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Recent tobacco use has widespread associations with adolescent white matter microstructure

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HIGHLIGHTS

- Tobacco use showed significant widespread associations with white matter.
- Cannabis use was negatively associated with white matter in one small cluster.
- Alcohol use was negatively associated with white matter integrity in females.
- Tobacco use was negatively associated with cerebellum gray matter in females.
- Tobacco use should always be considered when modelling adolescent substance use.

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ABSTRACT

Importance: Given the prevalence of alcohol, cannabis, and tobacco use during adolescence, it is important to explore the relative relationship of these three substances with brain structure.
Objective: To determine associations between recent alcohol, cannabis, and tobacco use and white and gray matter in a large sample of adolescents.
Design, Setting, and Participants: MRI data were collected in $N = 200$ adolescents ages 14–18 ($M = 15.82$ years; 67% male; 61% Hispanic/Latino). On average, during the past month, participants reported consuming 2.05 drinks per 1.01 drinking day, 0.64 g per 6.98 cannabis use days, and 2.49 cigarettes per 12.32 smoking days.
Main Outcomes and Measures: General linear models were utilized to examine past 30-day average quantities of alcohol, cannabis, and tobacco use, age, sex, and sex by substance interactions in skeletonized white matter (fractional anisotropy and axial, radial, and mean diffusivity) and voxel-based morphometry of gray matter (volume/density).
Results: Tobacco use was negatively associated with white matter integrity (radial and mean diffusivity) with peak effects in inferior and superior longitudinal fasciculi. Cannabis use was negatively associated with white matter integrity (axial diffusivity) in a small cluster in the left superior longitudinal fasciculus. No associations were observed between recent alcohol use and white or gray matter overall, but interactions showed significant negative associations between alcohol use and white matter in females.
Conclusions and Relevance: It is important to note that recent tobacco use, particularly given the popularity of e-tobacco/vaping in this age group, had widespread associations with brain structure in this sample of adolescents.

1. Introduction

The three most common substances used by adolescents are alcohol, cannabis, and nicotine, with 30%, 22%, and 21% (for vaping; 8% for smoking cigarettes) of 12th graders in the United States reporting consumption in the last 30 days, respectively (Johnston, Miech, O'Malley, Bachman, Schulenberg, & Patrick, 2019). Many existing studies have investigated each of these substances individually rather than modeling all three substances concurrently (Karoly et al., 2015), which may contribute to unclear or opposing substance use findings in

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adolescent neuroimaging research. Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that calculates water diffusion to describe white matter (WM) tracts using four scalar measurements: fractional anisotropy (FA; overall WM integrity), mean diffusivity (MD; diffusion in all directions), axial diffusivity (AD; diffusion parallel to a fiber), and radial diffusivity (RD; diffusion perpendicular to a fiber) (Beaulieu, 2002). Higher FA and AD and lower RD and MD are indicative of high axonal myelination (Cardenes et al., 2010). In typical development, FA and AD increase, while MD and RD decrease through adolescence (Bui et al., 2006; Eikenes, Lohaugen, Brubakk, Skranes, & Haberg, 2011), signifying the development of mature WM tracts and more efficient neural communication (Giedd, 2008; Suzuki, Matsuzawa, Kwee, & Nakada, 2003). Studies have also reported a positive correlation between FA and cognition, including working memory capacity, language, and reading ability (Beaulieu et al., 2005; Deutsch et al., 2005; Nagy, Westerberg, & Klingberg, 2004). Further, gray matter (GM) density increases with typical adolescent development, and females tend to have lower volumes but higher density than males throughout the brain (Gennatas et al., 2017). Given the accessibility of substances for this age group and ongoing questions about how changes in legislation may impact availability (Schmidt, Jacobs, & Spetz, 2016), understanding potential attendant harms on the developing brain remains an important public health concern (Feldstein Ewing, Lovejoy, & Choo, 2017).

Several adolescent DTI studies have shown lower FA, the most commonly reported WM measure, with alcohol use (Jacobus, Squeglia, Bava, & Tapert, 2013; McQueeny et al., 2009; Thayer, Callahan, Weiland, Hutchison, & Bryan, 2013). A large longitudinal study following 134 adolescents for 3.5 years found that adolescents who transitioned to heavy drinking ($n = 75$) showed attenuated WM growth in the corpus callosum and pons, as well as reduced frontal and temporal GM volumes, compared to nondrinkers (Squeglia et al., 2015). Studies have also reported smaller prefrontal cortex GM volume in adolescents with alcohol use disorder (AUD) (De Bellis et al., 2005; Medina et al., 2008); however, at least two cross-sectional studies have shown that adolescents with AUD have *increased* FA in the limbic system and corpus callosum compared to non-substance using adolescents (Cardenas et al., 2013; De Bellis et al., 2008) and a recent DTI study found that binge-drinking was positively associated with increased FA and AD in a small sample of college students (Kashfi et al., 2017).

