Curr Addict Rep (2014) 1:144–156
DOI 10.1007/s40429-014-0019-6

STIMULANTS, CANNABIS, AND CLUB DRUGS (AJ BUDNEY, R VANDREY AND D LEE, SECTION EDITORS)

Considering Cannabis: The Effects of Regular Cannabis Use on Neurocognition in Adolescents and Young Adults

Krista M. Lisdahl · Natasha E. Wright · Christopher Medina-Kirchner · Kristin E. Maple · Skyler Shollenbarger

Published online: 26 April 2014

Abstract Thirty-six percent of high-school seniors have used cannabis in the past year, and an alarming 6.5 % smoked cannabis daily, up from 2.4 % in 1993. Adolescents and emerging adults are undergoing significant neurodevelopment and animal studies suggest they may be particularly vulnerable to negative drug effects. In this review, we will provide a detailed overview of studies outlining the effects of regular (at least weekly) cannabis use on neurocognition, including studies outlining cognitive, structural, and functional findings. We will also explore the public health impact of this research.

Keywords Adolescence · Emerging Adult · Young Adult · Cannabis · Marijuana · MRI · fMRI · Diffusion Tensor Imaging · Neuropsychology · Cognition · Age of Onset · *FAAH* · *CNR1* · THC · Cannabidiol · Public health · Neurotoxic effects of cannabis

Introduction

Cannabis is the second most used drug after alcohol, with 22.9 % of high-school seniors and 20 % of college students using in the past month, and perhaps most alarmingly, one in every 15 seniors report using daily [1]. Research outlining the neurocognitive effects of chronic, regular (defined here as at least weekly) cannabis use in adolescents and young adults is of great public health concern. This review will summarize current findings regarding the neurocognitive consequences of cannabis use during the teenage and emerging adult years (focusing on ages 15–25 years). Studies utilizing neuropsychological assessment and structural and functional neuroimaging will be reviewed. Further, we will identify potential 'at-risk' groups who may experience more severe neurocognitive consequences of chronic cannabis use, such as those with early age of cannabis use onset and those with certain genotypic profiles, and will discuss the clinical and policy implications of this research.

K. M. Lisdahl (✉) · N. E. Wright · C. Medina-Kirchner · K. E. Maple · S. Shollenbarger
Department of Psychology, University of Wisconsin-Milwaukee, 2241 E. Hartford Ave, Milwaukee, WI 53211, USA
e-mail: krista.medina@gmail.com

Adolescence: A Sensitive Period?

Worldwide, most people start experimenting with drugs during the teenage years [2]. Adolescence is also a dynamic time marked by significant neurodevelopmental changes; brain regions underlying higher-order thinking and executive functioning, especially the prefrontal (PFC) and parietal cortex, undergo synaptic pruning into the mid-20s (see [3–6]). Quality and volume of white matter increase into the early 30s, which are associated with increased neural efficiency [7, 8]. This period of ongoing neurodevelopment may be a sensitive period in which drugs can exert a greater impact on the brain compared with exposure during adulthood (see [9]).

Impacts of Regular Cannabis Use on Neurocognition in Teens and Young Adults

Cognition

Although controversy exists in the adult literature, evidence is building to suggest that regular cannabis use during the teenage or emerging adult years (typically ages 15–25 years) is associated with cognitive deficits [10•]. Two longitudinal studies that followed adolescents with substance use disorders over 8 years found that increased cannabis use during the follow-up period significantly predicted poorer attention

[11•] and verbal memory [12•]. In the largest prospective, longitudinal study to date, Meier and colleagues [13••] followed a sample of 1,037 from birth to age 38 and found that 153 participants met criteria for cannabis-use disorders (CUD) at least once during the follow-up and individuals with more persistent cannabis use demonstrated the greatest reduction in IQ. Specifically, individuals who never regularly used cannabis had a slight increase (0.8 IQ point) in IQ from childhood into adulthood, while those diagnosed with cannabis dependence on at least three or more study occasions had an average loss of 5.8 IQ points. After controlling for gender, nicotine use, comorbid schizophrenia, and alcohol use, they also found specific deficits in executive functioning, sustained attention, verbal list learning, and psychomotor speed associated with persistent cannabis dependence [13••], findings that are generally consistent with cross-sectional studies [10•].

