CHAPTER 2

The Neurocognitive Impact of Alcohol and Marijuana Use on the Developing Adolescent and Young Adult Brain

Krista M. Lisdahl, Skyler Shollenbarger, Kelly A. Sagar, and Staci A. Gruber

Worldwide, most people start experimenting with drugs during the teenage years (Degenhardt et al., 2008). Alcohol is the most popular drug among youth, with 21% of 12th graders and 40% of young adults reporting recent binge drinking (Johnston, O'Malley, et al., 2017), which is defined as five standard drinks for males and four standard drinks for females per occasion. Although alcohol is typically initiated in adolescence, peak binge use occurs in the young adult years (Schulenberg & Maggs, 2002). The majority of adolescent drinkers (58%) also use marijuana (Martin, Kaczynski, Maisto, & Tarter, 1996), resulting in significant comorbidity between alcohol use disorder (AUD) and cannabis use disorder (CUD; Agosti, Nunes, & Levin, 2002). Of concern, during the past decade marijuana use is on the rise in youth in the United States, with 23% of high school seniors and approximately 20% of college students reporting past-year use (Johnston et al., 2017).

Adolescence is a period with an increase in risk-taking behaviors, such as experimentation with substances, which coincide with significant neurodevelopmental changes (Casey, Getz, & Galvan, 2008; Casey, Giedd, & Thomas, 2000; Eaton et al., 2006; Gardner & Steinberg, 2005). Gray matter continues

to mature, with areas associated with executive functioning, including the prefrontal cortex (PFC), maturing into the mid-20s (Giedd et al., 1996; Gogtay et al., 2004; Houston, Herting, & Sowell, 2014; Lenroot & Giedd, 2006; Mills, Goddings, Clasen, Giedd, & Blakemore, 2014; Schmitt et al., 2014; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Sowell et al., 2004; Sowell, Trauner, Gamst, & Jernigan, 2002). Preclinical animal studies have suggested that compared with adults, adolescent animals show increased neurotoxic effects following alcohol exposure (see Barron et al., 2005; Monti et al., 2005). Taken together, findings from preclinical studies (Rubino et al., 2009; see Rubino, Zamberletti, & Parolaro, 2012, for a review) have demonstrated greater microcellular changes associated with delta-9-tetrahydrocannabinol (THC) exposure, the primary psychoactive constituent in marijuana, during adolescence compared with adulthood. Therefore, the neurocognitive effects of chronic alcohol or marijuana exposure in youth are of great interest. In this chapter, we provide an overview of studies that examined the impact of adolescent and young adult binge drinking, AUD, and regular marijuana exposure. We also examine potential clinical and public health implications of these findings.

ADOLESCENT SUBSTANCE USE EXPOSURE AND RISKS FOR SUBSTANCE USE DISORDERS

Converging lines of evidence suggest that adolescence may represent a sensitive period during which exposure to substances increases the risk of substance use disorders (SUDs) and neurocognitive impairments compared with adult exposure (Brown & Tapert, 2004; Spear, 2015; Spear & Swartzwelder, 2014). Several studies have reported that adolescent alcohol exposure is associated with increased risk for developing an AUD (Dawson, Goldstein, Chou, Ruan, & Grant, 2008; DeWit, Adlaf, Offord, & Ogborne, 2000; Hingson, Heeren, & Winter, 2006; McGue, Iacono, Legrand, Malone, & Elkins, 2001; Robins & Przybeck, 1985; Winters & Lee, 2008). For example, one study reported that the odds of developing an AUD are decreased by 14% with each increasing year of age of alcohol use onset (Grant & Dawson, 1997). Earlier age of marijuana use has also been associated with increased risk for developing a CUD. In one study, Anthony (2006) reported that 17% of those who tried marijuana prior to age 17 became dependent, and a later survey study indicated that 11.5% of adults who reported having tried marijuana prior to age 14 met DSM-5 criteria for CUD as compared with only 2.6% of those who tried marijuana after age 18 (Substance Abuse and Mental Health Services Administration, 2013). Further, earlier onset of marijuana use has also been associated with higher rates of alcohol dependence as well as other SUDs (Brook, Brook, Zhang, Cohen, & Whiteman, 2002; Lynskey, Heath, Bucholz, & Slutske, 2003). Together, these findings support the hypothesis that adolescence is a vulnerable developmental

period in which individuals have a higher risk of developing an SUD following exposure to alcohol and marijuana.

NEUROCOGNITIVE CONSEQUENCES OF ADOLESCENT BINGE DRINKING

Binge drinking is typically defined as four or more standard alcohol drinks on an occasion for females and five or more drinks for males. In humans, converging evidence has also suggested that adolescent onset of regular alcohol exposure is associated with increased risk for neurocognitive deficits (see Jacobus & Tapert, 2013; Lisdahl, Gilbart, Wright, & Shollenbarger, 2013; Squeglia, Jacobus, & Tapert, 2009; Squeglia et al., 2015, for reviews). Below we provide an overview of the cognitive and brain structural and functional findings associated with human adolescent and young adult binge drinking.

