept	1.470 (10.092)	.884	-18.311	21.250
CU slope ←→ Exercise slope	.053 (.673)	.974	-3.080	3.186
Exercise intercept X CU slope→ DM slope	-.007 (.013)	.585	-.032	.018
CU intercept ←→ CU slope	43.620 (6.564)	<.001**	30.754	56.486
Exercise intercept ←→ Exercise slope	-2.865 (14.317)	.841	-30.925	25.196
DM intercept ←→ DM slope	-.095 (.673)	.888	-1.415	1.225
Sex→ CU intercept	-5.101 (1.824)	.005*	-8.676	-1.526
Sex→ CU slope	-2.239 (.497)	<.001**	-3.214	-1.264
Sex→ Exercise intercept	-2.841 (.862)	.001**	-4.531	-1.151
Baseline Age→ CU intercept	2.233 (.915)	.015*	.439	4.028
Estimated IQ → DM intercept	.152 (.022)	<.001**	.109	.195
Lifetime Alcohol T1 → Lifetime CU T1	.757 (.211)	<.001**	.344	1.170
Lifetime Alcohol T2 → Lifetime CU T2	.705 (.177)	<.001**	.358	1.053
Lifetime Alcohol T3 → Lifetime CU T3	.736 (.147)	<.001**	.448	1.024
Lifetime Alcohol T4 → Lifetime CU T4	.766 (.153)	<.001**	.466	1.066
Lifetime Alcohol T5 → Lifetime CU T5	.839 (.151)	<.001**	.543	1.135
Lifetime Nicotine T4 → Lifetime CU T4	.044 (.036)	.214	-.026	.115
Lifetime Nicotine T5 → Lifetime CU T5	.072 (.048)	.134	-.022	.166

**$p \leq .001$, *$p < .05$.

Note: DM = delayed memory; CU = cannabis use; CI = Confidence Intervals. Bidirectional arrows represent correlations and unidirectional arrows represent regression paths.

Table 12. Detailed estimates for covariate-adjusted latent interaction model examining interactive effect of exercise slope and cannabis slope on the immediate memory slope.

Parameter	Unstandardized Estimate (Standard Error)	*p*-value	Lower 95% *CI*	Upper 95% *CI*
IM intercept ←→ CU intercept	-15.463 (7.076)	.029*	-29.333	-1.594
CU intercept → IM slope	-.007 (.008)	.350	-.023	.008
IM Intercept → CU slope	-.087 (.043)	.043*	-.171	-.003
CU slope → IM slope	-.134 (.354)	.704	-.828	.559
IM intercept←→ Exercise intercept	-1.220 (2.544)	.632	-6.206	3.766
Exercise intercept→ IM slope	-.047 (.038)	.211	-.122	.027
Exercise slope → IM slope	.146 (1.786)	.935	-3.354	3.646
CU intercept ←→ Exercise intercept	3.936 (9.167)	.668	-14.032	21.904
CU slope ←→ Exercise slope	.492 (.901)	.585	-1.274	2.259
Exercise slope X CU slope→ IM slope	-.239 (.495)	.630	-1.209	.731
CU intercept ←→ CU slope	44.745 (6.582)	<.001**	31.844	57.646
Exercise intercept ←→ Exercise slope	-.101 (.542)	.852	-1.163	.962
IM intercept ←→ IM slope	-.081 (.671)	.904	-1.395	1.234
Sex→ CU intercept	-5.110 (1.829)	.005*	-8.694	-1.526
Sex→ CU slope	-2.231 (.501)	<.001**	-3.213	-1.250
Sex→ Exercise intercept	-3.192 (.900)	<.001**	-4.956	-1.429
Baseline Age→ CU intercept	2.174 (.916)	.018*	.377	3.970
Estimated IQ → IM intercept	.159 (.021)	<.001**	.118	.200
Lifetime Alcohol T1 → Lifetime CU T1	.755 (.213)	<.001**	.337	1.172
Lifetime Alcohol T2 → Lifetime CU T2	.707 (.178)	<.001**	.357	1.056
Lifetime Alcohol T3 → Lifetime CU T3	.741 (.147)	<.001**	.453	1.029
Lifetime Alcohol T4 → Lifetime CU T4	.773 (.153)	<.001**	.474	1.072
Lifetime Alcohol T5 → Lifetime CU T5	.847 (.151)	<.001**	.552	1.143
Lifetime Nicotine T4 → Lifetime CU T4	.045 (.036)	.207	-.025	.115
Lifetime Nicotine T5 → Lifetime CU T5	.072 (.048)	.131	-.022	.166

**$p \leq .001$, *$p < .05$.

Note: IM = immediate memory; CU = cannabis use; CI = Confidence Intervals. Bidirectional arrows represent correlations and unidirectional arrows represent regression paths.

Table 13. Detailed estimates for covariate-adjusted latent interaction model examining interactive effect of exercise slope and cannabis slope on the delayed memory slope.

Parameter	Unstandardized Estimate (Standard Error)	*p*-value	Lower 95% *CI*	Upper 95% *CI*
DM intercept ←→ CU intercept	-17.462 (6.937)	.012*	-31.058	-3.866
CU intercept → DM slope	.001 (.010)	.895	-.019	.021
DM Intercept → CU slope	-.133 (.044)	.002*	-.219	-.047
CU slope → DM slope	.038 (.129)	.772	-.216	.291
DM intercept←→ Exercise intercept	-3.615 (2.637)	.170	-8.784	1.554
Exercise intercept→ DM slope	.006 (.054)	.912	-.100	.112
Exercise slope → DM slope	.288 (1.276)	.821	-2.213	2.788
CU intercept ←→ Exercise intercept	2.830 (10.072)	.779	-16.912	22.571
CU slope ←→ Exercise slope	-.313 (1.271)	.806	-2.805	2.179
Exercise slope X CU slope→ DM slope	.059 (.104)	.567	-1.306	1.226
CU intercept ←→ CU slope	43.640 (6.495)	<.001**	30.910	56.371
Exercise intercept ←→ Exercise slope	-.228 (2.248)	.919	-4.633	4.177
DM intercept ←→ DM slope	-.040 (.646)	.951	-1.306	1.226
Sex→ CU intercept	-5.065 (1.830)	.006*	-8.653	-1.478
Sex→ CU slope	-2.222 (.499)	<.001**	-3.506	-1.245
Sex→ Exercise intercept	-3.149 (.906)	.001**	-4.925	-1.373
Baseline Age→ CU intercept	2.208 (.927)	.017*	.391	4.025
Estimated IQ → DM intercept	.152 (.022)	<.001**	.109	.195
Lifetime Alcohol T1 → Lifetime CU T1	.758 (.211)	<.001**	.345	1.171
Lifetime Alcohol T2 → Lifetime CU T2	.706 (.178)	<.001**	.357	1.054
Lifetime Alcohol T3 → Lifetime CU T3	.736 (.148)	<.001**	.447	1.025
Lifetime Alcohol T4 → Lifetime CU T4	.765 (.154)	<.001**	.464	1.066
Lifetime Alcohol T5 → Lifetime CU T5	.838 (.151)	<.001**	.541	1.135
Lifetime Nicotine T4 → Lifetime CU T4	.045 (.036)	.213	-.026	.115
Lifetime Nicotine T5 → Lifetime CU T5	.072 (.048)	.134	-.022	.167

**$p \leq .001$, *$p < .05$.

Note: DM = delayed memory; CU = cannabis use; CI = Confidence Intervals. Bidirectional arrows represent correlations and unidirectional arrows represent regression paths.

Table 14. Sample characteristics of participants included in Chapter III.

	Full Sample (n = 387)	Males (n = 209)	Females (n = 178)
Demographics	M ± SD or %	M ± SD or %	
Baseline Age	16.92 ± .78	16.96 ± 0.80	16.89 ± 0.77
Sex (% Male)	54.0	-	-
Race (% White)	77.0	84.21	88.2
Ethnicity (% Hispanic/Latino)	89.7	89.95	89.32
WRAT-4 Reading Standard Score	108.35 ± 14.79	110.06 ± 15.95	106.34 ± 13.06
Neurocognition 6-Month Follow-Up			
Cups Task, risky choices gain domain	17.15 ± 5,56	16.78 ± 5.67	17.59 ± 5.41
Cups Task, risky choices loss domain	17.11 ± 6.37	15.75 ± 6.39*	18.78 ± 5.95
Game of Dice Task, risky choices	5.37 ± 4.70	5.35 ± 4.84	5.40 ± 4.54
Iowa Gambling Task, Net Score	10.03 ± 28.60	8.90 ± 27.88	11.38 ± 29.46
Substance Use 6-Month Follow-Up	Md [IQR] or %	Md [IQR] or %	
Past 6-month Cannabis Use (Days)	14.00 [.00, 105.00]	10.00 [.00, 135.00]*	3.00 [.00, 49.25]
Past 6-month Alcohol Use (Days)	4.00 [1.00, 15.00]	1.00 [1.00, 15.00]	1.00 [1.00, 15.00]
Past 6-month Nicotine Use (Days)	.00 [.00, 2.00]	.00 [.00, 3.50]*	.00 [.00, 2.00]
Past 6-month Hallucinogen Use (Days)	.00 [.00, .00]	.00 [.00, .00]	.00 [.00, .00]
Past 6-month Benzodiazepine Use (Days)	.00 [.00, .00]	.00 [.00, .00]	.00 [.00, .00]
Past 6-month Cocaine Use (Days)	.00 [.00, .00]	.00 [.00, .00]	.00 [.00, .00]
Lifetime Cannabis Use (Days)	108.00 [8.50, 483.00]	313.00 [14.00, 588.00]*	111.50 [2.50,238.50]
Past 6-month Cannabis Use Disorder (%)	25.4	31.1*	18.5
Marijuana Problems Scale Score	2.00 [.00, 4.00]	2.00 [.00, 5.00]	1.00 [.00, 3.00]

*Denotes significant between-group difference at $p < .05$.

Note: M = mean; SD = standard deviation; Md = Median; IQR = interquartile range.

Table 15. Sample characteristics of ABCD study participants included in Chapter IV.

Characteristics (N = 7,733)	M ± SD or %
Demographics	
Age (years)	9.5 ± .5
Sex (% Male)	48.8
Race/Ethnicity	
African American	11.0
Caucasian	57.5
Hispanic/Latino	12.7
Other	18.2
Parental Education (years)	16.9 ± 2.6
Combined Household Income	
<$50K	22.7
≤$50K & <$100K	27.0
≥$100K	43.1
Neurocognitive Performance	
Fluid Intelligence Composite (uncorrected)	93.7 ± 9.6
Mental Health Performance	
CBCL Internalizing Problems	48.2 ± 10.4
CBCL Externalizing Problems	45.0 ± 10.0
Exercise Involvement	Md [IQR]
Number of Sports Endorsed	2.0 [1.0, 4.0]

Note: M = mean; SD = standard deviation; Md = Median; IQR = interquartile range.

Table 16. Confirmatory factor analysis for second-order frontoparietal network factor.

