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Associations between adolescent cannabis use frequency and adult brain structure:

a prospective study of boys followed to adulthood*

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Highlights

- Cannabis use was tracked prospectively in adolescence, with imaging in adulthood

- Adolescent cannabis users did not differ in adult brain structure

• Adolescent cannabis use is not associated with lasting structural brain differences

Abstract

Background: Few studies have tested the hypothesis that adolescent cannabis users show structural brain alterations in adulthood. The present study tested associations between prospectively-assessed trajectories of adolescent cannabis use and adult brain structure in a sample of boys followed to adulthood.

Methods: Data came from the Pittsburgh Youth Study -- a longitudinal study of ~1,000 boys. Boys completed self-reports of cannabis use annually from age 13-19, and latent class growth analysis was used to identify different trajectories of adolescent cannabis use. Once adolescent cannabis trajectories were identified, boys were classified into their most likely cannabis trajectory. A subset of boys (n=181) subsequently underwent structural neuroimaging in adulthood, when they were between 30-36 years old on average. For this subset, we grouped participants according to their classified adolescent cannabis trajectory and tested whether these groups showed differences in adult brain structure in 14 a priori regions of interest, including six subcortical (volume only: amygdala, hippocampus, nucleus accumbens, caudate, putamen, and pallidum) and eight cortical regions (volume and thickness: superior frontal gyrus; caudal and rostral middle frontal gyrus; inferior frontal gyrus, separated into pars opercularis, pars triangularis, and pars orbitalis; lateral and medial orbitofrontal gyrus).

Results: We identified four adolescent cannabis trajectories: non-users/infrequent users, desisters, escalators, and chronic-relatively frequent users. Boys in different trajectory subgroups did not differ on adult brain structure in any subcortical or cortical region of interest.

Conclusions: Adolescent cannabis use is not associated with structural brain differences in adulthood.

1. Introduction

Cannabis is, by far, the most commonly used illicit drug by adolescents. Data from the nationally representative Monitoring the Future study showed that 10.5%, 27.5%, and 35.9% of 8th, 10th, and 12th graders used cannabis in 2018, respectively (Johnston, 2019). These high rates of adolescent cannabis use are concerning, because adolescents might be particularly vulnerable to the effects of cannabis on brain structure and function. Specifically, it has been proposed that cannabis use disrupts critical brain changes that occur in adolescence, including myelination, synaptic pruning, and maturation of the endogenous cannabinoid system (Brumback et al., 2016; Lisdahl et al., 2013; Lisdahl et al., 2014; Lubman et al., 2015; Solowij and Battisti, 2008), making adolescent cannabis users susceptible to perhaps lasting structural and functional brain alterations. However, relatively few studies have examined associations between adolescent cannabis use and adult brain structure. The few studies that have examined this association have mainly relied on adult cannabis users' retrospective reports of age-of-onset of cannabis use (Ashtari et al., 2011; Battistella et al., 2014; Cousijn et al., 2012; Filbey et al., 2015; Gilman et al., 2014; Lorenzetti et al., 2014; Matochik et al., 2005; Pagliaccio et al., 2015; Wilson et al., 2000), which are subject to recall bias. Moreover, reports of age-of-onset of cannabis use do not capture important individual differences in frequency and duration of cannabis use in adolescence, which may be important for understanding adolescents' vulnerability to lasting cannabis effects. The present study redressed these limitations by obtaining prospective reports of cannabis use annually from age 13-19 and by assessing brain structure later in adulthood. To jointly account for age-of-onset, frequency, and duration of adolescent cannabis use, we mapped different trajectories of cannabis use over the adolescent years (e.g., infrequent use/non-use, desisting use, escalating use, chronic-relatively frequent use) and tested associations between trajectories of adolescent cannabis use and adult brain structure.

Case-control studies of adult cannabis users and comparison individuals have shown evidence of neuroanatomical differences, particularly in brain regions enriched with cannabinoid receptors, such as the hippocampus (Ashtari et al., 2011; Lorenzetti et al., 2015; Schacht et al., 2012; Yücel et al., 2008), amygdala (Lorenzetti et al., 2015; Schacht et al., 2012; Yücel et al., 2008), striatum (Pagliaccio et al., 2015), and prefrontal cortex (Battistella et al., 2014; Filbey et al., 2014). The most consistent finding is that cannabis users have lower

hippocampal volume (Batalla et al., 2013; Brumback et al., 2016; Lorenzetti et al., 2014; Lorenzetti et al., 2016; Rocchetti et al., 2013). Some of these studies examined associations between retrospectively- reported age-of-onset of cannabis use and adult brain structure (e.g., (Ashtari et al., 2011; Battistella et al., 2014; Cousijn et al., 2012; Filbey et al., 2015; Gilman et al., 2014; Matochik et al., 2005; Pagliaccio et al., 2015; Wilson et al., 2000). Reviews of these studies (Lorenzetti et al., 2014; Lorenzetti et al., 2016) have revealed that, although a few studies have found evidence of an association between an earlier age-of-onset of cannabis use and adult brain structure (e.g., (Battistella et al., 2014; Wilson et al., 2000), most studies have not (Ashtari et al., 2011; Cousijn et al., 2012; Filbey et al., 2015; Gilman et al., 2014; Lorenzetti et al., 2014; Matochik et al., 2005).