With regard to cannabis, one small cross-sectional DTI study found that adolescent cannabis users exhibited lower FA than matched non-using controls (Yucel et al., 2010). Cannabis use has also been associated with reduced GM volume in the caudate nucleus among young adults (Batalla et al., 2014), and in the medial orbital prefrontal cortex (Churchwell, Lopez-Larson, & Yurgelun-Todd, 2010) and whole brain GM volumes (Wilson et al., 2000) among adolescents. However, two studies reported associations between cannabis use and *greater* GM density in the amygdala and nucleus accumbens (Gilman et al., 2014; McQueeny et al., 2011) and an additional study reported increased cerebellar GM volume among cannabis users (Medina, Nagel, & Tapert, 2010). Finally, a systematic review of the DTI literature examining the impacts of nicotine on WM showed increased FA in adolescent and young adult cigarette smokers compared to nonsmokers, most commonly in the superior longitudinal fasciculus, internal capsule, and corpus callosum (Gogliettino, Potenza, & Yip, 2016). There has been a surprising lack of published literature on the effects of nicotine on GM volumes specifically in adolescents, but one study found reduced GM volume in the left thalamus and amygdala in young adult smokers compared to nonsmokers (Hanlon et al., 2016).

Few adolescent neuroimaging studies have examined alcohol, cannabis, and tobacco in conjunction. Structural studies have largely examined concomitant alcohol and cannabis use, and have continued to document differences in brain structure compared to nonusers. A 3-year longitudinal study found significant decreases in FA among adolescents who transitioned to heavy episodic drinking, and among adolescent binge drinkers with heavy cannabis use, compared to a matched control group of adolescents with minimal substance use (Jacobus et al., 2013). A previous study by the same group found that teens with a history of binge drinking alone and teens with a history of binge drinking and concomitant cannabis use showed diminished FA compared to their non-substance using peers but no differences in MD (Jacobus et al., 2009). Interestingly, the same study also found that teens who engaged in the heavy use of both cannabis and alcohol showed significantly higher FA than the binge drinking only group. Other research has indicated that adolescents who later went on to initiate use of both alcohol and cannabis showed lower cortical thickness at baseline compared to those who initiated alcohol only and non-using groups, but also did not show as much cortical thinning over time such that group differences were not present at follow up (Jacobus et al., 2016). Similarly, cumulative cannabis use was associated with higher cortical thickness at follow up, which may suggest interference with expected cortical thinning during adolescence (Jacobus et al., 2015). While the existing literature suggests associations between substance use and differences in brain structure in adolescence, a greater understanding of the relative impact of various substances may help inform prevention and intervention efforts.

The goal of the present study was to use MRI voxel-based morphometry (VBM) and DTI techniques in a large, racially/ethnically diverse sample of adolescents to explore associations between brain structure and substance use by incorporating alcohol, cannabis, and tobacco use within the same model. General linear models (GLMs) were conducted in whole-brain skeletonized WM (via DTI) and GM volume/density (via VBM) that included terms for recent (past month) alcohol, cannabis, and tobacco use, as well as age, sex, and intracranial volume. Given the equivocal results of previous studies and that none of these studies directly examined these three substances of abuse in the same continuous models, directional hypotheses were not established.

2. Methods

2.1. Sample and procedure

Participants were recruited from justice-related programs in the southwest United States and completed MRI scanning as part of a larger intervention study (Caouette, Hudson, Bryan, & Feldstein Ewing, 2018). Participants had to be 14–18 years old, fluent in English, and actively participating in a justice-related program. Exclusion criteria included antipsychotic/anticonvulsant medication use, head injury with loss of consciousness for > 5 min during the past 6 months, and standard MRI contraindications such as pregnancy. All procedures were approved by the participating Institutional Review Board, and participants were additionally protected by a federal Certificate of Confidentiality.

Both anatomical and DTI scans were completed by 247 adolescents. Exclusions occurred due to motion during DTI (greater than 4 mm of root mean square displacement in more than 10% of gradient directions; $n = 6$), missing substance use data ($n = 24$), and outliers over 3 standard deviations on substance use consumption variables (among those reporting use; $n = 17$), for a final sample size of $N = 200$.