Parameter	Standardized Loading	*p*-value
Second-Order Frontoparietal Network Factor		
Left Hemisphere Frontoparietal Network	.969	<.001
Right Hemisphere Frontoparietal Network	.969	<.001
First-Order Left Hemisphere Network Factor		
Transverse frontopolar gyrus and sulcus	.369	<.001
Middle frontal gyrus	.868	<.001
Frontomarginal gyrus and sulcus	.398	<.001
Superior frontal gyrus	.826	<.001
Supramarginal gyrus	.746	<.001
Inferior frontal sulcus	.874	<.001
Middle frontal sulcus	.802	<.001
Intraparietal sulcus and transverse parietal sulci	.755	<.001
Inferior part of the precentral sulcus	.837	<.001
First-Order Right Hemisphere Network Factor		
Transverse frontopolar gyrus and sulcus	.462	<.001
Middle frontal gyrus	.837	<.001
Frontomarginal gyrus and sulcus	.364	<.001
Superior frontal gyrus	.821	<.001
Supramarginal gyrus	.726	<.001
Inferior frontal sulcus	.868	<.001
Middle frontal sulcus	.826	<.001
Intraparietal sulcus and transverse parietal sulci	.759	<.001
Inferior part of the precentral sulcus	.844	<.001

Table 17. Confirmatory factor analysis for second-order salience network factor.

Parameter	Standardized Loading	*p*-value
Second-Order Salience Network Factor		
Left Hemisphere Salience Network	.989	<.001
Right Hemisphere Salience Network	.989	<.001
First-Order Left Hemisphere Network Factor		
Anterior insula	.758	<.001
Anterior cingulate gyrus and sulcus	.736	<.001
First-Order Right Hemisphere Network Factor		
Anterior insula	.743	<.001
Anterior cingulate gyrus and sulcus	.717	<.001

Table 18. Confirmatory factor analysis for second-order DMN factor.

Parameter	Standardized Loading	*p*-value
Second-Order DMN Factor		
Left Hemisphere DMN	.969	<.001
Right Hemisphere DMN	.969	<.001
First-Order Left Hemisphere Network Factor		
Frontomarginal gyrus and sulcus	.376	<.001
Middle frontal gyrus	.798	<.001
Superior frontal gyrus	.817	<.001
Anterior cingulate gyrus and sulcus	.636	<.001
Middle to posterior cingulate gyrus and sulcus	.725	<.001
Angular gyrus	.828	<.001
Precuneus	.854	<.001
Lateral superior temporal gyrus	.675	<.001
Middle temporal gyrus	.595	<.001
Superior frontal sulcus	.847	<.001
Subparietal sulcus	.797	<.001
Superior temporal sulcus	.849	<.001
First-Order Right Hemisphere Network Factor		
Frontomarginal gyrus and sulcus	.339	<.001
Middle frontal gyrus	.773	<.001
Superior frontal gyrus	.801	<.001
Anterior cingulate gyrus and sulcus	.630	<.001
Middle to posterior cingulate gyrus and sulcus	.716	<.001
Angular gyrus	.834	<.001
Precuneus	.827	<.001
Lateral superior temporal gyrus	.661	<.001
Middle temporal gyrus	.623	<.001
Superior frontal sulcus	.841	<.001
Subparietal sulcus	.813	<.001
Superior temporal sulcus	.865	<.001

Note: DMN = default-mode network.

Table 19. Detailed estimates for covariate-adjusted mediation model examining the indirect effect of frontoparietal network activation.

Parameter	Standardized Estimate (Standard Error)	*p*-value	Lower 95% *CI*	Upper 95% *CI*
Mediation Model				
Path a: Exercise→ FPN	.012 (.013)	.357	-.013	.037
Path b: FPN→ Fluid Intelligence	.092 (.012)	<.001	.068	.116
Path c': Exercise→ Fluid Intelligence	.029 (.012)	.019	.005	.053
Path a*b: Indirect Effect	.001 (.001)	.361	-.001	.003
Covariate Effects				
Sex→ FPN	-.010 (.013)	.456	-.036	.016
Sex→ Fluid Intelligence	.031 (.012)	.011	.007	.054
Parent Educ→ FPN	.035 (.017)	.036	.002	.068
Parent Educ→ Fluid Intelligence	.103 (.015)	<.001	.074	.133
Age→ FPN	.025 (.013)	.057	-.001	.050
Age→ Fluid Intelligence	.203 (.012)	<.001	.181	.226
Income→ FPN	.013 (.018)	.461	-.022	.049
Income→ Fluid Intelligence	.135 (.016)	<.001	.104	.166
Race→FPN	-.008 (.013)	.530	-.034	.018
Race→Fluid Intelligence	-.004 (.012)	.737	-.028	.020
Parental Monitoring→FPN	-.011 (.014)	.457	-.039	.018
Parental Monitoring→Fluid Intelligence	.049 (.013)	<.001	.023	.075
School Environment→FPN	-.014 (.016)	.389	-.046	.018
School Environment→Fluid Intelligence	-.055 (.015)	<.001	-.084	-.027
School Involvement → FPN	.018 (.016)	.268	-.014	.049
School Involvement→Fluid Intelligence	.074 (.015)	<.001	.044	.104
Internalizing Problems → FPN	-.007 (.016)	.690	-.038	.025
Internalizing Problems →Fluid Intelligence	.011 (.014)	.425	-.017	.040
Externalizing Problems → FPN	.001 (.016)	.942	-.031	.033
Externalizing Problems →Fluid Intelligence	-.065 (.015)	<.001	-.094	-.036

Note: FPN = frontoparietal network.

Table 20. Detailed estimates for covariate-adjusted mediation model examining the indirect effect of salience network activation.

Parameter	Standardized Estimate (Standard Error)	*p*-value	Lower 95% *CI*	Upper 95% *CI*
Mediation Model				
Path a: Exercise→ SN	.012 (.014)	.401	-.016	.040
Path b: SN→ Fluid Intelligence	.057 (.014)	<.001	.031	.084
Path c': Exercise→ Fluid Intelligence	.029 (.012)	.018	.005	.053
Path a*b: Indirect Effect	.001 (.001)	.410	-.001	.002
Covariate Effects				
Sex→ SN	.010 (.014)	.510	-.019	.038
Sex→ Fluid Intelligence	.029 (.012)	.016	.005	.053
Parent Educ→ SN	.025 (.018)	.178	-.011	.060
Parent Educ→ Fluid Intelligence	.105 (.015)	<.001	.075	.135
Age→ SN	.007 (.014)	.632	-.021	.035
Age→ Fluid Intelligence	.205 (.012)	<.001	.182	.228
Income→ SN	-.002 (.020)	.933	-.040	.037
Income→ Fluid Intelligence	.136 (.016)	<.001	.106	.167
Race→SN	-.003 (.014)	.818	-.032	.025
Race→Fluid Intelligence	-.005 (.012)	.697	-.029	.019
Parental Monitoring→SN	-.025 (.016)	.122	-.056	.007
Parental Monitoring→Fluid Intelligence	.050 (.013)	<.001	.024	.075
School Environment→SN	.018 (.018)	.335	-.018	.053
School Environment→Fluid Intelligence	-.058 (.015)	<.001	-.086	-.029
School Involvement → SN	.002 (.018)	.897	-.033	.037
School Involvement→Fluid Intelligence	.075 (.015)	<.001	.046	.105
Internalizing Problems → SN	-.013 (.018)	.455	-.048	.022
Internalizing Problems →Fluid Intelligence	.012 (.014)	.423	-.017	.040
Externalizing Problems → SN	.026 (.018)	.089	-.010	.062
Externalizing Problems →Fluid Intelligence	-.066 (.015)	<.001	-.096	-.037

Note: SN = salience network.

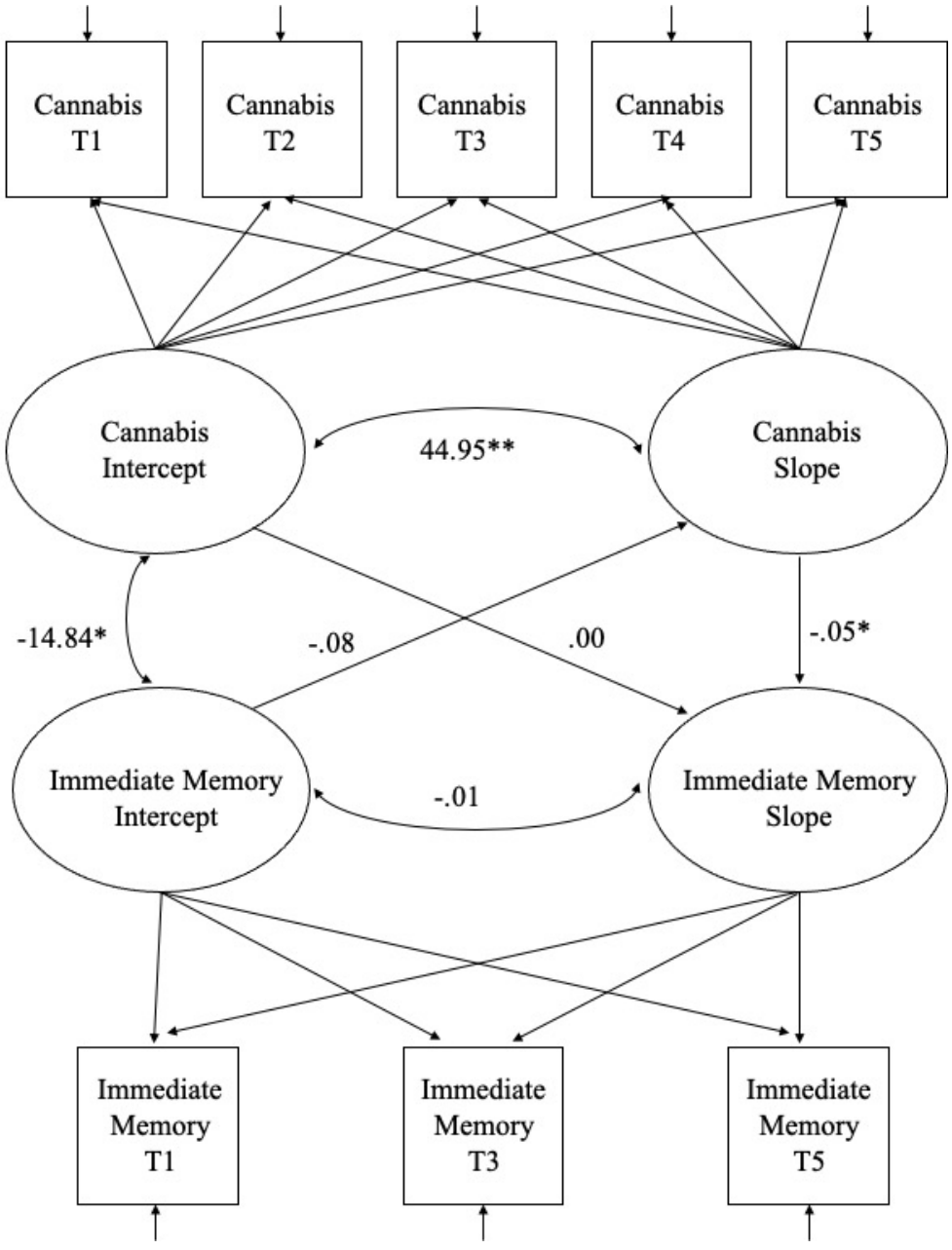
Table 21. Detailed estimates for covariate-adjusted mediation model examining the indirect effect of DMN activation.

