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Exploring Cannabis and Alcohol Co-Use in Adolescents: A Narrative Review of the Evidence

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Abstract

Objective.—Amidst evolving policy surrounding cannabis legalization in the United States, cannabis use is becoming increasingly prevalent as perceptions of harm decrease, particularly among adolescents. Cannabis and alcohol are commonly used by adolescents, and are often used together. However, developmental research has historically taken a “single substance” approach to examining the association of substance use and adolescent brain and behavior rather than examining co-(or poly-substance) use of multiple substances, such as cannabis and alcohol. Thus, the acute effects of cannabis and alcohol, and the impact of co-use of cannabis and alcohol on the adolescent brain, cognitive function and subsequent psychosocial outcomes remains understudied. This narrative review aims to examine the effects of cannabis and alcohol on adolescents across a number of behavioral and neurobiological outcomes.

Methods.—The PubMed and Google Scholar databases were searched for the last 10 years to identify articles reporting on acute effects of cannabis and alcohol administration, and the effects of cannabis and alcohol on neuropsychological, neurodevelopmental, neural (e.g., structural and functional neuroimaging), and psychosocial outcomes in adolescents. When adolescent data were not available, adult studies were included as support for potential areas of future direction in adolescent work.

Results.—Current studies of the impact of cannabis and alcohol on adolescent brain and behavior have yielded a complicated pattern. Some suggest that use of cannabis in addition to alcohol during adolescence may have a “protective” effect, yielding neuropsychological and structural brain outcomes that are better than those for adolescents who use only alcohol. However, other adolescent studies suggest that cannabis and alcohol co-use is associated with negative health and social outcomes such as poorer academic performance and impaired driving.

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Conclusion.—Variation in study methodologies, policy-level limitations and our limited understanding of the developmental neurobiological effects of cannabis preclude straightforward interpretation of the existing data on adolescent cannabis and alcohol use. Further research on this topic is requisite to inform the development of effective intervention and prevention programs for adolescent substance users, which hinge on a more comprehensive understanding of how cannabis —and its intersection with alcohol—impacts the developing brain and behavior.

Introduction

In the U.S., cannabis is the most commonly used substance among adults who drink alcohol (Subbaraman & Kerr, 2015), and not surprisingly, cannabis and alcohol are also the most commonly co-used substances among adolescents (Schulenberg, 2018). Co-using cannabis and alcohol is associated with increased quantity and frequency of drinking, more alcohol-related harms (Patrick et al., 2018; Subbaraman & Kerr, 2015), greater substance related problems for youth, including violence, driving under the influence, riding with an intoxicated driver (Lipperman-Kreda, Gruenewald, Grube, & Bersamin, 2017), and/or an incurring problems that result in needing to interface with the legal system (Green et al., 2016). In adolescents, co-use of cannabis and alcohol is also associated with poorer educational outcomes (Kelly, Evans-Whipp, et al., 2015) and increased psychological distress (Kelly, Chan, Mason, & Williams, 2015). Given the frequency and potential negative impact of cannabis and alcohol co-use among adolescents, it is important to consider how use of these drugs acutely affects behavior, neurodevelopment, and long-term outcomes.

However, at present, little is known about the acute effects of alcohol and cannabis on neurobehavioral phenotypes relevant to addiction (e.g., impulsivity, reward or cognitive control). Whereas some findings suggests synergistic or additive effects between cannabis and alcohol use in adults (Lukas & Orozco, 2001), others suggest that their combined effects in adults are no worse than the effects of alcohol alone (Ballard & de Wit, 2011; Ramaekers et al., 2011). No studies have explored acute co-effects of cannabis and alcohol in adolescents, and the limited studies exploring adolescent cannabis and alcohol co-use on neuropsychological development and brain structure and function have demonstrated inconsistent patterns. Some suggest that adolescent co-use of cannabis and alcohol is associated with worse neuropsychological performance (e.g., Jacobus, Squeglia, Infante, et al., 2015) and altered brain function (e.g., Claus et al., 2018); however, others suggest that cannabis and alcohol co-users may have better performance (e.g., Mahmood, Jacobus, Bava, Scarlett, & Tapert, 2010) and brain outcomes (e.g., Infante et al., 2018) than alcohol-only users.

Exploring the mixed findings of how cannabis and alcohol may interact within the developing brain and how this may impact public health outcomes for this age group is particularly timely in light of the changing legal landscape surrounding cannabis in the U.S. As of early 2019, 33 states and the District of Columbia have approved comprehensive medical cannabis programs whereby individuals with qualifying medical conditions can legally use cannabis for management of these issues. In addition, recreational use of cannabis has been legalized in 10 states and the District of Columbia, meaning that anyone age 21 or older is allowed to possess (in limited quantities) and consume cannabis purchased

through legal avenues (e.g., registered dispensaries). Legalization prohibits recreational cannabis use in adolescents, but across all age groups, cannabis use appears to be on the rise (National Academies of Sciences, 2017). Two factors that could contribute to increased use of cannabis by adolescents in U.S. states with recreational or medical legalization include increased cannabis availability and decreased perceived risk of the anticipated harms of cannabis (Feldstein Ewing, Lovejoy, & Choo, 2017).

Longitudinal studies spanning pre- and post-legalization have been a primary focus for elucidating the effects of legalization. The Monitoring the Future (MTF) report shows a decline in the perceived harmfulness of cannabis in 8th, 10th and 12th graders since 2006 and in the past year (Johnston et al., 2019). Annual prevalence assessed by the MTF, however, indicates stable cannabis use in these age groups, ranging from a 1.2% decrease (12th graders) to 0.2% increase in use (8th and 10th graders; Johnston et al., 2019). Focusing on states with recreational legalization provides mixed evidence; specifically, adolescents in Washington state reported less perceived harmfulness of cannabis and greater cannabis use post-legalization, but those in Colorado reported no changes in perceived harmfulness of cannabis use, perhaps due to the degree of commercialization of cannabis and the developed medical cannabis program pre-legalization in Colorado (Cerdá et al., 2017). In terms of the impact of medical cannabis legalization on adolescent use, four nationally representative U.S. datasets compared states before and after medical laws were passed to states that did not pass medical cannabis laws over the same time period, and these surveys suggest that changes in medical (as compared to changes in recreational) cannabis laws do not appear to significant impact adolescent cannabis use (Carliner, Brown, Sarvet, & Hasin, 2017), in the same way that recreational laws might impact perceived availability and decreased harm. Thus, the existing literature lacks clear evidence that cannabis legalization is associated with subsequent increases in adolescent cannabis use. However, one factor that complicates our capacity to examine these questions systematically is the existing status of cannabis as a Schedule 1 substance; many states with legal recreational and/or medical cannabis use, are not able to systematically examine how cannabis is impacting current behaviors in adolescents and adults due to federal restrictions on research. Thus, much of our current comprehension of cannabis- and cannabis-related behaviors is obstructed by limitations in federal policy around cannabis, and related implications in our capacity to truly measure the changing phenomenon of cannabis use in these regions (National Academies of Sciences, 2017).