There are a number of possible explanations for inconsistent or null findings regarding the relation between an earlier age-of-onset of cannabis use and adult brain structure. One explanation is that recall bias contributes to inaccurate retrospective reports of age-of-onset of cannabis use. In fact, a number of studies have shown evidence of recall bias in retrospective reports of age-of-onset of cannabis use and other substance use (Johnson and Schultz, 2005; Shillington et al., 2012). Another explanation is that different studies define age-of-onset differently, with some studies reporting on age of first use and other studies reporting on age of first regular use, with definitions of regular use also varying across studies (Lorenzetti et al., 2016). A third explanation is that reports of an earlier age-of-onset do not capture important individual differences in frequency and duration of cannabis use in adolescence that might be associated with risk for lasting brain alterations. For example, frequent cannabis use throughout adolescence is more likely to be associated with lasting brain alterations than short-term, infrequent cannabis use in adolescence. Consistent with this notion, some evidence suggests that cannabis users with the highest levels of cannabis exposure show the most pronounced brain differences (Ashtari et al., 2011; Batalla et al., 2013; Cousijn et al., 2012; Lorenzetti et al., 2016; Yücel et al., 2008). Importantly, the aforementioned explanations are not mutually exclusive. It is also possible that adolescent cannabis use might not have lasting effects on brain structure.

Few structural neuroimaging studies of adult cannabis users have taken account of both age-of-onset of cannabis use and level of cannabis exposure in adolescence, despite clear evidence of differences between adolescents in their patterns of cannabis use over time.

Longitudinal studies have consistently identified four prototypical subgroups of cannabis users based on their frequency of cannabis use over the adolescent years: (1) a large subgroup of non- users or infrequent users who never or rarely engage in cannabis use, (2) a subgroup of desisters who initiate cannabis use relatively early in adolescence but show declining use into young adulthood, (3) a subgroup of escalators who initiate cannabis use relatively late in adolescence and show increasing use into young adulthood, and (4) a small subgroup of chronic-relatively frequent users who initiate cannabis use early in adolescence and use relatively frequently into young adulthood (Brook et al., 2011; Brook et al., 2010; Lynne-Landsman et al., 2010). These different trajectories reflect differences not only in frequency and duration of adolescent cannabis use but also in developmental timing of adolescent use (earlier vs. later-onset adolescent use) that could potentially be important for understanding associations between adolescent cannabis use and adult brain structure.

The purpose of the present study was to test associations between different trajectories of adolescent cannabis use and adult brain structure in a cohort of boys followed to adulthood.

Participants completed self-reports of cannabis use annually from age 13-19, and a subset of participants underwent structural neuroimaging in adulthood, when they were between 30-36 years old on average. We classified boys into adolescent cannabis trajectory subgroups (non- users/infrequent users, desisters, escalators, chronic-relatively frequent users) using the full sample and compared adult brain structure across cannabis trajectory subgroups for the subset of participants who underwent neuroimaging as adults. Analyses focused on 14 brain regions for which theory and evidence suggest cannabis might have an effect: all six subcortical regions (volume only: amygdala, hippocampus, nucleus accumbens, caudate, putamen, pallidum) and eight prefrontal regions (volume and thickness: superior frontal gyrus; caudal and rostral middle frontal gyrus; inferior frontal gyrus, separated into pars opercularis, pars triangularis, and pars orbitalis; lateral and medial orbitofrontal gyrus). We tested the hypothesis that any differences in adult brain structure between adolescent cannabis trajectory subgroups would most likely emerge for adolescent chronic-relatively frequent users, because this subgroup engaged in relatively frequent cannabis use chronically throughout adolescence and, therefore, had the highest level of cannabis exposure.

2. Materials and Methods

2.1 Participants and Procedure

Participants were boys enrolled in the Pittsburgh Youth Study (PYS). The PYS is a longitudinal investigation of the development of substance use, delinquency, and mental health problems in 1,009 boys (55.1% Black, 41.1% White, 3.8% other). The sample was initially recruited from a list of students enrolled in 1st and 7th grades (referred to as the youngest and oldest cohorts, respectively) in Pittsburgh public schools in 1987-1988. Eligible boys participated in a multi-informant screening designed to assess early conduct problems (e.g., fighting, stealing). Scores on the screener were used to select boys for the PYS. The final sample included a random sample of boys in each cohort who scored in the upper third on the screener (youngest cohort: N=256; oldest cohort: N=257) and an approximately equal number of boys randomly selected from the remaining end of the distribution (youngest cohort: N=247; oldest cohort: N=249). Boys participated in eight (youngest cohort) or five (oldest cohort) biannual assessments, followed by nine (youngest) or ten (oldest) annual assessments. Boys in the youngest cohort were 7.5 years old (SD=0.6) at the first assessment after screening and 20.1 years old (SD=0.6) at the last annual assessment. Boys in the oldest cohort were 13.9 (SD=0.8) at the first assessment after screening and 25.9 years old (SD=0.8) at the last annual assessment.

Sample retention for all assessments was high and never dropped below 82%. The two cohorts were combined by aligning the data by age.