2.2. Measures

Participants completed questionnaires on demographics, substance use, and impulsivity and emotion regulation. Average substance use measures were derived from the 30-day Time-line Follow-back (TLFB) (Robinson, Sobell, Sobell, & Leo, 2014) and calculated for alcohol (i.e., drinks per drinking day), cannabis (i.e., grams per use day), and cigarettes (i.e., cigarettes per smoking day). Subscale scores related to risky behavior were calculated from the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) (Torrubia, Avila, Molto, & Caseras, 2001), Impulsive Sensation Seeking Scale (IMPSS) (Zuckerman, 1993), and Difficulties in Emotion Regulation Scale

(DERS) (Gratz & Roemer, 2004).

Scans were acquired on a 3T Siemens Trio (Erlangen, Germany) whole body scanner using 12-channel radio frequency coils. High-resolution T_1-weighted structural images were acquired using a 5-echo multi-echo MPRAGE sequence: TE = 1.64, 3.5, 5.36, 7.22, and 9.08 ms, TR = 2.53 s, TI = 1.2 s, flip angle = 7∘, excitations = 1, slice thickness = 1 mm, field of view = 256 mm, resolution = 256 × 256 × 176, voxel size 1 × 1 × 1 mm, pixel bandwidth = 650 Hz. DTI scans were acquired using a single-shot spin-echo echo planar imaging (EPI) sequence with a twice-refocused balanced echo to reduce eddy current distortions. Sequence parameters were: FOV = 256 × 256 mm, 128 × 128 matrix, slice thickness = 2 mm, NEX = 1, TE = 84 ms, and TR = 9000 ms. A 12-channel radiofrequency (RF) head-phased array coil was used, with GRAPPA (X2), 30 gradient directions, and b = 800 s/mm^2.

Imaging data were processed using FMRIB's Software Library (FSL; v5.0.1) (Smith et al., 2004) with default settings. DTI data were processed using Diffusion Toolbox (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007) including eddy current distortion and registration to a b = 0 s/mm^2 image using 6 degrees of freedom affine transformation. Diffusion tensor and index maps were calculated using Dtifit. Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) was then used to obtain a skeletonized 4D image for FA and mean, axial, and radial diffusivity (MD, AD, and RD, respectively). Voxel-based morphometry (VBM) processing was performed using the FSLVBM analysis pipeline (Ashburner & Friston, 2000; Good et al., 2001). T1-weighted images were brain-extracted using default BET brain extraction, and resulting GM images were aligned to Montreal Neurological Institute (MNI) standard space using the affine registration tool FLIRT, followed by nonlinear registration using FNIRT, and then averaged into a study-specific template. Native GM images were then non-linearly re-registered to this template using FNIRT. The registered partial volume images were then modulated by dividing the Jacobian of the warp field. The modulated segmented images were smoothed with an isotropic Gaussian kernel with a sigma of 3, yielding full-width half-maximum (FWHM) 3 × 2.3 mm = 6.9 mm.

2.3. Statistical analyses

Whole-brain univariate GLMs were used for all analyses and were run across each of the four DTI indices (FA, MD, AD, and RD) and VBM through FSL's Randomise function using 5000 permutations and threshold-free cluster enhancement with significance threshold of $p < 0.01$ and minimum cluster size ≥ 20 voxels. Terms were included for age, sex, alcohol use, cannabis use, and tobacco use, as well as intracranial volume in the VBM model. Significant clusters were identified for each term of interest (i.e., alcohol use, cannabis use, and tobacco use), and values were then extracted and examined in SPSS univariate GLMs in order to report significance values and effect sizes for all covariates. A sex by tobacco use interaction term was then added in SPSS for extracted clusters. Follow-up exploratory whole-brain univariate GLMs added a sex by substance interaction term to original models with a loosened significance threshold of $p < 0.05$.

