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The relation between cannabis use, dependence severity and white matter microstructure: A diffusion tensor imaging study

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Abstract

Despite the significant societal and personal burden of cannabis use, the impact of long-term use and Cannabis Use Disorder (CUD) on white matter microstructure is still unclear. Previous studies show inconsistent findings, in part due to heterogeneity in methodology, variable severity of cannabis use, and potential confounding effects of other mental health issues and substance use. The goal of this diffusion tensor imaging (DTI) study was to compare whole-brain white matter microstructure between 39 near daily cannabis users and 28 controls closely matched on age, sex, alcohol use, cigarette use and mental health. Within the group of cannabis users, associations between white matter microstructure and recent cannabis use, dependence severity, and age of onset and duration of weekly use were investigated. White matter microstructure did not differ between cannabis users and controls and did not covary with recent cannabis use, dependence severity, or duration of use. Earlier onset of weekly cannabis use was related to lower fractional anisotropy (FA) in various sections of the right inferior longitudinal fasciculus and uncinate fasciculus. These findings suggest that long-term near-daily cannabis use does not necessarily affect white matter microstructure, but vulnerability may be higher during adolescence. These findings underscore the importance of sample composition and warrant further studies that investigate the moderating role of age of onset in the impact of cannabis on the brain.

KEYWORDS
age of onset, cannabis, cannabis dependence, diffusion tensor imaging, white matter

1 | INTRODUCTION

Paralleling increases in cannabis potency[1] and decreases in risk perception,[2] worldwide cannabis policies show a tendency towards decriminalisation of medical and recreational use. Cannabis Use Disorders (CUDs) are among the most prevalent substance use disorders, especially in young adults, and global treatment demands have been increasing.[3] Regular cannabis use is a risk factor for comorbid mental health problems (i.e., psychosis, mood disorders and anxiety)[4] and remission rates among those seeking treatment are estimated at 17%.[5] Yet, the debate about potential harms and benefits is still ongoing and partially fuelled by mixed results

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regarding the impact of long-term cannabis use on brain structure and function.[6] The limited number of available studies, heterogeneity of the studied samples regarding severity of cannabis use, and potential confounding effects of other substance use and mental health issues currently prevent us from drawing strong conclusions.[4,7] It is important to strengthen the evidence base by conducting replication studies and investigating which characteristics of the cannabis users potentially affect the brain. Therefore, the goal of this diffusion tensor imaging (DTI) study was to compare white matter microstructure between cannabis-using young adults and non-cannabis-using controls closely matched on age, sex, alcohol use, cigarette use and mental health. Moreover, within the group of cannabis users we investigated associations between local white matter microstructure and recent cannabis use, dependence severity, and age of onset and duration of weekly use.

The main psychoactive compound of cannabis, Δ^9-tetrahydrocannabinol (THC),[8] primarily interacts with the brain's endogenous cannabinoid system by binding to the type 1 cannabinoid receptor (CB_1R). CB_1Rs are abundant throughout the brain and serve a complex role in short and long-term neuroplasticity through interaction with many other neurotransmitter systems.[9] Furthermore, the age during which cannabis use often starts and peaks[3] coincides with an important period of brain development. Both adolescents and young adults may be particularly vulnerable to the effects of cannabis use on white matter, as it continuously develops throughout the first three decades of life at least.[10] Although the precise mechanisms are unclear, cannabis use may specifically impact brain regions involved in learning, memory, reward and executive control, with larger effects in more frequent users.[4,7,for reviews see 11] Moreover, about one third of daily cannabis users develop a CUD.[12] Independently from effects of cannabis exposure itself, the development of a CUD may involve widespread plasticity in the same brain systems.[13]

DTI allows us to study white brain matter microstructure in vivo.[14] It measures restriction of water diffusivity in multiple directions from which we can derive directional coherence of diffusivity (fractional anisotropy, FA), mean diffusivity across all directions (MD), diffusivity perpendicular to white matter tracts (radial diffusivity; RD) and diffusion along the primary axis parallel to white matter tracts (axial diffusivity; AD). While FA is suggested to be sensitive to changes in axon density, diameter and myelination, AD may reflect axon damage, RD may reflect changes in axon myelination, and MD may reflect changes in membrane density.[15,16]

