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Aerobic Fitness Level Moderates the Association Between Cannabis Use and Executive Functioning and Psychomotor Speed Following Abstinence in Adolescents and Young Adults

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Abstract

Objectives: The high rate of cannabis (CAN) use in emerging adults is concerning given prior research suggesting neurocognitive deficits associated with CAN use in youth. Regular CAN use downregulates endocannabinoid activity, while aerobic exercise upregulates cannabinoid receptor 1 activity and releases endocannabinoids. Here we investigate the influence of regular CAN use on neuropsychological performance, and whether aerobic fitness moderates these effects. **Methods:** Seventy-nine young adults (37 CAN users) aged 16–26 participated. Groups were balanced for aerobic fitness level. Exclusion criteria included: left-handedness, past-year independent Axis-I disorders, major medical/neurologic disorders, prenatal issues, or prenatal alcohol/illicit drug exposure. After 3 weeks of abstinence, participants completed a neuropsychological battery and a maximal oxygen consumption test (VO_2 max). Multiple regressions tested whether past-year CAN use, VO_2 max, and CAN*VO_2 max interaction predicted neuropsychological performance, controlling for past-year alcohol use, cotinine, gender, and depression symptoms. **Results:** Increased CAN use was associated with decreased performance on working memory and psychomotor tasks. High aerobic fitness level was related to better performance on visual memory, verbal fluency, and sequencing ability. CAN*VO_2 max predicted performance of psychomotor speed, visual memory, and sequencing ability. **Conclusions:** Following monitored abstinence, increased CAN use was associated with poorer performance in working memory and psychomotor speed. Higher aerobic fitness level moderated the impact of CAN on visual memory, executive function and psychomotor speed, as more aerobically fit CAN users demonstrated better performance relative to low-fit users. Therefore, aerobic fitness may present an affordable and efficacious method to improve cognitive functioning in CAN users. (*JINS*, 2019, *25*, 134–145)

Keywords: Cannabis; Marijuana, VO_2 max, Neurocognition, Emerging adulthood, Aerobic fitness

INTRODUCTION

Cannabis (CAN) impacts the brain by interacting with the endogenous endocannabinoid (eCB) system, which includes cannabinoid receptor 1 (CB1R, primarily in CNS) and two endogenous ligands [anandamide (AEA) and 2-arachidonoylglycerol (2-AG)] (Di Marzo, De Petrocellis, & Bisogno, 2005; Eggan & Lewis, 2007; Herkenham et al., 1990). Regular exogenous CAN exposure downregulates the CB1Rs (Hirvonen et al., 2012) and is linked with neurocognitive deficits (see Lisdahl, Wright, Kirchner-Medina, Maple, & Shollenbarger, 2014). Despite these findings, daily CAN use amongst teens and young adults remains high (approximately 6% of 12th graders and 8% of young adults; Miech et al., 2017).

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Prior studies have often noted negative relationships between CAN use and neuropsychological functioning in emerging adults (for review, see Ganzer, Bröning, Kraft, Sack, & Thomasius, 2016; Lisdahl et al., 2014). More specifically, after periods of brief (12 + hr) abstinence, findings suggest deficits in learning and memory, working memory, planning, and decision-making (Becker et al., 2018) and in executive functioning (Dahlgren, Sagar, Racine, Dreman, & Gruber, 2016). However, studies such as these do not account for more long-term changes in cognitive functioning even after cessation of use. Thames, Arbid, and Sayegh (2014) found that, whether recent- (past 4 weeks) or past-use (greater than 4 weeks abstinence) and regardless of age, CAN users demonstrated decreased cognitive performance across attention, processing speed, and executive functioning, with mild recovery in the past-user group relative to the recent-user group.

Following a month of abstinence, emerging adult CAN users have also been found to have slower psychomotor speed, poorer complex attention, story memory, visual memory, visuospatial functioning, cognitive flexibility, working memory and sequencing (Jacobus, Squeglia, Sorg, Nguyen-Louie, & Tapert, 2014; Jacobus et al., 2015; Medina et al., 2007; Winward, Hanson, Tapert, Brown, 2014); similarly, we found poorer psychomotor speed, sustained attention, and cognitive inhibition in CAN users after a week of abstinence, with male users having greater psychomotor slowing (Lisdahl & Price, 2012). A recent meta-analysis of CAN studies of emerging adults concluded that cognitive deficits do not persist beyond 72 hr of abstinence (Scott et al., 2018). However, some studies included did not adequately control for other substance use, used non-standardized neuropsychological measures, did not exclude for psychiatric comorbidities, or did not assess for dose-dependent relationships. As these differences in study design may have obscured the relationship between the chronic effects of cannabis and cognitive functioning, further assessment of the chronic impact of cannabis is warranted with careful consideration of other variables that may be important moderators (e.g., fitness level). Given prior neuropsychological findings after withdrawal and excluding for psychiatric comorbidities, there is increased interest in investigating more chronic impacts of CAN use and examining potential ameliorative tools that may reverse cannabis-related cognitive deficits.

