BAKED AND BUZZED: INVESTIGATING THE INFLUENCE OF CO-USE OF CANNABIS AND ALCOHOL ON WHITE MATTER INTEGRITY IN EMERGING ADULTS

by

Natasha E. Wright

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ABSTRACT

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Objective: Growing evidence suggests alcohol and cannabis use independently alter neural structure and functioning, particularly during sensitive developmental time periods such as adolescence and emerging adulthood. However, there has been minimal investigation into the effects co-occurring use of these two substances, despite preliminary evidence of unique acute and psychopharmacological changes due to using alcohol and cannabis together.

Method: Data drawn from the IDEAA Consortium was utilized to assess white matter integrity as measured by FreeSurfer's TRACULA in emerging adults (n=192; 16-27 years old). Timeline Follow-Back was used to calculate past month cannabis use, alcohol use, co-use days, binge alcohol episode, and co-use-binge days. The Stroop task was administered and normed scores were used. Multiple regressions investigated white matter integrity by past month cannabis, alcohol, and co-use days, controlling for appropriate covariates (e.g., site, gender, education, length of abstinence). Analyses were run twice, once with alcohol as measured in standard units and once with binge episodes. Follow-up brain-behavior analyses assessed whether substance use or tracts that differed significantly by substance use then related to Stroop performance. Correction for multiple comparisons was conducted using Benjamini and Hochberg's (1995) False Discovery Rate correction method.

Results: Corrected for multiple comparisons, cannabis use was significantly related to increased mean diffusivity in 12 fronto-limbic and fronto-parietal tracts. Cannabis use also associated with poorer performance on Stroop word reading. Within the MJ+ALC group, increased mean diffusivity associated with better Stroop interference performance.

Discussion: The present study found cannabis use was associated with decreased white matter integrity, as measured by mean diffusivity, across fronto-parietal and fronto-limbic tracts. These results suggest a robust relationship between cannabis use and white matter integrity in this neurodevelopmentally sensitive time period. Despite our hypotheses, co-use, alcohol use, and binge drinking did not significantly predict any measures. Future research should further investigate the potential independent and interactive affects of these substances on preclinical and clinical levels. Efforts should be made to inform the public of the likely negative impact of cannabis on white matter quality.

To Ethan James Wade, who always encourages me to be better and learn more;

And to my family, who have supported me through the 21+ years of my education.

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LIST OF ABBREVIATIONS

2-AG	2-arachidonoyl-glycerol
ABCD	Adolescent brain and cognitive development study
ACC	Anterior Cingulate Cortex
AEA	Anandamide
ALC	Alcohol group participants
ATR	Anterior thalamic radiation
AUD	Alcohol Use Disorder
BAC	Blood alcohol content
CUD	Cannabis Use Disorder
CB1	Cannabinoid Receptor 1
CO	Group of individuals who co-used both cannabis and alcohol on the same day in the past month
DLPFC	Dorsolateral Prefrontal Cortex
DTI	Diffusion Tensor Imaging
eCB	Endogenous cannabinoid
FA	Franctional anisotropy
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
HC	Healthy Control
ILF	Inferior longitudinal fasciculus
IDEAA	Imaging Data in Emerging Adults Addiction

M	Mean
MD	Mean diffusivity of white matter
MJ	Cannabis or marijuana; Also, cannabis group
MJ+ALC	cannabis and alcohol co-use group
MRI	Magnetic resonance imaging
NO	Group of individuals who did *not* co-use both cannabis and alcohol on the same day in the past month
PFC	Prefrontal Cortex
THC	Delta-9-tetrahydrocannbinol
SD	Standard deviation
SLF	Superior longitudinal fasciculus
TLFB	Timeline Follow-back
TRACULA	Tracks Constrained by Underlying Neuroantomy
UCSD	University of California San Diego
UWM	University of Wisconsin Milwaukee
UTD	University of Texas Dallas
WM	White matter

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Introduction

Adolescents and emerging adults undergo ongoing neurodevelopment, including structural and functional neuronal changes (Giedd et al., 1996; Gogtay et al., 2004; Shaw et al., 2008), placing them at increased vulnerability to neurotoxins during this period (for review, see Bava & Tapert, 2010). Across the United States, almost one in fifteen 12th graders smoke cannabis daily, while one in four 12th graders have engaged in binge drinking (drinking 5 or more standard drinks on one drinking occasion) in the past two weeks (Miech, Johnston, O'Malley, Bachman, & Schulenberg, Patrick, 2017). Further, cannabis use is positively correlated with alcohol use (Johnston, O'Malley, Bachman, & Schulenberg, 2013) and 23% of high school seniors report simultaneously using both cannabis and alcohol in the past year, while 15.3% of young adults (age 18-29) report using both substances together in the past year, (Subbaraman & Kerr, 2015; Terry-McElrath, O'Malley, & Johnston, 2013). Therefore, there is a great public health need to better understand the neurological consequences of such co-occurring substance use. This is especially true when considering that both alcohol and cannabis use and abuse have been found to have a wide range of neurocognitive and neuronal consequences in adolescents (for review, see Lisdahl, Gilbart, Wright, & Shollenbarger, 2013).

The Developing Brain. Vast neurocognitive changes occur across the lifespan, particularly in adolescence and emerging adulthood (Gogtay et al., 2004). Improved executive functioning performance is associated with areas that undergo some of the most substantial development, including the prefrontal cortex (PFC), as well as through pruning of gray matter and cortical thinning (Giedd et al., 2015; Shaw et al., 2008) and white matter development (Gogtay et al., 2004). White matter development tends to follow an inverse 'U' shaped trajectory, with white matter integrity peaking in adolescence and young adulthood (Imperati et

al., 2011). In general, white matter tends to develop anterior to posterior and centrally to peripherally, though fronto-temporal tracts develop later in the maturation process (for review, see Yap et al., 2013). Understanding this neuroplasticity, particularly in regards to white matter, is key to facilitating healthy brain development in this time period (Spear, 2013). The sum of these neurodevelopmental and limbic system changes may make adolescents particularly vulnerable to engaging in risky behaviors as well as the neurotoxic consequences of substance use (for review, see Bava, Jacobus, Thayer, & Tapert, 2013; Bava & Tapert, 2010).

Endocannabinoid System, Cannabis & Alcohol. The main psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC), directly binds to cannabinoid receptor 1 (CB1) in cortical, limbic, and striatal regions (Sim-Selley, 2003). It is notable that the endogenous cannabinoid (eCB) system plays a role in neurodevelopment. The eCB system contains two endocannabinoids, arachidonoyl-ethanolamine (anandamide; AEA) and 2-arachidonoyl-glycerol (2-AG), which can activate CB1 (for review, see Breivogel & Sim-Selley, 2009). Cannabinoid receptors are located on glutamergic and GABAergic neurons, among others (Alger, 2012). Endocannabinoids act as neuromodulators; after being activated postsynaptically, they bind to CB1 receptors in the presynaptic terminal, which in turn prevent neurotransmitter release (see Hillard, 2015). The eCB system also undergoes neuromaturation in adolescence and emerging adulthood, making it more vulnerable to exogenous cannabinoids and their deleterious effects on the eCB system, morphological changes, and overall functioning (for review, see Schneider, 2008).

Chronic cannabis use in young adults has been found to downregulate CB1 receptors in cortical and limbic regions, but this appears to be reversible with a month of abstinence in humans (Hirvonen et al., 2012). Alcohol also moderates CB1 receptor activity through

interacting with neurotransmitters (e.g., glutamate, GABA), with the CB1 receptors in turn modulating dopamine and GABA receptors, particularly in reward and limbic regions (Pava & Woodward, 2012). Acutely, alcohol consumption in rats has been found to result in a greater release of endocannabinoids while, at times, also inhibiting eCB signaling (Rubio, McHugh, Fernandez-Ruiz, Bradshaw, & Walker, 2007). More chronic alcohol use, though, has been linked to reduction of CB1 levels in an irreversible manner in humans (Hirvonen et al., 2013).

As cannabis and alcohol both act on the same reward pathways, modulate similar neurotransmitter and ligand levels (e.g., GABA, dopamine, AEA, 2-AG; see Basavarajappa & Hungund, 2002; Cruz, Bajo, Schweitzer, & Roberto, 2008), and both downregulate eCB receptor activity (e.g., CB1), it may logically follow that there is potential for an additive or even synergistic effect when the two substances are used together. Indeed, the underlying mechanisms are similar enough that priming with one of these substances prior to use of the other substance, and vice-versa, has been shown to develop some level of cross-tolerance to either substance (for review, see Pava & Woodward, 2012). However, differences in these mechanisms also exist, alcohol stimulates GABA, while cannabinoids inhibit GABA transmission (Cruz et al., 2008). Pharmacologically, when looking at factors such as blood alcohol content (BAC), co-use of these substances may interact in such a way that they actually *reduce* BAC, as THC may slow alcohol absorption (Lukas et al., 1992). However, this may not always be the case; for example, Chesher and colleagues (1976) found BAC was *increased* when alcohol and THC were simultaneously administered in capsules. Ballard and de Wit (Ballard & de Wit, 2011), in contrast, found no pharmacokinetic difference when low doses of ethanol and capsule THC were administered in humans. When cannabis is used in combination with alcohol, plasma and blood THC levels increase (Hartman et al., 2015; Lukas & Orozco, 2001) and heart rate, a correlate of THC

absorption, remains higher (Ronen et al., 2010). Cannabinoids may also potentiate the deleterious effects of alcohol, as found in rodent youths through priming for apoptosis (Hansen et al., 2008). Therefore, chronic use of alcohol or cannabis in adolescent and emerging adult years may disrupt the role the eCB system plays in healthy neurodevelopment. However, there is currently too little evidence to be able to fully understand alcohol and cannabis co-use on neuropharmacology and their underlying mechanisms.

Co-Use of Cannabis and Alcohol. On a behavioral level, co-occurring use of alcohol and cannabis has generally been found to be linked to poorer outcomes, such as poorer treatment outcomes, higher rates of depression, and higher positive expectancies of use and, in turn, increased use of any substances (Aharonovich et al., 2005; Lopez-Quintero et al., 2011). One possible reason for these poorer outcomes is that combined use has been related to greater neurocognitive deficits. Studies examining the *acute* administration effects of cannabis and alcohol often suggest an additive effect on cognition, attention, memory, and motor functioning (Belgrave et al., 1979; Chait & Perry, 1994; Chesher, Franks, Jackson, Starmer, & Teo, 1977; Marks & MacAvoy, 1989), though not always (Ballard & de Wit, 2011; Bramness, Khiabani, & Morland, 2010; Ramaekers et al., 2011). Notably, almost all acute administration studies use very low doses of THC (1.3-3.0%; with the exception of Ramaekers et al., 2011), who used 11% THC), which may limit generalizability to contemporary doses of cannabis as found in the general population (averaging 12% THC; ElSohly et al., 2016).