Notably, recent evidence suggests that heavy alcohol use may impact the relationship between recreational legalization and cannabis use. Specifically, among emerging adults of legal purchasing age (college students) in Oregon, rates of cannabis use increased from pre- to post-recreational legalization and increases in cannabis use were significantly higher at universities in Oregon compared to universities in other states, but particularly among students who also reported recent heavy alcohol use (Kerr, Bae, Phibbs, & Kern, 2017). However, we are still missing systematic examination of these relationships among adolescents. If, as this study suggests, heavy drinking adolescents have broad substance use propensities and tend to increase cannabis use following recreational legalization, it will be particularly important to gain a better understanding of the potential consequences of adolescent alcohol and cannabis co-use as recreational cannabis laws become increasingly

common. In particular, numerous questions remain regarding the impact of adolescent cannabis and alcohol co-use on neurobehavioral addiction phenotypes, neuropsychological functioning, brain structure and function, and psychosocial outcomes.

Method

This review will discuss the burgeoning research exploring the effects of cannabis and alcohol co-use on the adolescent brain and behavior, including 1) acute effects on reward and cognitive/motor function, and 2) effects on neurodevelopment, including neuropsychological functioning, brain structure and brain function and 3) psychosocial outcomes. We will also comment on current challenges and recommendations for future research in this important emerging area. To select articles to include in this narrative review, PubMed and Google Scholar databases were searched for the last 10 years to identify articles reporting on cannabis and alcohol administration, patterns of use, and the effects of cannabis and alcohol on neuropsychological, neurodevelopmental, neuroanatomical (e.g., structural and functional neuroimaging), and psychosocial outcomes in adolescents. Because there are no existing adolescent studies exploring the *acute* effects of cannabis and alcohol on reward and cognition, adult studies have been included in the following sections to inform potential future adolescent work in this area.

Results

1. THC and Alcohol: Acute Effects

Overview—Preclinical and human studies of adults indicate that the different cannabinoids present in cannabis (specifically cannabidiol [CBD] and delta-9-tetrahydrocannabinol [THC]) render differential effects on the brain, cognition, and behavior, which may have additive or mitigating effects on subsequent substance use (Rømer Thomsen, Callesen, & Feldstein Ewing, 2017). However, as research on CBD is limited and the majority of recreational cannabis contains primarily THC and little-to-no CBD, we will focus on the effects of THC and alcohol throughout this review.

It is worth noting that administration studies exploring acute effects of cannabis on adults are limited by the current federal designation of cannabis as a Schedule 1 controlled substance. This prohibits scientists from administering cannabis to research participants unless the cannabis was grown at the DEA-licensed, National Institutes on Drug Abuse (NIDA)-funded farm at the University of Mississippi. Researchers can also administer THC using FDA-approved drugs such as Marinol, which contains synthetic THC as its active ingredient. Both of these options may lack external validity, given that NIDA-cannabis contains THC potencies that are considerably lower than cannabis typically consumed by recreational users (Hagerty, York Williams, Mittal, & Hutchison, 2015; Volkow, Baler, Compton, & Weiss, 2014), and plant-derived cannabis appears to confer unique effects that are not necessarily present in synthetic, THC-based drugs (Russo, 2019). Notably, fewer regulations exist outside the U.S. For instance, researchers in the Netherlands have studied slightly higher potency cannabis products (Ramaekers et al., 2006). However, given inherent ethical and legal issues that preclude acute administration for adolescents under any circumstances (Feldstein Ewing et al., 2017), some degree of reliance is needed upon adult

studies to examine the acute effects of cannabis on processes such as reward and cognition. This section will review results of acute cannabis administration studies in adults, (bolstered by preclinical rodent work where appropriate), which could inform our understanding of the effects of THC in adolescents. Given the limited number studies on this topic, we will include several older studies on cannabis and alcohol acute effects which are not within the 10-year search window applied to the adolescent neurodevelopment and psychosocial studies.

THC and Alcohol: Acute Effects on Reward Processes—THC reliably increases positive mood and measures of reward in humans (Cooper & Haney, 2008; Schacht, Selling, & Hutchison, 2009), likely in a THC-dose dependent fashion (Curran, Brignell, Fletcher, Middleton, & Henry, 2002; Gonzalez, 2007; Metrik et al., 2012; Wachtel, ElSohly, Ross, Ambre, & de Wit, 2002). Evidence spanning human and animal models points to potential pathways by which cannabis may also be associated with subsequent use of other substances, such as alcohol. Specifically, preclinical work suggests that, among adults, cannabis and alcohol activate the same neural reward pathways (Mechoulam & Parker, 2003). Decades of research have established that the mesolimbic dopamine system plays a major role in the reward circuitry in the adult brain, and is critically involved in the reinforcement produced by most addictive substances (Pierce & Kumaresan, 2006), including alcohol (Gonzales, Job, & Doyon, 2004) and cannabinoids (Gessa, Melis, Muntoni, & Diana, 1998) in adult samples. The nature of these interactions at the level of the developing, adolescent brain is not fully-understood (Silvers, Squeglia, Rømer Thomsen, Hudson, & Feldstein Ewing, 2019).

Preclinical studies demonstrate that THC can modulate reward centers of the brain (Pistis et al., 2004), likely due to the binding of THC to the cannabinoid receptor CB1, which densely populates mesolimbic dopamine regions implicated in alcohol use (Ranganathan & D'Souza, 2006). These cannabinoid receptors have been shown to regulate the reinforcing properties of alcohol (Mechoulam & Parker, 2003). For example, voluntary ethanol intake and drinking motivation can be increased by cannabinoid receptor agonists in rodent models (Colombo et al., 2002; Gallate, Saharov, Mallet, & McGregor, 1999), whereas cannabinoid receptor antagonists can inhibit ethanol intake (Arnone et al., 1997; Serra et al., 2001). Notably, the CB1 receptor appears to be more efficient in adolescence compared to adulthood (Rubino et al., 2015), suggesting that adolescents may be particularly vulnerable to the effects of THC (Bambico, Nguyen, Katz, & Gobbi, 2010; Rubino & Parolaro, 2016), and raising the question of whether THC increases the addictive effects of alcohol (via reward pathways, which are "under construction" in adolescence) and promotes future drinking among adolescents.