Animal models demonstrate numerous positive effects of aerobic exercise (AE) on brain health, including improved cognition, neurogenesis, and protection of the nervous system from injury in regions including the prefrontal cortex (PFC; Cotman, Berchtold, & Christie, 2007; Ding et al., 2004; Stranahan et al., 2010; van Praag, Christie, Sejnowski, & Gage, 1999; Vaynman, Ying, & Gomez-Pinilla, 2004). Pre-clinical research has shown that AE of moderate intensity resulted in greater neurogenesis compared to high-intensity interval training (Leasure & Jones, 2008) or anaerobic resistance training (Nokia et al., 2016). Notably, a series of studies have found that exercise blocks or reverses the negative effects of alcohol binge drinking on neurogenesis in the dentate gyrus and hippocampus in animals (Crews, Nixon, & Wilkie, 2004; Hamilton, Criss, & Klintsova, 2015; Helfer, Goodlett, Greenough, & Klintsova, 2009; Leasure & Nixon, 2010), although to date no such research exists in CAN exposure for animals or humans. There are multiple possible mechanisms underlying the benefits of aerobic fitness, including decreased inflammatory response and oxidative stress (Radak, Kumagai, Taylor, Naito, & Goto, 2007; Sakurai et al., 2009), increased c-FOS expression (Dragunow, 1996; He, Yamada, & Nabeshima, 2002; Sim et al., 2008; Vann, Brown, Erichsen, & Aggleton, 2000), increased CB1R activity in the hippocampus (Ferreira-Vieira, Bastos, Pereira, Moreira, & Massensini, 2014), and improved catecholaminergic function in brain regions such as the PFC and limbic system (Chaouloff, 1989; Dunn, Reigle, Youngstedt, Armstrong, & Dishman, 1996; Dunn & Dishman, 1991; Elam, Svensson, & Thoren, 1987; Heyes, Garnett, & Coates, 1985; Waters et al., 2005). Converging lines of evidence also suggest changes in growth factors, such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF), may underlie AE-related neurocognitive changes (Castrén, Berninger, Leingärtner, & Lindholm, 1998; Cotman & Berchtold, 2002; Egan et al., 2003; Kim, Lee, Kim, Yoo, & Kim, 2007; Lee et al., 2006; Li, Jarvis, Alvarez-Borda, Lim, & Nottebohm, 2000; Liu, Diorio, Day, Francis, & Meaney, 2000; Mueller et al., 2015; Whiteman, Young, Budson, Stern, & Schon, 2014). More specific to CAN users, Koltyn and colleagues has reported that AE results in release of circulating eCB concentrations (Koltyn, Brellenthin, Cook, Sehgal, & Hillard, 2014), resulting in improved mood (Brellenthin, Crombie, Hillard, & Koltyn, 2017). Therefore, AE may help restore circulating eCB concentrations in CAN users.

Prior research has suggested that AE may improve cognitive functioning in adolescents and young adults (for review, see Herting & Chu, 2017). Aerobic fitness has been linked to better executive functioning, spatial memory, psychomotor speed, and attention in adolescents (Lee et al., 2014; Wengaard, Kristoffersen, Harris, & Gundersen, 2017), and attention and working memory in young adults (Hwang, Castelli, & Gonzalez-Lima, 2017). VO_2 max (aka maximal oxygen consumption) provides a quantitative measure of one's capability and capacity for AE (Bassett & Howley, 2000). By definition, it is the highest amount of oxygen that an individual can consume to make energy aerobically. It also provides a good indication of overall fitness, in that it requires unified and high-level functioning of multiple systems including the ventilaory, cardiovascular, hematologic, and muscular systems (Bassett & Howley, 2000).

VO_2 max increases as a result of AE, such as running, walking, biking, etc. (Bassett & Howley, 2000). Therefore, the more aerobic activity a person engages in, the higher their VO_2 max will be. Other research has linked VO_2 max with neurocognitive function. For example, in healthy young adults, superior VO_2 max performance was related to larger entorhinal cortex volume, which was in turn associated with better memory (Whiteman et al., 2016).

The relationship between aerobic fitness and CAN use has been understudied. A longitudinal study (Henchoz et al., 2014) had young adult males self-report their frequency of exercise and complete a substance use screen. They found fewer cannabis use disorder (CUD) diagnoses and better mental health outcomes in those who maintained regular exercise habits, and lower prevalence of CUD in those who adopted new exercise routines. Another study of adult non-treatment seeking individuals with CUD found reduced cannabis use and craving following 2 weeks of AE (Buchowski et al., 2011). Whether aerobic fitness level may moderate cognitive functioning in CAN users have not been previously studied. To date, no one has reported whether aerobic fitness moderates measures of cognitive function in CAN-using youth.

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Here we aim to investigate the potential moderating effect of aerobic fitness level on neuropsychological outcomes in regular CAN users. We predict that following 3 weeks of monitored abstinence, greater past-year CAN use would be associated with greater cognitive deficits in a dose-dependent manner, especially on psychomotor speed, complex attention, and executive function tasks (Lisdahl & Price, 2012; Medina et al., 2007). We also predict that greater aerobic fitness would be associated with better neuropsychological performance. Finally, we hypothesize that CAN use would interact with aerobic fitness level, such that individuals with higher levels of past-year CAN use and lower VO_2 max would have worse neuropsychological performance relative to individuals with higher VO_2 max and greater levels of past-year cannabis use, and controls.