In addition to the biannual and annual interviews described above, a subset of 205 participants took part in a neuroimaging sub-study that was initiated to examine the neurobiological basis of violence in adulthood (youngest cohort: n=111, M=29.6 years, SD=1.23; oldest cohort: n=94, M=36.2 years, SD=1.52). Violent and non-violent men were recruited to the sub-study based on self-reported offending (Self-Report of Delinquency (Loeber et al., 1998); Violence History Questionnaire (Pardini and Phillips, 2010), and official criminal records). Specifically, men were recruited from the following three groups using annual data from age 11-25: men who never engaged in violence (n=75), men who engaged in violence for 1-3 years (n=74), and men who engaged in violence for 4+ years (n=56). Neuroimaging sub- study exclusion criteria were: (1) prior history of a psychotic disorder according to the Diagnostic Interview Schedule for DSM-IV (Robins et al., 1995); (2) use of psychotropic medications; (3) history of neurological disease, structural brain injury, post concussive syndrome,

and/or cardiovascular disease; (4) a full scale IQ below 70 on the Wechsler

Abbreviated Scale of Intelligence (PsychCorp, 1999); (5) irremovable ferromagnetic metal in the body; and (6) current incarceration. Further detail on participant selection, sample characteristics, and study methodology is available elsewhere (Pardini et al., 2014). In the current report, 24 participants were excluded from analyses (youngest: $n=9$; oldest: $n=15$) because of faulty neuroimaging data (e.g., claustrophobia, excess motion, poor segmentation upon visual inspection). This resulted in a final sample of 181 participants with analyzable neuroimaging data. As shown in Table 1, men with usable neuroimaging data from the sub-study differed from men in the larger PYS in terms of race, screening as high-risk for conduct problems at study outset, and years of violence from age 11-25. However, the magnitude of these differences was small (Cramer's $V <$ .10, Cohen's $d<.22$). All procedures were approved by the University of Pittsburgh Institutional Review Board, and informed consent was obtained from all participants. Parental consent was obtained for all boys prior to age 18.

2.2 Measures

2.2.1 Cannabis Use. Cannabis use from ages 13-19 was assessed with the youth-reported Substance Use Questionnaire (Loeber et al., 1998). Cannabis use from age 13-19 was the focus given the hypothesis that adolescents may be particularly vulnerable to cannabis effects (Brumback et al.,2016; Lisdahl et al., 2013; Lisdahl et al., 2014; Lubman et al., 2015; Solowij and Battisti, 2008). Participants reported the number of days they used cannabis in the past six months (biannual assessments) or in the past year (annual assessments). (For biannual assessments, reports were combined by summing adjacent assessments to create measures of past-year cannabis use.) Latent class growth analysis (LCGA) was used to identify trajectories of adolescent cannabis use in the full sample, and these analyses are described in section 2.3.1. Because of skew, cannabis frequency at each assessment was re-coded into a 5-level ordinal variable prior to LCGA: : 0=no use (0 days), 1=less than once per month (1-11 days), 2=at least monthly but not weekly (12-51 days), 3=1-3 times per week (52-156 days), and 4=more than 3 times per week (157-365 days) (Supplemental Table 1)[1].

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[1] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi: ...

2.2.2 Structural Magnetic Resonance Imaging. A subset of participants underwent structural magnetic resonance imaging using a Siemens 3T Allegra MRI scanner with a 32-channel head coil. Whole-brain high-resolution structural images were acquired using a T1-weighted 3D gradient echo imaging scan with a spoiled gradient recalled sequence in the axial plane (TR=1630 ms, TE=2.48 ms, slices=224; flip angle=8°, field of view=204 mm, number of excitations=1; bandwidth=210 Hz/pixel; echo spacing=6.8 ms; image matrix=256*256 mm, slice thickness=.8mm; 0mm gap). Image pre- processing, subcortical segmentation, and cortical parcellation were performed with FreeSurfer image analysis suite version 5.3.0 (http://surfer.nmr.mgh.harvard.edu). This automated processing pipeline has been detailed elsewhere (Dale et al., 1999; Fischl et al., 1999), and more information can be found in the Supplemental Text[*]. Cortical and subcortical measures from FreeSurfer exhibit very high reliability (cortical: intraclass correlation coefficient [ICCs]>0.87; subcortical: ICCs>0.95) (Liem et al., 2015). Further, there are high correlations between automated segmentation and manual tracing in structures such as the hippocampus (Morey et al., 2009). In fact, volumetric estimates from FreeSurfer have been reported as being statistically indistinguishable from hand-traced measures of the same structures (Fischl et al., 2002).

Our outcomes were 14 a priori regions of interest (ROIs): six subcortical regions (volume only; amygdala, hippocampus, nucleus accumbens, caudate, putamen, and pallidum) and eight prefrontal regions (volume and thickness: superior frontal gyrus; caudal and rostral middle frontal gyrus; inferior frontal gyrus, separated into pars opercularis, pars triangularis, pars orbitalis; lateral and medial orbitofrontal gyrus). All ROIs were automatically derived for each participant by FreeSurfer. Histograms of each brain structural volume were assessed for potential outliers, and no cases were discarded.

2.2.3 Covariates. Covariates were race (Black=1, White/Other=0), intracranial volume obtained from FreeSurfer (ICV; (consisting of gray matter, white matter, and cerebrospinal fluid), age at the time of neuroimaging, and years of prior violence. Race and ICV were included as covariates based on preliminary analyses showing that they were correlated with brain structure owing to systematic variation in head and whole-brain size (Walhovd et al., 2005). Number of years that participants engaged in at least one violent act from age 11-25 was included as a covariate to adjust for any differences in brain structure associated with oversampling

for violence in the neuroimaging sub-study, as described above.