Cognition

As previously reported in our work (Lisdahl, Gilbart, et al., 2013) and in several additional studies, adolescent and young adult binge drinking is associated with cognitive deficits across numerous domains. Youth who engage in binge drinking have been found to exhibit poorer verbal working memory (Parada et al., 2012), spatial working memory (Scaife & Duka, 2009; Townshend & Duka, 2005), sustained attention (Hartley, Elsabagh, & File, 2004), memory (Hartley et al., 2004; Parada et al., 2011; Scaife & Duka, 2009), perseverative responding (Parada et al., 2012), and decision making (Malone et al., 2014). In addition, poorer response inhibition and rule acquisition has been noted in adolescent female binge drinkers (Scaife & Duka, 2009; Townshend & Duka, 2005). Although slower psychomotor speed was also observed in one study (Hartley et al., 2004), two later studies reported faster motor speed (Scaife & Duka, 2009; Townshend & Duka, 2005; see Table 2.1).

For example, in a monozygotic co-twin controlled investigation, Malone and colleagues (2014) reported that among twin pairs who were discordant for alcohol use, adolescent binge drinkers demonstrated significantly poorer decision making on the Iowa Gambling Task; these differences were directly related to alcohol use status among twins, suggesting a causal effect of alcohol (Malone et al., 2014). In contrast, a longitudinal investigation (TRAILS) following 11- to 19-year-olds did not find executive functioning deficits (inhibition, working memory, sustained attention) associated with drinking status (nondrinkers compared with chronic heavy drinkers; Boelema et al., 2015). The authors suggested previous findings may be due to premorbid differences (i.e., differences that existed prior to drinking onset) that placed adolescents at risk for binge drinking. However, a 3-year longitudinal study (Jacobus et al., 2015) found that adolescents with concomitant alcohol and marijuana use

TABLE 2.1. Human Studies Reporting Neuropsychological Effects of Regular Alcohol and Marijuana Exposure in Adolescents and Emerging Adults

Authors	Teen onset worse?[a]	Cognitive findings (bingers vs. controls)
	Binge-drinking studies	
Boelema et al. (2015)		No differences in executive functioning
Hartley, Elsabagh, & File (2004)		↓ sustained attention, memory, and psychomotor speed
Malone et al. (2014)		↓ executive functioning
Parada et al. (2011)		↓ verbal memory, working memory, and executive functioning
Scaife & Duka (2009)		↓ verbal memory, spatial working memory, and executive functioning
Townshend & Duka (2009)		↓ spatial working memory and executive functioning; ↑ motor speed
	AUD studies	
Hicks, Durbin, Blonigen, Iacono, & McGue (2012)	Yes	↑ behavioral disinhibition
Lyvers, Czerczyk, Follent, & Lodge (2009)	Yes	↑ reward sensitivity and disinhibition
Lyvers, Duff, & Hasking (2011)	Yes	↑ reward sensitivity and disinhibition
White et al. (2011)		↓ executive functioning; ↑ disinhibition
Brown, Tapert, Granholm, & Delis (2000)		↓ verbal memory
Hanson, Medina, Padula, Tapert, & Brown (2011)		↓ verbal memory, visuospatial ability, and executive functioning
Thoma et al. (2011)		↓ processing speed
Koskinen et al. (2011)		↓ attention
Tapert & Brown (1999)		↓ attention
Giancola, Mezzich, & Tarter (1998)		↓ visuospatial ability
Sher, Martin, Wood, & Rutledge (1997)		↓ visuospatial ability
Tapert, Granholm, Leedy, & Brown (2002)		↓ visuospatial ability
Moss, Kirisci, Gordon, & Tarter (1994)		↓ language

(*continued*)

TABLE 2.1. (*continued*)

Authors	Teen onset worse?[a]	Cognitive findings (bingers vs. controls)
	Marijuana studies	
Meier et al. (2012)	Yes	↓ IQ, complex attention, verbal learning, psychomotor speed, and executive functioning
Pope et al. (2003)	Yes	↓ IQ
Ehrenreich et al. (1999)	Yes	↓ working memory
Dougherty et al. (2013)	Yes	↑ impulsivity; ↓ short-term memory
Dahlgren, Sagar, Racine, Dreman, & Gruber (2016)		↓ executive functioning
Fontes et al. (2011)	Yes	↓ executive functioning
Gonzalez et al. (2012)		↓ executive functioning
Grant, Chamberlain, Schreiber, & Odlaug (2012)		↓ executive functioning
Gruber & Yurgelun-Todd (2005)		↓ executive functioning
Gruber, Sagar, Dahlgren, Racine, & Lukas (2012)	Yes	↓ executive functioning and processing speed
Hanson, Thayer, & Tapert (2014)	Yes	↑ risk taking; ↓ executive functioning
Jacobus et al. (2015)	Yes	↓ executive functioning and processing speed
Sagar et al. (2015)	Yes	↓ executive functioning
Schuster, Crane, Mermelstein, & Gonzalez (2012)		↓ executive functioning; ↑ risky sexual behavior
Solowij et al. (2012)	Yes	↓ executive functioning
Tamm et al. (2013)	Yes	↓ executive functioning
Hanson, Winward, et al. (2010)		↓ complex attention, verbal memory, and executive functioning
Harvey, Sellman, Porter, & Frampton (2007)		↓ complex attention, verbal memory, and executive functioning
Lisdahl & Price (2012)		↓ complex attention, processing speed, sequencing ability, and cognitive inhibition
Medina, Hanson, et al. (2007)		↓ complex attention, processing speed, verbal memory, and executive functioning

TABLE 2.1. (*continued*)