No human adolescent studies have explored these questions, but insight can be gleaned from several small adult studies. In one study using NIDA-cannabis (1.26% and 2.53% THC), 22 healthy adult men who used cannabis and alcohol weekly were administered alcohol plus cannabis and placebo plus cannabis in the laboratory. They experienced the effects of cannabis more quickly and reported greater euphoria during the alcohol plus cannabis administration compared to the cannabis plus placebo administration (Lukas & Orozco, 2001). In a more recent study using NIDA cannabis (2.9 and 6.7% THC), alcohol was found

to potentiate the cannabis “high” in 19 healthy adult occasional-to-moderate cannabis smokers (Hartman et al., 2016). In another study of 11 healthy adults who were not regular cannabis or alcohol users, the combination of 2.5 mg synthetic THC and alcohol reduced participants desire for more alcohol compared to when they consumed alcohol alone (Ballard & de Wit, 2011). None of these studies explored whether cannabis use acutely increases alcohol consumption, but it has been hypothesized that the potentiation of rewarding effects of alcohol by cannabis could increase alcohol consumption. This question has not been explicitly explored in humans, although THC was found to dose-dependently blunt alcohol intake in rats (Nelson et al., 2018) and inhibit locomotor sensitization (a marker of alcohol dependence in rodents) induced by ethanol in mice (Filev, Engelke, Da Silveira, Mello, & Santos-Junior, 2017), suggesting that THC may paradoxically *decrease* acute alcohol consumption. Human research is needed to explore the acute effects of THC on alcohol consumption and reward (ideally using higher potency cannabis and larger sample sizes), and to examine how THC and alcohol co-use intersects with neural development in adolescents.

THC and Alcohol: Acute Effects on Cognitive and Motor Processes—Although the effects of cannabis on cognitive function in both adults adolescents are somewhat nuanced (Gorey, Kuhns, Smaragdi, Kroon, & Cousijn, 2019), with recent studies suggesting that cannabis is not associated with cognitive deficits across all domains (Broyd, van Hell, Beale, Yücel, & Solowij, 2016; Scott et al., 2018), alcohol has a well-established negative impact on performance across nearly all domains of cognition (Weiss, Singewald, Ruepp, & Marksteiner, 2014). Although cannabis and alcohol are frequently used together, few human studies have examined the effects of cannabis and alcohol co-use on cognition, and none have tested this relationship in adolescents. Understanding the effects of co-use on cognitive processes is particularly relevant in the context of adolescent impaired driving, a matter of great public importance (Oshri, Carlson, Bord, & Zeichner, 2017). We will thus briefly review the few adult studies that have explored the acute effects of THC and alcohol on cognitive and motor abilities, which have generated mixed results.

In one study of 11 healthy adults who were not regular cannabis or alcohol users, the combination of 2.5 mg synthetic THC and alcohol did not impact any of the cognitive effects tested (i.e., working memory, reaction time and non-specific impairment) over and above the effects of alcohol or cannabis consumed alone (Ballard & de Wit, 2011). However, in a non-US study of 21 heavy cannabis users consuming higher potency THC (400 μg/kg), the combination of cannabis and alcohol was associated with decreased performance on a task of divided attention compared to alcohol alone (Ramaekers et al., 2011). Overall, these studies provide conflicting evidence regarding the cognitive effects of THC combined with alcohol, with some studies indicating that THC worsens alcohol-related cognitive impairment and others suggesting that it has no effect. Although no existing research has explored the acute cannabis and alcohol effects in adolescents, numerous observational studies of adolescent cannabis and alcohol users have explored the impact of co-use on neuropsychological functioning and the adolescent brain.

2. Effects of Cannabis and Alcohol Co-Use on Adolescent Neurodevelopment

Adolescent neurodevelopment involves dramatic changes in brain structure and function. Gray matter volume reduces while white matter volume increases substantially during adolescence via pruning of synaptic connections (Giorgio et al., 2010). Cannabis and alcohol are the most commonly co-used substances among adolescents (Miech et al., 2017). Thus, understanding the impact of cannabis and alcohol co-use on brain structure and function during this sensitive developmental period is of great importance to public health. At present, the impact of structural brain differences on clinical outcomes for adolescent substance users is not fully understood. Exploring the intersection of developmental neuroscience and adolescent addiction and polysubstance use is thus an important topic for future investigation (Silvers et al., 2019).

To date, many studies on the effects of cannabis on adolescent brain structure and function have noted alcohol use as a potential confounding variable (Rocchetti et al., 2013) that could influence neural alterations in cannabis users or mediate cannabis-related effects on the brain (Lorenzetti, Chye, Silva, Solowij, & Roberts, 2019). Notably, some studies explicitly controlled for alcohol use in their analyses, though not in a systematic way (Batalla et al., 2013; Lorenzetti et al., 2016). The majority of insight in this area has come from single-substance studies focused on effects of *either* alcohol or cannabis on various neurodevelopmental phenotypes in adolescence, with few studies directly comparing dual- versus single-substance using adolescents (Silvers et al., 2019). The following sections provide a review of the limited studies from the past 10 years that have *explicitly* examined the effects of cannabis and alcohol *co-use* on neuropsychological, structural and functional brain outcomes in adolescents. Table 1 includes all co-use studies reviewed in the neuropsychological functioning, and brain structure and function sections.

