Poorer frontolimbic white matter integrity is associated with chronic cannabis use, FAAH genotype, and increased depressive and apathy symptoms in adolescents and young adults

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1. Introduction

Cannabis use remains the most popular illicit substance among youth, with 22.7% of high school seniors and roughly 20% of college students reporting past month use (Johnston et al., 2014). Considering the decline in perceived risk of use (Johnston et al., 2013), understanding the neurocognitive consequences of regular cannabis use in youth is a significant public health priority.

Consistent with high cannabinoid receptor 1 (CB1) frontolimbic receptor density, the endogenous endocannabinoid system is thought to regulate emotion-related memory, affective processing, stress response, and executive functioning (see Egerton et al., 2006; Horder et al., 2009; Marco and Laviola, 2012). Adult daily cannabis users demonstrate significant downregulation of CB1 density, especially within frontolimbic regions (Hirvonen et al., 2012). CB1 receptors are localized on axons in high concentrations as well as oligodendrocytes, which myelinate axons (see Mackie, 2005; Molina-Holgado et al., 2002; Moldrich and Wenger, 2000). Diffusion tensor imaging (DTI) provides in-vivo analysis of WM integrity, measured by fractional anisotropy (FA), and mean diffusivity (MD), quantifying the direction and coherence of WM fibers. In general, greater FA and lower MD values indicate highly cohesive WM bundles (see Johansen-Berg and Behrens, 2009). Adolescence and early adulthood are characterized by substantial increases in white matter (WM) volume, consisting of axons and oligodendrocytes, and improvements in the frontal and limbic networks (Ashtari et al., 2007; Barnea-Goraly et al., 2005; Bava et al., 2010a; Giorgio et al., 2008; Giorgio et al., 2010; Simmonds et al., 2014; Toga et al., 2006), which is associated with improved cognitive efficiency, especially in affective processing and complex executive functioning (Bava et al., 2010a; Blakemore and Choudhury, 2006; Nagy et al., 2004; Steinberg, 2005; Yurgelun-Todd, 2007). Further, this WM neurodevelopment...
Therefore, chronic cannabis exposure during adolescence and young adulthood may significantly disrupt frontolimbic WM integrity. However, to date, most studies examining white matter integrity in cannabis users have focused on the corpus callosum (fMinor), memory and sensory-motor relays, finding poorer integrity in the genu (Abou-Saleh, 2010; Arnone et al., 2008; Gruber et al., 2011; Gruber et al., 2014), internal capsule (Gruber et al., 2014), arcuate fasciculi (Ashtari et al., 2009), and tracts within the hippocampus (Yücel et al., 2010; Zalesky et al., 2012), but not the corona radiata (Gruber et al., 2014). Only a few studies have specifically examined WM integrity in frontal projecting fibers that underlie emotional regulation (such as the uncinate fasciculus, anterior thalamic radiation, and forceps minor; Blumenfeld, 2002) in cannabis users. For example, Clark et al. (2012) found lowered FA in PFC WM in adolescents with polysubstance use disorders (89% cannabis use disorder), including the frontal pole, frontal superior, frontal caudal middle, frontal rostral middle, and inferior frontal gyrus. In contrast, another study found increased apparent diffusivity coefficient in PFC regions in cannabis users and controls, with no differences in FA (DeLisi et al., 2006). Filbey et al. (2014) found increased FA in the forceps minor in heavy cannabis users, although this sample was on average 28 years old; therefore, results may be unique to this age group. Perhaps most relevant to the current study, Jacobs et al. (2013b) found reductions in white matter in cannabis users with comorbid alcohol use in a 3-year longitudinal investigation, with significant group by time interactions revealing decreased FA with cannabis use in the left anterior internal capsule and uncinate fasciculus.