3. Results

3.1. Participants

Sample characteristics are reported in Table 1. Participants were predominantly male (67%) and ethnically diverse. Of $N = 200$ total youth, $n = 184$ reported having ever tried alcohol at an average age of first use of 12.60 ($SD = 2.31$; range 7–17) years, and $n = 182$ reported having ever tried cannabis at an average age of first use of 11.83 years ($SD = 2.35$; range 7–17) years. Age of first use was not collected for tobacco, but $n = 113$ had used tobacco in the last 30 days. Participant substance use patterns for the past 30 days were as follows: $n = 41$ reported no substance use; $n = 8$ reported using only alcohol; $n = 21$ reported using only cannabis; $n = 39$ reported using only tobacco; $n = 17$ reported using alcohol and cannabis; $n = 7$ reported using alcohol and tobacco; $n = 27$ reported using cannabis and tobacco; and $n = 40$ reported using alcohol, cannabis, and tobacco. There were no sex differences in baseline TLFB measures. Females reported greater sensitivity to punishment (SPSRQ), and endorsed more anger and shame (DERS Nonacceptance) and difficulty feeling better (DERS Strategies) in response to being upset than males (all $p < 0.05$, FDR corrected). There were no sex differences in impulsivity or sensation seeking (IMPSS). In the whole sample and controlling for sex, no associations between behavioral measures (SPSRQ, IMPSS, DERS) and substance use survived FDR correction. Further, no associations between behavioral measures and substance use survived FDR correction when examined separately in females and males.

3.2. Cigarettes per smoking day

Average cigarette use per smoking day showed large clusters of positive association with MD and RD (see Table 2), such that greater cigarette use per smoking day was associated with poorer WM integrity with peak effect sizes of $\eta_p^2 = 0.12$–0.17. Peak associations were observed in long-range anterior-posterior tracts [e.g., superior longitudinal fasciculus (SLF) and inferior longitudinal fasciculus (ILF)]. Sex was a significant covariate in several clusters. Females showed higher diffusivity than males in left SLF and right anterior thalamic radiation, but lower diffusivity in right SLF and ILF. No associations exceeded the significance threshold in the VBM model.

3.3. Grams per cannabis day

One cluster of negative association between average cannabis use and AD in the left SLF exceeded the significance threshold, such that greater cannabis use was associated with worse WM integrity (see Table 2). Cannabis use was also a significant covariate with negative association with RD in left SLF. No associations exceeded the significance threshold in the VBM model.

3.4. Drinks per drinking day

No drinks per drinking day associations exceeded the $p < 0.01$ significance threshold for any DTI index or VBM models in direct contrasts. Alcohol use was a significant covariate in two clusters in corpus callosum and SLF (see Table 2).

3.5. Sex by substance interactions

Sex by tobacco use interactions were nonsignificant (all $p > 0.08$) in extracted clusters. Exploratory whole-brain interaction models were nonsignificant for tobacco use and cannabis use in TBSS. However, significant interactions were observed for sex by drinks per drinking day (see Table 3), such that average drinks per drinking day was positively associated with widespread MD and RD in females. In males associations were nonsignificant except in a left SLF cluster. Additionally, a VBM cluster in left cerebellum (I-IV) showed a significant sex by cigarettes per smoking day interaction [80 voxels, $t_{(1,192)} = 3.83$, $p < 0.001$, $\eta_p^2 = 0.07$], such that smoking was negatively associated with VBM in females [$t_{(1,60)} = -2.59$, $p = 0.01$, $\eta_p^2 = 0.10$] but not males [$t_{(1,128)} = 1.59$, $p = 0.11$, $\eta_p^2 = 0.02$]. No other significant interactions were observed in VBM.

4. Discussion

The current study sought to explore associations between brain structure and substance use in models incorporating alcohol, cannabis,

Table 1
Sample characteristics.