Parameter	Standardized Estimate (Standard Error)	*p*-value	Lower 95% *CI*	Upper 95% *CI*
Mediation Model				
Path a: Exercise→ DMN	.011 (.013)	.395	-.014	.036
Path b: DMN→ Fluid Intelligence	.067 (.012)	<.001	.043	.091
Path c': Exercise→ Fluid Intelligence	.029 (.012)	.018	.005	.053
Path a*b: Indirect Effect	.001 (.001)	.401	-.001	.002
Covariate Effects				
Sex→ DMN	-.015 (.013)	.250	-.041	.011
Sex→ Fluid Intelligence	.031 (.012)	.011	.007	.055
Parent Educ→ DMN	.025 (.017)	.139	-.008	.058
Parent Educ→ Fluid Intelligence	.105 (.015)	<.001	.075	.055
Age→ DMN	.007 (.013)	.594	-.018	.032
Age→ Fluid Intelligence	.205 (.012)	<.001	.182	.228
Income→ DMN	.006 (.018)	.724	-.029	.042
Income→ Fluid Intelligence	.136 (.016)	<.001	.105	.167
Race→DMN	-.011 (.013)	.411	-.037	.015
Race→Fluid Intelligence	-.004 (.012)	.736	-.028	.020
Parental Monitoring→DMN	-.013 (.014)	.359	-.042	.015
Parental Monitoring→Fluid Intelligence	.049 (.013)	<.001	.023	.075
School Environment→DMN	-.016 (.016)	.339	-.047	.016
School Environment→Fluid Intelligence	-.056 (.015)	<.001	-.084	-.027
School Involvement → DMN	.020 (.016)	.226	-.012	.051
School Involvement→Fluid Intelligence	.074 (.015)	<.001	.045	.104
Internalizing Problems → DMN	-.010 (.016)	.538	-.042	.022
Internalizing Problems →Fluid Intelligence	.012 (.014)	.420	-.017	.040
Externalizing Problems → DMN	.013 (.016)	.440	-.019	.045
Externalizing Problems →Fluid Intelligence	-.066 (.015)	<.001	-.095	-.037

Note: DMN = default-mode network

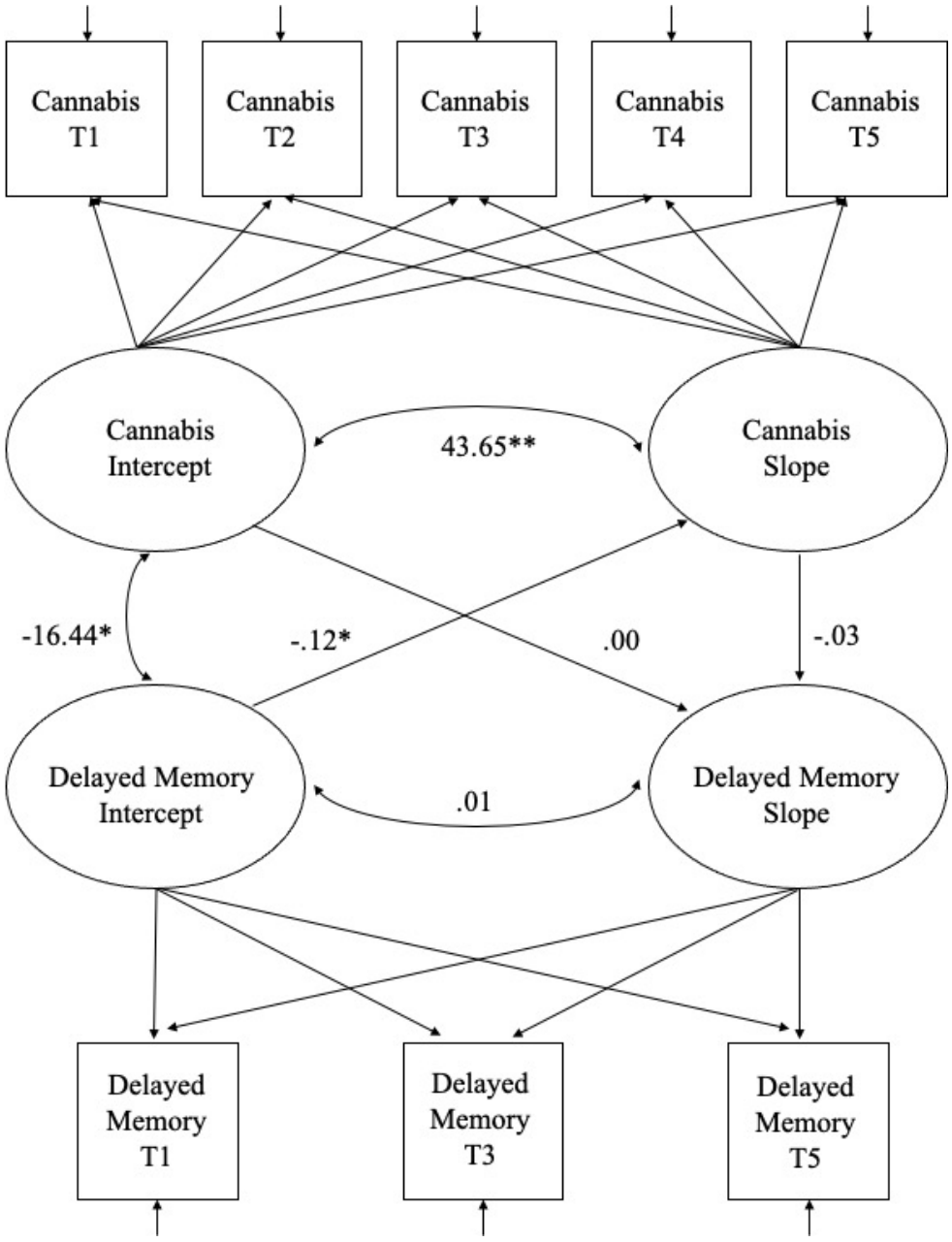
FIGURES

Figure 1. Covariate-adjusted parallel process LGCM of cannabis use and immediate memory performance.



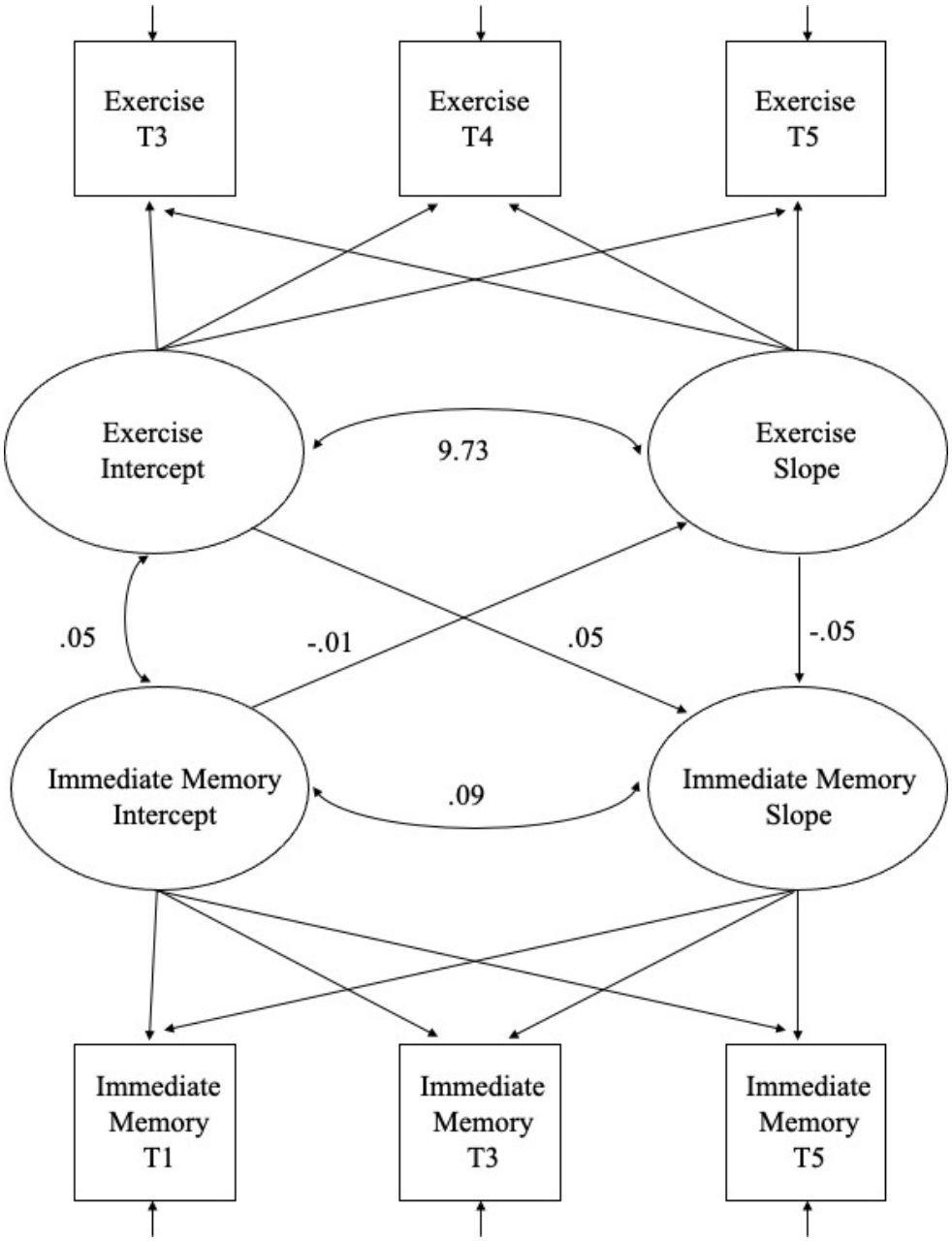
Note: *denotes significance at $p < .05$, **denotes significance at $p < .001$. All estimates represent unstandardized partial regression coefficients.

Figure 2. Covariate-adjusted parallel process LGCM of cannabis use and delayed memory performance.