Inconsistent findings in this literature may be related to methodological differences including decreased power associated with whole-brain analysis (DeLisi et al., 2006; Jacobs et al., 2013b) and sample age (Filbey et al., 2014). Alternatively, genes that regulate endocannabinoid signaling (ECS) may clarify variability in cannabis-related WM findings. An enzyme called fatty acid amide hydrolase (FAAH) is involved in decreasing CB1 receptor activation by degrading the naturally occurring agonist anandamide (AEA; see Ho and Hillard, 2005). As the PFC continues to develop during adolescence, persistent increases in the reliance of FAAH activity have been noted (Long et al., 2012), suggesting that variation in FAAH signaling may regulate white matter integrity in young cannabis users. The most common single nucleotide polymorphism (SNP) results in a missense from C to A at position 385 (rs324420) for the FAAH genotype. It is hypothesized that signiﬁcant correlations would exist between poorer white matter integrity and increased depressive and apathy symptoms in the cannabis users (Bloomfield et al., 2014; Degenhardt et al., 2003; Hayatbakhsh et al., 2007; Medina et al., 2007a; Medina et al., 2007b; Verdejo-Garcia et al., 2006).

2. Methods and materials

2.1. Participants

Participants included 67 (33 cannabis-users) right-handed adolescents and emerging adults from a larger imaging genetics study (PI: Lisdahl, NIDA R03 DA027457; see Lisdahl and Price, 2012 for additional details). Participants were between the ages 18–25 (35 males; see Table 1). The exclusions included current or past history of major neurologic, medical or Axis I disorders with the exception of substance use disorders; history of LD or special education; current psychoactive medication use; MRI contraindications; and failure to maintain abstinence for 7 days (for the detailed exclusion criteria see Lisdahl and Price, 2012). The eligible cannabis use criteria included more than 50 lifetime joints and more than 25 past year joints (on average, the group used 548 joints in the past year). Control status included less than or equal to 5 past year and 10 lifetime joints. Groups were matched as closely as possible on gender, age, education, verbal IQ, and ethnicity. Participants reporting >8 standard drinks per week on average as indicated in the Cahalan criteria as “very heavy drinkers” were excluded from the analyses.

2.2. Procedures

All aspects of the study were approved by the University of Cincinnati Institutional Review Board. Recruitment included advertisements in fliers and newspapers. Interested participants were phoned to assess the eligibility criteria. This included a semi-structured interview based on the DSM-IV-TR criteria for Axis I anxiety, mood, and psychotic disorders (determined by Dr. Lisdahl; First et al., 2001). Eligible participants then completed either one or two sessions. Those with considerable substance use completed the questionnaires, drug use interview, neuro-psychological battery and MRI scan in two sessions in order to ensure abstinence. Participants were paid $160 for two sessions and $110 for completing one session. They also received reimbursement for parking, images of their brain, and local substance treatment resource literature.
Drug use categories were as follows: alcohol, cannabis, nicotine: cigarettes, chewing tobacco/snuff/pipe, cigars/hookah, and ecstasy, inhalants, hallucinogens, sedatives, and opioids.

2.3.2. Biological samples
Participants completed a breathalyzer test and provided urine samples for assessing recent substance use and pregnancy testing. Individuals with positive drug and/or alcohol tests with the exception of cannabis and nicotine were not included in these analyses. THC metabolite levels were assessed via mass spectrometry testing in participants that tested positive; abstinence was ensured by subtracting the session effects related to substance use (Brown et al., 1998; Stewart and Brown, 1995).

2.4. Neuropsychological assessment

2.4.1. Premorbid intelligence
Estimates of verbal intelligence were measured by The Wide Range Achievement Test—4th Edition (WRAT-4) Reading subtest (Wilkinson, 2006), which may be sensitive to quality of education (see Manly et al., 2002). We controlled for this estimate in the analyses in order to reduce any pre-existing differences between groups.

2.5. Genotyping

2.5.1. FAAH
The FAAH variant was genotyped by a trained geneticist using the TaqMan (fluorogenic 5′ nuclease) assay (for an example see Egan et al., 2003). The primers and the probes were obtained from Applied Biosystems, and PCR was conducted via an ABI 9700 thermocycler. End-point results were scored using the ABI 7900HT Sequence Detection System. For these analyses, individuals fit into one of two FAAH genotype groups: C/C genotype or A carrier (e.g., C/A or A/A genotype).