Neuropsychological Functioning—Studies that assess adolescent use of cannabis and alcohol have generated a complicated and inconsistent pattern of neuropsychological differences compared to single-substance users or non-users. In one cross-sectional study, adolescents (age 16–18, $N = 128$, abstinent for 4 weeks prior to testing) were categorized into four groups based on lifetime substance use: 24 heavy episodic drinkers, 20 heavy cannabis users, 29 heavy episodic drinkers and cannabis users, and 55 controls. The heavy episodic drinking group and the cannabis using group each showed more difficulties with cognitive flexibility, verbal recall, and working memory compared to controls with minimal substance use. However, within these substance using subgroups, heavy episodic drinkers showed poorer performance on cognitive flexibility, verbal recall, semantic clustering, and reading while heavy cannabis users displayed worse performance in inhibition task accuracy, cued verbal memory, and psychomotor speed. Similar to the single-substance-using groups, adolescents who used both cannabis and alcohol had worse performance in cognitive flexibility, verbal recall and task accuracy compared to controls. Notably, the co-use group also performed worse than controls on working memory—a domain for which neither of the single-substance groups showed any decrements compared to controls. These findings suggest differential patterns of drinking and cannabis use on adolescent neurocognition. However, this picture appears to also be impacted by the nature of substance use for youth, insofar as greater lifetime cannabis and alcohol use, withdrawal symptoms from alcohol, and

earlier age of cannabis initiation were associated with greater disruptions in performance across all domains (Winward, Hanson, Tapert, & Brown, 2014).

Conversely, in another cross-sectional study of adolescents (65 with heavy cannabis use histories and 65 non-cannabis-using controls, ages 15.7–19.1 years, $N = 130$), greater alcohol hangover symptoms were associated with decreased performance on verbal learning and memory, but only among youth who did not use cannabis, despite the cannabis users reporting significantly *more* alcohol use than the non-cannabis users (Mahmood et al., 2010). The authors conclude that cannabis exposure may have neuroprotective effects against the detrimental effects of alcohol on learning and memory, particularly in the verbal domain, However, the cross-sectional nature of these studies makes it difficult to disentangle whether observed differences in cognitive performance could be due to pre-morbid differences, or whether they could be a sign of the deleterious impact of these substances on the developing brain. Longitudinal studies are one avenue to evaluate temporal evidence about the nature and timing of neuropsychological differences and their intersection with substance use.

In one longitudinal study, current cannabis- and alcohol-using adolescents ($n = 49$, ages 16–19 at baseline) were compared to minimal-substance-using controls ($n = 59$) on neuropsychological functioning at 18 and 36 months after baseline. Adolescents who were both heavy cannabis and alcohol users showed worse performance on complex attention, memory, processing speed, and visuospatial functioning, relative to minimal-substance-using controls. Additionally, frequency of cannabis use was inversely associated with overall cognitive functioning (Jacobus, Squeglia, Infante, et al., 2015). In another longitudinal study of young adolescents (7^{th} graders, $N = 3,826$) followed for 4 years, there was a negative within-subjects association between cannabis frequency on future inhibitory control, controlling for alcohol use. In addition, there was a concurrent negative within-subject association between cannabis frequency and delayed memory recall. Interestingly, there was no within-subject association between alcohol use and any cognitive domain. These results suggest that cannabis may have a negative impact on neuropsychological functioning (Morin et al., 2019). Based on these four studies, it appears that use of both cannabis and alcohol in adolescence interacts with performance across language, attention, memory, processing speed, and visuospatial functioning (Jacobus, Squeglia, Infante, et al., 2015; Winward et al., 2014). However, the exact pattern of effects is not well-understood, as there is some evidence to suggest that cannabis attenuates the damaging effects of alcohol on cognitive performance, though this is impossible to determine given the cross-sectional designs (Mahmood et al., 2010). Given that pre-morbid factors may impact potential cognitive performance (and interact with risk for transition to substance use), more research is necessary to determine the impact of cannabis and alcohol co-use on neuropsychological functioning, particularly in this critical window of neuropsychological development.

Structural Neuroimaging

Cortical Thickness.: The limited work exploring the impact of alcohol and cannabis co-use on cortical thickness consists of longitudinal studies which suggest that cannabis and alcohol co-use is associated with thicker cortices compared to alcohol-only users and minimal-

substance-using controls (Jacobus et al., 2016; Jacobus, Squeglia, Sorg, Nguyen-Louie, & Tapert, 2014; Jacobus, Squeglia, Meruelo, et al., 2015).

In one study, a sample of adolescents ($N = 69$) who were 13 years old prior to initiation of substance use at baseline and 19 years old at follow-up was divided into three groups: 23 alcohol-only initiators, 23 cannabis and alcohol initiators, and 23 minimal-substance using controls. A more substantial decrease in cortical thickness was observed in controls and alcohol-only initiators compared to the cannabis and alcohol initiators. Furthermore, the alcohol-only initiators and controls had thicker cortices at baseline in the frontal and parietal areas, suggesting pre-existing brain differences (Jacobus et al., 2016). Another 3-year follow up study of adolescents (ages 16–19 at baseline, $N = 68$) found that heavy alcohol and cannabis use was associated with thicker cortices across 23 brain regions, primarily in the parietal and frontal lobes compared to minimal-substance-using controls. In addition, greater lifetime cannabis use was associated with thicker cortices in the inferior temporal and entorhinal cortex, while greater lifetime alcohol use was associated with thinner cortices at the 3-year follow-up (Jacobus, Squeglia, Meruelo, et al., 2015). Similarly, in adolescents (ages 15–18, $N = 54$) measured before and after 28 days of monitored abstinence, group differences emerged between cannabis and alcohol users compared to non-using controls. Co-users had thicker cortices in the left entorhinal cortex and the medial temporal lobe. However, greater lifetime cannabis use was associated with thinner cortices while greater lifetime alcohol use was associated with thicker cortices (Jacobus et al., 2014). In sum, prospective longitudinal studies suggest that there may be some pre-morbid differences in cortical thickness among those who transition into initiating cannabis and alcohol compared to those who initiate alcohol-only or who do not initiate substance use during adolescence. How these differences coincide with neuropsychological function and other health sequalae remains an open question for future empirical inquiry.

White Matter Integrity.: Only four studies have examined the impact of cannabis and alcohol co-use on white matter integrity. Differences in results have been reported depending on how cannabis and alcohol use are defined. Two cross-sectional neuroimaging studies have examined the association of heavy cannabis and alcohol co-use on adolescent white matter integrity. In one study of adolescents (ages 16–19, $N = 36$) who use both cannabis and alcohol and controls with limited substance use histories, youth who used cannabis and alcohol had lower fractional anisotropy (FA; a marker of white matter integrity) in ten regions compared to controls. Decreased FA in temporal brain regions was associated with differential performance on attention, working memory, and processing speed. Among co-users, there was evidence for compensation in occipital brain regions, as the co-users displayed higher FA that was associated with better working memory and complex sequencing performance. Notably, white matter integrity in this region did not correlate with cognitive performance among controls, suggesting that perhaps changes within this region only optimize performance in the co-users (Bava, Jacobus, Mahmood, Yang, & Tapert, 2010). Another cross-sectional study of adolescents (ages 16–19, $N = 42$) compared non-users, binge-drinkers, and binge-drinking cannabis users on white matter integrity. Binge drinkers had lower FA in eight clusters compared to non-users, while binge-drinking cannabis users had lower FA than non-users in only three clusters. Co-users reported

significantly *higher* levels of alcohol use compared to the binge-drinking non-cannabis users (Jacobus et al., 2009).