Diffusion Tensor Imaging & White Matter Integrity. A common marker of brain health and function, as well as a key neurodevelopmental measure in emerging adulthood (Giedd, 2004; Gogtay et al., 2004), is the diffusion of water across white matter tracts in diffusion tensor imaging (DTI) (Basser, James, & LeBihan, 1994; Le Bihan, 2003). Such diffusion of water

indicates differences in neuromicrostructural integrity and architecture, and may be indicative of neural damage before other measures of brain health (e.g., volumetric analyses in gray matter; Soares, Marques, Alves, & Sousa, 2013). Healthy oligodendrocyte, and therefore white matter, development requires CB1 receptors protect progenitors from apoptosis (Molina-Holgado et al., 2002); thus, downregulation of CB1 receptors due to regular cannabis use (Hirvonen et al., 2012) may disrupt typical white matter development. Similarly, binge-like ethanol use in adolescent rats has been found to decrease protein levels (myelin basic protein and myelin oligodendrocyte glycoprotein) related to myelin development (Pascual, Pla, Minarro, & Guerri, 2014). Loss of axonal proteins, myelin proteins, and enzymes in mice have also been found following chronic intermittent ethanol exposure (Samantaray et al., 2015). Therefore, cannabis and alcohol may disrupt healthy white matter development in adolescents and emerging adults.

Effects of Cannabis, Alcohol, and Co-Use on White Matter. In young adult cannabis users, with few exceptions (Cousijn et al., 2012; Delisi et al., 2006), the majority of studies have reported poorer white matter integrity in cannabis users in comparison to healthy controls. Increased mean diffusivity (MD; (Arnone et al., 2008; Gruber, Dahlgren, Sagar, Gonenc, & Lukas, 2014; Shollenbarger, Price, Wieser, & Lisdahl, 2015) and decreased fractional anisotropy (FA; (Arnone et al., 2008; Ashtari et al., 2009; Bava et al., 2009; Clark, Chung, Thatcher, Pajtek, & Long, 2012; Gruber et al., 2014; Jacobus, Squeglia, Bava, & Tapert, 2013; Shollenbarger, Price, Wieser, & Lisdahl, 2015) have been found in prefrontal, parietal, cerebellar, corpus callosum, and temporal regions in regular cannabis emerging adult users.

In studies investigating the effects of alcohol use on WM integrity, a recent meta-analysis found substance-using adolescents to largely have deficits in white matter microstructure in neocortical, thalamic, and projection pathways (Baker et al., 2013). With one exception

(Cardenas et al., 2013), adolescent alcohol users have been found to have reduced white matter integrity relative to healthy controls in areas such as the corpus callosum, inferior longitudinal fasciculus (ILF), and superior longitudinal fasciculus (SLF) (Bava et al., 2013; Clark et al., 2012; Hill, Terwilliger, & McDermott, 2013; Jacobus et al., 2009; Lisdahl, Thayer, et al., 2013; Luciana, Collins, Muetzel, & Lim, 2013; McQueeny et al., 2009). Adolescent binge drinkers have also been found to have reduced white matter quality (McQueeny et al., 2009) and smaller cerebellar volumes (Lisdahl, Thayer, Squeglia, McQueeny, & Tapert, 2013).

Oftentimes cannabis users co-use alcohol, and vice versa. In studies investigating cannabis and alcohol co-use on WM, conflicting results are found. For example, Jacobus and colleagues (2013) found co-use to be worse than alcohol use alone as measured by poorer WM integrity in young adults who were not using substances in their late adolescence but transitioned into use in early adulthood (ages 19-22). Notably, this study was absent a healthy control group or a cannabis-only group, and had only 8 individuals per group. Another study (Bava et al., 2009) investigated WM integrity in 36 cannabis and alcohol users and in 36 healthy controls, finding 10 clusters with decreased FA and 3 with increased FA in the co-use group. Though they attempted to investigate the potential influence of cannabis, they did not have a cannabis- or alcohol-only group, making it difficult to tease apart the unique or even combined contributions of each substance. In another study, Jacobus and colleagues (2009) concluded that binge-and-cannabis users had poorer white matter integrity relative to binge alcohol users alone in a relatively small sample of 16-19 year olds (n=14 per group). However, the binge-and-cannabis group drank significantly more in their lifetime, though not in the past three months. Further, while the binge-and-cannabis group demonstrated better WM integrity than binge alone in some regions, increased alcohol use was also, at times, related to increased FA values. Together, this

shows overall aberrant results from what would typically be expected. De Bellis and colleagues (De Bellis et al., 2008) assessed WM deficits in 32 adolescents (12-18 years old) with an alcohol use disorder (AUD), 22 of whom also had a cannabis use disorder (CUD), in comparison to 28 healthy controls. The AUD subjects who also had CUD had greater differences in WM integrity; however, this was characterized by increased FA and decreased MD in the corpus callosum, which is in the opposite direction as expected and which the authors explained as being evidence of aberrant maturation of myelination perhaps as a sign of premature aging due to neurotoxicity. Importantly, the AUD subjects were not screened for psychiatric comorbidities, and even some of the healthy controls previously met criteria for other disorders, but did not currently meet diagnostic criteria. In an 18-month longitudinal investigation of 16 to 20 year olds who used any amount or variety of substances, Bava and colleagues (2013) found differences in WM integrity between substance users compared to non-users. In follow-up regression analyses, the onset of alcohol use, but not cannabis use, predicted reductions in white matter integrity in seven clusters: the left and right SLF, right posterior thalamic radiations, right prefrontal thalamic fibers, right superior temporal gyrus, right ILF, and the left posterior corona radiata. However, the extensive use of other illicit-substances confounds the potential to differentiate the relationship between each particular substance and WM integrity. More recently, Squeglia and colleagues (Squeglia et al., 2015) found general morphological differences in cannabis-and-alcohol users above and beyond that found in heavy alcohol-use-alone in comparison to healthy controls a longitudinal study, with greater attenuation in the medial frontal cortex and insula; however, they also found larger volumes in the corpus callosum when comparing cannabis-and-alcohol users to heavy-alcohol-users alone, leading to equivocal results. Importantly, the controls appropriately had very limited substance (alcohol or cannabis) use; however, there were no singular (alcohol OR

cannabis alone) groups, but one co-use (alcohol AND cannabis) group, limiting the ability to differentiate the influence of each substance. In addition, some participants in the co-use group had extensive histories of other illicit substance use beyond cannabis use.

In sum, these investigations have begun to tease apart the microstructural implications of adolescent and emerging adult substance co-use, but have been limited by a number of factors. Studies thus far have used group analyses rather than assessing *dose-dependent* relationships or the potential interactive effects of alcohol and cannabis in co-occurring use episodes. Only one co-use study (Winward, Hanson, et al., 2014) used an adequate sample, including a cannabis-only group and well-characterized and matched each substance group with the co-use group; however, this study investigated neurocognition alone, rather than neuroanatomy, and did not look at patterns of substance use. Studies often only looked at total amount of use or group status, rather than patterns of use (e.g., estimated number of lifetime uses per substance rather than the present study's number of co-occurring use events). Indeed, no known study to date has investigated patterns of use, which may be an important determinant of effects due to potential pharmacological differences in co-occurring use (Chesher et al., 1976; Lukas et al., 1992; Lukas & Orozco, 2001). Therefore, there is a need to have a well-powered analysis of the independent and interactive effects of cannabis and alcohol, while also investigating the patterns of co-use, on WM integrity in substance users and controls whose drug use patterns are clearly defined.

Substance Use and Executive Functioning. Executive functioning deficits are a suspected consequence of substance use in emerging adults (for review, see Lisdahl, Gilbart, et al., 2013). In regards to cannabis, this is likely due to the high level of CB1 receptors in the prefrontal cortex (Terry et al., 2009), as frontal regions have been shown to be activated during executive functioning tasks such as the Stroop task (Egner & Hirsch, 2005). Across adolescence,

neurodevelopmental changes in healthy adolescents have been linked to performance on a measure of executive functioning, the Stroop Task (Vijayakumar et al., 2014). Early onset of marijuana use has been found to be predictive of poorer Stroop performance relative to late onset use to healthy controls in a number of studies (Gruber, Sagar, Dahlgren, Racine, & Lukas, 2012; Sagar et al., 2015). Assessing brain-behavior relationships, several studies have also demonstrated altered functional processing of the Stroop task in MJ users, finding generally more disparate and diffuse activation in the DLPFC, PFC, and ACC is required for similar performance attainment (Banich et al., 2007; Gruber & Yurgelun-Todd, 2005; Sagar et al., 2015). In alcohol, disrupted prefrontal macro- and microstructure is a frequently reported finding (see Lisdahl, Gilbart, et al., 2013). Dysexecutive performance as measured through the Stroop task, then, makes logical sense. However, few studies in adolescents and young adults have found direct links between alcohol consumption and Stroop performance, with other studies containing null findings despite self-reported daily executive functioning deficits (Gil-Hernandez & Garcia-Moreno, 2016). Interestingly, one study administered the Stroop task in the fMRI scanner, finding no performance difference but less activation in the cuneus and precuneus in alcohol users (Thayer et al., 2015). Greater consideration of the executive functioning deficits associated with substance use are warranted.

Summary and Aims. Much remains to be discovered regarding co-occurring alcohol and cannabis use, given the nascent state of the literature. Indeed, even the studies that do exist often exclude for moderate use—a group that may have distinct qualitative characteristics or neuroanatomical or neurocognitive effects. However, preliminary studies suggest a potential additive affect of combined cannabis and alcohol use. CB1 receptor activity is downregulated by chronic cannabis (Hirvonen et al., 2012) and alcohol use (Hirvonen et al., 2013). Disrupted CB1

receptor activity may, in turn, affect white matter development, as healthy white matter is influenced by CB1 activity, and binge-like alcohol use (e.g., (Molina-Holgado et al., 2002; Pascual et al., 2014; Samantaray et al., 2015). Combined, alcohol and cannabis may have a cross-tolerance (see Pava & Woodward, 2012), and THC levels may increase while conflicting studies have shown reduced BAC (Lukas et al., 1992) *and* increased BAC (Chesher et al., 1976). A number of studies (Belgrave et al., 1979; Chait & Perry, 1994; Chesher et al., 1977; Marks & MacAvoy, 1989), though not all (Ballard & de Wit, 2011; Bramness et al., 2010; Ramaekers et al., 2011), have also found acute additive affects on cognition when the two substances are used together. Literature on chronic use is more limited. Given the potential for underlying mechanistic changes that may relate to anatomical and functional changes, more research into the effects of co-occurring cannabis and alcohol use is needed.