2.6. MRI data acquisition

2.6.1. Parameters
Images were obtained from a 4 T Varian, Unity MRI scanner. T1-weighted, 3-D SPGR anatomical brain scan was obtained using a modified driven equilibrium Fourier transform (MDEFT) sequence (FOV = 25.6 cm, 256 × 256 × 192 matrix, slice thickness = 1 mm, in-plane resolution = 1 × 1 mm, TR = 13 ms, TE = 5.3 ms, flip angle = 22°). Diffusion tensor imaging (DTI) was obtained using 12 diffusion directions with b ≈ 600 s/mm² (FOV = 25.6 cm, 64 × 64 × 30 matrix, resolution = 4 × 4 × 4 mm³, TR = 8000 ms, TE = 88.8 ms, flip angle 90°). A neuro-radiologist at CIR reviewed anatomical scans, and participants with noted abnormalities were excluded from this sample.

2.7. MRI processing

2.7.1. PFC underlying WM integrity
The WM pathways were reconstructed using voxel based 3 × 3 symmetric tensor matrices. ROI-based comparison was computed through FreeSurfer version 5.3 tractography software TRACULA providing both FA and MD for the following tracts: the corpus callosum forceps minor (fMinor), and bilateral: anterior thalamic radiation (ATR), and uncinate fasciculus (UNC) (see Fig. 1).

2.8. Data analysis
All analyses were conducted using SPSS. ANOVAs and Chi-square tests were run to examine potential demographic differences as well as differences in past year drug use histories between the drug and genotype groups. For the primary aim, general linear modeling (GLM) in SPSS was used to examine whether group, FAAH genotype, or a group × FAAH genotype interaction were significantly associated with average weighted FA and MD for each ROI. Standard least squares multiple regression was used; block one included covariates (WRAT-4 Reading score, age, gender, ethnicity, past year alcohol use, cotinine

### Table 1
Demographic & substance use information according to group & genotype.

<table>
<thead>
<tr>
<th></th>
<th>Cannabis users (N = 33)</th>
<th>Controls (N = 34)</th>
<th>FAAH carrier of A (N = 24)</th>
<th>FAAH C/C (N = 43)</th>
</tr>
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<tbody>
<tr>
<td>% Male</td>
<td>63.64%</td>
<td>41.18%</td>
<td>45.83%</td>
<td>55.81%</td>
</tr>
<tr>
<td>% ethnic minority</td>
<td>33.33%</td>
<td>32.35%</td>
<td>54.17**</td>
<td>20.93**</td>
</tr>
<tr>
<td>% FAAH C/C carriers</td>
<td>54.55%</td>
<td>73.53%</td>
<td></td>
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</tr>
<tr>
<td>WRAT-4 Reading, standard score</td>
<td>103.36 [73–134]</td>
<td>100.97 [81–120]</td>
<td>98.08* [81–120]</td>
<td>104.42* [73–134]</td>
</tr>
<tr>
<td>Beck Depression, Inventory Total-2</td>
<td>5.12* [0–17]</td>
<td>3.38* [0–14]</td>
<td>2.96* [0–8]</td>
<td>4.95* [0–17]</td>
</tr>
<tr>
<td>Past year nicotine use</td>
<td>1788.67* [0–7350]</td>
<td>469.26* [0–3680]</td>
<td>719.17 [0–3680]</td>
<td>1342.35 [0–7350]</td>
</tr>
<tr>
<td>Cotinine levels</td>
<td>3.89% [0–6]</td>
<td>1.32% [0–6]</td>
<td>3.04 [0–6]</td>
<td>2.33 [0–6]</td>
</tr>
<tr>
<td>Past year alcohol use</td>
<td>282.91* [0–1724]</td>
<td>104.26* [0–878]</td>
<td>193.25 [2–1724]</td>
<td>191.70 [0–1288]</td>
</tr>
<tr>
<td>Past year cannabis use</td>
<td>548.36* [26–3895]</td>
<td>.41* [0–5]</td>
<td>339.83 [0–1662]</td>
<td>231.49 [0–3895]</td>
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<tr>
<td>Past year other drug use</td>
<td>9.82 [0–171]</td>
<td>.12 [0–3]</td>
<td>1.0 [0–12]</td>
<td>7.07 [0–171]</td>
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Drug use categories were as follows: alcohol, cannabis, nicotine: cigarettes, chewing tobacco/snuff/pipe, cigars/hookah, and ‘other’ drug use, which was a total including all of the following categories: sedatives, ecstasy, stimulants, opioids, hallucinogens, inhalants, and other (anything else not mentioned). For this particular study, other was a sum of the following: stimulants, ecstasy, inhalants, hallucinogens, sedatives, and opioids.