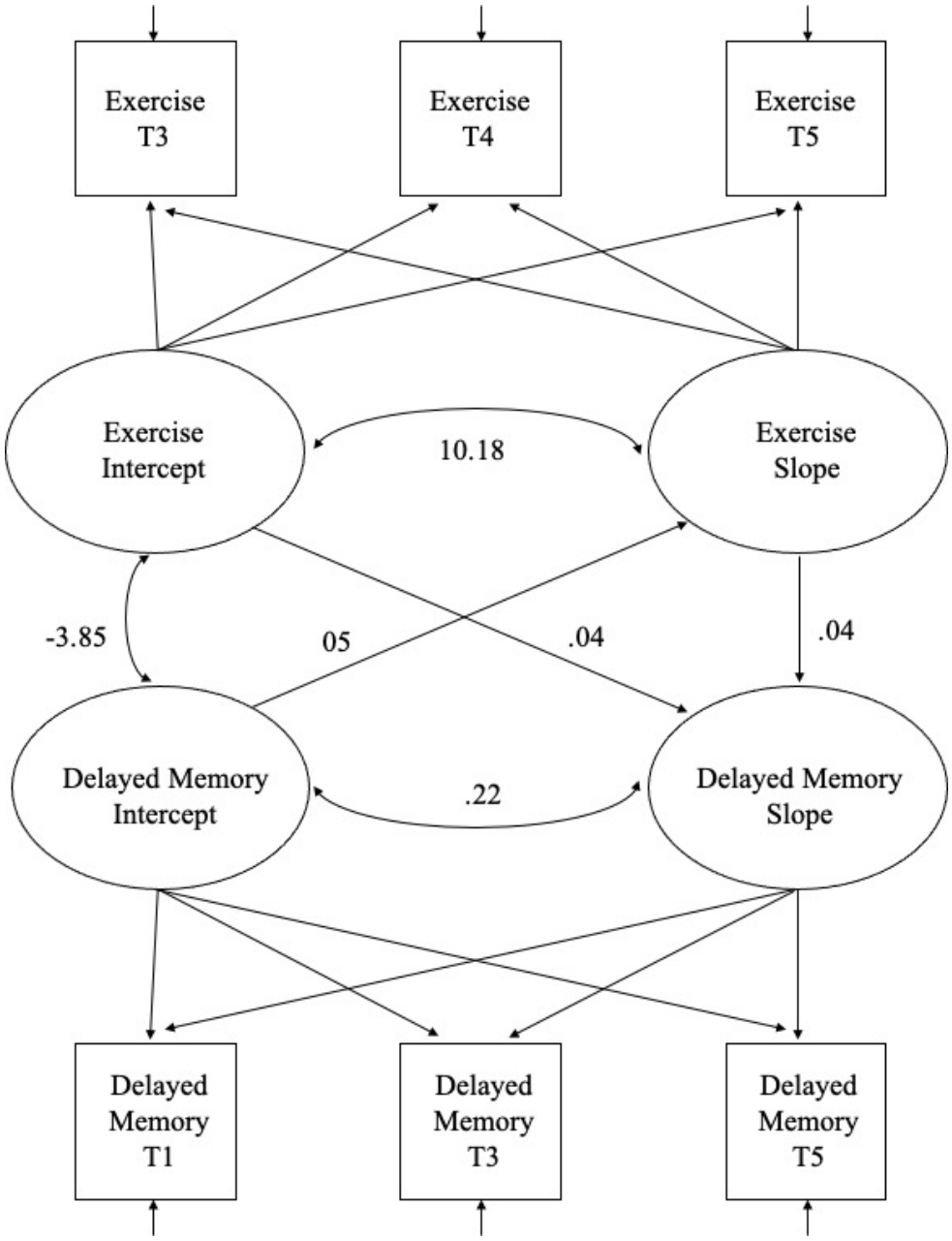
Note: *denotes significance at $p < .05$, **denotes significance at $p < .001$. All estimates represent unstandardized partial regression coefficients

Figure 3. Covariate-adjusted parallel process LGCM of exercise and immediate memory performance.



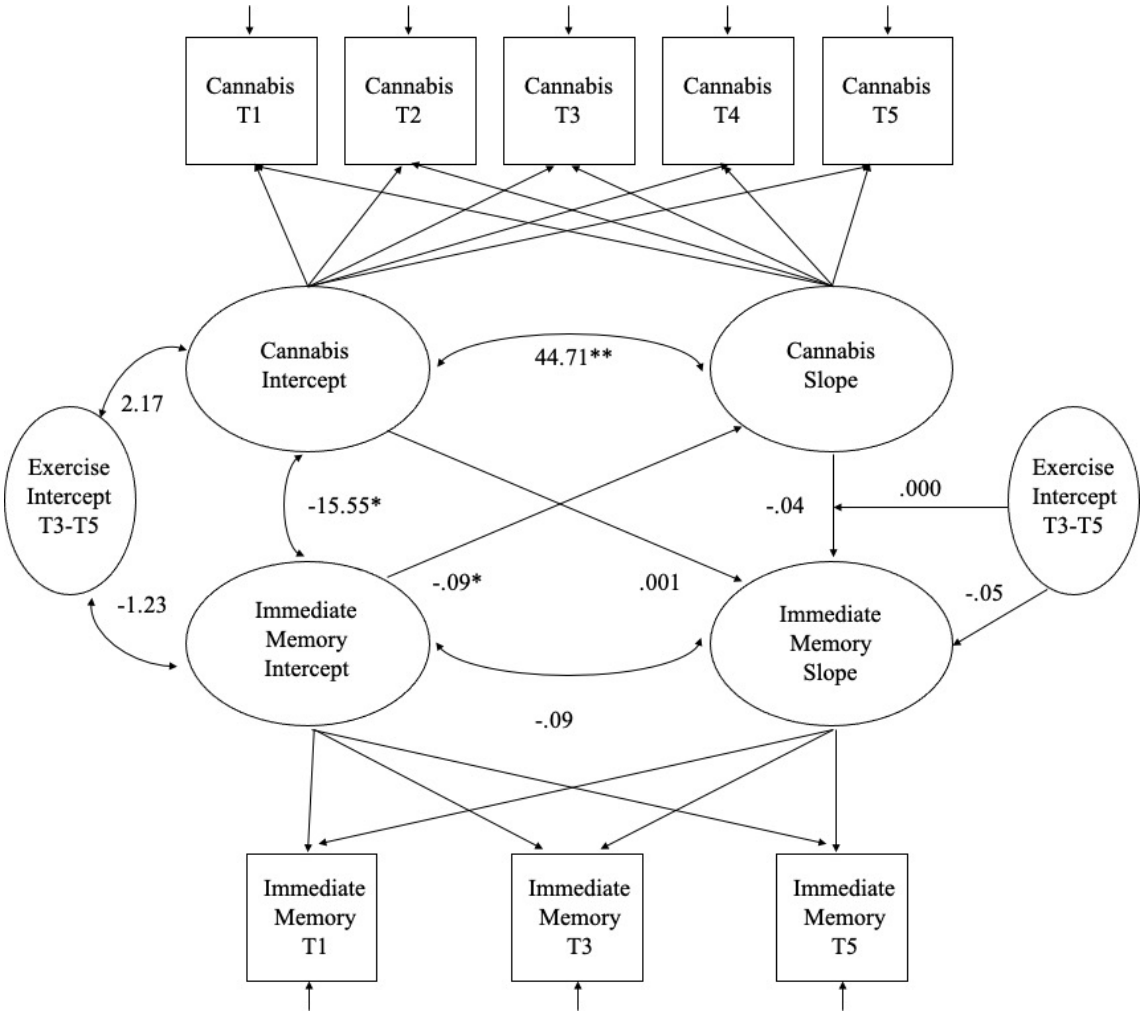
Note: *denotes significance at $p < .05$, **denotes significance at $p < .001$. All estimates represent unstandardized partial regression coefficients.

Figure 4. Covariate-adjusted parallel process LGCM of exercise and delayed memory performance.



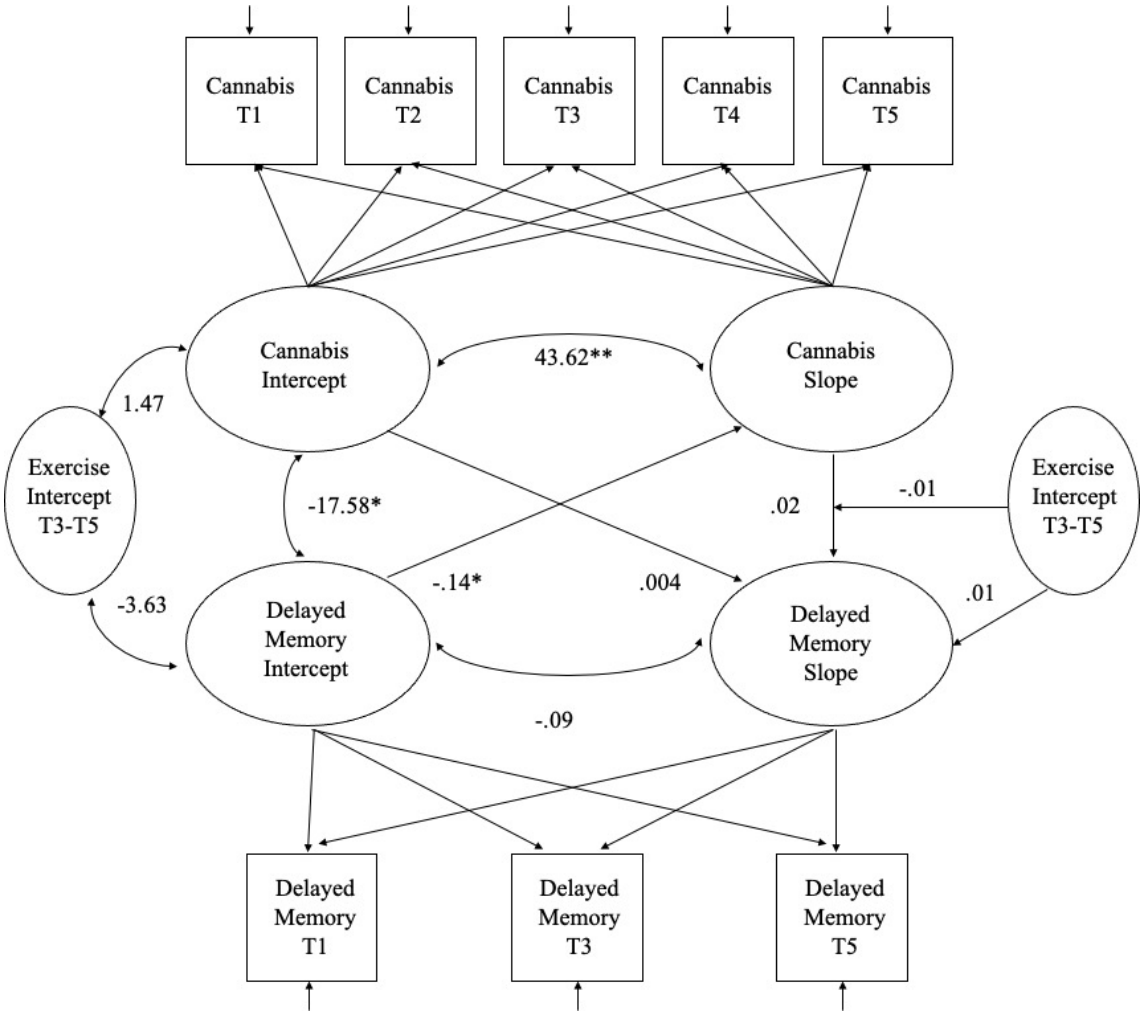
Note: *denotes significance at $p < .05$, **denotes significance at $p < .001$. All estimates represent unstandardized partial regression coefficients.

Figure 5. Covariate-adjusted multivariate LGCM examining the interactive effect of the exercise intercept and cannabis use slope on the immediate memory slope.