The present study examined structural connectivity in cannabis and alcohol using male and female adolescents and emerging adults utilizing DTI tractography to assess white matter integrity with a wide range of substance use patterns. The potential independent effects of alcohol, cannabis, and cannabis+alcohol co-occurring use on white matter integrity were assessed. In addition, in order to assess whether structural differences in white matter integrity between groups relate to functional performance, the relationship between performance on a neuropsychological task of executive functioning and white matter integrity was examined. Secondarily, to examine whether larger amounts of alcohol consumed in one episode may have differential effects, each analysis was repeated with number of binge drinking and MJ+binge episodes, rather than total alcohol consumed. It was hypothesized that greater recent cannabis use will predict increased MD and decreased FA in fronto-parietal tracts and fronto-limbic tracts (specifically, within the uncinate fasciculus; the cingulum angular bundle; the cingulum

cingulate gyrus; anterior thalamic radiation, or ATR; the corpus callosum forceps major and forceps minor; the SLF, both parietal and temporal portions; and the ILF; Ashtari et al., 2009; Clark et al., 2012; Gruber et al., 2014; Jacobus, Squeglia, Bava, et al., 2013; Shollenbarger et al., 2015). Similarly, it was hypothesized that greater recent drinking will predict increased MD and decreased FA in these same tracts (Bava et al., 2013; Jacobus et al., 2009). Another primary aim was to assess the combined effects of alcohol and cannabis co-occurring use on white matter integrity. Given the attenuation of THC metabolism (Hartman et al., 2015; Lukas & Orozco, 2001; Ronen et al., 2010) and the proposed potentiation of alcohol on THC neurotoxicity (Hansen et al., 2008), it was predicted that co-occurring MJ and alcohol use would have an additive effect, such that there would be greater decrements in white matter integrity in fronto-parietal and fronto-limbic tracts than alcohol or cannabis use alone. The secondary aim of the study was to assess brain-behavior relationships, predicting that, in tracts that are significantly related to alcohol use, cannabis use, or cannabis+alcohol co-use, poorer WM integrity will be associated with poorer cognitive performance (Anderson, Rabi, Lukas, & Teicher, 2010; Chanraud et al., 2009; Gruber et al., 2014; Gruber, Silveri, Dahlgren, & Yurgelun-Todd, 2011).

Methods

Overview. The present study analyzed data collected by the Imaging Data in Emerging Adults Addiction (IDEAA) Consortium (PIs: Krista Lisdahl, Ph.D., UWM site, Staci Gruber, Ph.D., McLean site, Francesca Filbey, Ph.D., UTD site, and Susan Tapert, Ph.D., UCSD site). One-hundred and ninety-two participants were included in one combined dataset drawn from the IDEAA Consortium PI's individual projects. Data from UCSD, UWM, and McLean were used in the present study.

Participants. Data from a total of 192 individuals, aged 16-27, were used for the present study and although the study focused on dose-dependent effects, participants were classified into distinct groups for selection of potential covariates (cannabis only, or MJ; alcohol only, or ALC; cannabis and alcohol co-use, or MJ+ALC; and healthy controls, or HC) and secondary brain-behavior analyses. The Institutional Review Boards at the University of Wisconsin-Milwaukee, Medical College of Wisconsin, McLean Hospital, and University of California San Diego have approved all aspects of this study, and all participants provided written informed consent. Groups were assessed for differences in sociodemographic information, such as gender, age, ethnicity, and education level. Any significant differences between groups were used as covariates in the subsequent analyses. Gender was the only variable that differed by substance group and, therefore, was included as a covariate; in the binge analyses, groups differed on education level and length of abstinence so these variables were included in those analyses as covariates.

All participants across sites were recruited for participation in a substance use study. For the current analysis, the following group definitions were used. MJ Criteria: MJ participants used at least half a gram of cannabis a week, on average, over the past month. They used less than 20 standards drinks of alcohol in the past month. ALC Criteria: ALC participants drank at least 20 standard drinks on average over the past month and used less than half a gram of cannabis a week. MJ+ALC Criteria: MJ+ALC participants exhibited patterns of regular substance use averaged over the past month (consuming =/> 20 standard drinks a month, use cannabis =/>0.5 gram a week). HC Criteria: Controls used less than 20 standards drinks of alcohol in the past month and less half a gram of cannabis per week on average over the last month.

Exclusion Criteria for All Participants: Current use of psychotropic medication, lifetime history of serious neurologic injuries or disorders, major medical illness, diagnosis of an

independent Axis I psychiatric disorder in past year (except for Substance Abuse or Dependence in any of the substance using groups), pregnancy, or MRI contraindications (e.g., metal anywhere in or on the body, greater than 250 lbs, claustrophobia). McLean allowed for left-handedness, and, therefore, three left-handed participants were included; all other sites excluded for left-handedness. Alcohol and breathalyzer screens verified .000 breath alcohol concentration at all study sessions. For McLean site *only*, recent binge drinking (defined as 4 or more drinks for a female, 5 or more drinks for a male, within a 2 hour period) was an exclusion criteria; therefore, McLean's participants were excluded from any binge-specific analyses.

Procedure. Eligible participants completed each respective parent study protocol and were asked to come to the MRI scanning center at each of the respective institutions. They were asked to remain abstinent from all substance use other than cigarettes for a minimum of 12 hours prior to session start. Participants were given breathalyzer and toxicology tests. UCSD and UWM also collected pregnancy tests for females; McLean Hospital relied on subject self-report of pregnancy. Positive results on either the pregnancy (when used) or breathalyzer tests regarded participants as ineligible, and they were subsequently given small compensation for their time. If negative, participants were given psychological questionnaires to assess mood and psychological variables. Participants then completed the neuroimaging and neurocognitive testing protocols. All participants were compensated for their time.

Recent Drug Use. At all sites, drug use history was collected using the Timeline Follow-Back (TLFB; Sobell & Sobell, 1992). Using a calendar to cue special dates and holidays, participants were asked to recount when they used alcohol (standard drinks), cannabis (grams), co-occurring alcohol and cannabis (days of co-use). Number of binge drinking episodes (≥4 drinks for females, ≥5 for males in one drinking occasion, not limited by hours) was also

calculated for UWM and UCSD site participants. Data for past month of use was averaged to the past month (30 days), as each site collected varying lengths of time. When available, length of abstinence was calculated (McLean site did not calculate this due to their short, 12 hour, period of time of required abstinence for participants).

Measures. A different set of neuropsychological measures were administered at each site; however, each used a version of the Stroop task (e.g., Comalli Stroop; Comalli, Wapner, & Werner, 1962), which is used in the present analyses. UWM and UCSD both administered the D-KEFS Color-Word Interference Task (Delis, Kaplan, & Kramer, 2001). It consists of four subtests: a word reading list, a color naming list, a color-word list, and a color-word+word reading list. Time to complete each condition was measured. Only the first three subtests are included in the proposed study to better match the other sites. McLean Hospital utilized the Comalli Stroop (Comalli et al., 1962), which allows a set amount of time to read and/or name as many words/colors as possible; total number of words/colors read was measured. Total reading score, total color naming score, and total color-word interference score were calculated. Each subject's performance was converted to the correct version's normed scores. It was then converted to a z-score, allowing for comparison across sites and versions.

MRI Data Acquisition. Each site used a standardized acquisition protocol on its respective 3T scanner (GE, Siemens, or Phillips). See Table 1 for specific structural acquisition parameters by site.

Diffusion Tensor (DTI) Image Acquisition. Diffusion Tensor Imaging (DTI) was similarly obtained standardized protocols at each site (see Table 2). Raw DTI data was then uploaded to the IDEAA server pre-processed all DTI data by the UWM site in order to ensure consistency and all DTI datasets underwent the same exact preprocessing pipeline on the same

computer system using a script capable of handling data from multiple scanner platforms. All structural data, including tracts of WM through FreeSurfer's Tracks Constrained by Underlying Neuroantomy (TRACULA), was processed by UWM, again to ensure consistency across datasets.

DTI Processing. FreeSurfer software was used to pre-process all T1-weighted 3D anatomical datasets, correcting for motion, non-parametric non-uniform intensity normalization, MNI transformation, removal of non-brain material, and skull-stripping. Whole-brain segmentation of white and gray matter was then completed. TRACULA (a software program within FreeSurfer) was then used to reconstruct white matter pathway from DTI images using a global probabilistic tractography program. This yields measures of white matter integrity, including fractional anisotropy (FA) and mean diffusivity (MD) (Yendiki et al., 2011). Each image underwent the following preprocessing steps: (1) Image Corrections (e.g., for B0 inhomogeneities, eddy currents, and simple head motion), (2) Further head motion correction, (3) Intra-subject and Inter-subject registration (4) Mask creation (white matter is extracted from FreeSurfer's segmentation and parcellation and combined into a mask), (5) Tensor fit, and (6) Estimation of pathways by combining the individual's data with an atlas. Following preprocessing, a ball-and-stick model of diffusion was fitted to the images. Markov Chain Monte Carlo sampling was used to measure diffusion in each voxel, then establishing the likelihood of locations of tract for each subject. From these estimated pathways, statistics on diffusion measures (average weighted FA and MD) within each individual were extracted and exported into SPSS for regression analysis. Correction for multiple comparisons was conducted using Benjamini and Hochberg's (1995) False Discovery Rate (FDR) correction method.

Data Analysis. All analyses were conducted in SPSS.

Preliminary Analyses. Although the primary analyses used dose-dependent independent variables, differences in demographic data and psychological indices were examined with ANOVA and chi-square analyses between groups (gender, age, education, race, ethnicity, handedness). Variables that differentiated the groups were included in subsequent analyses as covariates, along with study site; gender was the only variable that differed by group and therefore was include in each analysis for all participants. When investigating analyses by group with only binge data, length of abstinence and education differed, and so were included in all binge analyses.

Primary Analyses. A series of multiple regressions (FA and MD of specific hypothesized tracts) examined the study aims. For the first primary analysis (N=192), the independent variables included: past month drinking (standard drinks), past month cannabis (total grams), and co-occurring alcohol-cannabis smoking days. Covariates included study site and important demographics that may differ by group (i.e., gender). Next, the influence of binging was assessed by including past month binge episodes, past month cannabis, and number of co-occurring binge-cannabis days, and included covariates (i.e., study site, length of abstinence, and education) (N=134). All regression analyses were corrected for multiple comparisons by the FDR method (Benjamini & Hochberg, 1995).

Secondary Analyses. For secondary analyses, 167 of the 192 participants completed a version of the Stroop task. To assess brain-behavior relationship, multiple regressions were run, assessing whether differences in white matter integrity predict performance on a neuropsychological task of executive functioning, controlling for study site. As sites varied in versions of measures administered, each subject's normed performance on a task was transformed into a z-score. This was then used in all statistical analyses. Analyses were

completed by substance use group, to ensure that no significant differences would be obscured if relationships were in opposing directions.

In addition, the relationship between past month substance use and Stroop performance was examined. First, total past month alcohol (standard drinks; 1 ounce of liquor, 4 ounces of wine, 12 ounces of beer), cannabis (grams), and co-occurring alcohol-cannabis smoking days were investigated to see if they were associated with Stroop performance, when controlling for covariates. Next, past month binging episodes (number of binge drinking episodes; ≥4 drinks for females, ≥5 for males in one drinking occasion, not limited by hours), cannabis (grams), and co-occurring binging-cannabis episodes (co-occurring alcohol and cannabis, days of co-use-binge; binging defined as ≥4 drinks for females, ≥5 for males in one drinking occasion, not limited by hours), along with appropriate covariates, were investigated to see if they were associated with Stroop performance.