With one exception [14], several cross-sectional studies in cannabis-using youth without psychiatric comorbidities report cannabis-related cognitive deficits including reduced processing speed [15••, 16•, 17, 18•, 19••], complex attention [11•, 18•, 19••, 20••, 21, 22], verbal memory [12•, 15••, 19••, 20••, 21, 23–26], executive functioning [16•, 17, 18•, 19••, 21–23, 27, 28•, 29–31], and risky sexual behavior [30]. Takagi and colleagues [14] did not find differences in cognitive inhibition on a computerized task between inhalant users, cannabis users, and control adolescents. This may be partially due to a relatively small sample size (19 per group) and the authors did not report specific effect sizes obtained when comparing the cannabis users with controls. Cognitive deficits, including slowed processing speed, reduced verbal memory, sustained attention and sequencing ability, were measured following a month of monitored abstinence in one study [19••], although another found significant recovery following 4 months of abstinence [15••].

Brain Structure

Gray Matter

Several studies to date have demonstrated abnormalities in brain structure in adolescent and emerging-adult cannabis users. In a sample of adolescents (ages 16–19 years) without comorbid psychiatric, developmental, or neurologic conditions, we found that increased past-year cannabis use significantly predicted larger hippocampal volumes [32]. In similar adolescent samples followed over a month of closely monitored abstinence, we found that female cannabis users had larger posterior PFC [33], posterior inferior cerebellar vermis [34], and left amygdala [35] volumes. Male users also had larger posterior inferior cerebellar vermis volumes [34]. Churchwell and colleagues [36] found increased striatal volume in a sample of comorbid cannabis and methamphetamine users. Other groups have reported decreased right medial orbitofrontal cortex [37], reduced hippocampal [38, 39•, 40], reduced amygdala [39•, 40], and increased anterior cerebellar [39•] volumes in adolescent and young-adult cannabis users without comorbid psychiatric conditions. The above structural alterations in gray matter were associated with increased executive dysfunction [33, 34, 37], mood symptoms [35], poor verbal memory [38], and novelty seeking [36], suggesting that these structural abnormalities were not advantageous. In one of the most thorough structural studies, Lopez-Larson and colleagues [41•] measured cortical thickness in cannabis users and found decreased cortical thickness in right caudal middle frontal, bilateral insula, and bilateral superior frontal cortices with increased thickness in lingual, temporal, inferior parietal, and paracentral areas in the cannabis users compared with non-users. Another novel measurement of gray matter architecture is extent of gyrification, which is formed by horizontal cortical development and increasing tensions in the white matter [42]. Mata and colleagues [43•] found reduced cortical curvature in PFC regions in young adult cannabis users compared with non-using controls, suggesting reduced PFC complexity.

Taken together, these findings suggest that cannabis exposure during the adolescent years may lead to abnormalities in gray matter architecture, including reduced cortical gyrification complexity, increased volume that may reflect disrupted healthy gray matter pruning, and decreased structure that may reflect reduced dendritic branching or neuronal atrophy. Alternatively, increases in volume may be associated with abnormal connectivity patterns in adolescent cannabis users, perhaps reflecting compensation for less efficient cognitive performance. These structural abnormalities and resulting poorer cognitive functioning may signal a delay in neurodevelopment and underlying mechanisms need to be further examined in developmental animal studies.