Several studies have investigated white matter microstructure in cannabis users, showing inconsistent results.[17] Some cross-sectional studies found no differences between weekly cannabis users and non-using controls.[18,19] In contrast, others reported differences in weekly cannabis users compared to non-using controls in the forceps minor (higher FA and lower RD[20]; lower FA[21]; higher MD[22]), superior longitudinal fasciculus (SLF; lower FA[23]), bilateral hippocampus (lower FA[23]), the uncinate fasciculus (lower FA and higher MD[22]) and the frontal part of the corpus callosum (higher MD[18]). In individuals with a diagnosed CUD compared to non-using controls, one study found lower FA in various parietal and temporal white matter bundles,[24] while another study did not find any significant group differences.[25] Moreover, a 2-year longitudinal study in weekly cannabis users reported more widespread alterations over time in various frontal, temporal and parietal white matter tracts, which covaried with cannabis exposure over time.[26] Another longitudinal study in adolescents with CUD reported an FA reduction in the inferior longitudinal fasciculus (ILF) over time that correlated with cannabis exposure.[27] In sporadic cannabis users, Orr et al. (2016) did not find group differences in white matter microstructure, but an earlier age of onset was associated with lower FA and higher RD in the ILF, SLF, forceps major and forceps minor.[28] However, others reported non-significant effects of age of onset of cannabis use.[18,20,21,26,27,29]

These highly heterogenous results currently prevent us from drawing strong conclusions about the relation between cannabis use and white matter microstructure. Differences in CUD severity may in part explain differences between samples; however, associations with CUD severity have only been studied in the forceps minor by Filbey et al. (2014), who reported a non-significant effect.[20] Moreover, the difficulties of reliably assessing cannabis use history and potential confounding effects of other mental health issues and substance use could play an important role. Alcohol use, cigarette use and mental health problems are often more prevalent in the sampled cannabis users compared to controls, and both alcohol use[30] and depressive symptoms[22] have been found to covary with FA in white matter tracts that significantly differed between cannabis users and controls. This highlights the importance of replication studies that systematically assess the relation between white matter microstructure and different characteristics of cannabis use, including CUD severity, while taking these potential confounding factors into account. Therefore, the current study focused on young adult weekly to daily cannabis users with varying degrees of CUD severity and sporadically using controls carefully matched on alcohol use, cigarette use and mental health. We compared whole brain white matter microstructure between groups and investigated associations with cannabis use characteristics. Despite inconsistent results and a lack of studies investigating relations with CUD severity, previous studies preliminarily suggest that cannabis use may affect white mater microstructure depending on the severity of cannabis use, severity of CUD, and the age of onset of use, such that the impact of cannabis use would be more severe (i.e., lower FA and AD, but higher MD and RD) in more severe users that started at a younger age.

2 | MATERIALS AND METHODS

This study focused on DTI data that was collected as part of a neuroimaging study that aimed to replicate previous effects of cannabis use on brain structure and function, explicitly matching cannabis users and controls on alcohol use, cigarette use, and biological sex. All study protocols were approved by the local ethics committee of the University of Amsterdam Faculty of Social and Behavioral Sciences (2015-DP-6387) and all participants provided informed consent prior to testing.

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2.1 | Participants

DTI data was collected from 39 cannabis users and 31 matched non-using controls. All participants were young adults aged between 18 and 25 years. Similar to our previous study,[31,32] cannabis users were included if they used cannabis on more than 10 occasions per month, for at least two consecutive years, while controls were included if they sporadically used cannabis between 1 and 50 times during their life, but not during the past year. Potential participants were excluded if they had a self-reported clinical diagnosis or treatment history for any psychiatric disorder, smoked more than 20 cigarettes per day, scored higher than 12 on the Alcohol Use Disorder Identification test (AUDIT),[33] used any illicit or prescribed psychoactive substance during the past month, or met any MRI contraindication. Due to serious DTI data distortion, three controls were excluded from further analyses. The final sample consisted of 39 cannabis users and 28 controls (see Table 1 for sample characteristics).