Adding to these results, several longitudinal studies have examined the association of cannabis and alcohol co-use on adolescent white matter integrity. In a small study, adolescents (ages 16–18, $N = 16$) with minimal cannabis and alcohol use at baseline were followed for 3 years and separated into two groups after follow-up; alcohol-only escalators and cannabis and alcohol escalators. Adolescents who escalated in cannabis and alcohol had decreased FA compared to alcohol-only escalators. Cannabis and alcohol escalators had better or equal white matter integrity compared to the alcohol-only escalators at baseline, prior to substance escalation (Jacobus, Squeglia, Infante, et al., 2013). Conflicting results were found in another longitudinal study (ages 16–19, $N = 54$) which separated adolescents into three groups, based on substance use patterns over 3 years: heavy episodic drinkers, cannabis-using heavy episodic drinkers, and minimal-substance-using controls. Controls demonstrated higher FA compared to both substance-using groups after 3 years. No differences in FA were observed between the alcohol-only and co-using groups, despite the fact that the co-users actually reported significantly *higher* levels of alcohol use compared to the heavy episodic drinkers (Jacobus, Squeglia, Bava, & Tapert, 2013).

White matter integrity typically increases during adolescence, however, substance use during this critical developmental window likely impacts adolescent brain development. This is evidenced by studies that suggest that adolescents who use both cannabis and alcohol show differential white matter integrity compared to adolescents with minimal substance use histories as well as those who only drink alcohol (Bava et al., 2010; Jacobus et al., 2009; Jacobus, Squeglia, Bava, & Tapert, 2013; Jacobus, Squeglia, Infante, et al., 2013). When comparing adolescents who use both cannabis and alcohol to those with minimal substance use histories, studies suggest that co-users have lower FA or decreased FA over time (Bava et al., 2010; Jacobus et al., 2013; Jacobus, Squeglia, Infante, et al., 2013). However, results differ when comparing co-users to alcohol-only users. Two studies suggest that co-users had equal or better FA compared to alcohol-only users, even though the co-users reported more alcohol use compared to the alcohol-only users (Jacobus et al., 2009; Jacobus, Squeglia, Bava, et al., 2013). Conversely, another comparing adolescents who escalated both cannabis and alcohol over time to those who escalated only in alcohol use, found that cannabis and alcohol co-users had poorer FA (Jacobus, Squeglia, Infante, et al., 2013). As demonstrated, these results are nuanced, potentially based on the definition of alcohol or cannabis use. For example, escalators were defined by significant increases in only alcohol use or cannabis and alcohol. However, the other studies suggest that heavy episodic drinking or binge drinking only in combination with cannabis use may result in better FA compared to alcohol-only users. The way in which cannabis may alter or protect FA is unknown among heavy cannabis and alcohol users, and requires more research. However, these findings do not appear to be related to less alcohol use among co-users, as co-users typically report *greater* alcohol consumption compared to the alcohol only groups (Jacobus et al., 2009; Jacobus, Squeglia, Bava, et al., 2013).

Gray Matter.: Although this is a somewhat contentious topic, the limited data on cannabis and alcohol effects on gray matter suggest that cannabis may be protective against the

deleterious effects of alcohol use on gray matter volume among adolescents (Infante et al., 2018). One study reflected that cannabis and alcohol users have gray matter volume comparable to controls but differ from moderate alcohol users (Infante et al., 2018). Specifically, this study followed substance naïve adolescents (ages 12–14, $N = 69$) for 6 years and measured gray matter changes. Moderate alcohol-only users, moderate cannabis and alcohol users, and individuals with minimal substance use all had equivalent decreases in brain surface area over 6 years. However, a more substantial decrease was observed in the alcohol-only group compared to the cannabis and alcohol and minimal substance users in the bilateral medial orbitofrontal cortex and right insula. Importantly, significant differences in level of alcohol use were not found when comparing the cannabis and alcohol users to the alcohol-only users (Infante et al., 2018). This study suggests that alcohol appears to play a central role in differences observed in the developing brain, but these changes may depend upon interactions with cannabis. These results parallel prior systematic reviews that have arrived at similar conclusions (Feldstein Ewing, Sakhardande, & Blakemore, 2014). Future studies are needed to determine whether cannabis may indeed have protective neurodevelopmental effects among adolescent alcohol-users or whether there may be other individual differences between alcohol-only users and cannabis and alcohol co-users that may contribute to the above findings.

Functional Neuroimaging—Functional neuroimaging studies may be helpful for disentangling the conflicting results reported in studies comparing cannabis and alcohol co-users to nonusers or alcohol-only users. However, to date, research in this area is extremely limited. Overall, functional imaging work suggests that use of both cannabis and alcohol may differentially impact neural responses to executive function and risk-taking tasks compared to individual use of either cannabis or alcohol alone. In one study, adolescents (ages 14–18, $N = 132$) were separated into six groups: cannabis-only, tobacco-only, alcohol-only, cannabis and tobacco, cannabis and tobacco and alcohol, compared to past month non-using controls. Groups were compared on nucleus accumbens activation while completing the Monetary Incentive Delay (MID) task. All groups demonstrated comparable performance on the MID task, but brain activation differed between the tobacco-only group compared to the other groups. Notably, the polysubstance groups (tobacco and cannabis/cannabis and tobacco and alcohol) responses were similar to the non-using controls (Karoly et al., 2015).

Another study of adolescents (ages 14–18, $N = 198$) compared non/infrequent cannabis and alcohol using controls, alcohol-only, cannabis-only, and cannabis and alcohol users, and found that cannabis and alcohol users displayed decreased responses during the Balloon Analogue Risk Task (BART) task than controls in the insula, striatum, and thalamus. The cannabis and alcohol users, relative to controls, also showed differential response across dorsal anterior cingulate cortex, insula, striatum, and superior parietal lobe, ventral striatum and bilateral thalamus (Claus et al., 2018).