Authors	Teen onset worse?[a]	Cognitive findings (bingers vs. controls)
Mathias et al. (2011)		↓ complex attention and executive functioning
Tapert, Baratta, Abrantes, & Brown (2002)		↓ complex attention
Becker, Collins, & Luciana (2014)	Yes	↓ verbal memory, spatial working memory, spatial planning, and executive functioning
Crane, Schuster, & Gonzalez (2013)		↓ episodic memory (females) and executive functioning (males)
Crane, Schuster, Mermelstein, & Gonzalez (2015)	Yes	↓ episodic memory and IQ
Fried, Watkinson, & Gray (2005)		↓ verbal memory and processing speed
McHale & Hunt (2008)		↓ verbal memory and executive functioning
Schwartz, Gruenwald, Klitzner, & Fedio (1989)		↓ verbal memory
Solowij et al. (2011)		↓verbal memory and executive functioning
Tait, Mackinnon, & Christensen (2011)		↓ verbal memory
Thoma et al. (2011)		↓ verbal memory
Winward, Hanson, Tapert, & Brown (2014)	Yes	↓ verbal memory, psychomotor speed, and inhibition
Cousijn, Watson, et al. (2013)		↑ attentional bias to marijuana-related words
Takagi et al. (2011)		No differences reported
Comorbid marijuana + alcohol		
Jacobus et al. (2015)	Yes	↓ complex attention, memory, processing speeding, and visuospatial functioning
Winward et al. (2014)	Yes	↓ executive functioning, verbal memory, and working memory

[a] If "yes," analysis revealed that teenage age of onset (<16, 17, or 18 years of age) was associated with significantly poorer neurocognitive outcome; if "no," onset was not associated with outcome; if left blank, age-of-onset analysis was not conducted in this study.

performed significantly more poorly than controls in the neuropsychological domains of complex attention, memory, processing speed, and visuospatial functioning across three time points.

Brain Structure

Studies examining the impact of binge or heavy drinking on brain morphometry have generally found reduced gray matter volume, abnormal cortical thickness, and reduced white matter integrity in multiple brain regions (Lisdahl, Gilbart, et al., 2013). Specifically, increased alcohol use in adolescents has been linked with reduced cerebellar (Medina, Nagel, & Tapert, 2010; Lisdahl, Thayer, Squeglia, McQueeny, & Tapert, 2013); orbitofrontal cortex (Malone et al., 2014); ventromedial PFC and inferior frontal gyrus (Whelan et al., 2014); PFC, lateral frontal, and temporal cortex (Squeglia et al., 2015); total, PFC, and temporal gray matter volumes (Pfefferbaum et al., 2016); and larger middorsolateral PFC volume (Doallo et al., 2014). Other studies have reported abnormal cortical thickness, including increased cortical thickness in prefrontal, parietal, and temporal regions (Jacobus, Squeglia, Sorg, Nguyen-Louie, & Tapert, 2014) and thinner right-middle frontal gyrus (Luciana, Collins, Muetzel, & Lim, 2013); total, frontal, and temporal cortices (Pfefferbaum et al., 2016); and cingulate cortex (Mashhoon et al., 2014) in young binge drinkers. One longitudinal investigation (Squeglia et al., 2015) compared brain structure in 75 adolescents who transitioned into heavy drinking and 50 who remained light to nondrinkers over approximately 3.5 years—they found that the heavy-drinking adolescents demonstrated accelerated gray matter reductions in PFC and temporal volumes. Several studies to date have also demonstrated reduced white matter volume and integrity in young binge drinkers (Bava, Jacobus, Thayer, & Tapert, 2013; Jacobus et al., 2009; Jacobus, Squeglia, Infante, Bava, & Tapert, 2013; Luciana et al., 2013; McQueeny et al., 2009; Pfefferbaum et al., 2016; Squeglia et al., 2015). Notably, McQueeny et al. (2009) found that increased hangover symptoms and greater estimated peak blood alcohol concentration estimates were significantly correlated with poorer white matter quality in frontocerebellar tracts.

Brain Function

Studies have reported abnormal functional magnetic resonance imaging (fMRI) response in adolescent binge drinkers to spatial working memory (Squeglia et al., 2012; Squeglia, Schweinsburg, Pulido, & Tapert, 2011), decision-making (Gilman, Ramchandani, Crouss, & Hommer, 2012; Xiao et al., 2013), inhibitory control (Ahmadi et al., 2013, 2014; Wetherill, Squeglia, Yang, & Tapert, 2013), verbal memory (Schweinsburg, McQueeny, Nagel, Eyler, & Tapert, 2010), and figural memory (Dager et al., 2014) tasks. For example, Schweinsburg and colleagues (2010) reported that adolescent binge

drinkers, when compared with nondrinkers, failed to engage the hippocampus during a novel verbal encoding fMRI task. Two longitudinal investigations revealed that baseline differences in fMRI response to an inhibitory control and visual working memory task predicted initiation of heavy alcohol drinking in that adolescents who transitioned to heavy alcohol use showed blunted fMRI response at baseline in frontal and parietal regions (Squeglia et al., 2012; Wetherill, Squeglia, et al., 2013).

Taken together, these findings suggest that large doses of alcohol (binges) during the adolescent years are associated with cognitive, structural, and functional abnormalities. However, additional large-scale longitudinal studies are needed to confirm causation. These neurocognitive consequences, combined with other alcohol-related consequences (e.g., legal issues, poor sleep, hangover, emotional stress, interpersonal conflict), may significantly impact performance in the classroom, as previous research has reported that binge drinking is predictive of poorer end-of-semester grade-point averages (Read, Merrill, Kahler, & Strong, 2007).