2.2 | Assessments of substance use and psychological functioning

Severity of cannabis use and related problems during the past 6 months was assessed with the 8-item CUD Identification Test-Revised (CUDIT-R).[34] Current DSM-5 CUD symptoms were assessed through a short structured interview (Dutch translation of the SCID DSM-5 CUD).[35] Severity of alcohol use and related problems during the past 6 months was assessed with the 10-item AUDIT.[33] Severity of nicotine use and dependence during the past 6 months was assessed with the 6-item Fagerström Test for Nicotine Dependence (FTND).[36] We used an adapted Timeline Followback (TLFB) procedure to assess recent cannabis (grams), alcohol (standard units) and cigarette (total number) use during the past 14 days.[37] Furthermore, a detailed history of cannabis use was assessed, including self-reported age of onset of daily use, duration of daily use (years), and weekly use (days) for the cannabis users and total lifetime use for control participants. Participants were also

TABLE 1 Sample characteristics

	Controls ($n = 28$)	Cannabis users ($n = 39$)	*P*	BF_{01}
Age (years), mean (SD)	21.4 (2.0)	21.5 (2.3)	0.862	3.90
Female (*n*), %	16 (57)	17 (44)	0.274	1.86
Intelligence (sum WAIS matrix and similarities), mean (SD)	21.3 (4.3)	21.1 (4.2)	0.882	3.91
Alcohol use-related problems (AUDIT), mean (SD)	6.1 (3.3)	6.6 (4.4)	0.833[a]	3.88
Cigarette smokers (*n*), %	12 (43)	19 (49)	0.635	3.00
Nicotine dependence (FTND) among smokers, mean (SD)	2.4 (1.7)	2.7 (1.9)	0.700	2.73
Cannabis use and related problems (CUDIT-R), mean (SD)	0.5 (1.0)	13.7 (4.3)	**<0.001**[a]	**<0.01**
DSM-5 CUD symptom count	–	3.4 (1.6)	–	–
Weekly cannabis use (days)	–	4.7 (1.7)	–	–
Onset cannabis use (age), mean (SD)	16.5 (1.5)	15.33 (1.9)	**0.012**	**0.25**
Onset weekly cannabis use (age), mean (SD)	–	17.4 (2.0)	–	–
Duration weekly cannabis use (years), mean (SD)	–	4.1 (2.2)	–	–
Lifetime cannabis use (number of uses), mean (SD)	14.5 (37.8)	–	–	–
Cannabis use past 2 weeks (gram), mean (SD)	0.0 (0.0)	9.2 (10.7)	–	–
Alcohol use past 2 weeks (standard glasses), mean (SD)	15.0 (18.5)	12.5 (12.0)	0.904[a]	3.87
Cigarette use past 2 weeks (*n*), mean (SD)	65.9 (93.4)	70.9 (85.3)	0.327[a]	3.17
Lifetime Illicit substance (number of uses), mean (SD)	28.0 (118.5)	22.7 (29.9)	**<0.001**[a]	**0.05**
Depression (BDI), mean (SD)	3.8 (3.3)	5.4 (4.3)	0.099[a]	1.15
Anxiety (STAI) State, mean (SD)	31.2 (6.0)	31.1 (7.3)	0.504[a]	3.60
Anxiety (STAI) Trait, mean (SD)	33.6 (5.6)	35.1 (8.3)	0.593[a]	3.50
ADHD (CAARS), mean (SD)	16.3 (8.2)	17.2 (9.3)	0.760[a]	3.55
Impulsivity (BIS-11), mean (SD)	64.0 (6.2)	64.9 (7.6)	0.588	3.46

Note: *p* values reflect group comparison with independent sample *t* test, non-parametric Mann–Whitney U test or chi-square tests for categorical data. Abbreviations: SD, standard deviation; WAIS, Wechsler Adult Intelligence Scale; AUDIT, Alcohol Use Disorder Identification Test; FTND, Fagerström Test for Nicotine Dependence; CUDIT-R, Cannabis Use Disorder Identification Test-Revised; DSM-5, Diagnostic and Statistical Manual of Mental Disorders; CUD, Cannabis Use Disorder; BDI, Beck Depression Inventory; STAI, State–Trait Anxiety Inventory; CAARS, Conners Adult ADHD Rating Scale; BIS-11, Barratt Impulsiveness Scale; BF_{01}, Bayes factor likelihood H0 relative to H1 with default priors.
[a]Non-parametric Mann–Whitney U test.