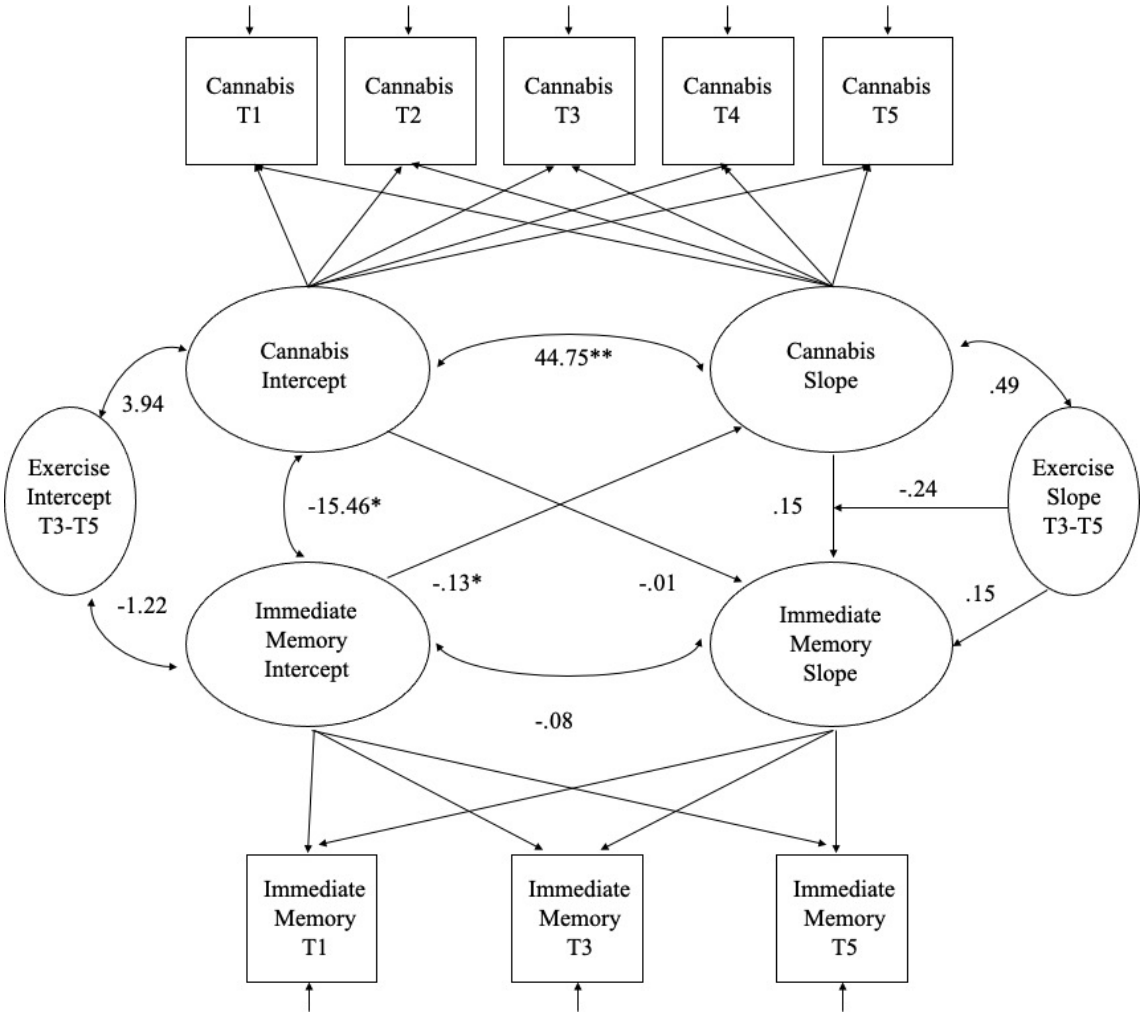
Note: *denotes significance at $p < .05$, **denotes significance at $p < .001$. All estimates represent unstandardized partial regression coefficients. Some paths not shown.

Figure 6. Covariate-adjusted multivariate LGCM examining the interactive effect of the exercise intercept and cannabis use slope on the delayed memory slope.



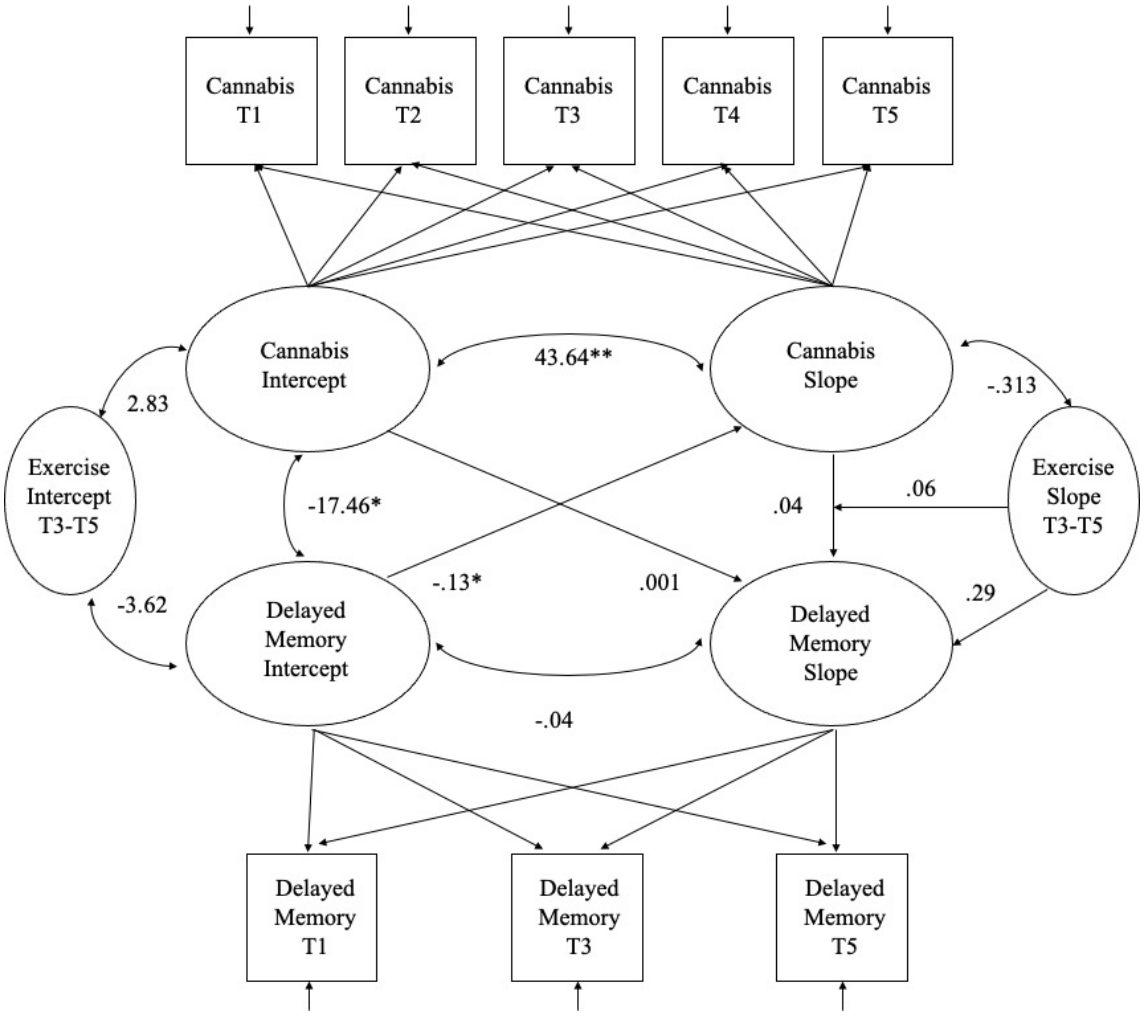
Note: *denotes significance at $p < .05$, **denotes significance at $p < .001$. All estimates represent unstandardized partial regression coefficients. Some paths not shown.

Figure 7. Covariate-adjusted multivariate LGCM examining the interactive effect of the exercise and cannabis use slopes on the immediate memory slope.



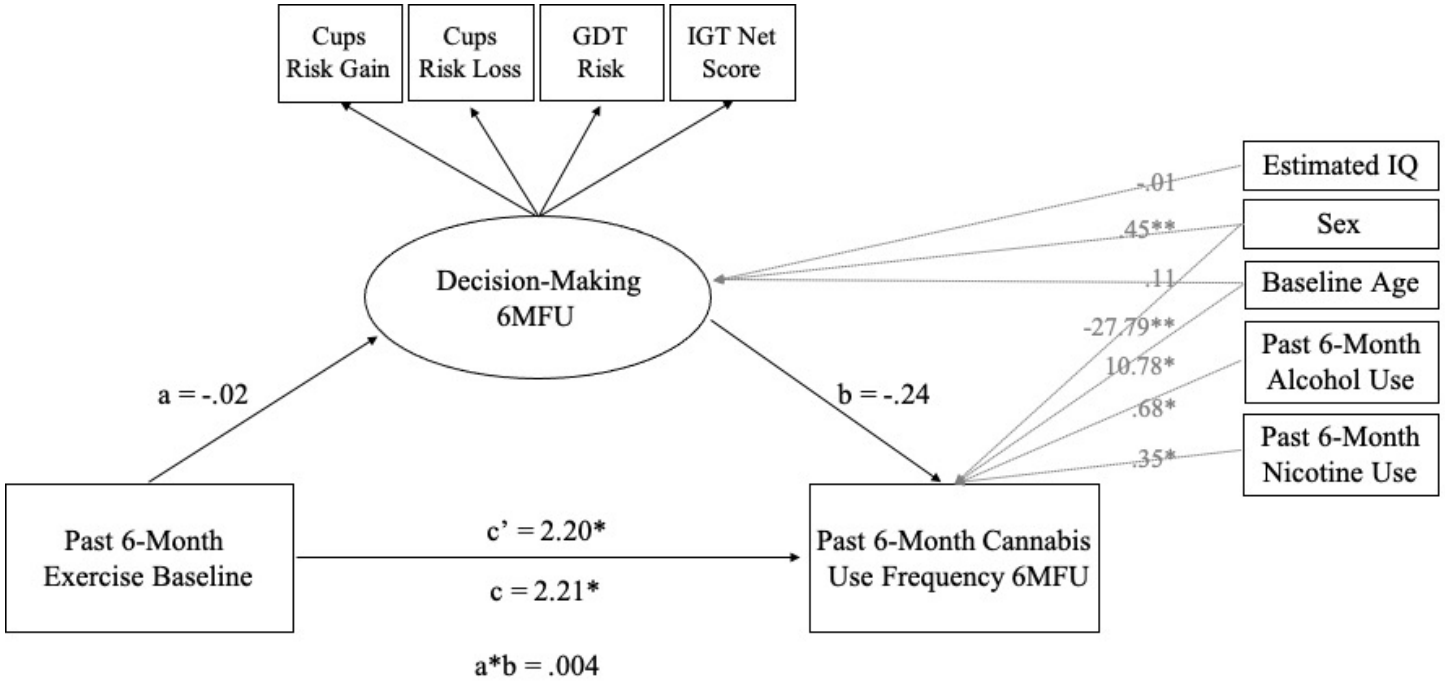
Note: *denotes significance at $p < .05$, **denotes significance at $p < .001$. All estimates represent unstandardized partial regression coefficients. Some paths not shown.

Figure 8. Covariate-adjusted multivariate LGCM examining the interactive effect of the exercise and cannabis use slopes on the delayed memory slope.