\( p < .05 \)

\( p < .01 \)
levels), group, and genotype; block two included the interaction between group and FAAH genotype. If the interaction (cannabis + FAAH genotype) was not significant, only block one was interpreted. All dependent variables were normally distributed and there was no evidence of multicollinearity. For the secondary analysis, Pearson correlations were run in the cannabis users between BDI-II depressive symptoms, FrSBE apathy symptoms, and WM ROIs that significantly differed between groups or by genotype × group interactions. Significance was determined if \( p < .05 \) for all analyses.

3. Results

3.1. Demographic & mood information

3.1.1. Demographics: drug group

ANOVAs and Chi-square tests revealed that groups did not differ in gender \( [\chi^2(1) = 3.39, p = .07] \), ethnicity \( [66.67\% \text{ Caucasian for cannabis users and 67.65\% controls}], \chi^2(1) = 0.07, p = .93 \), WRAT-4 Reading standard score \( [F(1,65) = .55, p = .46], \) age \( [F(1,65) = .03, p = .87], \) education \( [F(1,65) = 3.2, p = .08], \) annual income \( [F(1,65) = .05, p = .83], \) body mass index \( [F(1,65) = .45, p = .52], \) or FrSBE apathy T scores \( [F(1,65) = 1.7, p = .22]. \) As reported previously, cannabis users and controls significantly differed in BDI-II depressive symptoms \( [F(1,65) = 7.7, p = .007], \) alcohol \( [F(1,65) = 6.2, p = .02], \) and recent nicotine use measured by cotinine level \( [F(1,65) = 22.33, p < .001] \) (see Table 1). There was no difference between past year other drug use \( [F(1,65) = 3.48, p = .07] \) and past year drinking patterns \( [\chi^2(5) = 3.84, p = .57] \) between the groups. The cannabis group had an average age of regular (at least weekly for 6 months) cannabis use onset of 17.9 (range 10–24).

3.3.2. FAAH group

No differences in any drug use variable were noted between C/C carriers and A carriers.

3.4. Primary results

3.4.1. Primary aim: white matter integrity: cannabis group status

After controlling for the WRAT-4 Reading score, age, gender, ethnicity, past year alcohol use and cotinine levels, cannabis users demonstrated increased MD in fMinor \( (t(58) = 2.27, beta = −.41, p = .001) \) (see Figs. 2, 3 & 4).

3.4.1.1. FAAH genotype. FAAH genotype did not independently predict WM integrity.

3.4.1.2. Cannabis - FAAH interaction. FAAH genotype interacted with cannabis group status to significantly predict FA in fMinor and bilateral ATR. C/C cannabis users and A carrier controls demonstrated reduced bilateral FA in fMinor \( (t(58) = 2.43, beta = .31, p = .02], \) and C/C cannabis users demonstrated reduced bilateral ATR \( (t(58) = 1.99, beta = .25, p = .05]; \) left: \( (t(58) = 3.53, beta = .41, p = .001) \) (see Figs. 2, 3 & 4).

3.4.1.3. Covariates. Lower WRAT-4 Reading score \( (t(58) = −2.42, beta = −.32, p = .02], \) Caucasian ethnicity \( (t(58) = −2.55, beta = −.32, p = .01], \) and greater cotinine level \( (t(58) = 2.1, beta = .27, p = .04] \) predicted increased MD in the right ATR. Lower WRAT-4 Reading score \( (t(58) = −2.69, beta = −.37, p = .009] \) and
Caucasian ethnicity \( t(58) = -2.0, \beta = -0.26, p = .05 \) predicted increased MD in the left ATR. Caucasian ethnicity \( t(58) = -1.97, \beta = -0.26, p = .05 \) predicted increased MD in the left UNC. Lower WRAT-4 Reading score \( t(58) = -2.15, \beta = -0.28, p = .04 \) and Caucasian ethnicity \( t(51) = -2.2, \beta = -0.28, p = .03 \) predicted increased MD in fMinor.