	Whole Sample *Mean (SD; range)*	Females *Mean (SD; range)*	Males *Mean (SD; range)*
N	200	66	134
Ethnicity			
Hispanic/Latino	122	42	80
Biracial/Multiracial	33	13	20
White	23	2	21
African American	13	3	10
Native American	9	6	3
Age	15.79 (1.24; 14.00–18.00)	15.62 (1.30; 14.00–18.00)	15.87 (1.21; 14.00–18.00)
TLFB Alcohol Days	1.01 (2.09; 0.00–14.00)	1.06 (1.85; 0.00–8.00)	0.98 (2.20; 0.00–14.00)
Only in n = 72 current users[a]	2.79 (2.67; 1.00–14.00)	2.80 (2.04; 1.00–8.00)	2.78 (2.98; 1.00–14.00)
TLFB Drinks per Drinking Day	2.05 (3.41; 0.00–16.83)	1.94 (3.25; 0.00–13.17)	2.11 (3.49; 0.00–16.83)
Only in n = 72 current users[a]	5.70 (3.39; 0.50–16.83)	5.12 (3.41; 0.75–13.17)	6.01 (3.36; 0.50–16.83)
TLFB Cannabis Days	6.98 (10.47; 0.00–30.00)	5.53 (9.00; 0.00–30.00)	7.67 (11.08; 0.00–30.00)
Only in n = 105 current users[b]	13.29 (11.18; 1.00–30.00)	11.06 (10.07; 1.00–30.00)	14.31 (11.57; 1.00–30.00)
TLFB Grams per Cannabis Day	0.64 (0.94; 0.00–5.50)	0.53 (0.76; 0.00–2.89)	0.69 (1.02; 0.00–5.50)
Only in n = 105 current users[b]	1.21 (1.00; 0.06–5.50)	1.05 (0.79; 0.10–2.89)	1.29 (1.08; 0.06–5.50)
TLFB Cigarette Smoking Days	12.32 (13.59; 0.00–30.00)	11.17 (13.75; 0.00–30.00)	12.89 (13.52; 0.00–30.00)
Only in n = 113 current users[c]	21.80 (10.93; 1.00–30.00)	21.06 (12.13; 1.00–30.00)	22.14 (10.41; 1.00–30.00)
TLFB Cigarettes per Smoking Day	2.49 (3.61; 0.00–20.00)	2.29 (3.58; 0.00–20.00)	2.59 (3.64; 0.00–18.00)
Only in n = 113 current users[c]	4.41 (3.83; 0.00–20.00)	4.31 (3.93; 0.83–20.00)	4.46 (3.81; 0.00–18.00)
SPSRQ Sensitivity to Punishment*	11.18 (4.79; 0.00–22.00)	12.36 (4.66; 0.00–22.00)	10.59 (4.76; 1.00–22.00)
SPSRQ Sensitivity to Reward	12.78 (4.42; 1.00–23.00)	12.30 (4.04; 5.00–22.00)	13.01 (4.59; 1.00–23.00)
IMPSS Impulsive	3.91 (2.20; 0.00–8.00)	4.27 (2.22; 0.00–8.00)	3.72 (2.17; 0.00–8.00)
IMPSS Sensation Seeking	7.20 (2.48; 0.00–11.00)	7.53 (2.28; 1.00–11.00)	7.03 (2.56; 0.00–11.00)
DERS Nonacceptance[d,*]	11.63 (5.27; 4.00–30.00)	13.45 (5.82; 4.00–30.00)	10.72 (4.73; 6.00–30.00)
DERS Goals[d]	13.03 (4.65; 5.00–25.00)	13.45 (4.33; 5.00–23.00)	12.81 (4.80; 5.00–25.00)
DERS Impulse[d]	13.99 (5.14; 6.00–30.00)	14.70 (5.36; 6.00–30.00)	13.63 (5.01; 6.00–26.00)
DERS Awareness[d]	18.09 (5.95; 6.00–30.00)	17.77 (6.34; 6.00–30.00)	18.24 (5.76; 6.00–30.00)
DERS Strategies[d,*]	17.32 (7.10; 8.00–37.00)	19.09 (7.52; 8.00–36.00)	16.44 (6.73; 8.00–37.00)
DERS Clarity[d]	11.07 (3.97; 5.00–24.00)	11.65 (3.98; 5.00–21.00)	10.77 (3.95; 5.00–24.00)

SD: Standard Deviation.
TLFB: Timeline Follow-Back (30 days); SPSRQ: Sensitivity to Punishment and Sensitivity to Reward Questionnaire; IMPSS: Impulsive Sensation Seeking Scale; DERS: Difficulties in Emotion Regulation Scale
[a] 25 Females, 47 Males.
[b] 33 Females, 72 Males.
[c] 35 Females, 78 Males.
[d] $N = 197$; 66 Females, 131 Males.
* $p < 0.05$, Females > Males.

and tobacco. This sample of adolescents was predominantly male, Hispanic/Latino, and recruited from the juvenile justice system. GLMs in whole-brain skeletonized WM and GM VBM modelled recent alcohol use, cannabis use, and tobacco use as averages per use day, an important measure of potency of exposure (i.e., greater risk for those who tended to drink or use more at a time). Models also included age and sex. Recent tobacco use was negatively associated with WM integrity in large clusters in long-range tracts, particularly the SLF, and accounted for as much as 17% of variance in WM integrity. Cannabis use was negatively associated with WM integrity in the left SLF, but was not associated with GM volumes. Alcohol use was a significant covariate in two extracted WM clusters, but did not exceed significance thresholds in any direct contrasts. Age did not significantly contribute to any cluster. Finally, sex by drinks per drinking day interactions were observed such that females but not males showed significant negative associations between alcohol use and WM integrity, and one small cluster of negative association between smoking and VBM in left cerebellum.