We also considered a number of other covariates: screening as high-risk for childhood conduct problems at study outset, childhood socioeconomic status (SES), and alcohol and tobacco use trajectories. Screening as high-risk on childhood conduct problems at study outset was considered as a covariate because boys with conduct problems were initially oversampled at study outset. Childhood SES was considered as a covariate because some evidence suggests that SES is related to adult brain structure (McDermott et al., 2019). Alcohol and tobacco use were considered as covariates because they are correlated with cannabis use and could impact brain structure.

2.2.3.1 Childhood Conduct Problems Screener. Boys were considered high-risk for conduct problems if they scored in the upper third on the parent-, teacher-, and youth-reported conduct problems screener at study outset, as described in the procedure section (high risk=1; not high risk=0).

2.2.3.2 Childhood Socioeconomic Status (SES). Childhood SES was assessed at age 13 using the two-factor Hollingshead Index, which incorporates parental educational attainment and occupational status as reported by the boy's family (Hollingshead, 1975).

2.2.3.3. Alcohol and Tobacco Use. Alcohol and tobacco use were assessed with the youth-reported Substance Use Questionnaire (Loeber et al., 1998) from age 13-19. Participants reported the number of days they used alcohol and tobacco in the past six months (biannual assessments) or the past year (yearly assessments). (Biannual assessments were combined to create yearly measures of alcohol and tobacco use.) We used LCGA to identify trajectories of adolescent alcohol and tobacco use in the full sample. Because of skew, alcohol frequency at each assessment was re-coded into a 5- level ordinal variable prior to LCGA: (0=no use [0 days], 1=less than once per month [1-11 days], 2=at least monthly but not weekly [12-51 days], 3=1-3 times per week [52-156 days], and 4=more than 3 times per week [157-365 days]). Tobacco frequency at each assessment was re- coded into a three-level ordinal variable: 0=no use, 1=some use but not daily, 2=near daily or daily use. Alcohol and tobacco frequency data are shown in Supplemental Table 1[2].

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[2] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi: ...

2.3 Statistical Analyses

Analyses were conducted in two parts. First, we identified adolescent cannabis trajectories from age 13-19 in the full sample ($N = 989$; 98% of PYS participants) and grouped participants according to their adolescent cannabis trajectory subgroup. Second, we compared adolescent cannabis trajectory subgroups on adult brain structure using data from the subsample of participants who took part in the neuroimaging sub-study ($N = 181$).

2.3.1. Identification of Cannabis Trajectory Subgroups Using Latent Class Growth Analysis in The Full Sample. To identify adolescent cannabis trajectories, we conducted an LCGA of the cannabis frequency data from age 13-19 in Mplus 7.2 using maximum likelihood estimation with robust standard errors (Muthén and Muthén, 1998-2012). Maximum likelihood estimation uses all available data to generate parameter estimates. A series of sequential growth curves and model tests determined that cannabis use was best estimated with linear and quadratic growth factors (slopes). Latent intercepts and slopes were regressed on cohort (youngest versus oldest) to adjust for possible cohort effects. A successive number of latent classes was then specified with the optimal number of classes being determined by recommended criteria, including the sample- adjusted Bayesian Information Criterion, Vuong-Lo–Mendell–Rubin Likelihood Ratio Test, the Bootstrapped Likelihood Ratio Test, classification accuracy, parsimony, and interpretability (Muthen, 2004; Nylund et al., 2008). Once the optimal number of cannabis trajectories was determined, boys were classified into their most likely cannabis trajectory subgroup based on their highest posterior probability of subgroup membership. LCGA was conducted in the same way for the alcohol and tobacco use data.

2.3.2. Test of Associations Between Adolescent Cannabis Trajectory Subgroups and Adult Brain Structure. To compare adolescent cannabis trajectory subgroups on adult brain structure, we used mixed-model analyses of covariance (ANCOVAs), whereby cannabis trajectory subgroup was a between-subjects factor and hemisphere (left or right) was a within-subjects factor. If significant main effects of cannabis group emerged, we further investigated with post-hoc pairwise comparisons among the cannabis trajectory subgroups. We also examined whether the association between cannabis trajectory subgroup and ROIs differed by hemisphere by including an interaction between cannabis trajectory subgroup and a laterality marker (right versus left).

Statistical significance was evaluated against a Bonferroni-corrected p-value threshold, which was

determined based on the number of subcortical regions ($p < 0.05/6 = 0.008$) and cortical regions ($p < 0.05/8 = 0.006$) tested in each analysis. Race, ICV, age at neuroimaging, and prior violence were included as covariates in all analyses, and screening as high risk for childhood conduct problems, childhood SES, and alcohol and tobacco use trajectory subgroups were subsequently added as covariates in supplemental analyses.

3. Results

3.1 Adolescent Cannabis Trajectory Subgroups

Latent class growth analysis of the cannabis use frequency data from age 13-19 for the full sample showed that a four-class solution was best, based on fit statistics, face validity of classes, parsimony, and group size (>5%) (Supplemental Table 2)[3]. The specific cannabis trajectory subgroups for the four-class solution were: (1) infrequent use/no use (53%; N=524; average posterior probability [pp]=.881); (2) desisting use (10%; N=101; pp=.781); (3) escalating use (24%; N=238; pp=.806); and (4) chronic-relatively frequent use (13%; N=126; pp=.860).