METHODS

Participants

Seventy-nine participants (37 CAN users; 42 controls) were recruited through local newspaper advertisements and fliers placed around Milwaukee, Wisconsin, for the larger parent study (Pricipal Investigaror, Lisdahl; R01 DA030354). Efforts were made to balance for gender and physical activity levels across substance use groups. Individuals were considered healthy controls if they had smoked less than 5 joints (or their equivalent) in the past year and no more than 20 joints in their lifetime. CAN users had smoked at least 52 times in the past year (approximately weekly users). Furthermore, each participant was classified as being high-fit if they were above the 50th percentile in VO_2 max performance, and low-fit if they were below the 50th percentile by age and gender (Pescatello, 2014).

Inclusion criteria included being a fluent English speaker between 16 and 26 years old. Exclusion criteria for all participants included: being left handed, MRI contraindications, past-year co-morbid independent Axis-I disorders, major medical or neurologic disorders, prenatal issues (e.g., gestation <35 weeks) or prenatal alcohol (>4 drinks/day or >7 drinks/week) or illicit drugs (>10 uses), or excessive illicit drug use in lifetime (>50 uses of any drug category except nicotine, alcohol, or CAN). Participants confirmed 3 weeks of abstinence from all alcohol and drug use (other than tobacco) through self-report and drug toxicology screen. The University of Wisconsin Milwaukee and Medical College of Wisconsin IRBs approved all aspects of this study.

Procedure

Screening

Eligibility criteria were established through a two-step screening process. First, participants called in to a study line after seeing fliers around the community advertising for active and sedentary participants. After receiving oral consent from the participant, or oral consent from the parent/guardian and oral assent from the participant (if under 18), they completed a 5- to 10-min phone screen. Each parent and participant were screened separately to answer initial eligibility question (including age, ethnicity, MRI contraindications, and yes/no questions regarding psychiatric and substance use history).

Next, written consent/assent (if under 18) was received *via* mail and a 45-min detailed phone or in-person screen was scheduled. Participants then completed lifetime history of substance use *via* the Customary Drinking and Drug Use Record (CDDR) (Brown et al., 1998; Stewart & Brown, 1995). Participants and their parents separately completed youth psychiatric history though the Mini International Psychiatric Interview (MINI) or MINI-Kid (if under 18) (Sheehan et al., 1998). All participants and their parents were compensated $20 for their time during the phone screen. If eligible, participants were scheduled for study sessions. If ineligible, participants were not informed of the specific reason for ineligibility to protect study integrity.

Study sessions

Five sessions were scheduled over the course of 3.5–4 weeks for all eligible participants. The initial three sessions each occurred 1 week apart. They consisted of a mini-neuropsychological battery to assess impact of CAN withdrawal symptoms on cognitive function (data *not* examined here), psychological questionnaires, and urinalysis and drug patch analysis to ensure abstinence. The fourth session (data presented here) occurred 1 week after the third session and consisted of a 3-hr fully neuropsychological battery and a VO_2 max testing session. The final and fifth session occurred within 24–48 hr of the fourth session and consisted of MRI scanning. For the present study, only data from the fourth session, consisting of the neuropsychological battery and VO_2 max, are included, to ensure no potential withdrawal symptoms impact findings (Budney, Hughes, Moore, & Vandrey, 2004).

Verifying abstinence

Abstinence was evaluated at each study session to ensure participants remained abstinent from all alcohol and drugs (other than nicotine) for the duration of the study. The ACCUTEST SplitCup 10 Panel drug test was used to measure amphetamines, barbiturates, benzodiazepines, cocaine, ecstasy, methadone, methamphetamines, opiates, phencyclidine (PCP), and delta-9-tetrahydrocannabinol (THC). Urine samples were also tested using NicAlert to test cotinine level, a metabolite of nicotine. Participants also wore PharmChek Drugs of Abuse Patches which continuously monitor sweat toxicology for the presence of cocaine, benzoylecgonine, heroin, 6-monoacetylmorphine, morphine, codeine, amphetamines, methamphetamine, THC, and PCP.

At the start of each session, participants also underwent breathalyzer screens. If positive for THC at Sessions 1–3,

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participants were considered eligible to remain in the study if their THC level, as measured by the PharmChek patch, went down over time. If positive for any drug or having a breath alcohol concentration greater than .000 at the start of Session 4 (neuropsychology battery and VO_2 maximum testing) or Session 5 (MRI scan), participants were ineligible for study participation.

Measures

Psychiatric disorder screening

Participants and their parents separately completed youth psychiatric history though the Mini International Psychiatric Interview (MINI) (for 18 and older) or MINI-Kid (if under 18) (Sheehan et al., 1998).

Substance use

Lifetime Use. The CDDR (Brown et al., 1998; Stewart & Brown, 1995) was used to measure frequency/quantity of lifetime usage, age of first use, age of regular use, and symptoms of substance use disorder for alcohol, nicotine and cannabis. *Past-year Use*. A modified version of the Timeline Follow-Back (Lisdahl & Price, 2012; Sobell & Sobell, 1992) was used to measure past 365 days of CAN (joints), alcohol (standard drinks), and other drug use in standard units. For CAN, participants reported method and amount used (e.g., concentrates, hits, joints, etc.) and this was converted to a standard unit of joints. After being cued to memories, holidays, and personally significant events, participants recalled frequency and amount of drug use on each day or, if unable to recall day-by-day information, weekly averages. Last date of use was also captured to measure length of abstinence from substances other than tobacco.