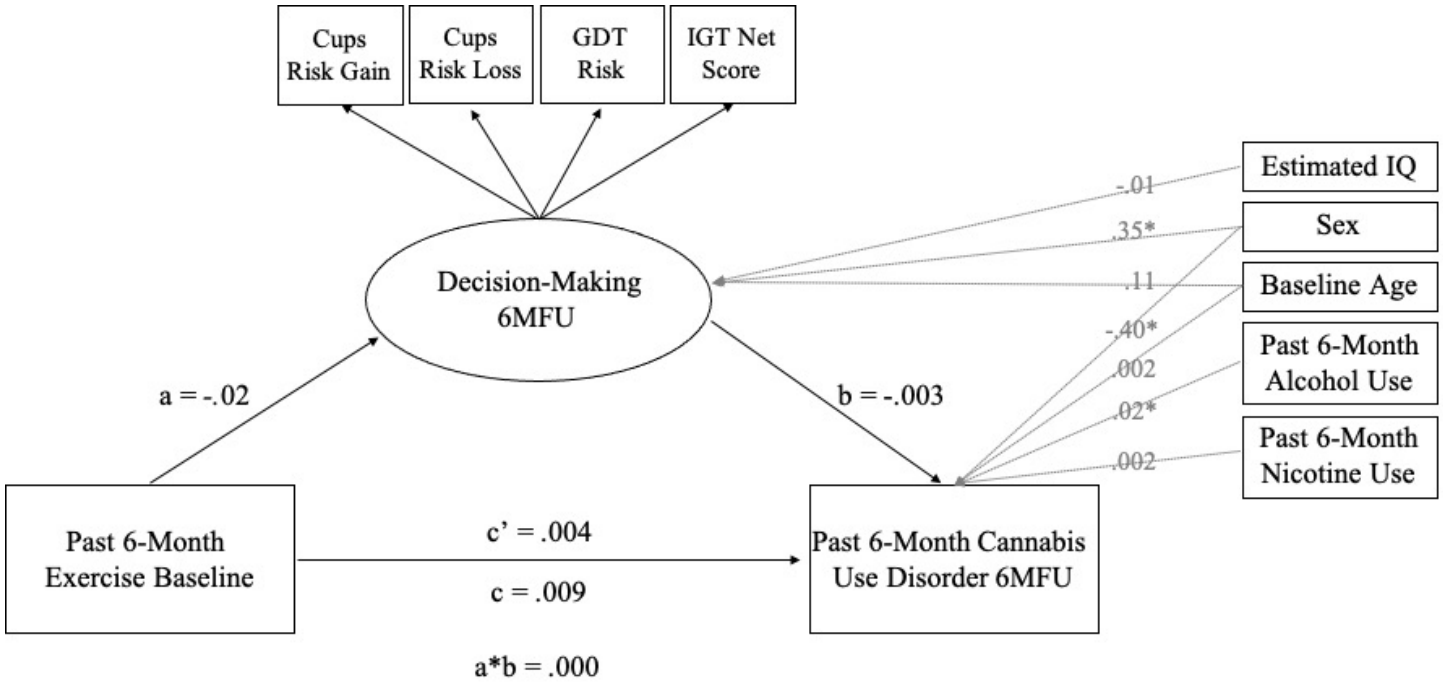
Note: *denotes significance at $p < .05$, **denotes significance at $p < .001$. All estimates represent unstandardized partial regression coefficients. Some paths not shown.

Figure 9. Covariate-adjusted mediation model examining decision-making as mediator of the association between baseline exercise and cannabis use frequency at the 6-month follow-up.



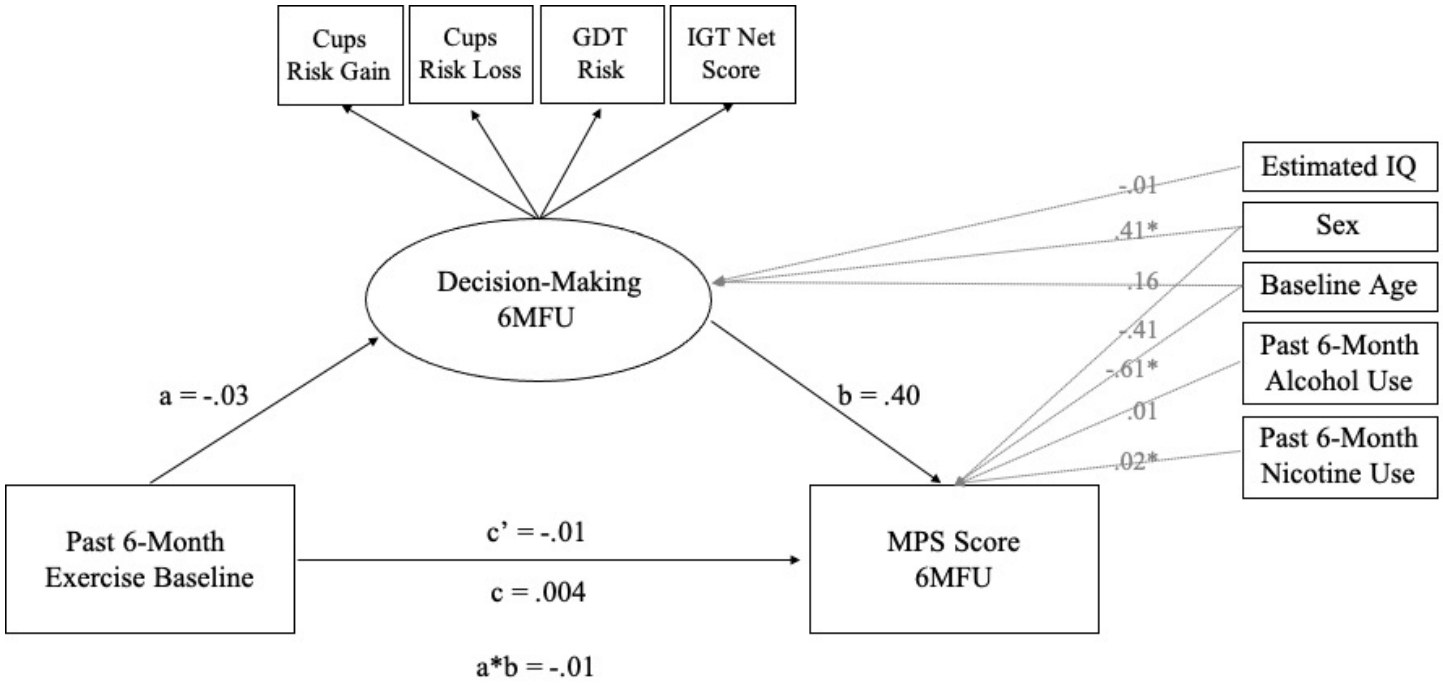
Note: All estimates represent unstandardized partial regression coefficients. Note: GDT = Game of Dice Task; IGT = Iowa Gambling Task; 6MFU = 6-month follow-up; ** denotes significance at $p < .001$; * denotes significance at $p < .05$.

Figure 10. Covariate-adjusted mediation model examining decision-making as mediator of the association between baseline exercise and presence of a cannabis use disorder assessed at the 6-month follow-up.



Note: All estimates represent unstandardized partial regression coefficients. Note: GDT = Game of Dice Task; IGT = Iowa Gambling Task; CUD = cannabis use disorder; 6MFU = 6-month follow-up; ** denotes significance at $p < .001$; * denotes significance at $p < .05$.

Figure 11. Covariate-adjusted mediation model examining decision-making as mediator of the association between baseline exercise and total MPS score at the 6-month follow-up.



Note: All estimates represent unstandardized partial regression coefficients. Note: GDT = Game of Dice Task; IGT = Iowa Gambling Task; MPS = Marijuana Problems Scale; 6MFU = 6-month follow-up; ** denotes significance at $p < .001$; * denotes significance at $p < .05$.

Figure 12. Sex as a moderator of the association between baseline exercise and past 6-month cannabis use frequency.