Adolescent cannabis trajectory membership (i.e., the percent of participants classified into each cannabis trajectory) was not different for participants who did versus did not take part in the neuroimaging sub-study (Table 1: $\times^2 = 6.28$, $p = .099$). Figure 1 shows the adolescent cannabis trajectory subgroups for the 181 participants in the neuroimaging sub-study. Each adolescent cannabis trajectory subgroup showed a different pattern of cannabis use over time. In addition, the cannabis trajectory subgroups differed from each other in terms of cumulative frequency of cannabis use from age 13-19 (Table 2: F (3) = 86.26, $p <.001$). For example, the infrequent/no- use group used cannabis for a total of 4 days, on average, from age 13-19, whereas the chronic-relatively frequent subgroup used cannabis for a total of 782 days, on average, from age 13-19 (Table 2). The cannabis trajectory subgroups also differed from each other in terms of screening as high-risk for conduct problems at study outset, years of violence from age 11-25, and alcohol and tobacco use trajectories from age 13-19 (Table 2), suggesting that these factors should be considered as covariates in analyses comparing trajectory subgroups on adult brain structure. (The results of the LCGA model comparisons for alcohol and

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[3] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi: ...

tobacco use trajectories from age 13-19 are shown in Supplemental Table 2[*], and the alcohol and tobacco trajectories for the 181 participants in the neuroimaging sub-study are shown in Figure 1).

3.2   Differences Between Adolescent Cannabis Trajectory Subgroups on Adult Brain Structure

We compared the adolescent cannabis trajectory subgroups on subcortical volume and cortical volume and thickness. These analyses were limited to the 181 participants who took part in the neuroimaging sub-study. All analyses adjusted for race, ICV, age at neuroimaging, and years of violence from age 11-25. There was no statistically significant main effect of adolescent cannabis trajectory subgroup, nor moderation by laterality, on subcortical volumes (Table 3), cortical volumes (Table 4), and cortical thickness (Table 5). We repeated analyses after adding childhood conduct problems, childhood SES, and alcohol and tobacco use trajectory subgroups as covariates (Supplemental Tables 3-5)[4], and results were similar. We also repeated cortical analyses using voxel-based morphometry instead of surface-based morphometry, because the different methods can produce different results. However, results were unchanged (results available on request).

4.   Discussion

We found that adolescent cannabis use was not associated with adult brain structure in a sample of boys followed prospectively to adulthood. Boys were classified into one of four prototypical adolescent cannabis trajectory subgroups based on prospective assessments of cannabis use frequency from age 13-19: infrequent use/no use, desisting use, escalating use, or chronic-relatively frequent use. These subgroups showed different patterns of cannabis use across adolescence and differed in terms of their overall cumulative exposure to cannabis. For example, the infrequent/no use subgroup had used cannabis, on average, on four total days from age 13-19, whereas the chronic-relatively frequent subgroup had used cannabis, on average, on 782 total days from age 13-19. We found no differences in adult brain structure for boys in the different adolescent cannabis trajectory subgroups. Even boys with the highest level of cannabis exposure in adolescence showed subcortical brain volumes and cortical brain volumes and thickness in adulthood that were similar to boys with almost no exposure to cannabis throughout adolescence.

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[4] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi: …

Our findings contribute to already mixed evidence regarding whether adolescent cannabis use is associated with lasting brain differences (Nader and Sanchez, 2018). Case-control studies of adult cannabis users and comparison adults have generally not found an association between an earlier age-of-onset of cannabis use and adult brain structure (Ashtari et al., 2011; Cousijn et al., 2012; Filbey et al., 2015; Gilman et al., 2014; Lorenzetti et al., 2014; Matochik et al., 2005), suggesting that adolescent cannabis use might not have lasting effects on brain structure, consistent with our findings. Relatedly, a number of studies have reported that cannabis-related brain and cognitive differences resolve with abstinence (Fried et al., 2005; Hanson et al., 2010; Hirvonen et al., 2012; Korponay et al., 2017; Schreiner and Dunn, 2012; Scott et al., 2018; Tait et al., 2011). However, animal studies have suggested that cannabis exposure in adolescence may have lasting effects (O'Shea et al., 2004; Rubino et al., 2009; Schneider and Koch, 2003; Verrico et al., 2014). Further, a number of human studies have suggested that adolescent cannabis users show persisting differences in brain structure, brain function, or cognitive functioning (Ashtari et al., 2011; Bolla et al., 2002; Ganzer et al., 2016; Jacobus et al., 2014; Lorenzetti et al., 2014; Medina et al., 2010; Meier et al., 2012; Padula et al., 2007; Pope et al., 2003; Schweinsburg et al., 2008; Tapert et al., 2007). Conflicting findings might be attributable to between-study methodological differences, such as the extent of the sample's cannabis exposure, length of cannabis abstinence at the time of testing, as well as inadequate control for covariates, such as alcohol use.

The present study has limitations. First, cannabis use was self-reported. Self-reports are common in cohort studies, because they are efficient and because biological assays are not sensitive enough to pick up on the lower levels of cannabis use common in adolescence (Bourque et al., 2018; Lorenzetti et al., 2016). Nonetheless, biological assays could have helped detect underreporting among heavier users. Relatedly, we obtained prospective reports of cannabis frequency but not cannabis quantity. Cannabis quantity is difficult to assess (Gray et al., 2009), and there is, as yet, no standardized means of assessing it (Lorenzetti et al., 2016).