Mood

Participants completed the 21-item Beck Depression Inventory - 2nd Edition (BDI) to measure current depressive symptoms from the past 2 weeks (Beck, 1996).

Neuropsychological battery

Cognitive tasks and variables included the following:

1. Select subtests from the Delis-Kaplan Executive Functioning Scale (D-KEFS; Delis, Kaplan, & Kramer, 2001) were used. Specifically: Color-Word Interference, which consisted of subtests with measuring reading of words, then colors, then two tasks which required inhibiting aspects of reading/naming (e.g., naming color without reading the word). Variables assessed included total reading time in seconds for word reading, color naming, color-word interference, and color-word interference with switching; Verbal Fluency, wherein the participant had 60 s to list as many words as they could that started with a specific letter (variable assessed: FAS total correct); and Trail Making Tests (TMT), which consisted of various connect-the-dot tasks designed to measure simple attention, psychomotor speed, information processing speed, and cognitive flexibility (variables included time to complete in seconds for each of the five conditions).
2. California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) is a 16-item verbal learning and recall measure with five learning trials, a distractor list, and both a brief and long delay. Variables assessed in this study included initial learning (trial 1), total learning (total trials 1–5), free recall (long delay free recall), and recognition (hits).
3. Rey Complex Figure Task (RCFT; Meyers & Meyers, 1995) is a figure which a participant first copies then later has to recall from memory. Variables assessed include visuospatial skills (direct copy score) and visual recall (immediate recall, long delay recall).
4. Penn Emotional Faces Memory Task of the Penn's Computerized Neurocognitive Battery (PennCNP; Gur et al., 2010) measures immediate recognition of faces following a learning trial and was assessed by facial memory total correct.
5. The Weschler Adult Intelligence Scale, Third Edition (WAIS-III; Wechsler, 1997) Letter-Number Sequencing (LNS) subtest was used to measure working memory through total raw sequencing score.
6. Conner's Continuous Performance Task, 2nd Edition (CPT-II; Conners, 2000) is a task designed to assess sustained attention. Number of omission errors and number of commission errors were used in the present analyses.
7. Iowa Gambling Task (IGT) is a measure of decision making through trying to maximize money in a gambling card task earned and examined here by total net money (won-borrowed; Bechara, Damasio, Damasio, & Anderson, 1994).
8. To estimate intelligence and quality of education (Manly, Jacobs, & Touradji, 2002), the Wide Range Achievement Test - 4th edition (WRAT-4) Word Reading subtest was used, with normed scores calculated. This test was only used for group comparisons in selection of covariates to ensure groups did not differ in premorbid IQ.

Neurocognitive variables that were not normally distributed (RCFT direct copy; CVLT-II long delay free recall; D-KEFS Trails Condition 4; CPT-II Omission errors) were log-transformed and used in all analyses. All raw scores were used, unless otherwise noted (i.e., WRAT-4 Word Reading). Measurement of Effort: An embedded effort measure from the CVLT-II, the Forced Choice trial, was assessed to ensure proper engagement by participants. No participants were below cutoff scores.

Body size and composition

Body height and mass were measured using standard procedures (Pescatello, 2014). In addition, a Tanita SC-331S Body

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Composition Monitor (Tanita, Arlington Heights, IL) was used to measure additional fitness characteristics, such as weight, body mass index (BMI), and fat percentage.

Aerobic fitness (VO_2 maximum)

Participants were asked to refrain from food and caffeine for 4 hr before the exercise tests. Before each exercise test, the metabolic measurement system, ParvoMedics TrueOne 2400 (ParvoMedics, Salt Lake City, UT) was calibrated according to the manufacturer's instructions using a 3-liter syringe for the pneumotachometer, and a two-point calibration for the gas analyzers (room air and a certified gas 4.08% CO_2, 115.98% O_2, balance N_2). Participants were fitted with the rubber mouthpiece connected to a Hans Rudolf 2700 series two-way nonrebreathing valve (Kansas City, MO), noseclip, and heart rate strap (Polar Wearlink 31, Finland) for the collection of expired gases and measurement of heart rate. Participants completed a maximal incremental exercise test on a treadmill (Full Vision Inc., TMX425C Trackmaster, Newton, KS) following the Bruce Protocol until volitional fatigue.

Expired gases were measured continuously using a ParvoMedics TrueOne 2400 metabolic measurement system (ParvoMedics, Salt Lake City, UT); this has been shown to be a valid measure of expired gases at rest and during increasing intensities of activity (Bassett et al., 2001). Trained exercise physiology research assistants, supervised by AS, used Howley, Bassett, and Welch (1995) criteria to determine attainment of VO_2 max. Metabolic data were averaged over 1 min and exported into a spreadsheet for analysis.