White Matter

Containing myelinated axons, white matter is responsible for efficient communication between and within brain regions. Although CB1 cannabinoid receptors are primarily found on neurons, they are also found on myelinating glial cells and are thought to play a significant role in structural connectivity [44]. Advances in diffusion tensor imaging (DTI) allow microstructural measurement of white matter integrity by assessing the extent to which water can diffuse across the axons. Poorer white matter quality is associated with slower processing speed and white matter disease. Structural [45] and micro-structural [46–48, 49••, 50, 51•, 52] reductions in white matter have also been observed in young cannabis users. Using DTI in a longitudinal study, Bava and colleagues [49••] found that at the 18-month follow-up, cannabis users with comorbid alcohol use demonstrated poorer white matter integrity in seven tracts (bilateral superior longitudinal

fasciculus, bilateral thalamic fibers, right superior temporal gyrus, right inferior longitudinal fasciculus, and left posterior corona radiate). However, in this sample, alcohol use during the interscan interval predicted reduced white matter integrity while cannabis did not. With only one exception [50], several studies have now reported reduced white matter quality in several PFC, limbic, parietal and cerebellar tracts in young cannabis users after controlling for alcohol use [46–48, 51•, 52, 53]. Additional research disentangling the unique effects of alcohol versus cannabis on white matter integrity is needed. In a study examining the relationship between psychological dysregulation, white matter integrity, and substance (including cannabis) use in teens, Clark et al. [53] tested mediation models and concluded that poorer white matter quality in frontoparietal networks was both a risk factor for psychological dysregulation and CUD-related symptoms, and a result of cannabis use.

Blood Flow/Neurochemical

Adolescent cannabis use has also been associated with reduced cerebral blood flow in PFC, insular, and temporal regions [54] and abnormal neurochemical markers of neuronal integrity [55•, 56]. Specifically, magnetic resonance spectroscopy research has shown alterations in glutamate, N-acetyl aspartate, creatine, and *myo*-inositol in the anterior cingulate [55•], reduced subcortical global *myo*-inositol/creatine ratios, and reduced white matter *myo*-inositol [56]. Taken together, these findings suggest that chronic cannabis use during the adolescent and emerging adult years may result in abnormal vascular functioning as well as neuronal and migroglia toxicity. Additional studies are needed to determine whether vascular and glial alterations underlie gray and white matter abnormalities observed in young cannabis users.

Brain Function

Several studies have reported inefficient brain activation patterns in young cannabis users. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies that assess brain activation patterns in adolescent cannabis users have reported abnormal PFC, parietal, insular, subcortical/limbic, and cerebellar activation in cannabis users during finger tapping [57•], attentional control [58], spatial working memory [59, 60•, 61], verbal working memory [62, 63•, 64], verbal learning [65], executive functioning [66, 67], and pleasant interoceptive stimuli [68] tasks. In the latter study, findings demonstrated that substance-using teens had blunted processing of pleasant stimuli but heighted sensitivity to reward processing in the insula [68].

In the past couple of years, novel fMRI analyses have revealed abnormal functional connectivity in young cannabis users compared with controls. Increased parietal-cerebellar, right hemispheric, and PFC [69•, 70•] and decreased frontal-cerebellar interhemispheric and temporal cortex [70•, 71•] resting state connectivity has been reported in adolescent cannabis users. Studies have also found increased functional connectivity between PFC-occipital [72•], and parietal-cerebellar [69•] brain regions in adolescent cannabis users while engaging in cognitive tasks. Authors note that observed increased connectivity patterns were associated with increasing task demands and poorer inhibitory control [69•, 72•] and patterns of reduced interhemispheric connectivity complement reports of reduced white matter integrity in these regions [70•]. Taken together, these findings suggest that during early cannabis exposure the brain may attempt to compensate by recruiting other neuronal regions, resulting in increased functional connectivity with similar task performance as controls, although such compensation may fail with increased task complexity (e.g., users demonstrate performance decrements in more difficult out-of-scan tasks assessing processing speed, verbal memory, inhibitory control, working memory, and attention; [10•]). Additional longitudinal studies examining how brain connectivity patterns change with increasing use in adolescents and young adults are needed.