NEUROCOGNITIVE CONSEQUENCES OF AUDS IN ADOLESCENTS

An estimated 2.7% of adolescents (ages 12–17) and 12.3% of young adults (ages 18–25) met past-year criteria for an AUD in 2014 (Center for Behavioral Health Statistics and Quality, 2015). Several studies have now shown that despite fewer years of drinking and less overall alcohol exposure than adults, adolescents and young adults with AUD demonstrate significant neurocognitive deficits.

Cognition

Studies examining the neuropsychological functioning in adolescents and young adults with AUD have demonstrated several cognitive deficits, including poorer verbal memory (Brown, Tapert, Granholm, & Delis, 2000; Hanson, Medina, Padula, Tapert, & Brown, 2011), attention (Koskinen et al., 2011; Tapert & Brown, 1999; Thoma et al., 2011), psychomotor speed (Thoma et al., 2011), language function (Moss, Kirisci, Gordon, & Tarter, 1994), visuospatial ability (Giancola, Mezzich, & Tarter, 1998; Hanson et al., 2011; Sher, Martin, Wood, & Rutledge, 1997; Tapert, Granholm, Leedy, & Brown, 2002), and executive functioning (Hanson et al., 2011; White et al., 2011). Further, three studies have reported that adolescent onset of binge drinking was associated with worsened executive functioning (disinhibition) and increased reward sensitivity (Hicks, Durbin, Blonigen, Iacono, & McGue, 2012; Lyvers, Czerczyk, Follent, & Lodge, 2009; Lyvers, Duff, & Hasking, 2011; see Table 2.1.) Consistent with McQueeny et al. (2009), withdrawal symptoms have predicted poorer

memory retrieval and visuospatial performance (Brown et al., 2000; Hanson et al., 2011; Tapert & Brown, 1999; Tapert, Granholm, et al., 2002), suggesting that drinking to the point of experiencing withdrawal may be related to an increased likelihood of neurocognitive deficits.

Brain Structure

Converging lines of evidence have shown structural abnormalities in adolescents with AUD, including smaller PFC (De Bellis et al., 2005; Medina et al., 2008), hippocampal (De Bellis et al., 2000; Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007; Nagel, Schweinsburg, Phan, & Tapert, 2005), and temporal and parietal (Fein et al., 2013) volumes. A recent study by Brooks and colleagues (2014) found that teens with AUD demonstrated reduced superior temporal gyrus brain volume, although AUD did not predict reductions in other areas, such as the hippocampus, after controlling for childhood trauma (Brooks et al., 2014), suggesting that reduced hippocampal volumes reported in other studies may partially be due to childhood trauma. Additional studies are therefore needed to examine the impact of childhood trauma and other related variables on structural brain findings.

Brain Function

FMRI studies in adolescents and young adults with AUD have revealed abnormal cortical activation during spatial working memory in girls (Tapert et al., 2001) (Caldwell et al., 2005) and verbal working memory tasks in males (Park et al., 2011). In summary, adolescents and young adults with AUD demonstrate mild to moderate neurocognitive impairments, especially in the executive function, memory, and visuospatial domains. They also have reduced cortical and subcortical volumes and abnormal brain activation to working memory tasks. These findings parallel what is seen in adults with AUD, despite youth having fewer drinking years and less overall exposure.

IMPACT OF ADOLESCENT MARIJUANA USE ON NEUROCOGNITION

The endogenous endocannabinoid (eCB) system has been shown to have an integral role in developmental brain processes, most importantly neuroplasticity, including neurogenesis and activity-dependent distinction and specificity of neuronal connections (Díaz-Alonso, Guzmán, & Galve-Roperh, 2012; Lee & Gorzalka, 2012; Nyilas et al., 2008). Several recent studies have reported a relationship between the eCB system and cognition and behavior, noting that increased eCB signaling is associated with improved executive functioning, reduced stress response, increased endogenous reward signaling, and improved

emotional regulation (Befort, 2015; Egerton, Allison, Brett, & Pratt, 2006; Filbey & DeWitt, 2012; Hill & McEwen, 2010; Hill & Tasker, 2012; Hillard, Weinlander, & Stuhr, 2012; Hurd, Michaelides, Miller, & Jutras-Aswad, 2014; Lee & Gorzalka, 2012; Pazos et al., 2013). However, exposure to *exogenous* cannabinoids, including delta-9-THC (or THC), a CB_1 agonist with strong binding affinity, has been shown to have deleterious effects on the brain. In particular, changes following THC exposure may alter the function and structure of brain regions rich in CB_1 cannabinoid receptors, especially during adolescence.

Cognition

As reported in recent reviews (Jacobus & Tapert, 2014; Lisdahl, Gilbart, et al., 2013; Lisdahl, Wright, Kirchner-Medina, Maple, & Shollenbarger, 2014), teenage onset of marijuana use is associated with greater neurocognitive deficits relative to those who begin marijuana use in adulthood. Increased frequency of marijuana use (weekly or more often) prior to age 18 has been associated with reduced performance on measures of IQ (Crane, Schuster, Mermelstein, & Gonzalez, 2015; Meier et al., 2012; Pope et al., 2003), spatial working memory (Becker, Collins, & Luciana, 2014; Cousijn, Watson, et al., 2013), visual scanning (Ehrenreich et al., 1999), memory (Becker et al., 2014; Crane, Schuster, & Gonzalez, 2013; Crane et al., 2015; Dougherty et al., 2013; Winward, Hanson, Tapert, & Brown, 2014), psychomotor speed (Jacobus et al., 2015; Winward et al., 2014), and executive functioning (Becker et al., 2014; Crane et al., 2013; Dahlgren, Sagar, Racine, Dreman, & Gruber, 2016; Dougherty et al., 2013; Fontes et al., 2011; Gruber, Dahlgren, Sagar, Gönenç, & Killgore, 2012; Hanson, Thayer, & Tapert, 2014; Jacobus et al., 2015; Sagar et al., 2015; Solowij et al., 2012; Tamm et al., 2013; Winward et al., 2014).