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asked the number of times they used any illicit substances during their life.

Depression, anxiety and ADHD often co-occur with cannabis use and CUD.[38] Presence and severity of depressive symptoms were therefore assessed with the 21-item Beck Depression Inventory-II (BDI),[39] anxiety symptoms with the 40-item State–Trait Anxiety Inventory for Adults (STAI),[40] and ADHD symptoms with the 23-item Conners' Adult ADHD Rating Scale (CAARS).[41] Finally, impulsivity was assessed with the 30-item Barratt Impulsiveness Scale (BIS)[42] and intelligence was estimated through administration of the matrix reasoning and verbal similarities subtests of the Wechsler Adult Intelligence Scale IV-NL.[43]

2.3 | Procedures

Participants were recruited via advertisements in local cannabis outlets and on social media. Over the course of data collection, recruitment became more targeted to ensure groups were matched on biological sex, alcohol use, cigarette use, and estimated intelligence. Potential participants were first interviewed by phone to screen for inclusion and exclusion criteria. All participants were asked to abstain from any alcohol or substance use (except for cigarettes) 24 h before testing. On the day of testing, a multi-panel urine drug test was conducted to increase abstinence compliance.[44] While this approach is insensitive to short-term cannabis abstinence, we confirmed abstinence for amphetamine, benzodiazepine, cocaine, and opioids in all participants. All testing took place in a single afternoon session and started with the urine drug test followed by the WAIS subtests. All other questionnaires were administered after the MRI session. All participants were financially compensated.

2.4 | Diffusion tensor image acquisition and preprocessing

DTI data was collected using a Philips 3 T Intera MRI scanner (Philips, Best, The Netherlands) with a 32-channel SENSE head coil and 80 mT/s gradient fields strength. Two separate DTI scans were acquired with the same echo planar imaging (EPI) acquisition parameters (pulse-gradient spin echo, TE = 71 ms, TR = 7329 ms, FOV = 240 × 240 × 150 mm, reconstructed voxel size = 1.875 mm, slice thickness = 2 mm, 75 slices, no slice gap, flip angle = 90°, SENSE reduction = 3, no cardiac gating), except for a reversed anterior–posterior direction of the k-space readout. One $b = 0$ (NSA = 4) and 30 diffusion-weighted volumes were acquired [$b = 1000 s/mm^2$ with uniformly distributed diffusion directions using the approach of Jones et al. (1999)[45]].

DTI image preprocessing was conducted with FMRIB's Diffusion Toolbox (FDT) and Tract-Based Spatial Statistics (TBSS),[46] part of FMRIB's Software Library (FSL) version 5.0.9.[47] Preprocessing included brain extraction, eddy current correction, EPI induced distortion correction and merging of the two DTI images with FSL TOPUP[48] and tensor fitting. The latter involved fitting of a diffusion tensor per voxel and resulted in four different indices of interest, representing directionality and size of water diffusion: Fractional Anisotrophy (FA; directional restriction of diffusion; relative difference largest λ compared to the other λs), Mean Diffusivity (MD; average λ_1, λ_2, λ_3), Radial Diffusivity (RD; average λ_2, λ_3; magnitude of diffusion perpendicular to white matter tracts), Axial Diffusivity (AD; λ_1; magnitude of diffusion along the primary axis, parallel to white matter tracts). Quality control of pre-processed images and TBSS analysis followed the freely available DTI protocol of the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Consortium (http://enigma.ini.usc.edu/ongoing/dti-workinggroup/) to allow for method harmonisation and potential data contribution to ENIGMA. The participants' FA images were nonlinearly registered to the ENIGMA-DTI template in standard space, which was derived from 400 adults scanned at four sites for optimal multisite harmonisation.[49] Skeletonized FA images were created by projecting participants' registered FA images to the ENIGMA-DTI template skeleton. From the individual FA skeletons, a mean FA skeleton was generated, which was thresholded at FA > 0.2. These FA registration and transformation parameters were subsequently used to create skeletonized MD, AD and RD images in standard space. As part of quality control, the DTI images were visually inspected before preprocessing, after tensor fitting, and after registration.