Cannabis, *FAAH/CNR1* and Neurocognition

Individual differences in candidate genes related to endogenous cannabinoid signaling such as the cannabis receptor-1 gene (*CNR1*) and fatty acid amide hydrolase (*FAAH*), which are related to CUD risk and healthy brain function (e.g., [73•]), may also moderate the effects of exogenous cannabis exposure on the young brain. Thus far, studies have linked the *CNR1* G allele with reduced bilateral hippocampal volumes [40] and increased cannabis cue-reactivity in PFC-cingulate regions [74], C allele with increased trait anxiety [75], withdrawal and negative affect following abstinence [76], and increased craving following cannabis cues [76] in young adult cannabis users. No links between *CNR1* genotype and behavioral problems, impulsivity [75] or amygdala volumes [40] have been found. Cannabis-using carriers of the *FAAH* C allele have demonstrated greater PFC, cingulate, and nucleus accumbens activation [74] and increased withdrawal [77] and craving [76] symptoms following cannabis cue exposure. *FAAH* C allele carriers also demonstrated greater withdrawal and negative affect following abstinence [76]. Results thus far have found no link between *FAAH* genotype and trait anxiety, impulsivity or behavioral problems [75]. In summary, these preliminary studies suggest that genetics, especially those related to reduced endogenous cannabinoid signaling such as the *FAAH* C allele, may place subgroups at greater risk for increased CUD severity and more severe neurocognitive consequences of cannabis exposure.

Age of Regular Cannabis Use Onset

Pre-clinical findings demonstrated greater microcellular changes, including altered dopamine, GABA and glutamate signaling, glial cell changes, decreased cAMP response element-binding protein (CREB) signaling in the PFC and hippocampus, abnormal neurotrophic release, and reduced dendritic branching (see [78] for review; [79]), associated with THC (delta-9-tetrahydrocannabinol, the major psychoactive chemical in cannabis) exposure during adolescence compared with adulthood, resulting in increased behavioral effects (e.g., [80–83]). Taken together, animal findings support increased structural alterations that result in poorer memory performance in adolescent THC-exposed animals compared with adults.

In a comprehensive review of human alcohol and cannabis studies, our group [10•] previously noted increasing evidence that teenage cannabis use onset (CUO) results in greater neurocognitive deficits compared with adult onset. Weekly cannabis use before age 18 has been linked with reduced performance on IQ [13••, 84••], attention [85], visual search [86] and executive functioning [16•, 17, 31, 87•, 88•] neuropsychological tasks. (See Table 1 for overview of studies.)

Perhaps most notable, in their prospective, longitudinal study, Meier and colleagues [13••] reported that adolescents with early CUO had the greatest reduction in IQ, going from a childhood 'average' to an adult 'low-average' IQ. Alarmingly, the individuals with early CUO did not return to their predicted intellectual trajectory. This is consistent with cross-sectional studies that have reported greater structural and functional brain abnormalities in early CUO. Wilson and colleagues [89] reported smaller gray matter and increased white matter cortical volumes in adults who initiated regular cannabis use in the teenage versus adult years. Adolescent CUO has also been linked with decreased right superior PFC thickness [41•], reduced PFC white matter integrity, and increased cognitive impulsivity [51•, 52]. With one exception [65], studies examining the impact of early cannabis use on brain function have revealed abnormal blood oxygenation level-dependent (BOLD) activation in PFC and parietal lobes [16•, 17, 63•, 64]. Finally, a recent study reported that dopamine (D2/D3) receptor availability and striatal dopamine release was not abnormal in adults with CUD; however, earlier CUO significantly predicted smaller baseline striatal dopamine release that may explain increased risk of dependence in adolescent CUO [94].

In sum, animal and human studies to date suggest that regular exposure to exogenous cannabinoids may disrupt healthy neurodevelopment, especially in the PFC and parietal cortices [16•, 17, 31, 37, 41•, 52, 63•, 87•], which underlie higher-order cognitive functioning. This early initiation during the sensitive period of adolescence may place individuals on a new neurodevelopmental trajectory, resulting in millions of youth who may not reach their full intellectual potential.

Future Research Directions

Recovery of Function with Abstinence?