Longitudinal studies have also assessed the association between marijuana use and cognitive performance in order to clarify the potential impact of adolescent marijuana use. While one study demonstrated that poorer inhibitory functioning at ages 12–14 was predictive of more frequent marijuana use at ages 17 and 18 (Squeglia, Jacobus, Nguyen-Louie, & Tapert, 2014), other longitudinal investigations have linked adolescent marijuana use to deficits in attention (Jacobus et al., 2015; Tapert, Granholm, et al., 2002), memory (Jacobus et al., 2015; Tait, Mackinnon, & Christensen, 2011), processing speed, and visuospatial functioning (Jacobus et al., 2015). Further, Jacobus and colleagues (2015) reported that *earlier onset* of marijuana use was associated with poorer processing speed and executive functioning at follow-up 3 years later. In a large prospective study (Meier et al., 2012), individuals assessed from childhood into adulthood diagnosed with marijuana dependence at three or more study visits exhibited an average loss of 5.8 IQ points; individuals with more persistent and early marijuana use demonstrated the greatest reduction in IQ. Although the final sample size for persistent marijuana dependence was small ($n = 23$), after controlling for potential confounding variables the authors also found

that deficits in executive functioning, sustained attention, verbal list learning, and psychomotor speed were associated with persistent marijuana dependence. Two more recent longitudinal studies have recently challenged the reported association between marijuana use and reduced IQ, however, suggesting that observed differences in IQ between marijuana users and nonusers may in fact be due to familial (Jackson et al., 2016) or other confounding factors (e.g., cigarette use; Mokrysz et al., 2016). Cross-sectional studies focused on examining marijuana-using youth and emerging adults have reported marijuana-related cognitive deficits with only one exception (Takagi et al., 2011). Overall, studies have reported an association between marijuana use and reduced processing speed (Fried, Watkinson, & Gray, 2005; Gruber, Dahlgren, Sagar, Gönenç, & Killgore, 2012; Jacobus et al., 2015; Lisdahl & Price, 2012; Medina, Hanson, et al., 2007), complex attention (Hanson, Winward, et al., 2010; Harvey et al., 2007; Lisdahl & Price, 2012; Mathias et al., 2011; Medina, Hanson, et al., 2007; Tapert, Baratta, et al., 2002), verbal memory (Becker et al., 2014; Dougherty et al., 2013; Fried et al., 2005; Hanson, Winward, et al., 2010; Harvey et al., 2007; McHale & Hunt, 2008; Medina, Hanson, et al., 2007; Schwartz, Gruenewald, Klitzner, & Fedio, 1989; Solowij et al., 2011; Tait, Mackinnon, & Christensen, 2011; Thoma et al., 2011; Winward et al., 2014), executive functioning (Becker et al., 2014; Crane et al., 2013; Dahlgren et al., 2016; Dougherty et al., 2013; Gonzalez et al., 2012; Grant, Chamberlain, Schreiber, & Odlaug, 2012; Gruber, Dahlgren, et al., 2012; Gruber & Yurgelun-Todd, 2005; Hanson et al., 2014; Hanson, Winward, et al., 2010; Harvey et al., 2007; Jacobus et al., 2015; Lisdahl & Price, 2012; Mathias et al., 2011; McHale & Hunt, 2008; Medina, Hanson, et al., 2007; Sagar et al., 2015; Schuster, Crane, Mermelstein, & Gonzalez, 2012; Solowij et al., 2012; Winward et al., 2014), attentional bias to marijuana cues (Cousijn, Watson, et al., 2013), and risky sexual behavior (Schuster et al., 2012; see Table 2.1.).

Brain Structure

Consistent with research documenting the association between cognitive deficits and adolescent onset of marijuana use, numerous cross-sectional studies have also observed structural alterations in those with adolescent marijuana onset, with few exceptions (Block et al., 2000; Weiland et al., 2015). Across studies, results are bidirectional in terms of increased or decreased gray matter, and findings are often dependent on the brain region under examination (see Batalla et al., 2013, for a review). Nonetheless, numerous studies document alterations among adolescent and early-onset users (Ashtari et al., 2011; Battistella et al., 2014; Gilman et al., 2012; Lisdahl et al., 2016; Mashhoon, Sava, Sneider, Nickerson, & Silveri, 2015; McQueeny et al., 2011; Schacht, Hutchison, & Filbey, 2012), which persist after 1 month of closely monitored abstinence (Medina et al., 2010). Moreover, several studies have linked gray matter alterations to increased executive dysfunction (Churchwell, Lopez-Larson, &

Yurgelun-Todd, 2010; Medina et al., 2009, 2010; Price et al., 2015), mood symptoms (McQueeny et al., 2011), poor verbal memory (Ashtari et al., 2011), and novelty seeking (Churchwell, Carey, Ferrett, Stein, & Yurgelun-Todd, 2012).