These results contrast with the existing literature, which has reflected *increased* WM integrity for adolescent and young adult tobacco users, as compared to those without tobacco use (Gogliettino et al., 2016); and decreased FA among adolescent drinkers and those with concurrent alcohol and cannabis use (Jacobus et al., 2009; Jacobus et al., 2013). Additional studies have found that adolescent tobacco users had greater WM integrity in the internal and external capsules and the right superior corona radiata (Yu et al., 2016). Among young adults (age 19–34 years) cigarette smoking has been shown to be associated with greater FA in bilateral frontoparietal tracts and in the superior longitudinal fasciculus (Liao, Tang, Liu, Chen, & Hao, 2012). It is possible that previous studies only examined FA, the most common measure used in DTI as an overall metric of WM integrity, and the current findings were observed only in diffusivity indices. However, it has also been suggested that a quadratic relationship may exist, such that WM integrity may increase with more limited nicotine exposure and then decrease with protracted exposure (Hudkins, O'Neill, Tobias, Bartzokis, & London, 2012). The adolescents in the current sample reported using cigarettes with much greater frequency than alcohol or cannabis (average of 12 out of 30 days, as compared to averages of 1 day of alcohol use and 7 days of cannabis use), which could account for observations of negative associations more similar to adult samples with greater exposure. Recent European studies have also underscored the contribution of adolescent tobacco use in health risk trajectories (Whelan et al., 2014). Further, this study indicates possible negative associations between cannabis use and both AD and RD in left SLF, in the context of significant positive associations of other substances. Future studies should consider exploring interactions of cannabis with alcohol and nicotine.

The current findings support sex differences in how substance use may interact with brain structure, which is well documented in the literature due to possible interactions with sex hormones during pubertal maturation (Feldstein Ewing et al., 2018; Gennatas et al., 2017). Preclinical research has shown that females may be particularly vulnerable to changes in neuronal structure and cognitive function with nicotine exposure during development (Cross, Linker, & Leslie, 2017),

Table 2
Clusters of significant ($p < 0.01$) association between structural measures and substance use ($N = 200$).

Region[a]	Cluster Size (voxels)	Cigarettes per Smoking Day			Grams per Cannabis Day			Drinks per Drinking Day			Sex			Age		
		t	*p*	η_p^2	*t*	*p*	η_p^2	*t*	*p*	η_p^2	*t*	*p*	η_p^2	*t*	*p*	η_p^2
Mean Diffusivity																
Superior longitudinal fasciculus L	6683	**6.10**	**< 0.01**	**0.16**	−1.46	0.15	0.01	0.50	0.62	0.00	−1.66	0.10	0.01	−1.77	0.08	0.02
Superior longitudinal fasciculus R	4181	**5.84**	**< 0.01**	**0.15**	−0.56	0.58	0.00	−0.70	0.48	0.00	1.55	0.12	0.01	−1.82	0.07	0.02
Superior longitudinal fasciculus R	70	**3.82**	**< 0.01**	**0.07**	0.75	0.46	0.00	−0.30	0.77	0.00	**2.15**	**0.03**	**0.02**	−1.58	0.12	0.01
Radial Diffusivity																
Superior longitudinal fasciculus L	11,392	**6.34**	**< 0.01**	**0.17**	−0.82	0.41	0.00	0.49	0.62	0.00	**−2.21**	**0.03**	**0.03**	−1.59	0.11	0.01
Superior longitudinal fasciculus R	7529	**5.75**	**< 0.01**	**0.15**	0.32	0.75	0.00	−0.68	0.50	0.00	−0.07	0.95	0.00	−1.48	0.14	0.01
Inferior longitudinal fasciculus L	1070	**5.44**	**< 0.01**	**0.13**	0.05	0.96	0.00	−0.43	0.67	0.00	0.10	0.92	0.00	−0.00	0.99	0.00
Superior longitudinal fasciculus R	396	**4.31**	**< 0.01**	**0.09**	−1.44	0.15	0.01	1.46	0.15	0.01	−1.18	0.24	0.01	−1.56	0.12	0.01
Corticospinal tract R	360	**5.09**	**< 0.01**	**0.12**	−1.06	0.29	0.01	1.07	0.29	0.01	−0.58	0.56	0.00	−1.83	0.07	0.02
Body of corpus callosum R	143	**2.78**	**< 0.01**	**0.04**	0.38	0.71	0.00	−0.27	0.79	0.00	−1.58	0.12	0.01	−1.67	0.10	0.01
Anterior thalamic radiation R	92	**3.28**	**< 0.01**	**0.05**	−1.41	0.16	0.01	1.07	0.28	0.01	**−1.95**	**0.05**	**0.02**	0.21	0.83	0.00
Superior longitudinal fasciculus L	29	**2.69**	**< 0.01**	**0.04**	**−2.37**	**0.02**	**0.03**	0.48	0.64	0.00	**−2.89**	**< 0.01**	**0.04**	−1.54	0.12	0.01
Genu of corpus callosum R	28	**2.60**	**0.01**	**0.03**	1.85	0.07	0.02	**−2.05**	**0.04**	**0.02**	0.06	0.95	0.00	1.11	0.27	0.01
Inferior longitudinal fasciculus R	21	**3.10**	**< 0.01**	**0.05**	−0.92	0.36	0.00	0.53	0.60	0.00	**3.10**	**< 0.01**	**0.05**	0.06	0.95	0.00
Axial Diffusivity																
Superior longitudinal fasciculus L	34	1.69	0.09	0.02	**−6.59**	**< 0.01**	**0.18**	**3.20**	**< 0.01**	**0.05**	0.70	0.49	0.00	−1.68	0.10	0.01