3.4.2. Secondary aim: brain–behavior relationships in cannabis users \((n = 33)\)

Greater symptoms of depression were associated with decreased FA in bilateral ATR (right: \( r = -0.36, p = .04 \); left: \( r = -0.35, p = .04 \)) and FA in the right UNC \( r = -0.34, p = .05 \), and increased MD in the left ATR \( r = 0.45, p = .009 \). Increased self-reported apathy symptoms were associated with decreased FA in bilateral UNC (right: \( r = -0.52, p = .002 \); left: \( r = -0.59, p < .001 \) see Fig. 5).

4. Discussion

The current study measured the relationship between cannabis group status, FAAH genotype, and frontolimbic WM integrity in a sample of adolescents and emerging adults (18–25 years old) without comorbid psychiatric disorders. Consistent with the predicted hypotheses, cannabis users had poorer WM integrity in fMinor and bilateral uncinate fasciculi (UNC) compared to controls. Further, consistent with proposed direction, cannabis users with the C/C genotype had reduced WM integrity in bilateral anterior thalamic radiation (ATR) compared...
to cannabis A carriers and controls. Examination of brain–behavior relationships noted that in cannabis users, greater self-reported depressive symptoms were significantly associated with poorer integrity in bilateral ATR and right UNC, while greater apathy scores were associated with poorer integrity in bilateral UNC, demonstrating a negative impact on affective processing.

The present findings are consistent with previous research examining regions of the fMinor, hippocampal, and internal capsule in young cannabis users (Abou-Saleh, 2010; Arnone et al., 2008; Gruber et al., 2011; Gruber et al., 2014; Jacobus et al., 2013b; Yücel et al., 2010; Zalesky et al., 2012). The PFC, especially the medial and orbital PFC, plays a vital role in regulating emotional, cognitive and behavioral functions (see Casey and Caudle, 2013; see Davidson, 2002), and such processes are fine-tuned with ongoing neurodevelopment, such that frontal regions exert greater top-down control over subcortical limbic regions (Phan et al., 2005). It has been previously proposed that the UNC has a bidirectional role in relaying associated memories of stimuli and emotions from the temporal lobes to the orbital frontal regions responsible for evaluating stimuli and rewards for the purpose of modifying behavior (see Von Der Heide et al., 2013). On balance, fMinor is composed of a collection of fibers that allow the exchange of both inhibitory and excitatory influences on the homologous region of the contralateral hemisphere within the PFC (see Bloom and Hynd, 2005; see van der Knaap and van der Ham, 2011). Thus, the observed reductions in fMinor and UNC integrity, tracts that connect the PFC to the limbic regions, may provide insight into mood and apathy symptoms related to cannabis use during this developmental period, perhaps influencing top-down abilities and affective processing in users (Bolla et al., 2005; Dorard et al., 2008; Gruber et al., 2009; Patton et al., 2002; Platt et al., 2010). As cortico-limbic tracts are one of the last to develop (Simonds et al., 2014), the present findings demonstrated compromise in these particular bundles, suggesting disruption of neurodevelopmental processes among cannabis using youth.

We also found moderations of WM integrity in cannabis users by FAAH genotype. Consistent with previous research suggesting greater risk associated with C/C genotype (Filbey et al., 2010; Haughey et al., 2008; Schacht et al., 2009; Tyndale et al., 2007), C/C status in cannabis users was associated with reduced WM integrity in bundles terminating on the prefrontal regions including the anterior cingulate and orbital frontal cortices, and previous studies have highlighted the role of such pathways in emotion processing, mood disorders, and reward-related behavior (Coenen et al., 2012; Lai and Wu, 2014; Paul et al., 2006). Filbey et al. (2010) examined functional changes between C/C and A carriers and found heightened activation in reward circuitry regions, including both anterior cingulate and orbital frontal cortex, among cannabis users with C/C genotype. Such findings suggest over-activation of limbic regions, which may be at the expense of reduced inhibitory response in the control regions of the PFC, and such patterns may occur in concert with poorer WM integrity in fMinor and ATR in cannabis using C/C carriers as observed in this study. In controls, the opposite pattern was observed, with those carrying at least one A allele demonstrating a pattern in reduced FA in the fMinor. Endocannabinoid signaling may impact myelination with evidence of communication between oligodendrocytes and neurons (Simons and Trajkovic, 2006). Therefore, the relationship between endocannabinoid signaling and neuronal health may be an inverse-U shaped curve, with too much or too little endocannabinoid involvement being associated with poorer WM integrity. Additional longitudinal studies characterizing the differences and influences of endocannabinoid signaling on WM development are needed.