Studies assessing cortical thickness in adolescent and young adult marijuana users have also reported bidirectional findings (Jacobus et al., 2014, 2015; Lisdahl et al., 2016; Mashhoon et al., 2015) that appear to be dependent on the brain region under study (Lopez-Larson et al., 2011) and age of onset of use. For example, an examination of cortical architecture in early- and late-onset marijuana users revealed that among early-onset users, continued years of marijuana use (i.e., longer duration of use) and increased current levels of marijuana use (in grams) were associated with thicker cortex measurements, while late-onset users who initiated use after age 16 exhibited thinner cortex measurements within the anterior dorsolateral prefrontal cortex (Filbey, McQueeny, DeWitt, & Mishra, 2015). Additional research is needed to clarify the impact of cortical thickness on cognitive functioning or other related variables.

Finally, recent studies have also investigated the extent of gyrification, folds in the cerebral cortex, or cortical curvature as a measure of gray matter architecture. Studies have reported reduced cortical curvature (Mata et al., 2010), decreased local gyrification in early- relative to late-onset users (Filbey et al., 2015), and reduced PFC gyrification (Shollenbarger, Price, Wieser, & Lisdahl, 2015a). Further, Shollenbarger and colleagues (2015a) found that this reduced cortical folding complexity was linked with poorer working memory in the cannabis users.

Although CB_1 cannabinoid receptors are primarily found on neurons, they also exist on myelinating glial cells and are thought to play a significant role in structural connectivity (Moldrich & Wenger, 2000). Perhaps not surprisingly, marijuana use during adolescence appears to affect the trajectory of white matter development. Structural (Medina, Nagel, Park, McQueeny, & Tapert, 2007) and microstructural (Arnone et al., 2008; Ashtari et al., 2009; Bava et al., 2009, 2013; Gruber, Dahlgren, Sagar, Gönenç, & Lukas, 2014; Gruber, Silveri, Dahlgren, & Yurgelun-Todd, 2011; Shollenbarger, Price, Wieser, & Lisdahl, 2015b) reductions in white matter have been observed both in adolescent marijuana users, as well as in adults who initiated marijuana use during adolescence. With only one exception (Delisi et al., 2006), several studies have reported reduced white matter quality in several PFC, limbic, parietal, and cerebellar tracts in adolescent and emerging adult marijuana users (Arnone et al., 2008; Ashtari et al., 2009; Bava et al., 2009; Clark, Chung, Thatcher, Pajtek, & Long, 2012; Epstein & Kumra, 2015; Gruber et al., 2011). Alterations in white matter have been identified as a potential risk factor for psychological dysregulation and CUD-related symptoms (Clark et al., 2012). In one of our own studies (Gruber et al., 2014), analyses revealed that lower white matter integrity was inversely correlated with higher impulsivity scores, specifically within early-onset marijuana smokers (marijuana use prior to age 16); this relationship was *not* detected within the late-onset marijuana group (marijuana use after

age 16), underscoring the importance of early intervention and education to help prevent adverse consequences associated with early-onset marijuana use.

Brain Function

With one exception (Cousijn et al., 2014), several studies have also reported altered brain activation patterns in young marijuana users (see Batalla et al., 2013; Jacobus & Tapert, 2014; Lisdahl, Gilbart, et al., 2013, for reviews). FMRI studies designed to examine brain activation patterns in adolescent marijuana users have reported abnormal PFC, orbitofrontal, cingulate, parietal, insular, subcortical/limbic, and cerebellar activation during attentional control (Abdullaev, Posner, Nunnally, & Dishion, 2010), implicit memory (Ames et al., 2013), spatial working memory (Schweinsburg et al., 2005), verbal working memory (Jacobsen, Mencl, Westerveld, & Pugh, 2004; Jacobsen, Pugh, Constable, Westerveld, & Mencl, 2007), verbal learning (Becker, Wagner, Gouzoulis-Mayfrank, Spuentrup, & Daumann, 2010), affective processing (Gruber, Rogowska, & Yurgelun-Todd, 2009), and reward processing tasks (Chung, Paulsen, Geier, Luna, & Clark, 2015; De Bellis et al., 2013; Jager, Block, Luijten, & Ramsey, 2013). Further, several recent papers specifically highlight altered activation patterns during the performance of executive functioning tasks in early-onset marijuana users relative to healthy controls, including decision making (Behan et al., 2014; Cousijn, Wiers, et al., 2013; De Bellis et al., 2013; Vaidya et al., 2012) and inhibitory control (Gruber, Sagar, Dahlgren, Racine, & Lukas, 2012; Sagar et al., 2015; Tapert et al., 2007) tasks. The majority of studies suggest that early marijuana exposure may result in the brain attempting to compensate via recruitment of additional neuronal regions, resulting in altered functional connectivity relative to healthy controls. However, this compensatory function may fail when challenged with increasing task complexity, as marijuana users often demonstrate reduced performance on more difficult tasks designed to assess processing speed, verbal memory, inhibitory control, working memory, and attention (Lisdahl, Gilbart, et al., 2013; Sagar et al., 2015).

Taken together, studies conducted to date suggest that regular exposure to eCBs may disrupt healthy neurodevelopment, especially in the PFC and parietal cortices, areas underlying higher-order cognitive functioning. These changes have been associated with poor neuronal efficiency and cognitive impairment across multiple domains. In particular, psychomotor speed, executive functioning, emotional control, learning, and memory appear to be most affected, even after a month of monitored abstinence from marijuana use. This is consistent with the finding that increased school difficulty, reduced grades, higher absenteeism, lower SAT scores, and reduced college degree attainment have been observed in marijuana-using teens and young adults (Maggs et al., 2015; Medina, Hanson, et al., 2007; Meier, Hill, Small, & Luthar, 2015). Early initiation of marijuana use may therefore impact the typical neurodevelopmental

trajectory, resulting in millions of youth who may not reach their full intellectual potential.