Data Analysis

To determine selection of covariates, two groups were formed: a CAN user group with at least an average of one joint per week over the past year, and a control group with less than 5 joints (or equivalent) in the past year and no more than 20 in their lifetime. Continuous variables reflecting total past-year CAN use (not groups) were used in the primary analyses. In addition, participants were again divided into a high (at or above 50th percentile) or low (below 50th percentile) fitness group, based on normed performance on VO_2 max (Pescatello, 2014), although again continuous variables, not group, were used in analyses. Between-group differences on demographic variables by both CAN group and fitness group were measured with analyses of variance and χ^2 tests. Controlling for potential confounds (i.e., past-year alcohol use, cotinine level, BDI-II score, gender, and BMI), multiple regressions were run to examine whether past-year cannabis use or VO_2 max performance independently related to cognitive functioning after the required abstinence period.

The potential interactive effect of past-year CAN use and VO_2 max performance was also assessed as a second block in the regression; for ease of presentation, the interaction term used is CAN*VO_2, though total past-year joints and actual VO_2 max performance, *not* groups, were used to calculate the interaction. Twenty-two separate multiple regressions were run, with covariates and independent variables assessed in the first block of the regression, and the interaction variable added in the second block. DFBetas were examined to rule out outliers. Notably, results remain consistent regardless of whether or not length of abstinence is included as a covariate. No correction for multiple comparisons was used due to power limitations.

RESULTS

Demographic, Drug Use, and Fitness Differences According to Drug Group

Demographics

Substance use groups did not differ significantly on age [$F(1,77) = .96$; $p = .33$], education [$F(1,77) = .87$; $p = .35$], reading level (from the WRAT-4) [$F(1,77) = .94$; $p = .34$], race ($\chi^2 = 5.81$; $p = .44$), or ethnicity ($\chi^2 = 3.00$; $p = .22$). They differed by gender ($\chi^2 = 3.98$; $p = .05$) and depression symptoms as measured by the BDI-II [$F(1,77) = 8.89$; $p = .004$] (these are included as covariates in all analyses). See Table 1. *Fitness Characteristics:* Substance use groups did not differ significantly in weight [$F(1,76) = .04$; $p = .85$], body fat percentage [$F(1,76) = 2.63$; $p = .11$], BMI [$F(1,76) = .00$; $p = .99$], height [$F(1,77) = .08$; $p = .78$], waist circumference [$F(1,76) = .99$; $p = .32$], or VO_2 max [$F(77) = 1.55$; $p = .22$]. *Drug Use Patterns:* CAN use groups differed significantly in drug use patterns, including past-year CAN use [$F(1,77) = 41.11$; $p < .001$], lifetime cannabis use [$F(1,77) = 31.48$; $p < .001$], cotinine level [$F(1,77) = 11.65$; $p = .001$], and past-year alcohol use [$F(1,77) = 17.26$; $p < .001$]. The latter two are covariates in all analyses.

Demographic, Drug Use, and Fitness Differences According to Aerobic Fitness Group

Demographics

Fitness groups did not differ significantly by age [$F(1,77) = .30$; $p = .59$], education [$F(1,77) = .02$; $p = .89$], reading level (from the WRAT-4) [$F(1,77) = 2.84$; $p = .10$], depression symptoms as measured by the BDI-II [$F(1,77) = .16$; $p = .69$], race ($\chi^2 = 6.87$; $p = .33$), or ethnicity ($\chi^2 = 3.54$; $p = .17$). They differed by gender ($\chi^2 = 11.67$; $p = .001$), which was included as a covariate for all multiple regression analyses. See Table 2. *Drug Use Patterns*: Fitness groups differed by cotinine level [$F(1,77) = 5.28$; $p = .02$] and past-year alcohol use [$F(1,77) = 6.58$; $p = .01$] (high-fit youth used more alcohol and had used nicotine more recently), but not past-year CAN use [$F(1,77) = .04$; $p = .84$] or lifetime CAN use [$F(1,77) = 3.57$; $p = .06$]. In addition, in individuals who had used CAN, fitness groups did not differ by age of first use ($\chi^2 = 4.23$; $p = .94$) or regular use ($\chi^2 = 6.85$; $p = .55$). *Fitness Characteristics:* Fitness groups did not differ significantly in weight [$F(1,76) = .08$; $p = .78$],

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Table 1. Demographics, substance use, and fitness characteristics by substance group

	Controls ($n = 42$) % or *M* (*SD*) Range	CAN ($n = 37$) % or *M* (*SD*) Range
Age (y)	20.86 (2.70) 16–25	21.41 (2.19) 17–26
Education (y)	14.26 (2.35) 9–19	13.84 (1.55) 11–18
Reading score (WRAT-IV)	106.64 (10.20) 87–133	104.14 (12.78) 72–133
BDI-II total*	2.71 (3.12) 0–10	5.32 (4.60) 0–19
Gender (% female)	55	32
% Caucasian	69	59
% Not Hispanic/Latino/a	88	78
Past-year cannabis use* (joints)	.38 (1.12) 0–5	427.73 (432.36) 53–2306
Lifetime cannabis use* (joints)	2.32 (4.89) 0–20	1162.49 (1341.16) 101–6000
Past-year alcohol use* (standard drinks)	103.90 (168.22) 0–698.50	318.37 (282.73) 0–1120.50
Cotinine level*	1.10 (.58) 0–3	2.08 (1.77) 0–6
Length of abstinence (days)	46.48 (26.68) 12–388	25.24 (7.96) 11–49
VO_2 max performance (mL/kg/min)	41.25 (10.27) 20.80–62.90	43.98 (9.05) 25.80–62.80
Weight (pounds)	148.85 (22.05) 108.8–194.8	149.91 (27.81) 103.4–213.4
Height (inches)	66.80 (3.60) 60.50–76.50	67.05 (3.99) 59.0–75.5
BMI (kg/m^2)	23.54 (3.80) 17.4–39.1	23.54 (4.24) 16.4–33.6
Body fat (%)	22.13 (10.09) 6.4–42.1	18.67 (8.47) 3.6–40.7