L = Left, R = Right.
[a] Peak association. Significant terms appear in bold.

and adolescent neuroimaging studies have fairly consistently reported that females show greater negative associations between brain structure and alcohol use (Feldstein Ewing, Sakhardande, & Blakemore, 2014). Importantly, alcohol associations were not observed in the current overall models and were only identified when modelling sex by substance interactions. Adolescent substance use research should continue to consider the range and impact of sexual development in neuroimaging studies (Silvers, Squeglia, Thomsen, Hudson, & Feldstein Ewing, 2019).

The overall lack of associations between GM volumes and substance use is also in contrast with the existing literature. Specifically, large cross-sectional studies have found smaller frontal and temporal cortical volumes among adolescent drinkers compared to those with low/no alcohol exposure (Pfefferbaum et al., 2016), and longitudinal studies have similarly found accelerated reductions in temporal and lateral frontal GM volumes among adolescents who transitioned to heavy drinking compared to their non-drinking peers (Squeglia et al., 2015). However, other studies in adolescents have found no associations between GM volumes and AUD (De Bellis et al., 2000; Nagel, Schweinsburg, Phan, & Tapert, 2005). With regard to cannabis, studies have found increased GM volumes (Orr et al., 2019), and significantly greater GM density (Gilman et al., 2014), in adolescent and young adult cannabis users compared to non-users, although a large study ($n = 781$) found no significant relationship between adolescent cannabis use and global or regional GM volume, thickness, or density (Scott et al., 2019). The differences between the existing literature and the current findings may reflect the overall low alcohol use in the sample (i.e., an average of one drinking day in the past 30 days with two drinks per drinking day, and a lower number of current alcohol users relative to cannabis and tobacco), but also highlight the importance of assessing tobacco use even in the context of other substances.

4.1. Clinical implications

The current findings indicate that tobacco use is associated with poorer WM integrity even in the context of relatively low alcohol and cannabis use; in turn, tobacco use should be assessed even when adolescents report minimal and infrequent use of other substances. E-cigarette and pod mod devices are common, with national data including Monitoring the Future suggesting that at least 30% of teens have used e-cigarettes (Johnston et al., 2019), and many e-tobacco delivery products may contain as much nicotine as a pack of cigarettes (Barrington-Trimis & Leventhal, 2018). Given that SLF WM integrity is associated with executive function, attention, and language in children and adolescents (Urger et al., 2015), the widespread associations between tobacco use and SLF observed in the current study underscore the importance of examining future impact on broader ongoing development with tobacco use.

Further, it is essential to note that many adolescents may use tobacco products without parent/guardian and other caregiver knowledge (DiFranza et al., 2000). Moreover, youth may be using heavily, but not show any symptoms of misuse, as tobacco is notable for its "non-symptomatic" nature even in the context of heavy use (Silvers et al., 2019). The current findings are particularly important in the context of rising rates of adolescent nicotine use in the form of vaping/juuling (National Academies of Sciences, 2018), wherein the user is exposed to concentrated levels of nicotine (Willett et al., 2019). Better forms of parent/caregiver monitoring/detection are an ongoing area of interest (Silvers et al., 2019), particularly in order to offer intervention in a timely way.