DOES CONTENT OF MARIJUANA (ESPECIALLY CANNABIDIOL VS. THC) MATTER?

Marijuana comprises hundreds of chemicals, including numerous distinct phytocannabinoids that modulate the endocannabinoid system. Different cannabinoids have unique effects on both physiological and psychological functioning, and the relative amount and ratio of each cannabinoid is especially important. THC is the major psychoactive constituent of marijuana and is mainly responsible for the subjective "high" felt by recreational marijuana users. Over the past two decades, while THC levels have steadily increased, levels of the major nonpsychoactive constituent of marijuana, cannabidiol (CBD), shown to have a variety of potential therapeutic and medicinal properties, have decreased (Burgdorf, Kilmer, & Pacula, 2011; ElSohly et al., 2016). Literature focused on *acute* exposure suggests that higher levels of CBD, as opposed to THC, may mitigate some of the negative effects of use (Niesink & van Laar, 2013), such as anxiety (Fusar-Poli et al., 2009; Winton-Brown et al., 2011), psychotic-like symptoms (Bhattacharyya et al., 2010; Englund et al., 2013; Winton-Brown et al., 2011), and memory impairment (Englund et al., 2013; Morgan, Schafer, Freeman, & Curran, 2010). Further, some suggest that CBD may moderate the effects of THC on affective processing (Bhattacharyya et al., 2010; Fusar-Poli et al., 2009), verbal memory and response inhibition (Bhattacharyya et al., 2010), and visual and auditory processing (Bhattacharyya et al., 2010; Winton-Brown et al., 2011). In addition, CBD may serve to mitigate some of the structural and neurochemical alterations related to THC (Lorenzetti, Solowij, & Yücel,, 2016; Yücel et al., 2016).

These findings are particularly salient given reports of sharply rising potency of recreational marijuana in the United States. The potency of recreational marijuana, expressed as the percentage of THC present, is estimated to have increased from 4% in 1995 to 12% in 2014 (ElSohly et al., 2016), raising concern about whether marijuana users may experience more pronounced cognitive deficits and alterations in brain structure and function. Further, data suggests that CBD content in recreational marijuana products has dropped precipitously; it is now estimated that the average ratio of THC to CBD in recreational marijuana strains has gone from 14:1 to 80:1 (ElSohly et al., 2016). National trends have also revealed an increase in the use of concentrates, including butane hash oil (BHO), as well as shatter, budder, and wax, particularly among younger populations, which can contain up to 90% THC (Bell et al., 2015). Further studies are needed to investigate the specific impact of high THC-containing compounds as they may confer additional risk, particularly among young recreational marijuana consumers. Similarly, studies should

assess the impact of CBD, both alone and in conjunction with THC, to determine whether it exerts protective properties and/or potentially mitigates the adverse effects associated with THC exposure.

"NORMALIZATION" WITH EXTENDED ABSTINENCE?

While some investigations of cognitive function in adolescents who drink alcohol or use marijuana report improvement in function following relatively brief abstinence periods (Fried et al., 2005; Pope, Gruber, & Yurgelun-Todd, 2001), little research is available to determine whether *extended* abstinence from alcohol and marijuana results in recovery of cognitive function and/or normalization of structural brain changes. However, findings to date appear promising. In binge drinkers, increased duration of abstinence has been associated with larger bilateral cerebellar volumes (Lisdahl, Thayer, et al., 2013). Hanson and colleagues (2011) also reported that increased days of abstinence from alcohol and drugs at a 10-year follow-up was associated with improved executive functioning, even after controlling for baseline executive functioning and education. Within adolescent marijuana users, short-term memory improved following 3–6 weeks of marijuana abstinence (Hanson, Winward, et al., 2010; Schwartz et al., 1989), while another study found that adolescent marijuana users who abstained for a minimum of 3 months demonstrated similar cognitive performance as healthy controls (Fried et al., 2005). Taken together, these data suggest that altered neurocognition observed in young marijuana users may begin to normalize after several weeks of abstinence. It is possible that extended periods of abstinence may allow for further reversal of the adverse consequences associated with early onset of alcohol and marijuana use. However, additional prospective research using longer periods of abstinence is necessary to more thoroughly examine the extent of recovery of neurocognitive function and reversal of structure abnormalities in adolescents. Nonetheless, these findings can be utilized to help increase motivation for abstinence in alcohol- and marijuana-using youth, as it is likely that continued abstinence will result in at least minimal improvements in attention, verbal memory, and neuronal processing speed.