Results

Demographics. Participants were recruited from different regions of the United States (59 from the West Coast; 75 from the Midwest; 58 from the East Coast). When including all three sites, groups significantly differed by gender ($F(187)=3.49$, $p=.02$); no other demographic variables were significantly associated with group status. When investigating analyses by group with only binge data (UWM and UCSD), length of abstinence ($F(121)=2.82$, $p=.04$) and education ($F(130)=2.73$, $p=.05$) differed, and so were included in all binge analyses.

In addition, participants were divided between those who had (CO) and had *not* (NO) used alcohol and cannabis on the same day in the past month, though these groups were used in

no analyses and were assessed strictly for descriptive purposes. They did not differ in age, education, gender, ethnicity, race, or handedness.

Substance Use Patterns. Participants exhibited a wide range of substance use in the past month (alcohol standard drinks: mean=19.68, SD=26.75, range=0-167.14; cannabis use in grams: mean=8.33, SD=18.14, range=0-139.91; number of binge episodes: mean=1.36, SD=2.85, range=0-15; see Table 5). Substance use differed significantly by group in past month cannabis use [$F(187)=30.67$, $p<.001$], alcohol use [$F(187)=80.95$, $p<.001$], binge episodes [$F(187)=27.40$, $p<.001$], co-use episodes [$F(179)=89.03$, $p<.001$], and co-use-binge episodes [$F(184)=27.73$, $p<.001$]. As expected, the ALC and MJ+ALC groups had significantly more past month alcohol use and binge episodes than either the MJ or HC groups while the MJ and MJ+ALC groups had significantly more past month cannabis use than the ALC or HC groups. For co-use and co-use-binge episodes, the MJ+ALC group had significantly more of each episode than the HC, MJ, or ALC groups. In addition, the MJ group had significantly more co-use episodes than the HC, though did not differ significantly from the ALC group.

In investigating co-use compared to no co-use, co-use groups differed significantly with past month substance use as exhibited by greater past month cannabis [$F(181)=59.92$, $p<.001$], alcohol [$F(181)=56.69$, $p<.001$], binge episodes [$F(181)=38.84$, $p<.001$], co-use episodes [$F(181)=140.78$, $p<.001$], and co-use-binge episodes [$F(181)=50.97$, $p<.001$] in the CO group (see Table 6). Groups also differed in maximum alcohol [$F(129)=7.71$, $p<.01$] and maximum cannabis use [$F(132)=76.05$, $p<.001$] in the past month in one episode, number of drinking days [$F(180)=25.71$, $p<.001$] and number of smoking days per month [$F(131)=130.17$, $p<.001$], average grams per smoking day in the past month [$F(131)=119.10$, $p<.001$]. However, CO v. NO

groups did not significantly differ on average drinks per drinking day in the past month [F(131)=2.22, p=.14].

Correlational analyses were run between past month substance use patterns. All substance use variables (alcohol use, cannabis use, binge episodes, co-use episodes, and co-use-binge episodes) were significantly correlated *except* past month binge episodes and past month cannabis use (see Table 7).

Study Site. As study site is a significant predictor of most variables (see below), an effort was made to better understand specific site characteristics. Importantly, prior research has established the reliability of combining data across multiple sites so long as site is a covariate (Pagani et al., 2010; Fox et al., 2012; Magnotta et al., 2012). Demographics by site are listed in Table 8. When assessing for demographic differences by study site, age [F(188)=45.79, p<.001], education [F(189)=69.83, p<.001], race [x^2=23.15, p=.01], and ethnicity [x^2=13.86, p=.01] significantly differed. When the whole-sample is assessed together by substance group, there is no longer a statistically significant difference in these variables (see Demographics section above).

Quantitative values of white matter integrity by Study Site were also pulled to see if there was any clear pattern (see Appendix I). In FA values, there was no clear pattern of better quality WM by site, as each site occasionally had higher FA values depending on the tract. In MD values, there was no clear pattern between UWM and McLean, but UCSD generally had a lower MD value.

In addition, group differences were assessed within each site. No significant differences by group were found within any of the sites. The one exception to this was in McLean's data, with gender being significantly different by group (F(42)=5.74, p<.01). This is consistent with

the broader findings of the whole combined sample, and is accounted for by covarying for gender in all whole-sample analyses.

Differences by study site were also found in substance use patterns (see Table 9). Sites differed in cannabis use [F(189)=9.64, p<.001], as McLean participants had significantly more past month cannabis use (in grams) than UWM or UCSD.

Primary Analysis: TRACULA.

Co-Use Data.

FA. **Primary Predictors** (see Table 10). Past month cannabis use was significantly associated with decreased FA in the following tracts: forceps minor [beta=.18, t=2.16, p=.03, FDR-p=.13], left ILF [beta=.21, t=2.41, p=.02, FDR-p=.13], left uncinate [beta=.22, t=2.57, p=.01, FDR-p=.13], and right SLF temporal [beta=-.19, t=-2.18, p=.03, FDR-p=.13], though no tracts survived correction for multiple comparisons. Neither past month alcohol or co-use were significantly associated FA in any tract.

Covariates. Study site was significantly associated with forceps major [beta=.25, t=3.35, p<.01, FDR-p<.01], forceps minor [beta=.23, t=3.25, p<.01, FDR-p<.01], left ILF [beta-.24, t=-3.26, p<.01, FDR-p<.01], left uncinate [beta=-.21, t=-2.99, p<.01, FDR-p<.01], left ATR [beta=.30, t=4.22, p<.001, FDR-p<.001], right ATR [beta=.47, t=7.15, p<.001, FDR-p<.001], left cingulum angular bundle [beta=-.24, t=-3.32, p<.01, FDR-p<.01], right cingulum angular bundle [beta=-.31, t=-4.26, p<.001, FDR-p<.001], left cingulum cingulate gyrus [beta=-.22, t=-3.04, p<.01, FDR-p<.01], right cingulum cingulate gyrus [beta=-.30, t=-4.07, p<.001, FDR-p<.001], left SLF parietal [beta=-.23, t=-3.14, p<.01, FDR-p<.01], right SLF parietal [beta=-.30, t=-4.11, p<.001, FDR-p<.001], left SLF temporal [beta=-.21, t=-2.93, p<.01, FDR-p<.01]. Gender was significantly associated with left uncinate [beta=-.24, t=-3.53, p<.01, FDR-p=.02].

Prior to correction for multiple comparisons, gender was also significantly associated with right uncinate [beta=-.14, t=-1.80, p=.07, FDR-p=.39] and left ATR [beta=-.14, t=-2.05, p=.04, FDR-p=.34]. In each of these instances, males exhibited higher FA compared to females.

MD. **Primary Predictors** (see Table 11). After correcting for multiple comparisons, past month cannabis use was significantly associated with increased MD in forceps major [beta=.14, t=2.18, p=.03, FDR-p=.04], left ILF [beta=.14, t=2.49, p=.014, FDR-p=.03], right ILF [beta=.15, t=2.70, p<.01, FDR-p=.02], right uncinate [beta=.16, t=2.39, p=.02, FDR-p=.03], left ATR [beta=.19, t=2.61, p=.01, FDR-p=.02], right ATR [beta=.17, t=2.41, p=.02, FDR-p=.03], left cingulum angular bundle [beta=16, t=2.15, p=.03, FDR-p=.04], right cingulum angular bundle [beta=.18, t=2.32, p=.02, FDR-p=.03], left cingulum cingulate gyrus [beta=.22, t=-2.80, p<.01, FDR-p=.02], right cingulum cingulate gyrus [beta=.19, t=2.32, p=.02, FDR-p=.03], left SLF parietal [beta=.20, t=2.87, p=.01, FDR-p=.02], right SLF parietal [beta=.22, t=3.33, p<.01, FDR-p=.01], left SLF temporal [beta=.20, t=3.04, p<.01, FDR-p<.02], right SLF temporal [beta=.21, t=3.28, p<.02, FDR-p=.01]. Neither past month alcohol or co-use were significantly associated with MD in any tract.

Covariates. Study site was significantly associated with forceps major [beta=-.66, t=-11.73, p<.001, FDR-p<.001], forceps minor [beta=-.76, t=-15.81, p<.001, FDR-p<.001], left ILF [beta=-.76, t=-15.48, p<.001, FDR-p<.001], right ILF [beta=-.78, t=-16.60, p<.001, FDR-p<.001], left uncinate [beta=-.63, t=-11.18, p<.001, FDR-p<.001], right uncinate [beta=-.64, t=-11.18, p<.001, FDR-p<.001] , left ATR [beta=-.57, t=-0.37, p<.001, FDR-p<.001], right ATR [beta=-.56, t=-9.15, p<.001, FDR-p<.001], left cingulum angular bundle [beta=-.52, t=-8.15, p<.001, FDR-p<.001], right cingulum angular bundle [beta=-.51, t=-7.93, p<.001, FDR-p<.001], left cingulum cingulate gyrus [beta=-.41, t=-6.06, p<.001, FDR-p<.001], right cingulum

cingulate gyrus [beta=-.38, t=-5.47, p<.001, FDR-p<.001], left SLF parietal [beta=-.60, t=-9.95, p<.001, FDR-p<.001], right SLF parietal [beta=-.65, t=-11.54, p<.001, FDR-p<.001], left SLF temporal [beta=-.65, t=11.61, p<.001, FDR-p<.001], and right SLF temporal [beta=-.69, t=-12.96, p<.001, FDR-p<.001].

Gender was significantly associated with left uncinate [beta=.12, t=2.07, p=.04, FDR-p=.64] prior to correction for multiple comparisons.

Co-Use-Binge Data.

FA. **Primary Predictors** (see Table 12). Past month cannabis use was significantly associated with decreased FA in the right cingulum angular bundle prior to correction for multiple comparisons [beta=-.28, t=-2.47, p=.02, FDR-p=.24]. Neither past month binge or co-use-binge were significantly associated with FA in any tract.

Covariates. Study site was significantly associated with forceps major [beta=.31, t=2.25, p=.03, FDR-p=.05], forceps minor [beta=.44, t=3.23, p<.01, FDR-p<.01], left ILF [beta-.36, t=-2.71, p=.01, FDR-p=.02], left ATR [beta=.45, t=3.40, p<.01, FDR-p<.01], right ATR [beta=.67, t=6.18, p<.001, FDR-p<.01], left cingulum angular bundle [beta=-.38, t=-2.73, p=.01, FDR-p=.02], right cingulum angular bundle [beta=-.43, t=-3.28, p<.01, FDR-p<.01], left cingulum cingulate gyrus [beta=-.31, t=-2.19, p=.03, FDR-p=.05], right cingulum cingulate gyrus [beta=-.53, t=-3.99, p<.001, FDR-p<.01], left SLF parietal [beta=-.29, t=-2.10, p=.04, FDR-p=.05], right SLF parietal [beta=-.45, t=-3.33, p<.01, FDR-p<.01], and left SLF temporal [beta=-.30, t=-2.16, p=.03, FDR-p=.05].