Note. Length of abstinence measures last use of any substance other than tobacco. Length of abstinence data were missing from nine controls as they denied any history of substance use.
*$p < .05$.
BMI = body mass index; *M* = mean; *SD* = standard deviation.

but as expected they did differ by fat percentage [$F(1,76) = 26.20$; $p < .001$], BMI [$F(1,76) = 6.23$; $p = .02$], height [$F(1,77) = 19.40$; $p < .001$], and VO_2 max performance [$F(77) = 136.89$; $p < .001$]. BMI was included as a covariate to control for potential impact of body composition on cognition.

Table 2. Demographics, Substance Use, and Fitness Characteristics by Fitness Group

	Low-fit ($n = 35$) % or *M* (*SD*) Range	High-fit ($n = 44$) % or *M* (*SD*) Range
Age (y)	20.94 (2.65) 16–26	21.25 (2.35) 16–25
Education (y)	14.03 (2.13) 9–18	14.09 (1.94) 10–19
Reading score (WRAT-IV)	103.06 (11.54) 72–133	107.39 (11.18) 90–133
BDI-II total	4.14 (4.77) 0–19	3.77 (3.47) 0–13
Gender* (% female)	66	27
% Caucasian	51	75
% Not Hispanic/Latino/a	77	89
Past year cannabis use (joints)	209.96 (453.17) 0–2306	193.03 (278.46) 0–1394
Lifetime cannabis use (joints)	292.07 (453.17) 0–1668	747.43 (1350.06) 0–6000
Past year alcohol use* (standard drinks)	125.65 (195.17) 0–800	266.95 (275.27) 0–1120.50
Cotinine level*	1.17 (.75) 0–3	1.86 (1.65) 0–6
Length of abstinence (days)	36.90 (32.14) 20–197	34.10 (57.45) 11–388
VO2 max performance* (mL/kg/min)	33.83 (5.45) 20.80–43.80	49.44 (6.21) 39.20–62.90
Weight (pounds)	148.46 (26.82) 103.4–213.4	150.05 (23.16) 108.2–190.8
Height* (inches)	65.04 (2.76) 59–71	68.41 (3.81) 61–76.5
BMI* (kg/m^2)	24.75 (4.60) 17.4–33.9	22.56 (3.13) 16.4–33.6
Body fat* (%)	25.82 (8.92) 6.4–42.1	16.23 (7.62) 3.6–36.8

Note. Length of abstinence measures last use of any substance other than tobacco. Length of abstinence data were missing from three high-fit and six low-fit participants as they denied any history of substance use.
*$p < .05$.
BMI = body mass index; *M* = mean; *SD* = standard deviation.

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Primary Outcomes

All results are on cognitive performance at a single time point following a 3-week period of abstinence.

CAN results

Greater past-year CAN use was significantly associated with decreased LNS performance (beta = -.39; t = −2.89; $p = .005$; $f^2 = .12$) and slower time to complete TMT motor sequencing task (beta = .31; t = 2.35; $p = .02$; $f^2 = .08$).

VO_2 max results

Better VO_2 max performance significantly related to better verbal fluency (beta = .32; t = 2.16; $p = .03$; $f^2 = .07$), TMT motor sequencing (beta = -.31; t = −2.26; $p = .03$; $f^2 = .07$), and facial memory recognition (beta = .45; t = 3.14; $p = .003$; $f^2 = .14$).

CANVO_2 results*

CAN interacted with VO_2 max to predict CVLT Trial 1, TMT switching, TMT motor sequencing, and RCFT delayed recall. CAN interacted with VO_2 max in association with CVLT Trial 1 performance (beta = -.25; t = −1.94; $p = .05$; $f^2 = .06$), with more fit controls having better initial learning, while cannabis users' performance remained the same regardless of fitness level. On TMT switching (beta = -.29; t = −2.37; $p = .02$; $f^2 = .08$), individuals with higher past-year CAN use and higher VO_2 max and individuals with less (or no) cannabis use and lower VO_2 max exhibited faster performance than either low-fit users or high-fit controls (see Figure 1). On TMT motor sequencing (beta = -.32; t = −2.86; $p = .006$; $f^2 = .12$), individuals who used more CAN in the past year and had better on VO_2 max performed more quickly than either individuals with high past-year CAN use and low VO_2 max or controls. On RCFT delayed recall (beta = .26; t = 2.02; $p = .05$; $f^2 = .06$), individuals with more past-year CAN use and with higher VO_2 max attained the highest raw score (see Figure 2).