Recently, a PET study demonstrated significant recovery of CB1 receptor downregulation in adult daily cannabis users following 1 month of monitored abstinence [95], suggesting alterations in the endogenous cannabinoid system may recover with abstinence. Still, there is little research that has attempted to answer whether neurocognitive functioning returns with sustained abstinence in youth. In adolescent cannabis users, verbal memory significantly improved following three 3–6 weeks of abstinence [24, 27]. Fried and colleagues [15••] demonstrated that adolescent cannabis users no longer had cognitive deficits following 4 months of abstinence [15••]. Schweinsburg and colleagues [60•] demonstrated that recent cannabis users had greater insular and PFC brain activation compared with ex-users, suggesting inefficient processing may recover with sustained abstinence. Although these brief longitudinal studies demonstrate some recovery, the largest prospective longitudinal study to date reported that individuals who began using cannabis early in the teenage years never fully returned to their predicted pre-drug exposure IQ trajectory, even with abstinence in adulthood [13••]. Therefore, data to date suggests that some cognitive recovery may occur with sustained abstinence although additional prospective longitudinal research is needed to determine whether adolescents who begin regularly using cannabis can recover fully or if their neurocognitive trajectory is permanently altered.

Does Neurocognition Predict Treatment Outcomes?

Using cannabis may lead to CUD, with 17 % of individuals who tried cannabis before age 17 years becoming dependent (NIDA [96]). In 2010, 49.9 % of all drug treatment admissions reported a CUD, and 86.8 % had an early teenage CUO [97]. Recent studies have attempted to utilize neuroimaging to predict treatment outcomes in youth with early CUO. For example, in a sample of young adolescents (14–17 years old) seeking outpatient treatment for CUD that included psychiatric comorbidities, De Bellis and colleagues [92•] found increased BOLD activation in left superior lobule, lateral occipital, and bilateral precuneus to a risky decision-making task. In the youth with CUD, increased relapse risk and more chronic use was associated with reduced left orbitofrontal activation to reward. In a sample without comorbid psychiatric disorders [91•], decreased BOLD response at baseline in the dorsolateral PFC and anterior cingulate to a stimulus

response compatibility task, designed to parallel real-world approach-bias (tendency to approach drug-related cues), predicted increased CUD problem severity 6 months later.

In the most integrated translational project to date, Feldstein Ewing and colleagues [93••] utilized fMRI to measure the impacts of psychological treatment (change talk versus counterchange talk) on brain activation to cannabis cues following treatment in teenage cannabis users. They found that change talk increased BOLD activation in areas that underlie introspection (posterior cingulate, precuneaus) during exposure to cannabis cues, and this increase in activation was associated with superior 1-month treatment outcomes (frequency of cannabis use, marijuana-related problems, CUD symptoms). Additional studies utilizing neuroimaging and neurocognitive measures to assess the long-term impact of various treatments on neurocognition and to predict treatment outcomes in adolescent substance users are needed.

Does Content of Cannabis (especially CBD vs THC) Matter?

There are numerous chemicals in cannabis, including at least 60 cannabinoids. Historically, users have primarily sought plants with high THC content to enhance the subjective 'high,' and a recent analysis of California cannabis revealed that levels of THC are increasing while levels of cannabidiol (CBD) are decreasing [98]. This is of concern as an emerging literature focused on *acute* exposure is suggesting that increasing the CBD versus THC in cannabis plants may decrease some of the negative effects of use [99], such as anxiety [100, 101], psychotic-like symptoms [101–103], and memory impairment [103, 104]. Further, CBD may moderate effects of THC on affective [100, 102], verbal memory [102], response inhibition [102], visual processing [102], and auditory processing [101, 102] brain activation patterns. Two studies to date have measured THC and CBD levels from hair; one found that individuals with high THC and low CBD had increased symptoms of depression and anxiety [105] and both found worse verbal memory associated with THC, but not CBD [90•, 105]. Further, Demirakca and colleagues [90•] found reduced hippocampal volumes in cannabis users, although increased CBD levels were associated with *increased* gray matter concentration in bilateral hippocampi. Additional preclinical and human research examining the impact of chronic CBD versus THC exposure on the developing brain is needed, especially as state governments are considering legalization.