MD. **Primary Predictors** (see Table 13). After correcting for multiple comparisons, past month cannabis use was significantly associated with increased MD in the right SLF temporal [beta=.11, t=3.29, p<.01, FDR-p=.02]. Prior to, but not after, corrections, past month cannabis

use was significantly associated with left ILF [beta=.09, t=2.20, p=.03, FDR-p=.12], right ILF [beta=.07, t=2.03, p=.04, FDR-p=.12], right ATR [beta=.076, t=2.031, p=.05, FDR-p=.12], right SLF parietal [beta=.08, t=2.57, p=.01, FDR-p=.07], left SLF temporal [beta=.12, t=2.51, p=.01, FDR-p=.07], and right SLF temporal [beta=.11, t=3.29, p<.01, FDR-p=.02].

Past month co-use-binge was significantly associated with decreased MD in the left ILF [beta=-.11, t=-2.10, p=.04, FDR-p=.15], and right ILF [beta=-.11, t=-2.45, p=.02, FDR-p=.15] before correction for multiple comparisons.

Covariates. Study site was significantly associated with forceps major [beta=-.81, t=-11.68, p<.001, FDR-p<.001], forceps minor [beta=-.82, t=-11.17, p<.001, FDR-p<.001], left ILF [beta=-.89, t=-19.34, p<.001, FDR-p<.001], right ILF [beta=-.87, t=-22.12, p<.001, FDR-p<.001], left uncinate [beta=-.83, t=-14.18, p<.001, FDR-p<.001], right uncinate [beta=-.82, t=-16.44, p<.001, FDR-p<.001], left ATR [beta=-.84, t=-18.99, p<.001, FDR-p<.001], right ATR [beta=-.86 t=-20.05, p<.001, FDR-p<.001], left cingulum angular bundle [beta=-.77, t=-11.43, p<.001, FDR-p<.001], right cingulum angular bundle [beta=-.72, t=-9.36, p<.001, FDR-p<.001], left cingulum cingulate gyrus [beta=-.82, t=-13.56, p<.001, FDR-p<.001], right cingulum cingulate gyrus [beta=-.75, t=-11.32, p<.001, FDR-p<.001], left SLF parietal [beta=-.86, t=-18.16, p<.001, FDR-p<.001], right SLF parietal [beta=-.87, t=-22.98, p<.001, FDR-p<.001], left SLF temporal [beta=-.86, t=-17.07, p<.001, FDR-p<.001], and right SLF temporal [beta=-.86, t=-21.90, p<.001, FDR-p<.001].

Education was significantly associated with right ILF [beta=.09, t=2.18, p=.03, FDR-p=.07], right uncinate [beta=.14, t=2.77, p=.01, FDR-p=.03], left ATR [beta=.12, t=2.72, p=.01, FDR-p=.03], right ATR [beta=.11, t=2.54, p=.01, FDR-p=.04], right cingulum cingulate gyrus

[beta=.16, t=2.43, p=.02, FDR-p=.04], right SLF parietal [beta=.12, t=3.20, p<.01, FDR-p=.03], and right SLF temporal [beta=.11, t=2.80, p=.01, FDR-p=.03].

Prior to correction for multiple comparisons, length of abstinence was significantly associated with left cingulum cingulate gyrus [beta=.08, t=-1.81, p=.07, FDR-p=.24], right Cingulum Cingulate [beta=.09, t=1.90, p=.06, FDR-p=.24], right SLF parietal [beta=.07, t=2.66, p=.01, FDR-p=.14], and right SLF temporal [beta=.06, t=2.38, p=.02, FDR-p=.15].

Secondary Analysis: DTI-Stroop.

Co-Use Data.

Stroop. Within the MJ+ALC group, multiple regression analyses revealed significant positive relationships between MD tracts and Stroop performance, after correcting for multiple comparisons. Specifically, forceps major [beta=.54, t=2.72, p=.01, FDR-p=.02], left ILF [beta=.51, t=2.54, p=.02, FDR-p=.02], right ILF [beta=.61, t=2.59, p=.01, FDR-p=.02], right uncinate [beta=.49, t=2.58, p=.01, FDR-p=.02], left ATR [beta=.48, t=2.65, p=.01, FDR-p=.02], right ATR [beta=.45, t=2.47, p=.02, FDR-p=.02], left cingulum angular bundle [beta=.38, t=2.17, p=.04, FDR-p=.04], right cingulum angular bundle [beta=.39, t=2.28, p=.03, FDR-p=.03], left cingulum cingulate gyrus [beta=.44, t=2.78, p=.01, FDR-p=.02], right cingulum cingulate gyrus [beta=.42, t=2.60, p=.01, FDR-p=.02], left SLF parietal [beta=.49, t=2.82, p=.01, FDR-p=.02], right SLF parietal [beta=.48, t=2.41, p=.02, FDR-p=.03], left SLF temporal [beta=.49, t=2.64, p=.01, FDR-p=.02], and right SLF temporal [beta=.50, t=2.45, p=.02, FDR-p=.02] were significantly associated with better Stroop color-word interference performance. No other groups revealed significant relationships between tracts and Stroop performance.

Co-Use-Binge Data.

Multiple regressions were run by group, controlling for study site, to assess whether the one tract that was associated with cannabis use (right SLF temporal MD) significantly related to Stroop performance. No significant results were revealed.

Secondary Analysis: Substance Use Patterns-Stroop.

Co-Use Data**.**

Word reading performance was significantly negatively related to past month cannabis use [beta=-.23, t=-2.64, p=.01], and marginally positively related to by past month alcohol use [beta=.177, t=1.97, p=.05]. Color naming and color-word interference were not significantly associated with any primary predictors.

Co-Use-Binge Data.

Color naming, word reading, and color-word interference were not related to any primary variables.

Discussion

The present study found a number of significant and robust relationships between past month cannabis use and poorer white matter integrity (measured by increased MD). However, contrary to our hypotheses, we did not see any influence of co-use episodes, past month alcohol use, past month binge episodes, or co-use-binge episodes. Secondary brain-behavior relationships were assessed, finding that, within only the MJ+ALC group, increased MD was positively associated with Stroop performance on the color-word interference subtest. Finally, analyses assessed the influence of substance use on Stroop performance, finding again that

cannabis use was the only substance significantly associated with word reading when assessed in the whole sample.

Consistent with prior findings in adolescent and emerging adult MJ users (Arnone et al., 2008; Ashtari et al., 2009; Gruber et al., 2014; Shollenbarger et al., 2015), we found increased MD was associated with past month cannabis use. Our findings are consistent and robust across fronto-limbic and fronto-parietal networks (specifically, within the uncinate fasciculus; the cingulum angular bundle; the cingulum cingulate gyrus; anterior thalamic radiation; the corpus callosum forceps major and forceps minor; the SLF, both parietal and temporal portions; and the ILF tracts). Such disrupted WM may be indicative of damage to myelination due to cannabis use during this sensitive neurodevelopmental time period. Indeed, MJ use downregulates CB1 activity (Hirvonen et al., 2012) and cannabinoid receptors are important for WM development (Molina-Holgado et al., 2002), suggesting a potential underlying mechanism of these findings.

This increased MD is likely an indication of altered processing that can be broken down by pathway types. It is interesting to hypothesize about potential functional implications of structural differences, though the present study assessed only one specific function. First, the association tracts (SLF, ILF, uncinate fasciculus, and the cingulum) connect distant regions within the same hemisphere and are involved in key functions such as higher cognitions, emotion regulation, memory, and visuospatial processing (Catani & Thiebaut de Schotten, 2012; Hua et al., 2009). The SLF connects the frontal, parietal, and temporal lobes, and is generally involved in language, visuospatial skills, and working memory. The ILF connects the occipital and temporal lobes, the amygdala, and the hippocampus, and is involved in functions such as perception, visual memory, and aspects of language. The uncinate fasciculus connection the anterior temporal lobe with the orbitofrontal cortex and is key to the function of the limbic

system. The cingulum connects the frontal, parietal, temporal, and occipital lobes to different portions of the cingulate cortex, leading to the limbic system and functions such as attention, memory, and emotion. As many of these pathways relate to fronto-limbic and cognitive functioning, increased dysexecutive symptoms and poorer mood regulation may be expected. Indeed, this is what is commonly seen in the cannabis literature; specifically, in MJ users, our group previously found poorer WM integrity in the bilateral uncinate to be predictive of increased mood and apathy symptoms (Shollenbarger et al., 2015). Others have similarly found cannabis users to have either decreased WM integrity in association tracts (Arnone et al., 2008; Ashtari et al., 2009; Delisi et al., 2006), or deficits in cognitive (Lisdahl & Price, 2012; Solowij et al., 2011) or emotional (McQueeny et al., 2011; Wright, Scerpella, & Lisdahl, 2016) functioning, or both structural and functional deficits (Maple et al., under review; Gruber et al., 2014; Gruber et al., 2011). Admittedly, the present study did not find this relationship with executive functioning due directly to substance use. As this was a single measure in a secondary analysis, a more thorough neuropsychological battery may have revealed such relationships.

The commissure pathways connect the two hemispheres through the corpus callosum and here are divided between the corpus callosum forceps major and forceps minor (Catani & Thiebaut de Schotten, 2012). The forceps minor encompasses the genu and rostrum, within the PFC and OFC respectively. The forceps major includes the splenium in the occipital cortex, with some fibers reaching the parietal and temporal lobes (Catani & Thiebaut de Schotten, 2012). Our group (Shollenbarger et al., 2015) and others (Gruber et al., 2014) previously found increased MD in the forceps minor and anterior portions of the corpus callosum in cannabis users, though the present study did not find any results related to the forceps minor. More consistent with the present findings, Bava and colleagues (Bava et al., 2009) found poorer WM integrity in the

splenium in MJ+ALC users relative to controls, while Jacobus, Squeglia et al. (Jacobus, Squeglia, Bava, et al., 2013) found decreased WM in the splenium in both heavy drinkers and heavy drinkers-and-MJ users relative to controls. Given the role of the forceps major in visuospatial processing and deficits in visuospatial processing with disrupted WM in this region (Lunven et al., 2015) and other research suggesting disrupted visuospatial skills in MJ users (Huestuegge et al., 2002; Smith et al., 2010), future research should more directly assess potential brain-behavior relationships with the forceps major in substance using populations.

The projection pathways connect cortical and subcortical regions, allowing for communication of sensory and motor information (Catani & Thiebaut de Schotten, 2012). Here we found cannabis use was related to increased MD in the bilateral ATR, a region key for limbic functions and communication between the thalamus and PFC. Similarly, Becker and colleagues (2015) found young adult heavy cannabis users had reduced WM growth in a range of projection and other pathways over a three year period, relative to controls, and that this reduced growth was predictive of poorer verbal learning performance. Here again, then, it is suggested that underlying microstructural integrity may be altered by cannabis use, and, while not seen in the present study, such microstructural changes may lead to functional impairment.