Covariate results

Alcohol: Past-year alcohol was related to increased D-KEFS FAS total correct raw score (beta = .32; t = 2.65; $p = .01$; $f^2 = .10$), quicker D-KEFS inhibition/switching Stroop completion (beta = -.27; t = −2.13; $p = .04$; $f^2 = .07$), and fewer commissions in CPT (beta = -.32; t = −2.56; $p = .01$; $f^2 = .10$). *Gender:* Females performed better than males on Penn CNP facial memory recognition (beta = .44; t = 3.19; $p = .002$; $f^2 = .15$).

DISCUSSION

The present study aimed to investigate the impact of adolescent and emerging adult CAN use on neuropsychological functioning following 3 weeks of monitored abstinence, and to assess whether aerobic fitness level moderated the impact of CAN on cognitive function. We found that past-year CAN use, in a *dose-dependent* manner, was associated with poorer working memory and psychomotor speed following a monitored 3-week abstinence period. In addition, we found that the novel interaction between cannabis use and aerobic fitness level was associated with performance on working memory, sequencing ability, psychomotor speed, and visual

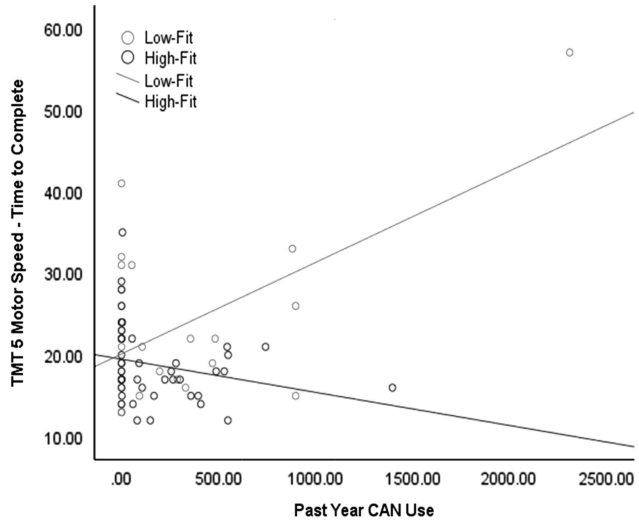

Fig. 1. TMT condition 5 (motor speed) by CAN and VO_2 max. Notes: D-KEFS TMT condition 5 psychomotor speed measured in time to complete (seconds), with quicker performance indicating better psychomotor speed. While continuous variables were used in the interaction term for the MJ*VO_2 interaction, for the sake of presentation here, VO_2 max performance is presented as a categorical variable.

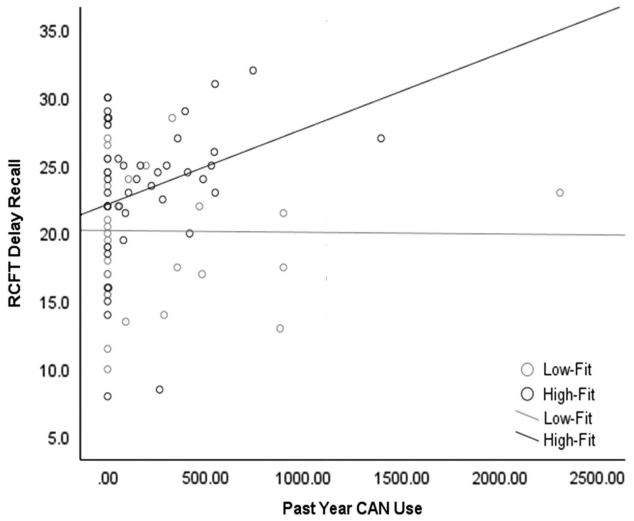

Fig. 2. RCFT delayed recall by CAN and VO_2 max. Notes: RCFT Delayed Recall for visual memory, with higher scores indicating better recall. While continuous variables were used in the interaction term for the MJ*VO_2 interaction, for the sake of presentation here, VO_2 max performance is presented as a categorical variable.

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memory. In general, CAN users who had higher aerobic fitness level performed better on these cognitive tasks than CAN users who had lower aerobic fitness level.

Consistent with prior findings (Lisdahl & Price, 2012; Medina et al., 2007; Thames et al., 2014), we found a significant relationship between increased CAN use and poorer attention/working memory and psychomotor speed, even after a monitored abstinence period of 3 weeks. Inconsistent with prior research (Becker, Collins, & Luciana, 2014; Fried, Watkinson, & Gray, 2005; Jacobus et al., 2015; Medina et al., 2007; Solowij et al., 2011), we did not find a significant relationship between past-year CAN use and memory in the present study. However, we previously did not find a relationship between verbal memory and CAN in a separate sample (Lisdahl & Price, 2012) and attributed this finding to the likely recovery of verbal memory function (Hanson et al., 2010) and hippocampal volume (Yucel et al., 2016) within the first couple weeks of abstinence from CAN.

