**Supplementary Methods**

**Supplementary Procedures**

*Detailed Phone Screen—*Interested individuals were asked for demographic information (e.g., sex, race, ethnicity, educational attainment, etc.) and screened through an initial semi-structured interview for independent lifetime and past-year Axis I Disorders—other than substance use disorder—over the phone [Mini International Psychiatric Interview (Sheehan et al., 1998)], lifetime drug use patterns [Customary Drinking and Drug Use Record (Brown et al., 1998)], recent physical activity [IPAQ (Fogelholm et al., 2006)], and aerobic testing safety [PAR-Q (Thomas, Reading, & Shephard, 1992)]. If eligible, study staff obtained written consent from participants (aged 18 or older). All minors below 18 years of age provided written assent after parent consent was obtained. Additionally, parents of participants were consented for a parent-administered phone interview that screened for medical, psychiatric, and prenatal history before an in-person session was conducted.

**Supplementary Session Measures.**

*Physical Activity*—Extent of physical activity was assessed with the IPAQ (Fogelholm et al., 2006) and physical ability to engage in VO2 max testing was assessed with the PAR-Q (Thomas et al., 1992).

*Lifetime substance use*—To determine lifetime patterns of drug and alcohol use, participants were given the Customary Drinking and Drug Use Record (CDDR) (Brown et al., 1998) at baseline to measure frequency of alcohol, nicotine, cannabis, and other drug use, SUD symptoms, and the age of onset for first and regular (weekly) use.

*Mini Psychiatric Interview*—Participants and parents of minors were interviewed using the Mini International Psychiatric Interview (MINI) (Sheehan et al., 1998) or MINI-Kid (Sheehan et al., 2010) to screen out for psychiatric comorbidities.

*Processing pipeline—*T1-weighted 3D anatomical datasets underwent an automatic pipeline for motion correction, nonparametric non-uniform intensity normalization, Montreal Neurologic Institute transformation, removal of non-brain materials, skull-stripping, and automated topology correction (http://surfer.nmr.mgh.harvard.edu/fswiki/recon-all); white matter voxels were detected based off voxel intensity and the surface boundary between grey and white matter (white surface) was created based of voxel intensity gradients; surface was deformed and expanded to fit the grey and CSF boundary (pial surface) intensity gradient utilizing localized curvature to reduce error [see Sullivan, Wallace, Wade, Swartz, and Lisdahl (2020) for more details]. Subcortical segmentations were computed using a validated volume based stream and labelled using subject-independent probabilistic Desikan-Killiany Atlas (Desikan et al., 2006; Fischl et al., 2002; Fischl et al., 2004). Preprocessed scans were quality-checked by a team of three trained research staff where scans of varying quality were flagged and then discussed as a team. Manual edits were made by the team when deemed necessary.

*Power Analysis*—The parent study (R01-DA030354; PI: Lisdahl) conducted a priori power analyses to determine a sample size of 100. For the present study, a post-hoc power analysis was conducted using G\*Power 3 (Faul, Erdfelder, Lang, & Buchner, 2007) Based on the presented analysis, a fixed linear multiple regression model will be run with medium effect size of *f2* = 0.15, an error probability of α = 0.05, and a total sample size of n=74. With nine predictors in our models, this results in a power (1-β) equal to 0.91. However, it is worth mentioning that post-hoc power analyses have noted limitations (Levine & Ensom, 2001).

**Supplementary Results**

**Exploratory Brain-Behavior Correlations**

**VO2 Correlations.** PASAT total score was positively correlated with left cerebellum (r=0.37, *p*=0.001), left caudate (r=0.25, *p*=0.035), two left inferior parietal regions (r=0.24, *p*=0.036; r=0.34, *p*=0.003), and right fusiform (r=0.29, *p*=0.01) volumes (See Supplementary Table 2).

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**Supplementary Table 1.** Brain Morphology Findings

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | *t* | Size (mm2) | x | y | z | *cwp* | *Effect Size* |
| *Volume* |  |  |  |  |  |  |  |
| **Cannabis\*Sex Finding** |  |  |  |  |  |  |  |
| Left Lateral Orbitofrontal | -3.99 | 941.0 | -17.1 | 46 | -14.5 | .019 | -.29 |
| Left Inferior Temporal | -2.73 | 960.3 | -49.5 | -20.4 | -32.2 | .017 | -.28 |
| Left Precuneus | -2.67 | 857.3 | -8.6 | -50.4 | 46.4 | .034 | -.29 |
| Left Caudal Middle Frontal | -2.40 | 1468.9 | -33 | 1.5 | 52.3 | .0003 | -.27 |
| Right Superior Frontal | 4.42 | 1407.7 | 13.9 | 18.5 | 57.3 | .001 | -.30 |
| Right Paracentral | 3.19 | 1197.7 | 13.9 | -12.4 | 43.3 | .0047 | -.29 |
| **VO2 Finding** |  |  |  |  |  |  |  |
| Left Inferior Parietal | 5.21 | 1545.4 | -27 | -63.6 | 34.7 | .0001 | .37 |
| Left Inferior Parietal | 4.31 | 1982.9 | -46.9 | -63.3 | 10.5 | .0001 | .32 |
| Left Rostral Middle Frontal | 2.89 | 843.9 | -30.9 | 46.6 | 11.7 | .039 | .27 |
| Right Inferior Parietal | 3.40 | 898.6 | 45.1 | -57 | 26.5 | .035 | .30 |
| Right Fusiform | 3.11 | 1383.8 | 38.4 | -42 | -21.4 | .001 | .29 |
| Right Precuneus | 3.06 | 972.8 | 9.4 | -54 | 47.9 | .02 | .29 |
| **Cannabis\*VO2 Finding** |  |  |  |  |  |  |  |
| Left Superior Temporal | -3.58 | 1906.8 | -58.8 | -21.9 | -2.3 | .0001 | -.30 |
|  | | | | | | |  |

**Supplementary Table 2.** Significant Correlations Between Aerobic Fitness Volumetric Regions and Neurocognitive Performance.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Neurocognitive  Measure | *r* | *p* |
| **VO2 Finding** |  |  |  |
| Left Cerebellum | *PASAT Total* | .37 | .001 |
| Left Caudate |  | .25 | .035 |
| Left Inferior Parietal |  | .24 | .036 |
| Left Inferior Parietal (2) |  | .34 | .003 |
| Right Fusiform |  | .29 | .01 |
| *Note:* PASAT = Paced Auditory Serial Addition Task | | | |

**Supplementary Figure 1.** *Cannabis\*VO2 Finding*.Lateral view of CAN and VO2 interaction observed within left superior temporal volume. Non-using controls demonstrated a positive association between VO2 max and increased volume, whereas no relationship was observed within CAN-using participants.

|  |
| --- |
|  |

**Supplementary Figure 2.** *Cannabis\*Sex Finding*. Interaction plots of CAN-by-sex findings.