Interestingly and contrasting our hypotheses, FA was not significantly related to substance use patterns. Unlike others (Ashtari et al., 2009; Delisi et al., 2006; Gruber et al., 2014; Shollenbarger et al., 2015) we did not find differences in FA by MJ use. FA is known to be a sensitive measure of overall microstructural integrity in WM as measured through directional cohesion, but does not offer much information related to type of change (Alexander et al., 2007). In contrast, MD measures the diffusion rate and free diffusion (Soares et al., 2013). Previously, our group has found MD to be particularly sensitive in MJ users (Shollenbarger et al., 2015), and

others have suggested MD is also a more sensitive measure in other clinical samples (e.g., in epilepsy patients; Kreilkamp, Weber, Richardson, & Keller, 2017). Perhaps MJ damages WM microstructure in specific ways that are lost when looking at an overall value, such as FA.

Also contrary to our hypotheses, we did not find any significant relationships between alcohol use and white matter integrity, despite previous findings (Cardenas et al., 2013; De Bellis et al., 2008; Lisdahl, Thayer, et al., 2013; Luciana et al., 2013; McQueeny et al., 2009; Squeglia et al., 2015). Further, the lack of findings around binging and co-use-binge episodes may initially be surprising given prior studies (Lisdahl, Thayer, et al., 2013; McQueeny et al., 2009). However, given the limited amount of co-use-binge in the sample (mean=1.77 in the past month), there may not have been enough variance to detect real change based on limited use. Other studies have also found results to be more robust when investigating MJ use rather than by alcohol use (Lisdahl & Price, 2012; Wright et al., 2016), perhaps indicating MJ is a more reliable predictor of such deficits. This does not negate the importance of measuring alcohol use and such findings as these are not always the case (e.g., Jacobus, Squeglia, Bava, et al., 2013; Lisdahl, Thayer, et al., 2013), but underscores the need to measure cannabis and alcohol use with careful quantitative techniques that enable assessment of the unique influence of each substance.

Co-use episodes, whether or not considering alcohol binges, were not significantly related to any DTI outcomes once we corrected for multiple comparisons. This is in contrast to our expectations and to other studies that have shown acute additive cognitive deficits (Belgrave et al., 1979; Chait & Perry, 1994; Chesher et al., 1977; Marks & MacAvoy, 1989) and chronic cognitive deficits due to co-use (Winward, Hanson, et al., 2014), though none of these studies investigated WM differences. Given the somewhat equivocal results of human pharmacological studies (Chesher et al., 1976; Hartman et al., 2015; Lukas et al., 1992; Lukas & Orozco, 2001)

and even acute (Raemakers et al., 2011) and chronic studies (Mahmood et al., 2010), this may not be a surprising finding. Acutely, alcohol may increase endocannabinoid levels (Alvarez-Jaimes, Stouffer, & Parsons, 2009; Rubio, McHugh, Fernandez-Ruiz, Bradshaw, & Walker, 2007), which may offset the effects of MJ, even though chronic alcohol use may downregulate CB1 activity (Hirvonen et al., 2013). However, the nascent literature of the pharmacological interactive effects of MJ and alcohol, the preliminary evidence of acute deficits, and the equivocal findings of chronic effects (as suggested here, and in Winward, Hanson, et al., 2014) highlight the great need of more research in this area. These studies should consist both of preclinical work, as well as carefully categorizing and accounting for co-use of substances in human subjects.

As may be expected, almost all substance use measured was significantly correlated. The exception to this was between past month number of binge episodes and past month grams of cannabis used. Substance use groups may then be qualitatively different in how they approach substance consumption. Subjectively, when cannabis and alcohol are consumed together at low doses, the alcohol may be prolonging the effects of THC (Hartman et al., 2016); however, this relationship has not been assessed at a higher dose. Perhaps with larger dosing the effects are less pleasant, deterring more people from both binging and smoking marijuana together. As Guttmannova and colleagues suggest (Guttmannova et al., 2016), however, co-use of substances is a complex topic with many nuanced indicators due to policy and environmental factors, warranting more research in this area.

Limitations of the current study should be noted. Study site significantly related to most analyses, although it is notable that prior studies suggest that combining data across different sites and even scanner brands to be reliable (Fox et al., 2012; Magnotta et al., 2012; Pagani et al.,

2010), if properly accounted through statistically covarying. The present study was designed with the intent to broaden external validity, including a range of demographics and substance use patterns across sites. Inherent in increasing external validity is reduced internal validity. Even so, results regarding MJ use and WM integrity are very robust, after controlling for study site and gender. This perhaps suggests the strong influence of cannabis use on WM integrity, despite differences in population makeup and locale. While every effort was made to carefully measure the past month of substance use, particularly for assessing same-day substance use, we were not able to account for whether or not the substances were used simultaneously or even within hours of one another. Future research should more carefully determine simultaneous use. The present study did not have consistent tobacco use information across study sites and, therefore, tobacco use was not accounted for in the present analyses, despite the potential influence of tobacco use on brain structure and function. Not all sites excluded for learning disabilities, and, therefore, performance on the Stroop task may have been influenced by potential inclusion of individuals with a learning disability. While brain-behavior analyses were initially examined, we only used a single neurocognitive task, despite the range of cognitive deficits that may be affected by cannabis or alcohol use; future studies should include a full neuropsychological battery. Finally as a cross-sectional study, causal relationships cannot be established; future studies, such as the Adolescent Brain and Cognitive Development (ABCD) study, are needed to assess causality.

Conclusion. In conclusion, the present study found that greater past month cannabis use was associated with decreased WM integrity, as measured by MD, across fronto-parietal and fronto-limbic tracts. These robust findings suggest abnormal WM quality related to cannabis use, after accounting for study site, gender, alcohol use, and alcohol and cannabis co-use days. Though hypothesized, we did not find evidence for an independent or additive impact of co-

occurring same-day alcohol and cannabis use. More careful research into the *combined* effects of cannabis and alcohol, especially simultaneous use, and their potential psychopharmacological interactions is also needed on both preclinical and clinical levels. Given the mainstream popularity of cannabis use and its perceived safety and benefits, greater communication of potential harms to laymen and experts alike is of great need.

Table 1. Structural MRI Acquisition: Across IDEAA Sites

	Slices	Thick-ness	TR	TI	TE	FOV	Flip	Frequency x Phase	Time
UWM	176	1 mm	2.53	1100	3.39	256	12	256x256	8 min
McLean	150	1 mm	8.20	450	3.40	240	12	256x256	9 min
UCSD	172	1 mm	7.78	450	2.99	240	12	256x192	7 min

Notes: Structural MRI acquisition parameters by study site. Slices: Number of slices per structural MRI scan; Thickness: Thickness per slice; TR: Repetition time; TI: Inversion time; TE: Echo time; FOV: Field of view; Flip: Tip angle; Time: Time for whole structural scan.

Table 2. DTI Acquisition: Across IDEAA Sites

	Slices	Thick-ness	TR	TE	# b0	b value	# directs	Pixel spacing	Avg
UWM	60	2 mm	9300	89	7	700	48	1/1	1
McLean	60	2 mm	9300	89	7	700	48	2/2	1
UCSD	34	3 mm	10900	93.1	1	1500	61	1.9/1.9	1

Notes: DTI acquisition parameters by study site. Slices: Number of slices per structural MRI scan; Thickness: Thickness per slice; TR: Repetition time; TE: # directs: Number of diffusion gradients.

Table 3. Group Demographics by Substance Use Group.

	Controls n = 92	MJ n = 33	ALC n = 27	MJ+ALC n = 39
	% or M (SD) *Range*	% or M (SD) *Range*	% or M (SD) *Range*	% or M (SD) *Range*
Age	19.93 (2.73) *16-25*	19.96 (2.59) *16-27*	21.17 (2.30) *17.25-25*	19.75 (2.48) *16-26*
Education	13.39 (2.52) *9-21*	13.02 (1.69) *11-16*	14.33 (1.78) *11-17*	13.04 (2.07) *10-18*
Gender* (% Female)	50%	24%	48%	28%
Race (% Caucasian)	71%	76%	74%	79%
Ethnicity (% Hispanic)	15%	12%	15%	15%
Left-Handed	n = 1	n = 1	n = 0	n = 1
Stroop – Color	.57 (.67) *-2.00-2.00*	.42 (.61) *-1.00-1.67*	.59 (.61) *-1.33-2.00*	.47 (.63) *-1.33-1.50*
Stroop – Word	.74 (.74) *-1.67-2.00*	.35 (.91) *-1.45-1.67*	.72 (.60) *-.67-1.67*	.59 (.92) *-2.33-2.18*
Stroop - Interference	.92 (.74) *-.67-2.33*	.90 (.82) *-1.07-2.22*	1.03 (.53) *-.33-1.67*	.91 (.80) *-2.00-3.48*

Notes: Demographic and normed Stroop performance by substance use group. Groups were not used for analyses, but to better approximate patterns of use and to establish appropriate covariates. M = mean, SD = standard deviation, *</=.05. **</=.01. ***</=.001

Table 4. CO and NO Group Demographic Information.

	No-CO n = 115	CO n = 68
	% or M (SD) *Range*	% or M (SD) *Range*
Age	20.19 (2.68) *16-25*	19.96 (2.54) *16-27*
Education	13.59 (2.38) *9-21*	12.99 (1.92) *10-18*
Gender (% Female)	47%	34%
Race (% Caucasian)	74%	71%
Ethnicity (% Hispanic)	12%	21%
Left-Handed	n = 2	n = 1
Stroop – Color	.58 (.62) *-2.00-2.00*	.41 (.69) *-1.33-2.00*
Stroop – Word	.69 (.72) *-1.67-2.00*	.50 (.90) *-2.33-2.18*
Stroop - Interference	.98 (.68) *-.67-2.33*	.81 (.83) *-2.00-2.48*

Notes: Demographic information by co-use and no-co-use groups. These groups were not use in any analyses, but were explored for qualitative purposes to better understand the use patterns of those who co-use compared to those who do not. M = mean, SD = standard deviation, *</=.05. **</=.01. ***</=.001.

Table 5. Past Month Substance Use by Substance Use Group.