2.5 | Statistical analyses

Scores on questionnaires and sample characteristics were compared between groups with parametric or non-parametric (in case normality assumptions were violated) t-tests and chi-square tests for categorical data. Complementary Bayesian analyses were run to estimate evidence strength for H0 (i.e., no group difference) relative to H1 with default priors (BF_{01}), following Jeffreys' benchmarks for the interpretation of evidence strength.[50] These analyses were run in JASP version 0.9.2 (JASP team 2019, Amsterdam, The Netherlands).

Regarding diffusion data, voxelwise differences in FA, MD, RD and AD were first compared between cannabis users and controls. Next, a series of analyses were run in cannabis users only, investigating the linear relationship of FA, MD, RD and AD with recent cannabis use (total grams used during the past 2 weeks), severity of dependence (DSM-5 CUD symptom count), onset of weekly cannabis use (age) and duration of weekly cannabis use (years). These analyses were performed in skeleton space using randomise, FSL's tool for general linear model-based non-parametric permutation inferences,[51] using a total of 5000 permutations. A threshold-free cluster enhancement (TFCE)[52] correction for multiple comparisons was applied with a familywise error (FWE) rate of $p < 0.05$. Given the limited age range and equal distribution of males and females in both groups, analyses were initially performed without correction for age and sex. When a significant effect was found,

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a multiple regression analysis was performed using the extracted peak diffusion values to investigate if the effect survived additional correction for age, sex, recent cannabis, alcohol and nicotine use (TLFB), and lifetime illicit substance use.

3 | RESULTS

3.1 | Sample characteristics

Table 1 provides an overview of the sample characteristics. Compared to the control group, cannabis users did not significantly differ in age, estimated intelligence, alcohol and cigarette use during the past 2 weeks, severity of alcohol use-related problems, anxiety, ADHD, and impulsivity, with moderate evidence strength ($BF_{01} > 3$). There was insufficient evidence to support or refute a group difference in sex, severity of nicotine dependence within smokers and depression (*p*s < 0.099, BF_{01} 1.15–2.73). Cannabis users used cannabis 4.7 days per week on average. The majority of cannabis users met diagnostic criteria for CUD (no CUD = 4, mild = 17, moderate = 15, severe = 3). Besides our sampled differences in cannabis use measures, there was strong evidence for a group difference in lifetime illicit substance use *(median cannabis users = 12; median controls = 0*, $U = 236$, $p < 0.001$, $d = 0.57$, $BF_{01} = 0.047$). Of note, illicit substance use mainly reflected MDMA use, with nobody using cocaine on more than 15 occasions or any opiates.

3.2 | Group comparisons

FA, MD, RD and AD did not significantly differ between cannabis users and controls (TFCE corrected, FWE $p < 0.05$).

3.3 | Associations with cannabis use and dependence

Within the group of cannabis users, FA, MD, RD and AD was not significantly associated with recent cannabis use (TLFB total grams used during the past 2 weeks), severity of dependence (DSM-5 symptom count) or duration of weekly cannabis use (years). However, FA in various clusters of two white matter tracts in the right temporal lobe related negatively to age of onset of weekly cannabis use; ILF (near occipital-temporal fusiform gyrus, 46 voxels, $p_{\text{-max}} = 0.037$, contrast of parameter estimate = 0.019, $x_{\text{-max}} = 33$, $y_{\text{-max}} = -47$, $z_{\text{-max}} = -14$; near superior temporal gyrus, 30 voxels, $p_{\text{-max}} = 0.048$, contrast of parameter estimate = 0.014, $x_{\text{-max}} = 48$, $y_{\text{-max}} = -13$, $z_{\text{-max}} = -6$) and uncinate fasciculus (53 voxels, $p_{\text{-max}} = 0.045$, contrast of parameter estimate = 0.017, $x_{\text{-max}} = 39$, $y_{\text{-max}} = 9$, $z_{\text{-max}} = -28$). As can be seen in Figure 1, a younger age of onset was associated with lower FA, however, all FA values still fell within the FA range of the control group. Post hoc multiple regression analysis with extracted peak FA values showed that this association was still significant after correction for age, sex and recent cannabis, alcohol and cigarette use (i.e., TLFB)