4.2. Limitations and conclusions

Important considerations should be taken into account as context for the current results. First, these data are cross-sectional, and it cannot be determined whether differences in white matter are the result of or

Table 3
Clusters of significant ($p < 0.05$) sex by alcohol use interaction.

Region[a]	Cluster Size (voxels)	Drinks per Drinking Day*Sex			Drinks per Drinking Day, Females ($n = 66$)			Drinks per Drinking Day, Males ($n = 134$)		
		t	p	η_p^2	t	p	η_p^2	t	p	η_p^2
Mean Diffusivity										
Body of corpus callosum L	10,326	**−5.38**	**< 0.01**	**0.13**	**4.99**	**< 0.01**	**0.29**	−1.61	0.11	0.01
Radial Diffusivity										
Superior corona radiata L	10,267	**−5.36**	**< 0.01**	**0.13**	**5.62**	**< 0.01**	**0.34**	−1.02	0.31	0.01
Inferior fronto-occipital fasciculus R	6432	**−5.07**	**< 0.01**	**0.12**	**4.34**	**< 0.01**	**0.24**	−1.18	0.24	0.01
Inferior fronto-occipital fasciculus L	1165	**−4.51**	**< 0.01**	**0.10**	**4.01**	**< 0.01**	**0.21**	−1.51	0.13	0.02
Inferior longitudinal fasciculus L	397	**−3.63**	**< 0.01**	**0.06**	**2.84**	**< 0.01**	**0.12**	−0.48	0.63	0.00
Superior longitudinal fasciculus L	150	**−4.45**	**< 0.01**	**0.09**	**3.57**	**< 0.01**	**0.17**	−1.13	0.26	0.01
Superior longitudinal fasciculus L	115	**−4.27**	**< 0.01**	**0.09**	**2.80**	**< 0.01**	**0.11**	**−2.36**	**0.02**	**0.04**
Posterior corona radiata L	42	**−2.57**	**0.01**	**0.03**	**3.19**	**< 0.01**	**0.14**	−0.53	0.60	0.00
Inferior fronto-occipital fasciculus L	31	**−3.48**	**< 0.01**	**0.06**	**3.07**	**< 0.01**	**0.13**	−1.17	0.25	0.01

L = Left, R = Right.
[a] Peak association. Significant terms appear in bold.

preceded substance use behavior. To decrease concerns about reliability of self-report data, substance use measures focused on recent (past month) substance use. Participants reported average first use of alcohol and cannabis around age 12, or approximately 3–4 years prior to participation on average. Age of first use was not available for tobacco, and no other lifetime history of substance use was collected. It is possible that duration of tobacco or other substance use could be a confounding effect for the current results, especially if adolescents initiated tobacco use prior to alcohol or cannabis use. Other substances, such as opioid use, were also not examined, which at the time of this study (2010–2016) were not as relevant; however, studies are increasingly reflecting the importance of integrating metrics of prescription opioid use into examinations of adolescent substance use (Caupp et al., 2018; Dash, Wilson, Morasco, & Feldstein Ewing, 2018; Monitto et al., 2017). It is also worth noting that data collection did not include objective measures of recent use (i.e., analysis of hair or urine samples), and data are entirely based on self-report. It is also possible that concomitant use of products that contain both cannabis and tobacco may have been only reported as cannabis use.

In addition, these adolescents were recruited from juvenile justice settings that may capture a higher end of the distribution of internalizing/externalizing risk and behaviors (Kang, Wood, Eno Louden, & Ricks, 2018). The current study collected behavioral measures related to internalizing/externalizing but did not fully assess history of psychopathology beyond exclusions for severe mental health conditions. U.S. justice-involved youth represent a critical and very large higher-risk group that is often missed in developmental neuroscience research (Bryan, Gillman, & Hansen, 2016; Feldstein Ewing et al., 2016). Further, juvenile justice youth are disproportionately of color, experience more health disparities, and internalizing and externalizing symptoms/behaviors are associated with experience of ethnic/racial discrimination (Loyd et al., 2019). In this respect, the current study represents an endeavor to overcome an important disparity in representative sampling.

Recent interest has been focused on the effect of alcohol and cannabis on the adolescent brain; however, results from the current study suggest that tobacco use may have widespread associations for adolescents who are otherwise not heavy alcohol or cannabis users on average. Particularly in an age of increasing exposure to nicotine among adolescents due to vaping, this is highly relevant for public health programming.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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