Thus far, only two studies have compared co-users of cannabis and alcohol to other substance-using groups. On a MID task, co-use of alcohol, cannabis, and tobacco had similar nucleus accumbens activation to controls and single-substance users (with the exception of tobacco-only users; Karoly et al., 2015). However, on a risk-taking task,

cannabis and alcohol users displayed decreased responses compared to controls and had differential response in several other brain regions (Claus et al., 2918). More research is needed to understand functional brain differences among those who use both cannabis and alcohol compared to controls or single-substance users in the domains of attention, memory, learning, and executive function.

Summary: Effects of Cannabis and Alcohol on Adolescent Neurodevelopment—Overall, the literature exploring the impact of cannabis and alcohol-co use on neuropsychological development, brain structure and function is largely inconsistent and quite limited. Some studies suggest that vulnerabilities may exist before substance use initiation, such that these pre-existing differences may drive differences in cognitive performance along, brain structure and/or brain function in cannabis and alcohol users vs. single-substance users or non-users (Jacobus & Tapert, 2014; Squeglia, Jacobus, Nguyen-Louie, & Tapert, 2014).

However, many of these studies are complicated by the wide variance in the nature of substance use queries and metrics (Feldstein Ewing et al., 2017; Rømer Thomsen, Blom Osterland, Hesse, & Feldstein Ewing, 2018; Silvers et al., 2019). When reviewing the literature as a whole, cannabis and alcohol variables are quantified in different ways. For example, heavy/frequency cannabis use has been quantified as greater than 200 (e.g., Jacobus & Tapert, 2014), 100 (e.g., Winward et al., 2014), and 50 (e.g., Infante et al., 2018) episodes. In addition, the amount of time required for participants to be abstinent from substances in each study varied from 24 hours (e.g., Claus et al., 2018) to 28 days (e.g, Winward et al., 2014). Furthermore, in general, cannabis and alcohol co-users tend to drink more alcohol compared to alcohol-only users (Jacobus et al., 2009; Jacobus et al., 2013; Jacobus et al., 2013; Jacobus et al., 2016; Karoly et al., 2015), which further complications the interpretation of these results. There is also the inherent complication that adolescents cannot obtain cannabis legally, and are thus not always certain of the component cannabinoids they are consuming (e.g., THC potency, presence of other cannabinoids such as CBD). It is for this reason that in the field of adolescent cannabis use, cannabis is often measured as a function of frequency (number of cannabis use days), but not quantity, given variability in types of administration and potency. In contrast, adolescent alcohol use is quantifiable both in terms of frequency (number of alcohol use days), heavy use/misuse (binge drinking), and quantity (based on blood alcohol levels or self-reported number of drinks consumed). Establishing a psychometrically valid and widely used common metric for adolescent cannabis use quantity will be a critical step toward understanding the potential impact of cannabis use on adolescent neurodevelopment.

3. Psychosocial Correlates of Adolescent Cannabis and Alcohol Use

Although the impact of adolescent cannabis and alcohol co-use on the phenotypes discussed above appears to be somewhat nuanced—with conflicting evidence regarding whether cannabis worsens or ameliorates the effects of alcohol on the brain and behavior—there is consistent emerging evidence suggesting that adolescents who use both cannabis and alcohol may face significant psychosocial problems. Specifically, a longitudinal study that followed adolescents (ages 10–23, $N = 2,287$) across three cohorts, classified as mainly-alcohol users,

non-substance users, or polysubstance users (typically of alcohol, cannabis, and tobacco), found that polysubstance users were more likely to have low academic performance and less likely to complete high school compared to the other groups (Kelly, Evans-Whipp, et al., 2015). Using the same substance use classifications (among adolescents ages 12–14, N = 10,273), another study found that polysubstance users reported greater psychological distress than the mainly-alcohol or non-user groups (Kelly, Chan, et al., 2015).

One of the most critical behaviors impacted by adolescent cannabis and alcohol use is impaired driving. The existing data, primarily collected among adults, demonstrate that co-use is associated with a dose-related impairment in driving performance, such that co-users may be significantly impaired at low doses of cannabis and/or alcohol that would not produce impairment when consumed alone (Sewell, Poling, & Sofuoglu, 2009). The combination of cannabis and alcohol significantly increases crash culpability rates and crash risk (Ramaekers, Berghaus, van Laar, & Drummer, 2004; Ramaekers, Berghaus, van Laar, & Drummer, 2009), and this increased culpability has even been demonstrated for drivers who were below the legal alcohol limit, suggesting that co-use is not only a risk for heavy drinkers, but for anyone combining cannabis and alcohol while driving (Romano, Voas, & Camp, 2017). Similarly, a study of 80 recreational cannabis- and alcohol-using adults found that consumption of low potency cannabis (1.8% and 3% THC) in addition to alcohol was associated with impaired driving simulation performance compared to when either substance was consumed alone (Downey et al., 2013). Thus, regardless of the amount of alcohol or cannabis consumed, co-use of these substance poses a significant risk, even for experienced drivers.

This risk is likely heightened among adolescents, for whom driving is a new skill. One study compared low, medium, and high doses of cannabis and alcohol (using a controlled puffing procedure on cannabis cigarettes containing 19 mg THC from NIDA) among novice (ages 18–21) and experienced drivers (ages 25–40). This study found that novice drivers had a poorer vehicle control (e.g., greater steering variability and higher speed deviations) than experienced drivers, and impairment increased as the level of cannabis increased (Lenné et al., 2010). Adolescent risky driving is also impacted by the presence of peers (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011), which could intersect with substance use in potentially dangerous ways (Caouette & Feldstein Ewing, 2017). For example, in a large sample of adolescents (ages 11–15 years, N = 23,212) approximately 10% reported driving after cannabis or alcohol use and 21% report being a passenger with a driver under the influence of cannabis or alcohol (Pickett et al., 2012). Overall, the psychosocial outcomes associated with adolescent cannabis and alcohol co-use are somewhat more straightforward than the effects of co-use on the brain and behavior. Further research is needed to link neural and behavioral effects to psychosocial outcomes.