Nevertheless, future research should consider deriving adolescent cannabis trajectories based on both quantity and frequency of cannabis use. Second, although we identified a subgroup of chronic-relatively frequent adolescent cannabis users in the cohort who used cannabis, on average, approximately two days per week for seven years, it is possible that lasting brain structural differences will emerge only with more frequent use (e.g.,

daily), which our study, and others (Meier et al., 2018; Miech et al., 2018), suggest is rare in adolescence. Third, neuroimaging data were collected only once in adulthood. Thus, it is unclear if cannabis-related structural brain differences were apparent in adolescence or early adulthood, as some (Batalla et al., 2013; Brumback et al., 2016; Churchwell et al., 2010; Gilman et al., 2014; Lopez-Larson et al., 2011), but not all (Rocchetti et al., 2013; Weiland et al., 2015), studies have found. Importantly, several case-control studies have found brain structure differences in adolescent or young-adult cannabis users with cumulative levels of cannabis exposure comparable to the levels of cannabis exposure reported here for the chronic-relatively frequent subgroup (Gilman et al., 2014; Jacobus et al., 2014). However, it was unclear from those studies if brain structure differences among the adolescent or young-adult cannabis users persisted into later adulthood.

Our study suggests they might not. Relatedly, we also could not test if adolescent cannabis was associated with longitudinal changes in brain structure, which is a focus of the ongoing Adolescent Brain Cognitive Development Study (https://abcdstudy.org/).

Fourth, we did not examine associations between adolescent cannabis use and other brain morphometry measures (e.g., grey matter shape and density, white matter integrity) or functional brain differences in adulthood, which have been shown to be related, in some studies, to earlier- onset cannabis use (Filbey et al., 2014; Gruber et al., 2014; Orr et al., 2016). Fifth, the size of some of the adolescent cannabis trajectory subgroups was small, limiting power to detect differences. Still, subgroup means were nearly identical, suggesting any effects of cannabis were trivial. Sixth, findings are limited to a subset of boys from a single cohort study who, as adults, took part in a neuroimaging sub-study on the neurobiological basis of violence. Participants in the neuroimaging sub-study were over-selected for violence and, therefore, had more years of violence than the full cohort. Sub-study participants also had more conduct problems in childhood at study outset and were more likely to be Black. Effect sizes for these differences were small, but findings might not generalize to samples that are predominantly White or other races/ethnicities or to samples with fewer years of violence. Relatedly, findings might not generalize to girls and to younger cohorts who will be exposed to the now higher levels of THC in cannabis (ElSohly et al., 2016; Rigucci et al., 2016). Seventh, this study focused on adolescent cannabis use as a predictor of adult brain structure and did not take account of patterns of cannabis use in

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adulthood.

4.1 Conclusion

This study has a number of implications. First, the patterns of cannabis use typically seen in community-dwelling adolescents do not appear to have lasting effects on brain structure, as we found no association between prospectively-assessed adolescent cannabis use and subcortical brain volume and cortical brain volume and thickness in adulthood. Second, however, longitudinal studies are needed to examine associations between adolescent cannabis use and changes in both brain structure and function from before to after cannabis initiation. Third, findings should be interpreted in the context of research suggesting that adolescent cannabis use might have lasting effects on white matter integrity and brain function, as well as research suggesting that adolescent cannabis use increases risk for psychotic symptoms and psychosis (Arseneault et al., 2002; Bechtold et al., 2016; Bourque et al., 2018), academic problems (Meier et al., 2015; Silins et al., 2014), social, economic, and occupational problems (Cerdá et al., 2016), and cannabis use disorder (Chen et al., 2009; Silins et al., 2014). Because adolescent cannabis use appears to be associated with functional impairment, encouraging adolescents to delay use or quit is prudent.

Author Disclosures

Contributors

DP conceived the study and collected the data. RS, JB, and JH conducted data analyses. RS and MM drafted

the manuscript. All authors revised the manuscript and approved the final article.

Conflict of Interest

No conflict declared.

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Figure Legend

Figure 1. Adolescent cannabis, alcohol, and tobacco trajectories for the participants in the neuroimaging sub-study (N=181).
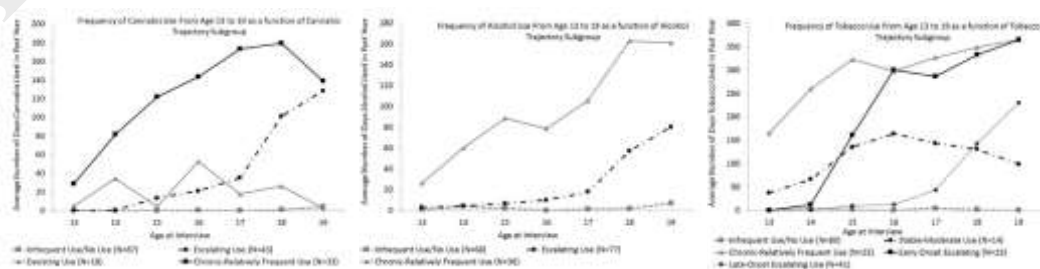
Table 1: Comparisons between participants in the initial PYS sample and those who participated in the neuroimaging sub-study