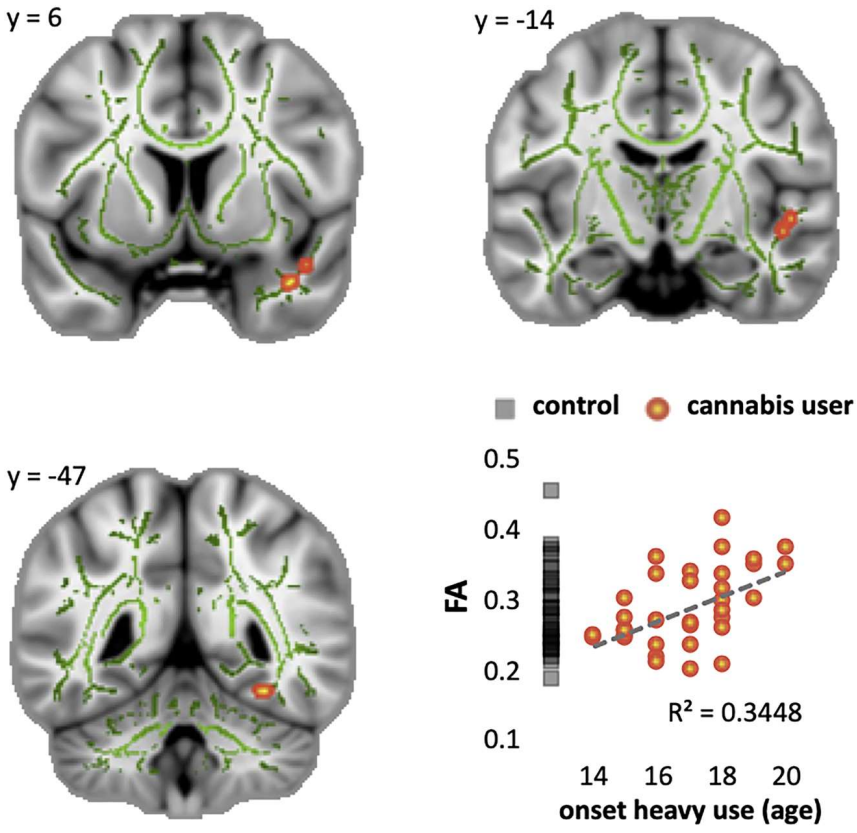

FIGURE 1 Association of onset of weekly cannabis use and fractional anisotropy (FA) in right temporal lobe. Significant clusters in the inferior longitudinal fasciculus and uncinate fasciculus (threshold-free cluster enhancement corrected with $p < 0.05$ familywise error rate) are shown superimposed on average white matter skeleton (green) and standard MNI 152 T1. Scatterplot depicts FA at peak voxel ($x = 33$, $y = -47$, $z = -14$) in cannabis users (red/orange dots) relative to onset age and in controls (grey squares) for reference

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and lifetime illicit substance use, with age of onset explaining 18% of the variance in FA ($p = 0.004$, t (31) = 3.11, $b = 0.58$). MD, RD and AD did not significantly relate to onset of weekly use.

4 | CONCLUSIONS

Despite the significant societal and personal burden of cannabis use,[3,4,53] the impact of long-term use and CUD on white matter microstructure is still unclear. Previous DTI studies are limited in number and inconsistent in findings, in part due to heterogeneity in methodology, assessed severity of cannabis use and CUD, and potential confounding effects of other substance and mental health related issues.[17] This study aimed to further elucidate the relation between cannabis use and white matter microstructure in weekly to daily young adult cannabis users with varying levels of CUD. Relative to the existing evidence base, clear strengths of this study include the matching of cannabis users and controls on alcohol use, number of cigarette users, and mental health, as well as the systematic whole-brain investigation of associations with dependence severity, onset, duration and frequency of use. White matter microstructure did not differ between near daily cannabis users and sporadic cannabis using controls and did not covary with recent cannabis use, duration of use, and CUD symptom severity. However, earlier onset of weekly cannabis use related to lower FA in various sections of the right ILF and uncinate fasciculus. These results suggest that near-daily cannabis use does not necessarily influence white matter microstructure in young adults, but, in line with previous findings, those starting weekly use relatively young may be at an increased risk.[28,54] These results and their implications are elaborately discussed below.