We also found that CAN use and aerobic fitness level interacted to predict performance on neuropsychological tasks measuring psychomotor speed, visual memory, and sequencing ability. No other studies to date have examined these relationships. More specifically, when looking at the CAN users, high-fit CAN users performed better than low-fit CAN users on tests of sequencing ability, psychomotor speed, and visual memory. Other groups have found reduced symptoms of CUD and reduced craving in CAN users who exercise (Buchowski et al., 2011; Henchoz et al., 2014). The underlying mechanism for this finding is likely multifactorial. Engaging in aerobic activity, which improves overall aerobic fitness, may counteract the downregulation of regular CAN use on CB1R (Ferreira-Vieira et al., 2014; Hirvonen et al., 2012), especially in frontal and parietal cortical regions. Engaging in AE may also increase circulating eCB levels (Koltyn et al., 2014), which are linked with cognitive function (Egerton, Allison, Brett, & Pratt, 2006; Lee & Gorzalka, 2012). AE also results in release of neurotrophic growth factors such as BDNF, IGF-1, and VEGF (Castrén et al., 1998; Cotman & Berchtold, 2002; Egan et al., 2003; Kim et al., 2007; Lee et al., 2006; Li et al., 2000; Liu et al., 2000; Mueller et al., 2015; Whiteman et al., 2014), improved catecholaminergic (dopamine, norepinephrine, and epinephrine) function (Chaouloff, 1989; Dunn et al., 1996; Dunn & Dishman, 1991; Elam et al., 1987; Heyes et al., 1985; Waters et al., 2005), increased c-FOS expression (Dragunow, 1996; He et al., 2002; Sim et al., 2008; Vann et al., 2000), decreased inflammatory response and oxidative stress (Radak et al., 2007; Sakurai et al., 2009), and increased CB1R activity in the hippocampus (Ferreira-Vieira et al., 2014).

Another surprising result was the lack of relationship between alcohol use and neuropsychological outcomes, and occasional positive relationships. One reason for this may be the present study's assessment of total use, rather than patterns of use that may be more neurotoxic (e.g., frequency, heavy episodic or binge drinking). Others have found age of onset of use (Nguyen-Louie et al., 2017), frequency (Nguyen-Louie et al., 2015), or binge drinking patterns (Nguyen-Louie et al., 2016) to be related to decrements in neuropsychological functioning, none of which were specifically investigated here. Alternatively, the socially facilitative nature of initial alcohol experimentation (see Varlinskaya & Spear, 2015) may lead to better social and, by extension, neuropsychological outcomes, as has been indicated across the lifespan (see Kang, Boss, & Clowtis, 2016).

Given the present results, aerobic fitness may be an exciting and low-cost means of intervening to improve psychological and cognitive functioning in CAN users, as has been suggested by our group (Lisdahl, Gilbart, Shollenbarger & Wright, 2013) and others (Brellenthin & Koltyn, 2016). Augmentation of existing cognitive behavioral and motivational interviewing interventions for substance using youth with AE may boost youth's ability to process, manipulate, and retain information, leading to superior outcomes. There is also potential opportunity to use AE as a prevention technique, as improving youth's executive function, processing speed, and memory may reduce risk for substance use initiation.

There are limitations to consider. While relationships between CAN use, fitness, and neuropsychological functioning were found, causality cannot be established due to the cross-sectional nature of this study; longitudinal studies, such as the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org/), are needed to clarify directionality of relationships. Recent research has indicated that CAN users included in studies such as this are *not* representative of the "typical" CAN user (e.g., lack of psychiatric co-morbidity, lower frequency of use; Rosen, Sodos, Hirst, Vaughn, & Lorkiewicz, 2018); therefore, these results may not generalize and/or may not reveal the true extent of relationships between CAN use and cognition in higher-risk groups. Even in domains where deficits were found, these were modest effects well below the typical 1.5 *SD*s associated with clinical significance; the real-world functional implications about such relative declines are lesser known, although CAN users have reported lower academic achievement (Fergusson & Boden, 2008; Horwood et al., 2010; Suerken et al., 2016), reduced salaries (Fergusson & Boden, 2008), and reduced life satisfaction (Fergusson & Boden, 2008; Grevensteine & Kroninger-Jungaberle, 2015).

Another limitation is that, while participants were encouraged to exercise as long as possible, only 80% reached their true VO_2 max as defined by Howley and colleagues (1995); therefore, their predicted performance is used in lieu of maximum performance. In addition, while VO_2 max is the gold standard in assessing cardiorespiratory health and is typically highly correlated with recent aerobic activity, it does not indicate exact levels of physical activity or sedentary behaviors. Other factors also influence VO_2 maximum performance (gender, genetics, age, body composition, etc.). In this sample, adiposity (body fat composition) was too highly correlated with VO_2 max (r's $> .65$) to be included in the same regressions due to multicollinearity, although gender and age were controlled for in the regressions. Larger

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samples may want to consider examining the unique influences of adiposity, levels of physical activity, and aerobic fitness on neurocognition in cannabis users.

Taken together, our results provide further evidence of increased CAN use being related to poorer working memory, sequencing ability, and psychomotor speed, even after 3 weeks of monitored abstinence. Most notably, our results also suggest aerobic fitness may moderate these effects, such that individuals with higher VO_2 max and more past-year CAN use may have better neuropsychological performance than low-fit users. AE, therefore, may be a promising ameliorative cognitive intervention for regular CAN users, although future research is needed to assess causality and effectiveness of such an approach.

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