	Entire PYS sample		Participants in neuroimaging sub-study		Comparison between those who did and did not participate in neuroimaging sub-study
	N/M	%/SD	N/M	%/SD	
Black Race	557	55.2	132	64.4	$x^2 = 8.14$, $p = .004$, Cramer's V = .091
High risk on conduct problems screener[a]	513	50.8	120	58.5	$x^2 = 5.26$, $p = .022$, Cramer's V = .072
Childhood SES	37.4	12.2	36.5	11.1	$t(245.25) = 1.09$, p=.277, d=.092
Years of Violence[b]	1.8	2.30	2.20	2.43	$t(244.41) = -2.57$, p=.011, d=.219
Cannabis LCGA					$x^2 = 6.28$, $p = .099$, Cramer's V = .080
Infrequent use/no use	524	53.0	87	48.1	
Desisting use	101	10.2	18	9.9	
Escalating use	238	24.1	43	23.8	
Chronic-relatively frequent use	126	12.7	33	18.2	
Alcohol LCGA					$x^2 = 1.74$, $p = .420$, Cramer's V = .042
Infrequent use/no use	403	40.7	68	37.6	
Escalating use	419	42.4	77	42.5	
Chronic-relatively frequent use	167	16.9	36	19.9	
Tobacco LCGA					$x^2 = 2.75$, $p = .600$, Cramer's V = .053
Infrequent use/no use	456	46.1	80	44.2	
Early-onset escalating	130	13.1	23	12.7	
Stable-moderate use	90	9.1	14	7.7	
Late-onset escalating use	183	18.5	41	22.7	
Chronic-relatively frequent use	130	13.1	23	12.7	

Note. LCGA=latent class growth analysis. a. High risk on conduct problems screener refers to scoring high on the conduct problems screener at the study outset. b. Years of violence refers to the number of years a participant had engaged in violent behavior using annual data from age 11 to 25.

Table 2: Comparison of adolescent cannabis trajectory subgroups on covariates for participants in the neuroimaging sub-study.

| Covariates | Adolescent Cannabis Trajectory Subgroups | | | | Statistical Test of Group Differences |
	Infrequent Use/No Use N=87	Desisting Use N=18	Escalating Use N=43	Chronic-Relatively Frequent Use N=33	
Race (% Black)	60.9	72.2	72.1	60.6	$x^2 = 2.26$, $p = .520$, Cramer's V = .112
Conduct problems screener[a] (% High Risk)	43.7	83.3	65.1	75.8	$x^2 = 17.28$, $p = .001$, Cramer's V = .309
Childhood SES (M [SD])	37.74 (10.66)	33.92 (9.55)	37.50 (12.26)	32.90 (11.08)	F (3) = 1.70, $p = .169$, $\eta^2 = .033$
Years of Violence[b] Ages 11-25 (M [SD])	1.02 (1.75)	3.72 (2.69)	3.12 (2.78)	3.51 (2.18)	F (3) = 17.45, $p < .001$, $\eta^2 = .228$
Cumulative Days of Cannabis Use From Age 13 to 19 (M [SD])	4.48 (13.89)	127.33 (193.56)	269.79 (268.97)	782.00 (446.42)	F (3) = 86.26, $p < .001$, $\eta^2 = .594$
Alcohol Trajectory	63.2% Infrequent use/no use	38.9% Infrequent use/no use	9.3% Infrequent use/no use	6.1% Infrequent use/no use	$x^2 = 103.12$, $p < .001$, Cramer's V = .532
	33.3% Escalating	38.9% Escalating	76.7% Escalating	24.2% Escalating	
	3.4% Chronic	22.2% Chronic	14.0% Chronic	69.7% Chronic	
Tobacco Trajectory	66.7% Infrequent use/no use	27.8% Infrequent use/no use	23.3% Infrequent use/no use	21.1% Infrequent use/no use	$x^2 = 73.30$, $p < .001$, Cramer's V = .367
	2.3% Early-onset escalating	11.1% Early-onset escalating	25.6% Early-onset escalating	24.2% Early-onset escalating	
	5.7% Stable-moderate use	16.7% Stable-moderate use	4.7% Stable-moderate use	12.1% Stable-moderate use	
	23.0% Late-onset escalating use	16.7% Late onset-escalating use	37.2% Late-onset escalating use	6.1% Late-onset escalating use	

| 2.3% Chronic | 27.8% Chronic | 9.3% Chronic | 36.4% Chronic |

Note. a. High risk on conduct problems screener refers to scoring high on the conduct problems screener at the study outset. b. Years of violence refers to the number of years a participant had engaged in violent behavior using annual data from age 11 to 25.

Table 3: Adolescent cannabis trajectory subgroup differences and moderation by laterality on subcortical volumes

Brain Region	Infrequent Use/No Use ($n = 87$)		Desisting Use ($n = 18$)		Escalating Use ($n = 43$)		Chronic-Relatively Frequent Use ($n = 33$)		Main Effect of Trajectory Subgroup	Trajectory Subgroup x Laterality
	M	(SE)	M	(SE)	M	(SE)	M	(SE)	F (p)	F (p)
Amygdala	1.46	(0.02)	1.46	(0.04)	1.46	(0.03)	1.43	(0.03)	0.22 (.880)	1.03 (.381)
Hippocampus	3.69	(0.04)	3.71	(0.09)	3.65	(0.06)	3.70	(0.06)	0.23 (.878)	0.64 (.591)
Nucleus Accumbens	0.62	(0.01)	0.61	(0.02)	0.61	(0.01)	0.61	(0.02)	0.12 (.947)	0.24 (.866)
Caudate	4.03	(0.05)	4.02	(0.11)	3.99	(0.07)	4.02	(0.08)	0.07 (.979)	1.88 (.135)
Putamen	6.02	(0.07)	6.10	(0.14)	6.05	(0.09)	5.99	(0.10)	0.14 (.935)	0.65 (.583)
Pallidum	2.03	(0.03)	2.04	(0.06)	1.99	(0.04)	2.11	(0.05)	1.29 (.280)	1.24 (.298)

Note. Subcortical volume values are x 10^3. Means represent the average between the left and right hemispheres of each region and are adjusted for race, ICV, age at neuroimaging, and years of violence from age 11-25. Significance of trajectory subgroup main effect and trajectory subgroup by laterality interaction were evaluated using a Bonferroni correction (α= .05 / 6 subcortical regions = .008). In addition to testing the main effect of cannabis trajectory, we also conducted pairwise comparisons between the chronic-relatively frequent subgroup and the infrequent/no use subgroup. None of these pairwise comparisons were statistically significant.