Potential Limitations

Without additional large-scale prospective longitudinal studies, it can be difficult to tease apart the influence of premorbid factors versus direct effects of cannabis exposure on neurocognition in youth. Most of the studies outlined in this review controlled for potentially confounding variables, such as family history of substance use disorders and Axis I disorders; however, subclinical symptoms or neurocognitive correlates of risk factors [27, 53, 106–111] may still explain at least a portion of the brain abnormalities reported in cross-sectional studies of cannabis users. For example, Cheetham and colleagues [112•] found that abnormalities in the orbitofrontal cortex, but not limbic and anterior cingulate areas, predated and predicted the onset of cannabis use in a 4-year, prospective, longitudinal study. Yet, preclinical findings show consistent effects of chronic THC exposure in animal models (e.g., [81]), and the recent large prospective longitudinal study by Meier and colleagues [13••], suggests that reductions in IQ, executive functioning, sustained attention, verbal list learning, and psychomotor speed, areas reportedly impaired in several cross-sectional studies, were related to cannabis exposure after controlling for any premorbid factors. Additional longitudinal research in adolescents *prior* to cannabis use initiation is needed to determine the specific influence of cannabis exposure on the developing brain.

Conclusions

Increase Prevention and Treatment

According to the most recent Monitoring the Future Study, an alarming 6.5 % of high-school seniors smoke cannabis daily, up from 2.4 % in 1993 [1]. This review article summarizes numerous studies that, taken together, suggest regular cannabis use during the adolescent and emerging adult years may disrupt brain function and result in poor cognitive functioning. Even subtle reductions in sustained attention, new learning, psychomotor speed, and executive functioning may result in significant psychosocial consequences during a neurodevelopmental period that is typically rich in new learning and continued education and training. Further, most of the studies examined youth following a period of abstinence and excluded individuals with comorbid disorders; therefore, these findings may underestimate functioning of young cannabis users who may be experiencing withdrawal symptoms, poor sleep quality, comorbid psychiatric symptoms, and stress associated with increased legal issues.

It is becoming increasingly critical to publicize these research findings in any settings that serve adolescents and young adults (e.g., schools, military, mental-health clinics, medical schools, and to parents). It needs to be emphasized that regular cannabis use, defined here as once a week, is *not* safe and may result in addiction and neurocognitive damage, especially in youth. National websites do produce high-quality education materials outlining the effects of regular cannabis use on the brain and are available for free (e.g., www.nida.nih.gov, www.thecoolspot.gov, www.drugfreeamerica.org, www.Teen-Safe.org). However, psychoeducation alone may not be effective. Additional

Table 1 Summary of primary findings from human studies reporting neurocognitive effects of regular cannabis use in adolescents and emerging adults (organized by cognitive, structural or functional consequences and clustered according to functional category) (Adapted and modified from [10•])

Cited cannabis studies	Neuropsychology findings	Brain structure findings	Blood flow/neurochemistry findings	Brain function findings
[14]	No difference			
*[13••]	↓IQ			
*[84••]	↓IQ			
*[86]	↓visual search			
*[87•]	↓executive functioning			
[29]	↓ executive functioning			
*[16•, 17]	↓ executive functioning			
[28•]	↓ executive functioning			
[30]	↓ executive functioning; ↑risky sexual behavior			
*[31]	↓executive functioning			
*[88•]	↓ decision making Early onset MJ: ↓executive functioning in sample with and without ADHD			
*[85]	↓attention			
[15••]	↓ processing speed, verbal memory			
[20••]	↓ complex attention, verbal memory			
[21]	↓ complex attention, verbal memory, executive functioning			
[18•]	↓ complex attention, processing speed, sequencing ability, cognitive inhibition			
[22]	↓ complex attention, executive functioning			
[19••]	↓ complex attention, processing speed, verbal memory, sequencing ability			
[11•]	↓complex attention			
[23]	↓ verbal memory, executive functioning			
[24]	↓verbal memory			
[25]	↓verbal memory, executive functioning			
[12•]	↓verbal memory			
[26]	↓verbal memory			
[75]	↑trait impulsivity in *CNR1* C carriers in cannabis users			
[76]	↑ withdrawal, negative affect, craving with cues, *CNR1* C carriers ↑ withdrawal, negative affect, craving with cues, *FAAH* C carriers			
*[89]		↓ total GM; ↑ total WM		
*[37]	↓ executive functioning	↓ right medial OFC		
*[41•]		↓ right caudal, PFC, insula ↑lingual, temporal, inferior parietal, paracentral thickness		