Finally, although numerous risks can be present for youth engaging in polysubstance use that can put them on a riskier trajectory, it is important to note that there are aspects of the developing brain that are adaptive and reflect the unique to capacity to learn and thrive during adolescence (Cousijn, Luijten, & Feldstein Ewing, 2018). The nature of this phase is still not fully understood, but likely involves adolescents' ability to adapt and learn from their environment, arising from a complex interplay of unique developmental factors,

including enhanced social attunement, affective processing, and neural plasticity (Cousijn et al., 2018; Giedd, 2015; Silvers et al., 2019). More studies are needed to explore this heightened window of both risk and resilience to substance use, particularly in the context of cannabis and alcohol co-use.

Discussion

Numerous challenges face researchers and clinicians at the intersection of adolescent cannabis and other substance use (Feldstein Ewing et al., 2017). An ideal way to examine the impact of a substance on the brain and behavior is through administration studies, an approach that is complicated for Schedule 1 substances (*National Academy of Sciences*, 2017). Further, the amount of THC available in recreational cannabis is now much higher than in decades prior, which decreases generalizability of the results from prior studies (Rømer Thomsen et al., 2017). For example, the average potency for Colorado legal market cannabis is 16–19% THC, with strains up to 30% THC commonly available (Orens, Light, Lewandowski, Rowberry, & Saloga, 2018; Vergara et al., 2017). In addition, because the effects of cannabis on the brain and body are highly variable depending on route of administration (e.g., smoking, vaping, edible cannabis), potency (high THC vs. low THC), and content (THC, CBD, and over 100 other potential chemical compounds; Rømer Thomsen et al., 2017), it is virtually impossible to fully capture and evaluate the extent of the effects of cannabis on the developing brain and behavior. For example, THC, CBD, or any of the other potential chemical compounds of cannabis may explain the mixed results reported in studies of cannabis and alcohol co-use in adolescence.

Importantly, one path toward disaggregating the causal stream of adolescent cannabis and its intersection with other substance use is through large-scale longitudinal studies, including The National Consortium on Alcohol and Neurodevelopment in Adolescence (N-CANDA), the Imagen Consortium, and the Adolescent Brain Cognitive Development (ABCD) project (Brown et al., 2015; Jernigan, Brown, & ABCD Consortium Coordinators, 2018; Whelan et al., 2012). These studies have large sample sizes and the ABCD study explicitly incorporates a twin design to better assess the nature and progression of substance use onset and its intersection with genetic, familial, peer, and other environmental factors. These projects are promising in terms of truly advancing the field of developmental neuroscience from one that has been largely cross-sectional (Feldstein Ewing et al., 2014) and complicated by small sample sizes to one that can empirically interrogate data over time to answer causal questions (Bjork, 2018).

Clinical Significance.

In line with evolving theory on the nature of the adolescent brain and its intersection with substance use (Silvers et al., 2019), it is important to note that we are still operating largely without the data that can guide best practices for next steps in prevention and intervention. An important concern is that without a comprehensive picture of how cannabis—and particularly its intersection with alcohol—impacts the developing brain and behavior, it is difficult to understand how best to approach prevention and intervention approaches to best mitigate the harms that befall youth as they are experimenting with substances during the

adolescent years, in order to best protect and redirect them towards prosocial health and development. While most youth naturally desist or decrease substance use with the onset of adult roles and responsibilities (Cousijn et al., 2018), there are numerous risks that adolescents can face while experimenting and exploring these substances. One of the major concerns facing practitioners is that adolescents show impaired decision-making while intoxicated that can lead to irrevocable consequences, such as physical accidents leading to injury to themselves or others, impaired academic/occupational functioning, or involvement with the justice system. Future research actively examining and reporting the effects of alcohol and cannabis co-use will be critical to disaggregating how different substances might impact and interact within the developing brain (Silvers et al., 2019).

While we can only imagine how our ability to study cannabis and alcohol will progress with declassification of cannabis from Schedule 1; in the interim, cross-cultural and collaborative work with regions that have different clinical and research policies such as Canada and Europe may provide useful data. Additionally, large scale longitudinal projects such as ABCD may offer another important perspective on the natural trajectory of adolescent cannabis and alcohol use and its impact on brain and behavior (Bjork, 2018; Lisdahl et al., 2018).

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Table 1.

Studies Assessing the Impact of Cannabis and Alcohol Co-Use on Neuropsychological Functioning, and Structural and Functional Neuroimaging

Study	Age (*N*)	Substance Use Groups & Definitions	Abstinence	Measure	Main Findings	Level of Alcohol Use Across Groups
Neuropsychological Studies						
Winward et al., 2014	Ages 16–18, (*N* = 128)	29 CA + ALC (*>100 alcohol and cannabis episodes*), 24 ALC (*>100 alcohol episodes, <25 cannabis episodes*), 20 CA (*<25 alcohol episodes, >100 cannabis episodes*), 55 CON (*<10 alcohol episodes, <5 cannabis episodes*)	4 weeks	EF, Learning and memory, visuospatial construction, working memory, attention, psychomotor speed, language and achievement	CA + ALC poorer cognitive flexibility, verbal recall, poorer task accuracy, and working memory compared to CON. ALC poorer cognitive flexibility, verbal recall, semantic clustering, and reading skills compared to CON. CA poorer inhibition task accuracy, cued verbal memory, and psychomotor speed compared to CON.	CA + ALC, ALC > CON, CA ($p < .05$)
Mahmood et al., 2010	Ages 15–19, (*N* = 130)	65 CA (*≥60 cannabis episodes*), 65 CON (*<5 cannabis episodes*)	4 weeks for cannabis, 13 days for alcohol	Achievement, verbal intelligence, verbal learning and memory, and visual learning and memory	Greater post-drinking effects was associated with poorer performance on verbal learning and memory for CON, but not CA.	CA > CON ($p < .01$)
Jacobus, Squeglia, Infante, et al., 2015	Ages 16– 19 at baseline, 3 year follow-up, (*N* = 108)	49 CA + ALC (*≥60 cannabis episodes*), 59 CON (*≤9 cannabis episodes and minimal alcohol use*)	1 day	Complex attention, processing speed, verbal memory, visuospatial functioning, and EF	CA + ALC significant worse than CON in complex attention, memory, processing speed, and visuospatial functioning.	CA + ALC > CON ($p < .05$)
Morin et al., 2018	$Mean_{age}$ = 12.7, 4 year follow-up, (*N* = 3,826)	Continuous measure of cannabis and alcohol frequency x quantity	Not reported	Spatial working memory, delayed recall memory, perceptual reasoning, and inhibitory control	Within-subject effect of CA frequency on poorer inhibitory control later, while controlling for alcohol. Concurrent within-subject associations between cannabis and delayed memory recall. No within-subject effects of alcohol on cognition.	Not applicable
Structural Neuroimaging: Cortical Thickness						
Jacobus et al., 2016	Ages 12– 14 at baseline, 6-year follow up, (*N* = 69)	23 CA + ALC (*>monthly* CA *use, >50 cannabis episodes*), 23 ALC (*<40 cannabis episodes*), 23 CON (*<3 alcohol episodes, 0 cannabis episodes*)	Not reported	Complex attention, processing speed, verbal memory, visuospatial functioning, EF, and cortical thickness	CON and ALC performed better on complex attention compared to CA + ALC. ALC and CON greater decrease in left hemisphere compared to CA + ALC.	CA + ALC > ALC, CON ($p < .05$)