Table 4: Adolescent cannabis trajectory subgroup differences and moderation by laterality on cortical volumes

Brain Region	Infrequent Use /No Use (n = 87)		Desisting Use (n = 18)		Escalating Use (n = 43)		Chronic-Relatively Frequent Use (n = 33)		Main Effect of Trajectory Subgroup	Trajectory Subgroup x Laterality
	M	(SE)	M	(SE)	M	(SE)	M	(SE)	F (p)	F (p)
Superior Frontal	2.30	(0.02)	2.28	(0.05)	2.30	(0.03)	2.22	(0.03)	1.35 (.261)	1.68 (.173)
Caudal Middle	0.65	(0.01)	0.66	(0.02)	0.65	(0.01)	0.63	(0.02)	0.75 (.523)	0.98 (.403)
Rostral Middle	1.64	(0.02)	1.61	(0.04)	1.68	(0.03)	1.65	(0.03)	0.91 (.437)	1.62 (.187)
Pars Opercularis	0.46	(0.01)	0.47	(0.01)	0.46	(0.01)	0.44	(0.01)	1.20 (.311)	0.88 (.451)
Pars Triangularis	0.41	(0.01)	0.40	(0.01)	0.41	(0.01)	0.40	(0.01)	0.53 (.662)	0.21 (.893)
Pars Orbitalis	0.24	(0.00)	0.24	(0.01)	0.24	(0.00)	0.25	(0.01)	0.23 (.878)	0.96 (.414)
Lateral OF	0.78	(0.01)	0.76	(0.02)	0.79	(0.01)	0.77	(0.01)	0.73 (.535)	0.20 (.900)
Medial OF	0.53	(0.01)	0.52	(0.01)	0.54	(0.01)	0.52	(0.01)	1.60 (.192)	0.43 (.735)

Note. Cortical volume values are x 10^4. Means represent the average between the left and right hemispheres of each region and are adjusted for race, ICV, age at neuroimaging, and years of violence from age 11-25. Significance of trajectory subgroup main effect and trajectory subgroup by laterality interaction were evaluated using a Bonferroni correction (α= .05 / 8 Cortical regions = .006). In addition to testing the main effect of cannabis trajectory, we also conducted pairwise comparisons between the chronic-relatively frequent subgroup and the infrequent/no use subgroup. None of these pairwise comparisons were statistically significant.

Table 5: Adolescent cannabis trajectory subgroup differences and moderation by laterality on cortical thicknesses

Brain Region	Infrequent Use /No Use (*n* = 87)		Desisting Use (*n* = 18)		Escalating Use (*n* = 43)		Chronic-Relatively Frequent Use (*n* = 33)		Main Effect of Trajectory Subgroup	Trajectory Subgroup x Laterality
	M	*(SE)*	*M*	*(SE)*	*M*	*(SE)*	*M*	*(SE)*	*F* (*p*)	*F* (*p*)
Superior Frontal	2.70	(0.01)	2.69	(0.03)	2.67	(0.02)	2.65	(0.02)	1.12 (.341)	0.75 (.521)
Caudal Middle	2.57	(0.01)	2.59	(0.03)	2.52	(0.02)	2.51	(0.02)	2.63 (.052)	1.12 (.342)
Rostral Middle	2.35	(0.01)	2.36	(0.03)	2.32	(0.02)	2.32	(0.02)	0.95 (.416)	1.23 (.301)
Pars Opercularis	2.63	(0.01)	2.62	(0.03)	2.59	(0.02)	2.56	(0.02)	2.44 (.066)	0.41 (.750)
Pars Triangularis	2.47	(0.02)	2.47	(0.04)	2.46	(0.02)	2.44	(0.03)	0.32 (.808)	0.15 (.929)
Pars Orbitalis	2.64	(0.02)	2.67	(0.04)	2.64	(0.03)	2.61	(0.03)	0.51 (.677)	1.34 (.262)
Lateral OF	2.56	(0.01)	2.54	(0.03)	2.53	(0.02)	2.55	(0.02)	0.41 (.746)	0.43 (.730)
Medial OF	2	(0.	2	(0.	2	(0.	2	(0.	1.05	0.87

									(.373)	(.460)
. 4 1	01)	. 4 4	03)	. 3 9	02)	. 3 8	02)			

Note. Cortical thickness values are x 10^3. Means represent the average between the left and right hemispheres of each region and are adjusted for race, ICV, age at neuroimaging, and years of violence from age 11-25. Significance of trajectory subgroup main effect and trajectory subgroup by laterality interaction were evaluated using a Bonferroni correction ($\alpha = .05 / 8$ Cortical regions = .006). In addition to testing the main effect of cannabis trajectory, we also conducted pairwise comparisons between the chronic-relatively frequent subgroup and the infrequent/no use subgroup. None of these pairwise comparisons were statistically significant.