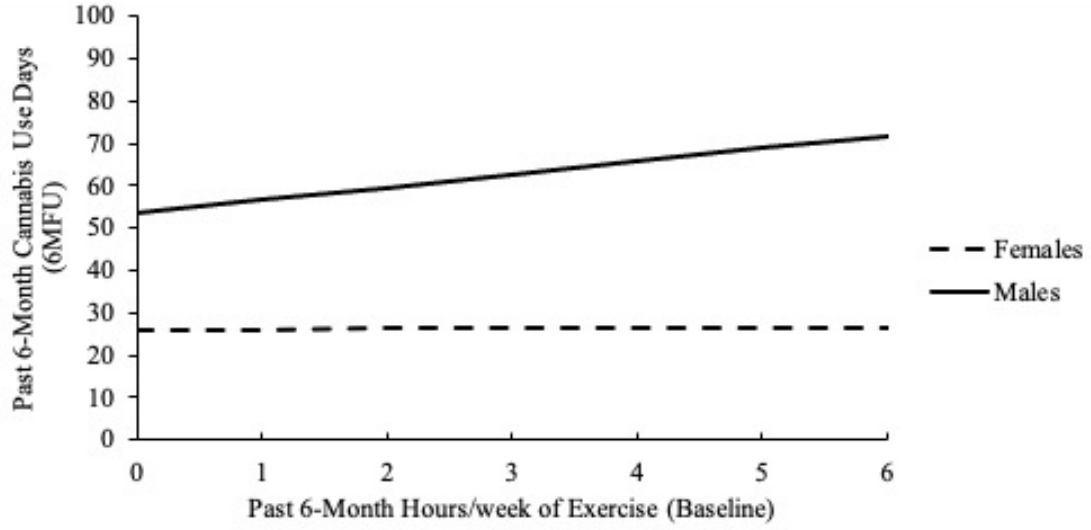
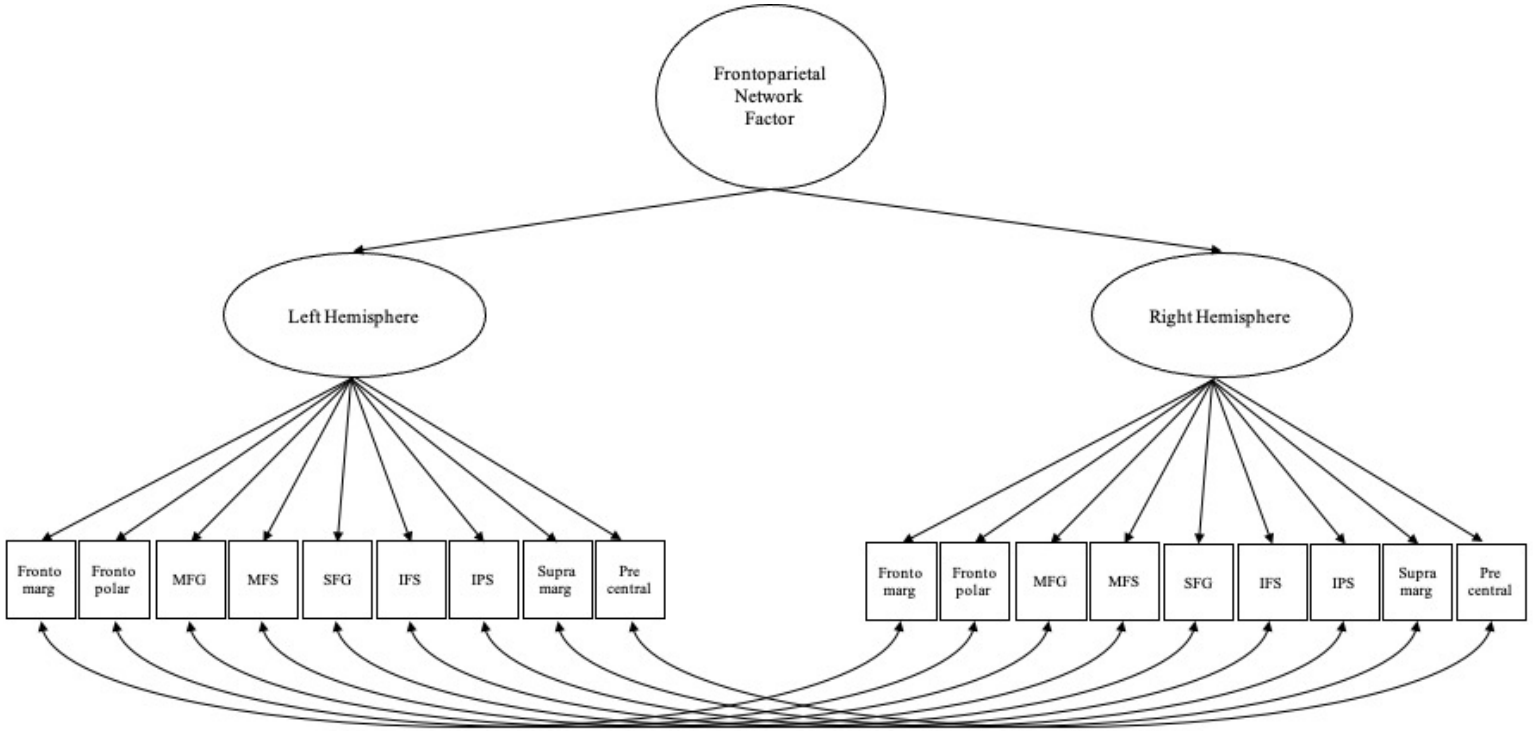
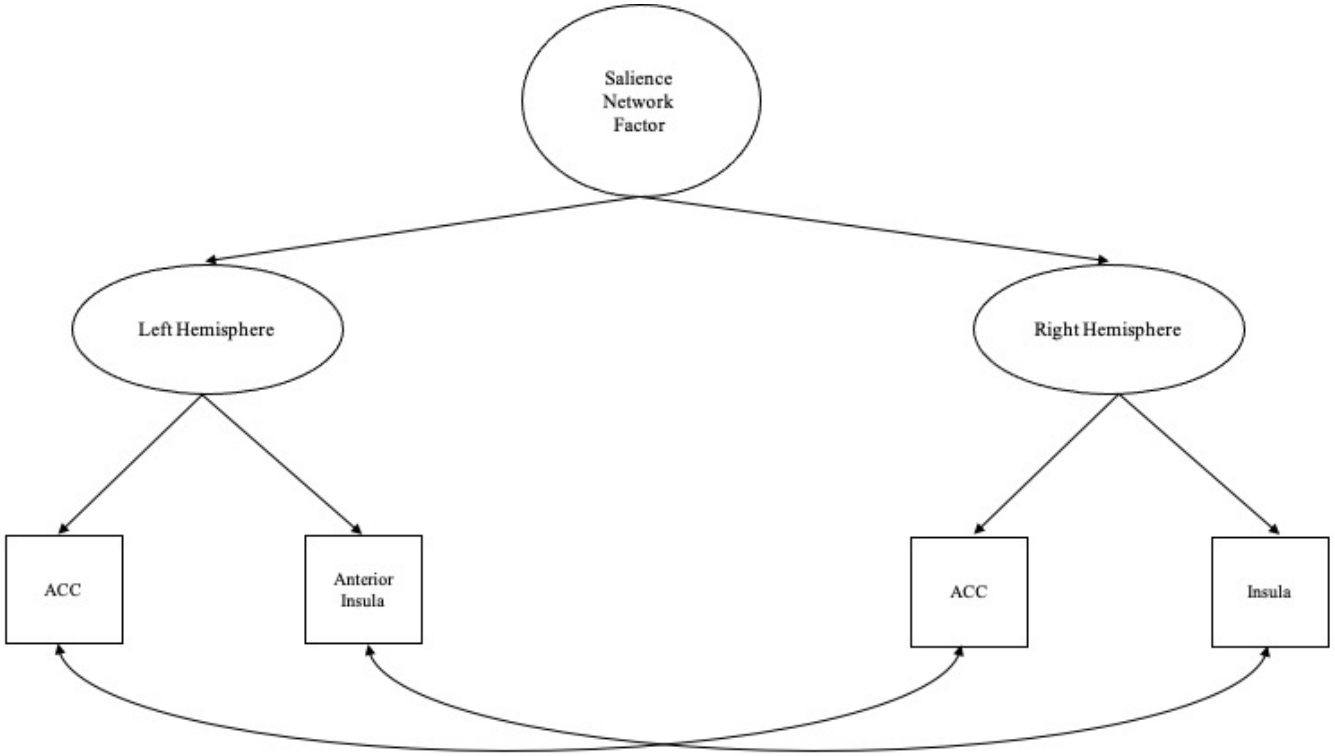


Figure 13. Second-order latent frontoparietal network factor.



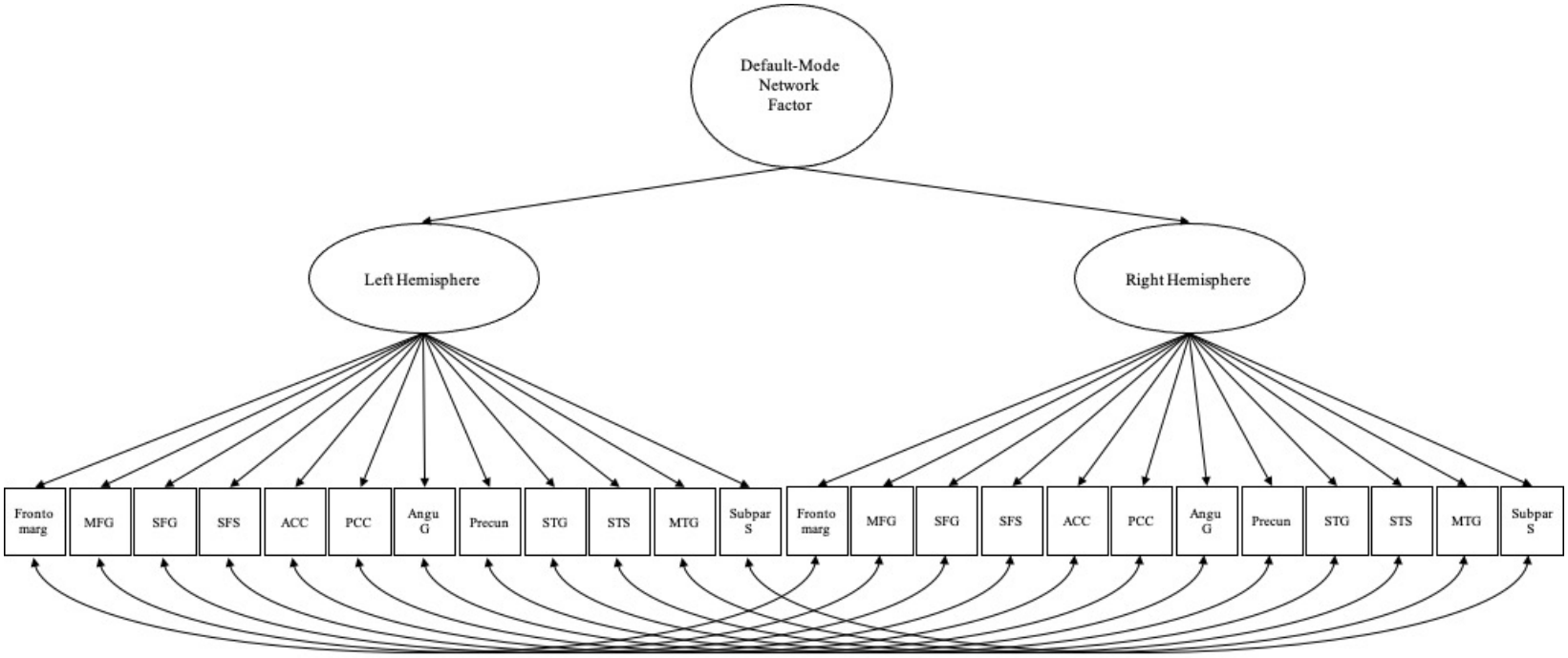
Notes. Frontomarg = frontomarginal gyrus and sulcus; Frontopolar = transverse frontopolar gyri and sulci; MFG = middle frontal gyrus; MFS = middle frontal sulcus; SFG = superior frontal gyrus; IFS= interior frontal sulcus; IPS = intraparietal sulcus and transverse parietal sulci; Supramarg = supramarginal gyrus; Precentral = inferior part of the precentral sulcus.

Figure 14. Second-order latent salience network factor.



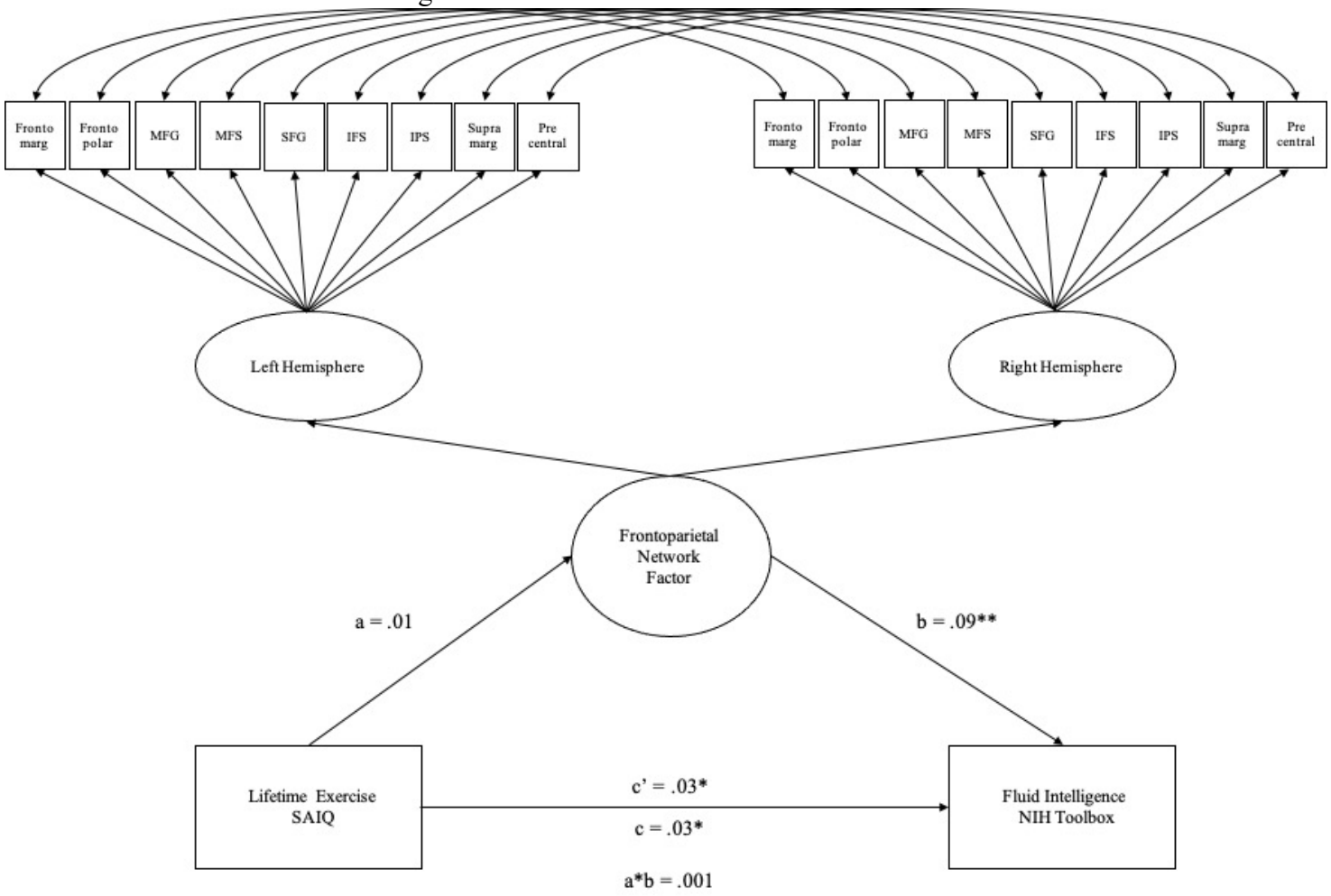
Note: ACC = anterior cingulate gyrus and sulcus; Anterior insula = Anterior segment of the circular sulcus of the insula