Table 1 (continued)

Cited cannabis studies	Neuropsychology findings	Brain structure findings	Blood flow/neurochemistry findings	Brain function findings
[33]	↓ executive functioning	Females: ↑ inferior PFC volume		
[38]	↓verbal memory	↓ HC volume		
[90•]		↓ HC volume with ↑THC ↑ HC GM with ↑CBD		
[45]		↑ left HC volume		
[35]	↑depressive symptoms	Females: ↑ left AMYG		
[40]		↓HC, AMYG volumes ↓HC in *CNR1* G allele		
[36]	↑ novelty seeking in MJ+ methamphetamine users	↑ left putamen volume		
[34]	↓ executive functioning	↑ inferior cerebellar vermis volume		
[39•]		↑ GM volume in cerebellum; no WM differences		
[50]		No WM differences detected		
[46]		↓ WM integrity (CC)		
[47]		↓ WM integrity (arcuate fasciculus)		
[48]		↓ WM integrity in 10 regions (PFC, parietal cortex); ↑WM integrity in occipital cortex		
[49••]		↓ WM FA in R PFC, thalmic fibers, plenium, and posterior corona; ↑ MD, RD, and AD in 7 regions		
*[52]	↑ impulsivity	↓ WM integrity in PFC		
*[51•]	↑ impulsivity	↓ FA in L and R genu of CC, L internal capsule, ↑ mean diffusivity in CC		
[45]	↑depressive symptoms	↓ global WM in MJ users with depressive sx		
[54]			↓ blood flow in temporal, insular and PFC regions	
[55•]			↓ ACC glutamate, N-acetyl aspartate, creatine, *myo*-inositol	
[56]			↓ subcortical GM *myo*-inositol/ creatine; WM *myo*-inositol	
[58]				↑ PFC BOLD during attentional control task
*[64]				↑ left superior PFC BOLD during working memory task in early onset
[65]				↑ left parahippocampal BOLD during learning task
[69•]				↑ connectivity in frontal-parietal-cerebellar network in Go/No-Go task; ↑ connectivity in parietal and cerebellar in RS fMRI
[53]				↓ PFC and parietal WM FA
[91•]	↑ problem severity			↓ DLPFC and ACC in heavy users
[92•]				↑L superior lobule, lateral occipital cortex, L and R precuneus in risky decision-making task
[93••]				↑ insula, parahippocampal, caudate, ACC, and IFG in response to change talk, predicting treatment outcomes

Table 1 (continued)

Cited cannabis studies	Neuropsychology findings	Brain structure findings	Blood flow/neurochemistry findings	Brain function findings
[74]				↑ PFC, ACC, nucleus accumbens in *FAAH* C carriers
*[16•, 17]				↓ ACC fMRI BOLD during inhibition task in early onset
[72•]				↑ PFC and occipitoparietal connectivity as task demands increase
[71•]				↑ PFC activation in RS fMRI
[62]				↓ PFC, parietal connectivity during verbal working memory task
[54]				↓ CBF in temporal lobe, insula, and PFC
*[63•]				↑ PFC BOLD during working memory task
[57•]				↓ ACC, cerebellar BOLD during finger tapping
[68]				↓ bilateral posterior insula, R PFC ↑ anterior insula to interoceptive stimulation
[59]				↓ PFC, occipital ↑ parietal BOLD during SWM task
[60•]				↑ PFC, insula ↓ precentral BOLD during SWM task in recent MJ users
[61]				↑ inferior, middle PFC BOLD during SWM task
[66]				↑ PFC, parietal, occipital BOLD during inhibitory task
[70•]				↑ right low-frequency and ↓ frontal-cerebellar interhemispheric connectivity in RS fMRI
[67]				↑ventral medial PFC, cerebellar PET rCBF during IGT task

* analysis revealed that teenage cannabis use age of onset (<16, 17 or 18 years of age) was associated with significantly poorer neurocognitive outcomes.