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Study	Age (*N*)	Substance Use Groups & Definitions	Abstinence	Measure	Main Findings	Level of Alcohol Use Across Groups
					ALC thicker cortices at baseline in frontal and parietal areas compared to CA + ALC.	
Jacobus, Squeglia, Meruelo, et al., 2015	Ages 16– 19 at baseline, 3 year follow-up, (*N* = 68)	CA + ALC (*>120 cannabis episodes, ≥ 22 alcohol episodes*), CON (*≤9 cannabis episodes, ≤20 cannabis episodes*)	Not reported	Cortical thickness	CA + ALC greater cortical thickness than CON, especially in frontal and parietal lobes.	CA + ALC > CON ($p < .05$)
Jacobus et al., 2014	Ages 15– 18, (*N* = 54)	24 CA + ALC (*>200 cannabis episodes*), 30 CON (*<7 cannabis episodes*)	28 days	Cortical thickness	CA + ALC thicker cortices than CON in left entorhinal cortex, after adjusting for alcohol use. More lifetime ALC use linked to thicker cortices in all four lobes.	CA + ALC > CON ($p < .05$)
Structural Neuroimaging: White and Gray Matter						
Bava et al., 2010	Ages 16–19, (*N* = 72)	36 CA + ALC (*180 – 1800 cannabis episodes, 50 – 700 drinks*), 36 CON (*<5 cannabis use, <50 drinks, <2 episodes of other drug use*)	24 hours (cannabis), 3 days (for binge drinking)	WM integrity (FA)	CA + ALC lower FA in 10 clusters compared to CON.	CA + ALC > CON ($p < .001$)
Jacobus et al., 2009	Ages 16– 19, (*N* = 42)	14 CA + ALC (*180 – 1800 cannabis episodes, 1 episode of binge drinking*), 14 ALC (*1 episode of binge drinking, <9 episodes of cannabis*), 14 CON (*< 5 episodes of cannabis, 0 binge drinking episodes*)	23 days (cannabis), 3 days (alcohol)	WM integrity (FA)	ALC significantly lower FA in 8 clusters compared to CON. CA + ALC significantly lower FA in 3 clusters compared to CON.	CA + ALC > ALC, CON ($p < .05$)
Jacobus, Squeglia, Bava, et al., 2013	Ages 16– 19, 1.5 and 3 year follow-ups, (*N* = 54)	21 CA + ALC (*≥3 binge drinking episodes, >200 cannabis episodes*), 17 ALC (*≥ 3 binge drinking episodes, <150 alcohol episodes, <10 cannabis episodes*), 16 CON (*<10 cannabis episodes, <20 alcohol episodes*)	28 days	WM integrity (FA)	CA + ALC and ALC lower FA in 14 clusters compared to CON. No differences in FA between CA + ALC and ALC.	CA + ALC > ALC > CON ($p > .05$)
Jacobus, Squeglia, Infante, et al., 2013	Ages 16– 18, 3 year follow-up, (*N* = 16)	8 CA + ALC (*significant increase in* CA *and ALC*), 8 ALC (*significant increase in ALC*)	28 days	WM integrity (FA)	CA + ALC significant decrease in FA. ALC no significant changes in FA.	CA + ALC > ALC ($p > .05$)
Infante et al., 2018	Ages 12–14, 6 year follow-up, (*N* = 69)	23 CA + ALC (*>50 cannabis episodes, >20 alcohol episodes*), 23 ALC (*<40 cannabis episodes, >20 alcohol episodes*), 23 CON (*0 cannabis episodes, <3 alcohol episodes*)	Not reported	GM volume	ALC more substantial decrease in GM surface area in orbitofrontal cortex compared to CA + ALC. CA + ALC and CON greater surface area in general than ALC.	CA + ALC, ALC > CON, ($p < .05$)
Functional Neuroimaging						
Karoly et al., 2015	Ages 14– 18, (N = 132)	17 CA + TB + ALC (*≥10 cannabis use days, ≥27 tobacco use days, ≥2 alcohol use days*), 17 CA + TB (*≥10 cannabis days, ≥27 tobacco use days*), 14 CA (*≥10 cannabis use*	3 hours	MID	TB decreased bilateral nucleus accumbens activation compared to other groups, including polysubstance users. No	CA + TB + ALC > ALC > CA + TB, CA, TB ($p > .05$)

Study	Age (*N*)	Substance Use Groups & Definitions	Abstinence	Measure	Main Findings	Level of Alcohol Use Across Groups
		days), 34 TB (*≥27 tobacco use days*), 12 ALC (*≥2 alcohol use days*)			differences emerged between the CA + TB + ALC compared to CON, CA, ALC, CA + TB.	
Claus et al., 2018	Ages 14–18, (N = 198)	90 CA + ALC (*>1 cannabis using and drinking days in past month*), 23 ALC (*>1 drinking days in past month*), 39 CA *(>1 day of cannabis use in past month*), 37 CON (*≤1 day of cannabis and alcohol use in past month*)	24 hours	BART	CA + ALC decreased response on during BART compared to CON in insula, striatum, and thalamus. CA + ALC differential response dACC, insula, striatum, and superior parietal lobe, ventral striatum, and bilateral thalamus.	CA + ALC, ALC > CA, CON ($p < .05$)

Note. The far-right column indicates alcohol consumption across substance-use groups for each study, as well as whether differences in reported alcohol consumption were significantly different. CA = cannabis; ALC = alcohol; TB = tobacco; CON = controls; EF = executive function; WM = white matter; FA = fractional anisotropy; GM = gray matter; MID = monetary incentive delay task; BART = Balloon Analogue Risk-Taking; dACC= dorsal anterior cingulate cortex.