Figure 15. Second-order latent DMN factor



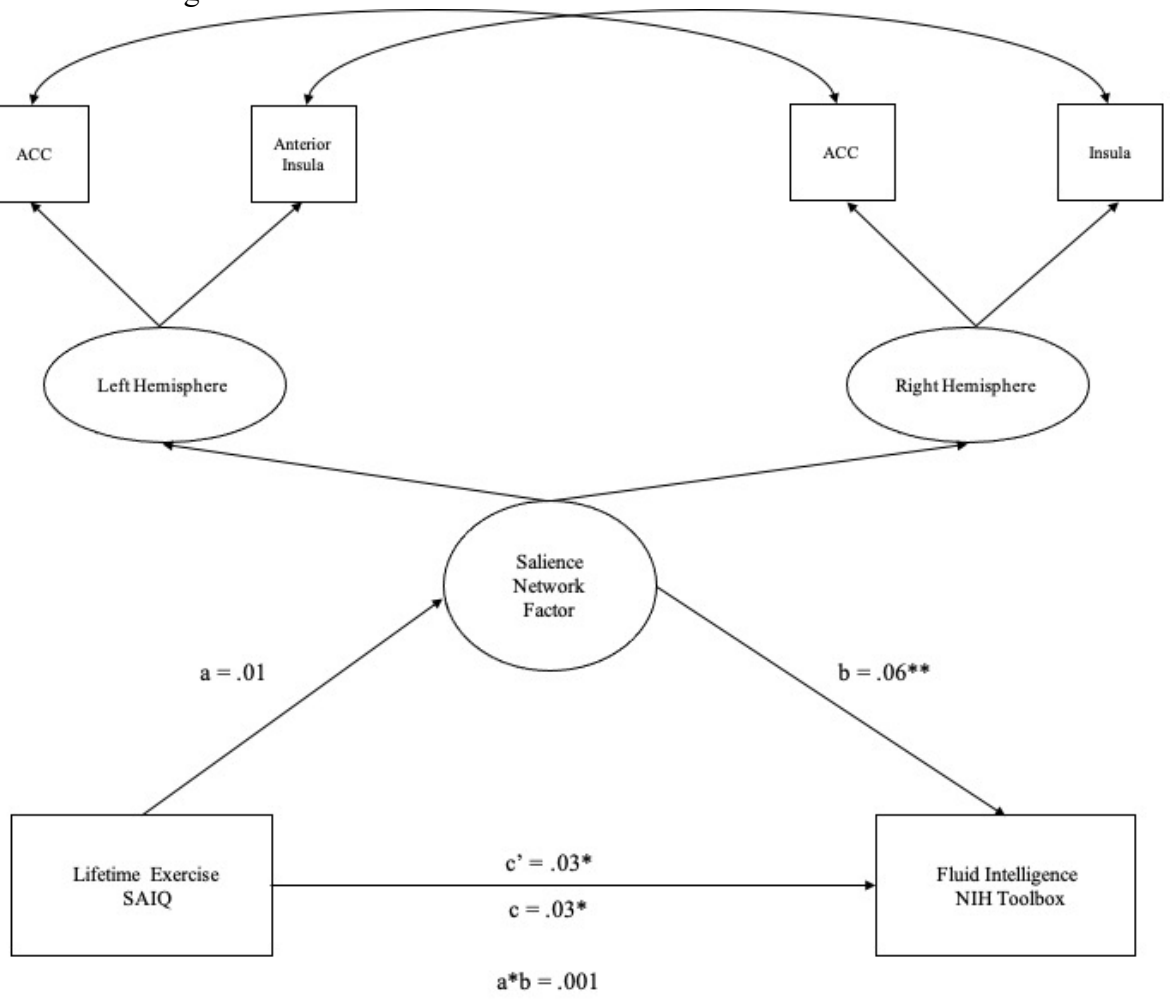
Notes. Frontomarg = Frontomarginal gyrus and sulcus; MFG = middle frontal gyrus; SFG = superior frontal gyrus; ACC = anterior cingulate gyrus and sulcus; PCC = middle to posterior cingulate gyrus and sulcus; AnguG = angular gyrus; Precun = precuneus; STG = superior temporal gyrus; STS = superior temporal sulcus; MTG = middle temporal gyrus, SubparS = subparietal sulcus.

Figure 16. Covariate-adjusted mediation model examining frontoparietal network activation as mediator of the association between exercise and executive functioning.



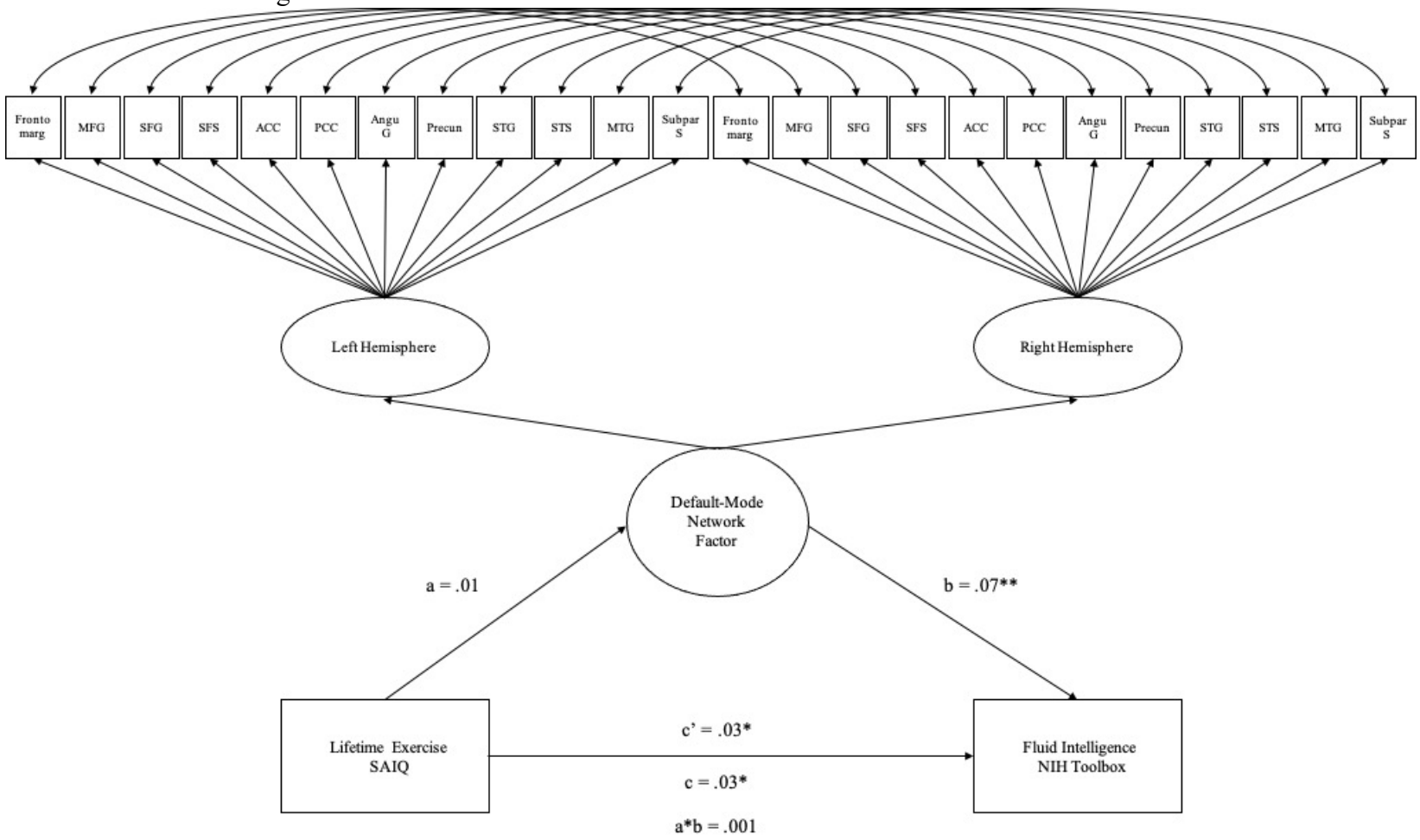
Note: *denotes significance at $p < .05$; ** denotes significance at $p < .001$; Frontomarg = frontomarginal gyrus and sulcus; Frontopolar = transverse frontopolar gyri and sulci; MFG = middle frontal gyrus; MFS = middle frontal sulcus; SFG = superior frontal gyrus; IFS = interior frontal sulcus; IPS = intraparietal sulcus and transverse parietal sulci; Supramarg = supramarginal gyrus; Precentral = inferior part of the precentral sulcus; SAIQ = Sports and Activity Involvement Questionnaire

Figure 17. Covariate-adjusted mediation model examining salience network activation as mediator of the association between exercise and executive functioning.



Note: *denotes significance at $p < .05$; ** denotes significance at $p < .001$; ACC = anterior cingulate gyrus and sulcus; Anterior insula = Anterior segment of the circular sulcus of the insula; SAIQ = Sports and Activity Involvement Questionnaire

Figure 18. Covariate-adjusted mediation model examining DMN activation as mediator of the association between exercise and executive functioning.



Note: *denotes significance at $p < .05$; ** denotes significance at $p \leq .001$; Frontomarg = Frontomarginal gyrus and sulcus; MFG = middle frontal gyrus; SFG = superior frontal gyrus; ACC = anterior cingulate gyrus and sulcus; PCC = middle to posterior cingulate gyrus and sulcus; AnguG = angular gyrus; Precun = precuneus; STG = superior temporal gyrus; STS = superior temporal sulcus; MTG = middle temporal gyrus, SubparS = subparietal sulcus; SAIQ = Sports and Activity Involvement Questionnaire

VITA

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SELECTED PUBLICATIONS

Pacheco-Colón, I., Hawes, S. W., Duperrouzel, J. C., & Gonzalez, R. (*in press*). Causal Evidence Lacking for Cannabis Users Slacking: A Longitudinal Analysis of Adolescent Cannabis Use and Motivation. *Journal of the International Neuropsychological Society.*

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