The cannabis users in the current study used on average 5 days per week, 50% started using cannabis weekly before the age of 18, and 90% met criteria for at least a mild CUD. Cannabis users and controls did not differ in alcohol use, cigarette use, anxiety, ADHD, and impulsivity (moderate evidence strength), but there was insufficient evidence to support or refute a group difference in severity of nicotine dependence within smokers (FTND) and depression (BDI). In contrast to most previous studies in weekly young adult cannabis users,[18,20,22,26,30] we did not find group differences in regional white matter microstructure (but see previous work[19]). However, almost all of these studies reported significant differences in alcohol and/or cigarette use, which suggests that these white matter alterations may be a result of differences in alcohol and cigarette use. Indeed, a DTI study in polysubstance users demonstrated that cannabis use is associated with strong reductions in bilateral uncinate fasciculus FA only when alcohol and cocaine are also heavily used.[55] Regarding mental health, while most studies do not report their confounding effect, Shollenbarger et al. (2015) reported differences in depressive symptoms correlating with FA in the left uncinate fasciculus.[22] The absence of group differences between relatively closely matched near daily cannabis users and sporadic cannabis using controls in the current study highlight the importance of control group composition. Statistical approaches that correct for variance explained by other substance use and mental health issues may not be sufficient to reveal cannabis use specific associations. Since comorbidities are a rule rather than an exception in these populations, researchers are encouraged to embrace the heterogeneous nature of substance using and dependent samples and select control samples accordingly.

Despite the lack of group differences, earlier onset of weekly cannabis use related to lower FA in the right uncinate fasciculus and ILF near the occipital-temporal fusiform gyrus and superior temporal gyrus. Orr et al. (2016) reported a similar association between onset of use and FA in the right ILF in occasional cannabis users (i.e., >100 lifetime uses)[28] and Epstein et al. (2015) reported reductions in FA in the left ILF over time correlating with cannabis exposure in adolescents with a CUD.[27] Our results were independent of age, sex, lifetime illicit substance use and recent cannabis, alcohol and cigarette use. Moreover, duration of cannabis use was not associated with white matter microstructure, suggesting a developmental sensitivity period during which younger adolescents in particular may be more vulnerable to effects of cannabis use. Early onset has been associated with higher risk to develop CUD[56] and differences in brain function and structure between cannabis users and controls seem to be more pronounced in early versus late onset users.[57] Rodent studies directly comparing adolescent versus adult chronic THC exposure suggest reduced THC aversion, but increased vulnerability to learning impairments during adolescence (for a systematic review see[11]). The endocannabinoid system plays a complex role in brain development[9] and early onset of cannabis use may lead to local hyperconnectivity.[58] Moreover, weekly cannabis use may regionally accelerate age-related loss of fibre integrity.[59]

The FA values in the ILF and uncinate fasciculus in the cannabis group fell within range of the control group (see Figure 1). To further explore the role of age of onset, we ran a post-hoc multiple regression analysis investigating if FA at the peak significant voxel ($x = 33$, $y = -47$, $z = -14$) related to age of first cannabis use across the full sample of cannabis users and controls. No association was found ($b = 0.07$, $t = 0.47$, $p = 0.64$), which may indicate that the onset of a more regular pattern of cannabis use is driving the observed effects. Indeed, a tractography study in near-daily cannabis users showed correlations between onset of regular cannabis use (i.e., at least twice per month) and RD and AD in the right fimbria and commissural fibre independent of the duration of cannabis use.[60] However, local effects of early sporadic cannabis exposure undetectable by our test protocol may still be present. Diffusion Tensor Imaging may underestimate diffusion directionality in voxels with crossing fibres.[61] Future studies will benefit from recent developments in multi-shell diffusion imaging, as this technique has been shown to be more sensitive to changes in white matter microstructure over time.[62] Moreover, structural tractography studies may shed further light on the relationship between cannabis use and structural connectivity.