↑ increase, ↓ decrease, *ACC* anterior cingulate cortex, *ADHD* attention-deficit hyperactivity disorder, *AMYG* amygdala, *BOLD* blood oxygenation level-dependent, *CBD* cannabidiol, *CBF* cerebral blood flow, *CC* corpus callosum, *DLPFC* dorsolateral prefrontal cortex, *FAAH* fatty acid amide hydrolase, *fMRI* functional magnetic resonance imaging, *GM* gray matter, *HC* hippocampus, *IFG* inferior frontal gyrus, *L* left, *MJ* marijuana, *OFC* orbitofrontal cortex, *PET* positron emission tomography, *PFC* prefrontal cortex, *R* right, *RS* resting state, *SWM* spatial working memory, *IGT* Iowa Gambling task, *THC* delta9-tetrahydrocannabinol, *WM* white matter

prevention research that is effective at *delaying the onset* of regular cannabis use is needed.

Cannabis Policy Considerations

Adolescence has been named the "gateway to adult health outcomes" [113] and presents a "golden opportunity for public policy intervention to improve health outcomes that last throughout adulthood" [10•]. The cannabis policy in the US is rapidly changing [114] and two states (CO, WA) have recently legalized cannabis. In order to inform policy, we need further research determining whether specific frequency of use (e.g., >monthly, monthly, weekly, daily) and dose of THC or THC/CBD ratios may be considered safe for adults. Additional work is also needed to determine at what age cannabis use is no longer or minimally associated with significant neurocognitive harm (e.g., we know use before 18 is associated with increased neurocognitive deficits, but data is not clear as to whether the age limit should be set at 21, or closer to 25 when significant gray matter neurodevelopment is complete).

It is estimated that with legalization, cannabis cost will go down and consumption will go up [114] and we have already seen reductions in perceived risk of cannabis in youth [1]. Clearly, we will need additional research to help determine the impact of cannabis legalization or other policy decisions on patterns of use, age of onset, and treatment needs. With easier access to cannabis, it is particularly critical to educate the public about potential health effects of acute and regular use as they relate to youth. It is imperative that the scientific

community increase dissemination and communication of cannabis-related research findings with policy makers in order to impact critical decisions regarding legal age cut-offs, enforcement of under-age laws, potency decisions (e.g., THC vs CBD ratio), and distribution of prevention and treatment resources as governments begin to consider cannabis legalization. This may be a rare opportunity to help develop policies that can improve public health outcomes (see [114] for discussion of policy considerations).

The largest lessons the scientific community can share are that we need to (i) invest resources to *delay the onset* of cannabis use past the sensitive period of significant neuromaturation (i.e., close to age 25), (ii) increase resources for prevention, screening, and early intervention for regular cannabis users (especially targeting youth), and (iii) invest in more research regarding the impact of cannabis content and dosage on addiction risk and neurocognition (i.e., following up on preliminary evidence that higher levels of CBD and limiting THC content may reduce public health impact of cannabis use). In order to optimize neuronal development and reduce the prevalence of cannabis use disorders, empirically validated interventions aimed at lowering and preventing cannabis use in youth need to be consistently implemented to minimize the impact of regular cannabis use on the developing brain.

Acknowledgments During manuscript preparation, Dr. Lisdahl was supported by the NIDA-funded grant R01DA030354.

Compliance with Ethics Guidelines

Conflict of Interest Due to Krista Lisdahl's efforts, the University of Wisconsin-Milwaukee has received money in the form of grants from NIH/NIDA for the current work. Dr. Lisdahl declares consultancy work for the NIH/NIDA and travel, accommodations or meeting expenses paid by INS, APA and NIDA, outside of the submitted work.

Natasha E. Wright, Christopher Medina-Kirchner, Kristin E. Maple and Skyler Shollenbarger declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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