POTENTIAL LIMITATIONS OF THE EXISTING LITERATURE

Although converging lines of evidence are increasingly convincing that adolescent and young adult alcohol and marijuana use are associated with neurocognitive deficits, limitations of the research to date must be considered. Several of the aforementioned studies did balance or statistically control for potential

confounding factors, such as family history of SUD or subclinical symptoms of depression or other mood problems, and most excluded participants with comorbid psychiatric disorders. However, it is still difficult to disentangle the impact of premorbid factors (differences prior to onset of use) from causal drug exposure influence. Indeed, risk factors associated with substance use initiation (e.g., inhibitory control, conduct disorder, attention problems, and family history of SUD) are also related to neurocognitive abnormalities (Aronowitz et al., 1994; Kelly et al., 2016; Hanson, Medina, et al., 2010; Hill, Kostelnik, et al., 2007; Hill, Muddasani, et al., 2007; Nigg et al., 2004; Ridenour et al., 2009; Schweinsburg et al., 2004, 2008; Spadoni, Norman, Schweinsburg, & Tapert, 2008; Tapert, Baratta, et al., 2002; Tapert & Brown, 2000), and some evidence exists that preexisting brain structural and functional abnormalities predate and predict the onset of regular drug exposure (e.g., Cheetham et al., 2012; Squeglia et al., 2014; Wetherill, Castro, Squeglia, & Tapert, 2013). It is notable, however, that prospective longitudinal studies have provided evidence for additional cognitive and brain abnormalities following the onset of regular alcohol or marijuana use that extend beyond premorbid differences in personality, cognition, and brain structure (Hicks et al., 2012; Maurage, Pesenti, Philippot, Joassin, & Campanella, 2009; Meier et al., 2012; Squeglia et al., 2012; Wetherill, Squeglia, et al., 2013; White et al., 2011). Reversal effects also support causal relations, as do marijuana constituent (THC vs. CBD) studies. Still, additional prospective, longitudinal, twin-informed studies are needed to truly determine whether exposure to alcohol and marijuana causes these neurocognitive abnormalities.

CONCLUSIONS AND RECOMMENDATIONS

Summary: It's Worth the Wait

Adolescence is considered the "gateway to adult health outcomes" (Raphael, 2013). From a public health perspective, this is worrisome, as alarming numbers of youth regularly binge drink and use marijuana (Johnston et al., 2017) despite evidence that alcohol and marijuana use during this critical period of neurodevelopment negatively impacts cognition, brain structure, and function in otherwise healthy teens and emerging adults. In fact, the research presented in this chapter suggests that binge drinking, AUD, and chronic marijuana use during the teenage and emerging adult years results in gray and white matter micro- and macrostructural abnormalities that have often correlated with cognitive deficits. The current body of research should also be utilized to inform public health policy. The issue of adolescent alcohol and marijuana use is not solely confined to cognition and brain health, but is likely to have overarching affects on adolescents' lives. The combined negative impact of both drug- and alcohol-related consequences—which include sleep deprivation/disruption (Cohen-Zion et al., 2009), hangovers, emotional stress, and intoxication while

at school—may result in problems related to school functioning and emotional well-being. Information presented in class or "on the job" may be missed or misinterpreted as a result of reduced learning or processing speed, as well as difficulties with attention and working memory. Research study findings are consistent with this theory, as youth who use substances have lower than expected academic performance, increased school problems, risky decision making, and poorer emotional regulation (Kloos, Weller, Chan, & Weller, 2009; Lynskey & Hall, 2000; Medina, Hanson, et al., 2007).

In moving forward with prevention strategies, we know that the "just say no" policy was unsuccessful. It is imperative to shift the outdated message of pure refusal or abstinence to a more realistic stance, especially in light of shifting attitudes regarding marijuana. Instead, the focus should be on *delaying* the onset of use, in order to allow the most vulnerable period of neurodevelopment to pass. Although "just say no" was not well received by our nation's youth, "just not yet" is likely a more easily adopted and embraced message, especially if paired with meaningful data that resonate personally with adolescents.

Increase Screening and Personalized Feedback

In order to reduce the likelihood of regular alcohol or marijuana use, it is critical to disseminate research findings to high school and college students, young military enlistees, therapists, teachers, child psychiatrists, pediatricians, parents, and consumers across the nation. Materials focused on the effects of alcohol and drugs on the brain, including pamphlets specifically designed for teens and young adults, are readily available at no cost through government institutes (National Institute on Drug Abuse, National Institute on Alcohol Abuse and Alcoholism) as well as teen-centered (*www.thecoolspot.gov, www.drugfreeamerica.org*) and university websites such as Teen Safe (*www.Teen-Safe.org*), which also includes an excellent parent resource center. In addition to providing general information and related statistics, personalized feedback regarding the effects of alcohol and marijuana that is tailored to individuals is likely to improve outcomes among youth (see Larimer & Cronce, 2007). Further, screening for youth utilizing measures such as the CRAFFT screening tool (Knight, Sherritt, Shrier, Harris, & Chang, 2002), which asks subjects six questions and reveals a teen's risk for problematic, abusive, or dependent use patterns (*www.ceasar.org/teens/test.php*), should be widely implemented. After utilizing the screening tool, physicians and therapists could then employ brief motivational interviewing (described in Part II of this volume) to help educate youth further about the potential negative effects of alcohol and marijuana use. Additionally, therapists or other practitioners could employ neuropsychological testing, tailored specifically to the cognitive domains known to be most affected by alcohol and/or marijuana use, which would provide personalized feedback regarding the youth's cognitive status. Current prevention, screening, and treatment programs should leverage the invaluable data acquired from

cognitive neuroscience and general psychoeducation, coupled with personalized feedback regarding the potential effects of chronic drug use on cognition and brain health. Most importantly, empirically validated interventions aimed at delaying, decreasing, and ultimately preventing alcohol and marijuana use in youth must be consistently implemented to optimize neurodevelopmental trajectories and minimize the impact of alcohol and marijuana use on the developing brain.

ACKNOWLEDGMENTS

During manuscript preparation, Krista M. Lisdahl was supported by grant No. R01DA030354 and Staci A. Gruber by Grant No. R01DA032646 from the National Institute of Drug Abuse.

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