The functional implications of structural alterations remain to be determined. Lower FA could reflect multiple white matter alterations, such as damage to the axon or myelin membrane, reduced axonal coherence, or reduced axonal density.[61] The uncinate fasciculus connects temporal areas with the orbitofrontal cortex, which allows

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integration of (affective) memory associations into decision processes.[63] Psychopathology is mostly associated with abnormalities in the left uncinate fasciculus, except for antisocial behaviour and psychopathy.[63] Similar to the current study, the few existing studies that found associations between cannabis use and FA in the uncinate fasciculus report bilateral[22] or right side[24,64] effects, but functional implications of hemispheric differences are unknown. The ILF connects occipital with temporal areas and is suggested to play an important role in visual guidance of cognition.[65] A functional hypothesis could be that lower FA in the uncinate fasciculus and ILF plays a role in the biassed cognitions in response to (visual) cannabis cues towards cannabis use that are often observed in heavy cannabis users.[66–68] However, this is a speculative notion and more research is needed to investigate the implications and mechanisms underlying the current findings.

CUD treatment demands have increased 75% over the last 10 years in Europe,[3] sharply contrasting with the lack of studies specifically investigating CUD-related mechanisms. Since Filbey et al. (2014)[20] focused on the forceps minor only, our study is the first to assess association between CUD severity and white matter microstructure across the whole brain. In contrast to our expectations, CUD severity did not relate to FA, MD, RD or AD. One explanation for this could be that CUD duration was too short and CUD severity too mild to induce white matter changes. Our sample was relatively young (i.e., below 25), and while most had a mild to moderate CUD, none of them were seeking treatment. Indeed, a study including slightly older (22–35) individuals with a CUD history, found more widespread FA differences[24] and another study showed stronger relations between white matter microstructure and cannabis exposure in older users.[21] The clear CUD research gap needs to be addressed in future studies, including assessments in clinical populations and investigations of distinct vulnerability periods across the lifespan.

Some limitations of the current study should be considered. First, this is a cross-sectional study and longitudinal studies are needed to verify if the association between age of onset and ILF and uncinate fasciculus microstructure is causal or consequential (i.e., a risk factor for early cannabis escalation). Second, we included sporadic cannabis users rather than cannabis naïve individuals in the control group. While the lack of associations between measures of cannabis exposure and white matter microstructure in the current study would argue against effects of sporadic cannabis use on white matter microstructure, a comparison to a cannabis naïve control group is needed to verify this. Third, while lifetime illicit substance use was relatively low in both groups with no use of opiates and limited use of cocaine, the median use differed between cannabis users (i.e., 12) and controls (i.e., 0). This could be a potential confound; however, controlling for illicit substance use did not affect the current findings. Fourth, despite the absence of significant group differences, cannabis use may have interacted with anxiety and depression symptoms in cannabis users,[4] which may also affect the association between cannabis use and white matter microstructure. While our sample size is relatively large compared to existing studies in near-daily cannabis users,[17] our study is insufficiently powered to study such interaction effects or to detect small effects, highlighting the general need for larger neuroimaging studies and replication efforts.[69] Fifth, while recent cannabis use did not relate to FA, MD, RD or AD, we did not quantify cannabis metabolites in urine and cannot exclude potential sub-acute effects. The difficulty of reliably assessing history of cannabis use is a general problem in cannabis studies, potentially contributing to mixed findings. The lack of a standardised cannabis unit and the diversity in cannabis products and methods of administration affect the validity of self-reports both within and between studies.[70] Objective measures like blood, hair and urine analysis are limited to recent use. A strength of our study is the homogeneous method of cannabis use, since all our participants reported to smoke joints made from cannabis bought in Dutch Coffeeshops. The average potency of herbal cannabis in the Netherlands is ~16% THC,[71] which is high compared to the European average.[72] Nevertheless, there is great variability in strength and strain of the available cannabis in Coffeeshops and supply is unregulated.[71] Regional factors (e.g., cannabis product, legislation and risk perception) should be considered and efforts to standardise cannabis research should be encouraged.

In conclusion, the lack of group differences between cannabis users and controls relatively closely matched on alcohol use, cigarette use, and mental health suggests that long-term near-daily cannabis does not necessarily affect white matter microstructure. However, the association between age of onset and ILF and uncinate fasciculus microstructure imply distinct vulnerability periods during development. These findings underscore the importance of sample composition and warrant further studies that investigate the moderating role of age of onset in the impact of cannabis on the brain.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

JC designed and directed the study. JC and YT conducted the analyses with aid from LV and AK and all authors contributed to the interpretation of the results. JC wrote the manuscript with input from all authors. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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