We found that poorer WM integrity was significantly associated with increased self-reported symptoms of depression and apathy in the cannabis users. These brain–behavior findings are consistent with our previous finding that reduced WM volume was associated with increased depressive symptoms in adolescent cannabis users (Medina et al., 2007b), longitudinal studies linking cannabis use with depressive disorders (Patton et al., 2002), and studies linking white matter integrity with apathy in individuals with HIV (Kamat et al., 2014). Consistent with our previous findings (Medina et al., 2007a), cannabis users as a group did not significantly differ from controls in symptoms of apathy; however, cannabis users with poorer white matter integrity did demonstrate increased apathy symptoms. Therefore, white matter integrity in frontolimbic pathways may mediate apathy symptoms in cannabis users. The reward system may also be involved, as cannabis-using youth demonstrated a relationship between increased apathy and decreased dopamine production in the striatum (Bloomfield et al., 2014), a subcortical region high in CB, density (Terry et al., 2009). These WM pathways have been shown to impart top-down executive control (see Davison, 2002; Phan et al., 2005) and previous studies in adolescents highlight the influence they have on affective activation (Swartz et al., 2014).
et al., 2014); thus, frontal regions may not effectively regulate affective processing in young cannabis users. Future studies may want to examine frontolimbic functional connectivity differences in affective processing between young cannabis users and non-users.

There are limitations to the present study. Alcohol and cannabis are the most frequently used substances among youth (Johnston et al., 2014). The current study excluded individuals meeting the Cahalan criteria for “very heavy” alcohol use, and we statistically controlled for alcohol in the main analyses; however, it is possible that the effects of simultaneous or combined cannabis and alcohol use on WM may be influencing the observed results. For example, studies comparing non-using controls with groups reporting alcohol only or combined alcohol and cannabis use suggest that alcohol does indeed have damaging effects on WM in the frontal and temporal regions (Bava et al., 2009; Bava et al., 2010b; Bava et al., 2013; Jacobus et al., 2009; Jacobus et al., 2013a), though those transitioning to combined use may have greater WM abnormalities (Jacobus et al., 2013b). Jacobus et al. (2013b) examined WM quality in youth prior to initiation of heavy cannabis and/or heavy alcohol use and found significant reductions in WM integrity in those with combined alcohol and cannabis use compared to those that initiated heavy alcohol use alone. Thus, combined cannabis and alcohol use appears to be detrimental to WM health in youth. Similarly, cannabis users indicated greater nicotine use than controls, consistent with reported rates of co-use in youth, and associated with mood symptomatology (see Ramo et al., 2012). We also found that recent nicotine use measured by saliva cotinine levels predicted WM integrity in the right ATR, such that higher levels were associated with reduced integrity. Because this is a cross-sectional study, it is not possible to determine whether results are due to premorbid differences. A longitudinal study found that weekly or greater cannabis use during the teenage years doubled the risk of later depression and anxiety, whereas depression and anxiety as a teenager did not predict later cannabis use (Patton et al., 2002), suggesting that mood symptoms may be related to long-term regular use with earlier onset. Therefore, prospective, longitudinal studies are needed to disentangle potential causal influences on findings from cross-sectional datasets. Additionally, despite lack of differences observed in genotype between cannabis users and controls, there were significant differences in age between C/C genotype and A carriers. Although age was statistically controlled for, this may have important implications related to the degree of development reached between genotypes. Finally, ethnicity (coded as Caucasian or not) significantly predicted white matter when the FAAH genotype was included in regressions; due to power, we were not able to examine ethnicities separately. Larger cohorts may remedy this and address developmental differences between genotypes.

5. Conclusions

In conclusion, this study found that regular cannabis use is associated with poorer frontolimbic WM integrity, and these findings were moderated by the FAAH genotype. This reduced WM integrity was associated with negative mood and greater apathy symptoms in cannabis users. As use is predicted to rise in youth (Caulkins et al., 2012) in the context of decreases in perceived risk (Johnston et al., 2013), it remains an important public health priority to delay the onset of regular cannabis use until neuronal maturation has been reached (see Lisdahl et al., 2013).

Conflict of interest

None.

Acknowledgments

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References