	Controls n = 92	MJ n = 33	ALC n = 27	MJ+ALC n = 39
	M (SD) *Range*	M (SD) *Range*	M (SD) *Range*	M (SD) *Range*
Alcohol***	4.59 (5.47) *0-19.35*	7.12 (5.02) *0-17.16*	41.37 (21.85) *23.57-107.42*	50.88 (33.72) *21.43-167.14*
Cannabis***	.06 (.27) *0-1.94*	21.98 (29.77) *2.36-139.91*	.38 (.64) *0-1.94*	20.74 (18.19) *2.09-90.89*
Binge***	.28 (.60) *0-2.90*	.12 (.42) *0-1.94*	3.07 (3.34) *0-11.61*	3.85 (4.47) *0-15*
Co-Use***	.04 (.21) *0-1.07*	1.87 (2.22) *0-8.58*	.59 (1.03) *0-3.87*	7.26 (4.65) *0-17.16*
Co-Use-Binge***	.01 (.11) *0-1.07*	.44 (.94) *0-4.29*	.48 (.80) *0-2.90*	3.63 (4.56) *0-17.14*

Notes: Past month substance use by substance group in standardized units. Groups were not used for analyses, but to better approximate patterns of use and to establish appropriate covariates. Alcohol: Standard drinks; 1 ounce of liquor, 4 ounces of wine, 12 ounces of beer. Cannabis: grams. Co-Use: Co-occurring alcohol and cannabis, days of co-use. Binge: Number of binge drinking episodes; ≥4 drinks for females, ≥5 for males in one drinking occasion, not limited by hours. Co-Use-Binge: Co-occurring alcohol and cannabis, days of co-use-binge; binging defined as ≥4 drinks for females, ≥5 for males in one drinking occasion, not limited by hours. M = mean, SD = standard deviation, *</=.05. **</=.01. ***</=.001.

Table 6. CO and NO Group Past Month Substance Use Information.

	No-CO n = 115	CO n = 68
	M (SD) *Range*	M (SD) *Range*
Alcohol***	9.15 (12.30) *0-61.94*	37.21 (35.48) *.99-167.14*
Cannabis***	.98 (3.42) *0-20.74*	16.98 (22.40) *.08-139.91*
Binge***	.49 (1.13) *0-5.81*	2.99 (4.08) *0-15*
Co-Use***	0 (0) *0-0*	4.77 (4.32) *.97-17.16*
Co-Use-Binge***	0 (0) *0-0*	2.47 (3.72) *0-17.14*

Notes: Past month substance use by co-use and no-co-use groups in standardized units. These groups were not use in any analyses, but were explored for qualitative purposes to better understand the use patterns of those who co-use compared to those who do not. Alcohol: Standard drinks; 1 ounce of liquor, 4 ounces of wine, 12 ounces of beer. Cannabis: grams. Co-Use: Co-occurring alcohol and cannabis, days of co-use. Binge: Number of binge drinking episodes; ≥4 drinks for females, ≥5 for males in one drinking occasion, not limited by hours. Co-Use-Binge: Co-occurring alcohol and cannabis, days of co-use-binge; binging defined as ≥4 drinks for females, ≥5 for males in one drinking occasion, not limited by hours. M = mean, SD = standard deviation, *</=.05. **</=.01. ***</=.001.

Table 7. Correlations Between Substance Use Patterns.

Variables	1	2	3	4	5
1. Alcohol[a]	-				
2. Cannabis[b]	.30***	-			
3. Co-Use[c]	.60***	.54***	-		
4. Binge[d]	.82***	.14	.43***	-	
5. Co-Use-Binge[e]	.61***	.29***	.68***	.70***	-
M	19.68	8.33	1.77	1.36	.88
SD	26.75	18.14	3.50	2.85	2.51
Range	0-167.14	0-139.91	0-17.16	0-15	0-17.14

Notes: Correlations of substance use for all participants. Each variable is for past month substance use in standard units or episodes. [a]Past month number of standard alcohol drinks; [b]past month number of grams of cannabis used; [c]past month number of episodes using both alcohol and cannabis, regardless of amount used; [d]past month number of binge episodes (=/>4 standard drinks for females, =/>5 standard drinks for males, on one drinking occasion); [e]past month number of episodes using both binge-level alcohol and cannabis. M = mean, SD = standard deviation, *</=.05. **</=.01. ***</=.001.

Table 8. Demographics by Study Site.

	UWM n = 75	UCSD n = 59	McLean n = 58
	% or M (SD) *Range*	% or M (SD) *Range*	% or M (SD) *Range*
Age***	21.23 (2.53) 16-26	17.83 (.81) 16.25-19	20.83 (2.52) 16-27
Education***	14.34 (2.17) 9-21	11.20 (.76) 10-13	14.30 (1.70) 11-18
Gender (% Female)	47%	36%	40%
Race* (% Caucasian)	68%	68%	88%
Ethnicity ** (% Hispanic)	12%	27%	5%
Stroop – Color	.74 (.66) -2.00-2.00	.18 (.65) -1.33-1.00	.50 (.46) -.50-1.50
Stroop – Word	.86 (.74) -1.67-2.00	.36 (.81) -2.33-1.33	.54 (.80) -1.59-2.18
Stroop - Interference	1.06 (.67) -.67-2.00	.51 (.76) -2.00-2.00	1.08 (.68) -1.07-2.48

Notes: Demographics and normed Stroop performance by study site. M = mean, SD = standard deviation, *</=.05. **</=.01. ***</=.001

Table 9. Past Month Substance Use by Study Site.

	UWM n = 75	UCSD n = 59	McLean n = 58
	M (SD) *Range*	M (SD) *Range*	M (SD) *Range*
Length of Abstinence (Days)	29.38 (23.44) *5-197*	26.69 (2.63) *12-28*	--
Cannabis***	3.36 (8.17) *0-47.42*	6.70 (12.99) *0-60.54*	16.43 (27.23) *0-139.91*
Alcohol	19.29 (26.87) *0-132.58*	21.54 (32.82) *0-167.14*	18.26 (18.76) *0-98.67*
Binge	1.73 (2.96) *0-11.61*	2.20 (3.56) *0-15*	0 (0) *0-0*
Co-Use	1.14 (2.73) *0-15.48*	2.25 (3.95) *0-17.14*	2.17 (3.87) *0-17.16*
Co-Use-Binge	.44 (1.19) *0-5.81*	2.25 (3.95) *0-17.14*	0 (0) *0-0*

Notes: Past month substance use by study site. Alcohol: Standard drinks; 1 ounce of liquor, 4 ounces of wine, 12 ounces of beer. Cannabis: grams. Co-Use: Co-occurring alcohol and cannabis, days of co-use. Binge: Number of binge drinking episodes; ≥4 drinks for females, ≥5 for males in one drinking occasion, not limited by hours. Co-Use-Binge: Co-occurring alcohol and cannabis, days of co-use-binge; binging defined as ≥4 drinks for females, ≥5 for males in one drinking occasion, not limited by hours. M = mean, SD = standard deviation, *</=.05. **</=.01. ***</=.001

Table 10. Co-Use Data in FA

Tract	Variable	p	FDR-p
Forceps Major	--	-	-
Forceps Minor	Cannabis	.03*	.128
Left ILF	Cannabis	.017*	.128
Right ILF	--	-	-
Left Uncinate	Cannabis	.011*	.128
Right Uncinate	--	-	-
Left ATR	--	-	-
Right ATR	--	-	-
Left Cingulum Angular Bundle	--	-	-
Right Cingulum Angular Bundle	--	-	-
Left Cingulum Cingulate Gyrus	--	-	-
Right Cingulum Cingulate Gyrus	--	-	-
Left SLF Parietal	--	-	-
Right SLF Parietal	--	-	-
Left SLF Temporal	--	-	-
Right SLF Temporal	Cannabis	.030*	.128

Multiple regression FA results for co-use data with cannabis, alcohol, and co-use cannabis and alcohol days as primary variables; covarying for gender and study site. FDR-p = corrected for multiple comparisons. *p<.05

Table 11. Co-Use Data in MD.

Tract	Variable	p	FDR-p
Forceps Major	Cannabis	.031*	**.038***
Forceps Minor	--	-	**-**
Left ILF	Cannabis	.014*	**.028***
Right ILF	Cannabis	.008*	**.021***
Left Uncinate	--	-	-
Right Uncinate	Cannabis	.018*	**.028***
Left ATR	Cannabis	.010*	**.023***
Right ATR	Cannabis	.017*	**.028***
Left Cingulum Angular Bundle	Cannabis	.033*	**.038***
Right Cingulum Angular Bundle	Cannabis	.021*	**.028***
Left Cingulum Cingulate Gyrus	Cannabis	.006*	**.019***
Right Cingulum Cingulate Gyrus	Cannabis	.021*	**.028***
Left SLF Parietal	Cannabis	.005*	**.019***
Right SLF Parietal	Cannabis	.001*	**.008***
Left SLF Temporal	Cannabis	.003*	**.016***
Right SLF Temporal	Cannabis	.001*	**.008***

Multiple regression MD results for co-use data with cannabis, alcohol, and co-use cannabis and alcohol days as primary variables; covarying for gender and study site. FDR-p = corrected for multiple comparisons. *p<.05

Table 12. Co-Use-Binge Data in FA

Tract	Variable	p	FDR-p
Forceps Major	--	-	-
Forceps Minor	--	-	-
Left ILF	--	-	-
Right ILF	--	-	-
Left Uncinate	--	-	-
Right Uncinate	--	-	-
Left ATR	--	-	-
Right ATR	--	-	-
Left Cingulum Angular Bundle	--	-	-
Right Cingulum Angular Bundle	Cannabis	.015*	.240
Left Cingulum Cingulate Gyrus	--	-	-
Right Cingulum Cingulate Gyrus	--	-	-
Left SLF - Parietal	--	-	-
Right SLF - Parietal	--	-	-
Left SLF - Temporal	--	-	-
Right SLF - Temp	--	-	-

Multiple regression results for co-use data with cannabis, binge episodes, and co-use-binge cannabis and binge days as primary variables; covarying for education, length of abstinence, and study site. FDR-p = corrected for multiple comparisons. *p<.05

Table 13. Co-Use-Binge Data in MD

Tract	Variable	p	FDR-p
Forceps Major	--	-	-
Forceps Minor	--	-	-
Left ILF	Cannabis	.030*	.12
	Co-Use-Binge	.038*	.152
Right ILF	Cannabis	.044*	.12
	Co-Use-Binge	.02*	.152
Left Uncinate	--	-	-
Right Uncinate	--	-	-
Left ATR	--	-	-
Right ATR	Cannabis	.045*	.12
Left Cingulum Angular Bundle	--	-	-
Right Cingulum Angular Bundle	--	-	-
Left Cingulum Cingulate Gyrus	--	-	-
Right Cingulum Cingulate Gyrus	--	-	-
Left SLF - Parietal	--	-	-
Right SLF - Parietal	Cannabis	.012*	.069
Left SLF - Temporal	Cannabis	.013*	.069
	Co-Use-Binge	.036*	.152
Right SLF - Temp	Cannabis	.001*	**.016***
	Co-Use-Binge	.022*	.152

Multiple regression results for co-use data with cannabis, binge episodes, and co-use-binge cannabis and binge days as primary variables; covarying for education, length of abstinence, and study site. FDR-p = corrected for multiple comparisons. *p<.05

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Appendix: DTI values by Study Site

FA

Tract	UWM	McLean	UCSD
	M (SD) *Range*	M (SD) *Range*	M (SD) *Range*
Forceps Major	.508 (.028) *.441-.564*	.559 (.060) *.407-.670*	.541 (.070) *.354-.706*
Forceps Minor	.390 (.049) *.237-.539*	.447 (.056) *.337-.588*	.426 (.071) *.242-.533*
Left ILF	.452 (.024) *.387-.503*	.489 (.043) *.384-.624*	.428 (.037) *.228-.473*
Right ILF	.459 (.026) *.387-.522*	.497 (.041) *.405-.595*	.450 (.040) *.234-.519*
Left Uncinate	.367 (.021) *.320-.438*	.398 (.044) *.321-.525*	.345 (.053) *.198-.417*
Right Uncinate	.369 (.021) *.317-.418*	.392 (.039) *.317-.496*	.363 (.045) *.172-.430*
Left ATR	.377 (.019) *.337-.411*	.400 (.035) *.326-.486*	.398 (.023) *.335-.461*
Right ATR	.381 (.018) *.347-.427*	.369 (.035) *.308-.461*	.424 (.030) *.352-.501*
Left Cingulum Angular Bundle	.332 (.030) *.264-.420*	.283 (.050) *.197-.437*	.309 (.051) *.173-.404*
Right Cingulum Angular Bundle	.334 (.036) *.200-.438*	.279 (.050) *.175-.383*	.300 (.050) *.168-.396*
Left Cingulum Cingulate Gyrus	.546 (.055) .386-.646	.491 (.077) .331-.730	.519 (.039) *.444-.593*
Right Cingulum Cingulate Gyrus	.502 (.046) .382-.634	.463 (.068) .331-.618	.469 (.037) *.398-.551*
Left SLF Parietal	.419 (.029) *.350-.476*	.418 (.041) *.322-.506*	.400 (.039) *.228-.482*
Right SLF Parietal	.444 (.032) *.352-.530*	.411 (.044) *.321-.511*	.420 (.032) *.362-.498*
Left SLF Temporal	.436 (.025) *.380-.503*	.454 (.038) *.363-541*	.415 (.051) *.230-.488*
Right SLF Temporal	.437 (.028) *.363-.523*	.413 (.040) *.323-.515*	.426 (.038) *.253-.512*

MD

Tract	UWM	McLean	UCSD
	M (SD) *Range*	M (SD) *Range*	M (SD) *Range*
Forceps Major	.000823 (.000044) *.000742-.001060*	.000871 (.000079) *.000758-.001145*	.000634 (.000066) *.000552-.000887*
Forceps Minor	.000901 (.000087) *.000794-.001238*	.000864 (.000089) *.000756-.001183*	.000651 (.000053) *.000545-.000834*
Left ILF	.000811 (.000087) *.000748-.000886*	.000847 (.000051) *.000744-.000992*	.000617 (.0000386) *.000558-.000797*
Right ILF	.000814 (.000029) *.000750-.000900*	.000841 (.000044) *.000761-.000954*	.000614 (.000033) *.000552-.000724*
Left Uncinate	.000814 (.000030) *.000738-.000877*	.000867 (.000081) *.000747-.001083*	.000646 (.000043) *.000584-.000763*
Right Uncinate	.000812 (.000030) *.000758-.000881*	.000881 (.000080) *.000772-.001087*	.000635 (.000038) *.000588-.000815*
Left ATR	.000748 (.000027) *.000696-.000809*	.000843 (.000085) *.000717-.001148*	.000585 (.000028) *.000527-.000670*
Right ATR	.000755 (.000029) *.000706-.000831*	.000864 (.000088) *.000724-.001133*	.000584 (.000028) *.000529-.000670*
Left Cingulum Angular Bundle	.000825 (.000042) *.000703-.000905*	.000936 (.000115) *.000728-.001168*	.000661 (.000049) *.000596-.000891*
Right Cingulum Angular Bundle	.000823 (.000050) *.000721-.000970*	.000928 (.000115) *.000756-.001174*	.000664 (.000050) *.000593-.000867*
Left Cingulum Cingulate Gyrus	.000690 (.000038) *.000605-.00792*	.000863 (.000011) *.000676-.001093*	.000546 (.000028) *.000492-.000635*
Right Cingulum Cingulate Gyrus	.000682 (.000038) *.000575-.000779*	.000853 (.000103) *.000680-.001067*	.000556 (.000030) *.000502-.000642*
Left SLF Parietal	.000719 (.000026) *.000659-.000797*	.000816 (.000058) *.000721-.000947*	.000564 (.000031) *.000510-.000670*
Right SLF Parietal	.000726 (.000026) *.000683-.000797*	.000809 (.000054) *.000724-.000938*	.000556 (.000023) *.000514-.000617*
Left SLF Temporal	.000735 (.000026) *.000679-.000803*	.000809 (.000056) *.000718-.000958*	.000570 (.000038) *.000510-.000695*
Right SLF Temporal	.000734 (.000026) *.000685-.000820*	.000799 (.000047) *.000714-.000910*	.000561 (.000028) *.000511-.000663*

Curriculum Vitae

Natasha E. (Wright) Wade

EDUCATION

2017-Present **Psychology Intern**
VA Puget Sound American Lake, Tacoma, WA.
Rotations: (1) Mental Health Neuropsychology; (2) Geriatric Research, Education, and Clinical Care; (3) Residential Substance Treatment

2014-Present **Doctor of Philosophy, Psychology**
University of Wisconsin-Milwaukee, Milwaukee, WI.
Clinical Psychology Track, Emphasis in Neuropsychology
Advisor: Krista M. Lisdahl, Ph.D.

Dissertation: *Baked and buzzed: Investigating the influence of co-use of marijuana and alcohol use on white matter integrity in emerging adults*
Defended: August 3, 2017

2012-2014 **Master of Science, Psychology**
University of Wisconsin-Milwaukee, Milwaukee, WI.
Clinical Psychology Track

2008-2012 **Bachelor of Arts, Psychology and Philosophy-Theology**
Point Loma Nazarene University, San Diego, CA.

PUBLICATIONS (listed as Wright, N.E. or Wade, N.E.)

1. **Wade, N.E.**, Padula, C.B., Anthenelli, R., Nelson, E., Eliassen, J., & Lisdahl, K.M. (2017). Amygdala hyperactivity and blunted functional connectivity during a stress task in alcohol dependent individuals. *Neurobiology, 7,* 74-79.
2. **Wright, N.E.**, Scerpella, D., & Lisdahl, K.M. (2016). Marijuana use and gender are associated with behavioral approach, anxiety, and depressive symptoms in adolescents and emerging adults. *PLOSOne, 11(11)*, e0166005.
3. **Wright, N.E.**, Strong, J.A., GIlbart, E.R., Shollenbarger, S.G., & Lisdahl, K.M. (2015). *5-HTTLPR* genotype, gender, ecstasy, and cannabis use interact to predict memory in adolescent and emerging adults. *PLOSOne, 10(7)*, e0134708.
4. Lisdahl, K.M., **Wright, N.E.,** Kirchner-Media, C., Maple, K.E., & Shollenbarger, S. (2014). Considering cannabis: The impact of regular cannabis use on cognition, brain structure and function in adolescents and emerging adults. *Current Addictions Report, 1*, 144-156.

5. Lisdahl, K.M., Gilbart, E.R., **Wright, N.E.,** & Shollenbarger, S. (2013). Dare to delay?: The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure and function. Invited review for Special Topic issue *Brain Reward and Stress Systems in Addiction. Frontiers in Psychiatry, 4,* 53.

Under Review

6. **Wade, N.E.,** Thomas, A.M., Gruber, S.A., Tapert, S.F., Fillbey, F.M., & Lisdahl, K.M. (Under Review). Baked and buzzed: Investigating whether co-use of cannabis and alcohol relates to white matter integrity in emerging adults.

BOOK CHAPTERS

1. **Wright, N.E.,** Maple, K.E., & Lisdahl, K.M. (2017). Effects of cannabis use on neurocognition in adolescents and emerging adults. In V.R. Preedy (Eds.), The Handbook of Cannabis and Related Pathologies: Biology, Diagnosis, Treatment, and Pharmacology. Academic Press.
2. Maple, K.E., **Wright, N.E**., & Lisdahl, K.M. (2017). Effects of cannabis use on neurocognition in adolescents and emerging adults with psychiatric comorbidities. In V.R. Preedy (Eds.), The Handbook of Cannabis and Related Pathologies: Biology, Diagnosis, Treatment, and Pharmacology. Academic Press.

ORAL PRESENTATIONS (listed as Wright, N.E. or Wade, N.E.)

1. **Wade, N.E.**, Wallace, A.L., Swartz, A.M., & Lisdahl, K.M. (February, 2018). Aerobic Fitness and Marijuana Use interact to Predict Neuropsychological Functioning in Emerging Adults. Paper to be presented at the annual International Neuropsychological Society conference in Washington, D.C.
2. **Wright N.E.**, Padula, C.B., Maple, K.E., Anthenelli, R.M, Nelson, E.G., & Lisdahl, K.M. (June, 2014). *Alcohol dependence, gender, and cortisol response predict amygdala response pattern to fMRI stress task*. College on Problems of Drug Dependence, San Juan, Puerto Rico.
3. Shollenbarger, S., **Wright, N.E**., Lisdahl, K.M. (June, 2013). *FAAH genotype and MJ use interact to predict executive functioning in adolescents and emerging adults.* The College on Problems of Drug Dependence, San Diego, CA.
4. **Wright, N.E.** & Oakes Mueller, R. (April, 2012). *Predicting prosocial behavior: Disgust as an obstacle to service*. Western Psychological Association, San Francisco, CA.
5. **Wright, N.E.** & Oakes Mueller, R. (April, 2012). *The elicitors and effects of disgust: Exploring the reciprocal relationship of emotion and prosocial behavior*. Point Loma Nazarene University Honors Conference, San Diego, CA.

POSTER PRESENTATIONS (listed as Wright, N.E. or Wade, N.E.)

1. Wallace, A.L., **Wright, N.E.**, Gilbart, E.R., & Lisdahl, K.M. (June, 2017). ADHD symptoms and marijuana exposure predict sustained attention accuracy. Poster presented at the College on Problems of Drug Dependence in Montreal, Canada.
2. Gilbart, E.R., **Wright, N.E.**, Lisdahl, K.L. (February, 2017). Marijuana Use, Aerobic Fitness, Mood, and Disinhibition in Emerging Adults. Poster presented at the annual International Neuropsychological Society conference in New Orleans, LA.
3. **Wright, N.E.**, Kangsier, M.E., Vitucci, S., Gill, E., & Lisdahl, K.M. (June, 2016). Adolescent and young adult alcohol, marijuana, and gender effects on depression, anxiety, and apathy. Poster presented at the Research Society on Alcoholism conference in New Orleans, LA.
4. **Wright, N.E.,** Scerpella, D., & Lisdahl, K.M. (February, 2016). Young adult marijuana use and gender effects on frontolimbic function: Depression, anxiety, impulsivity, and executive dysfunction. Poster presented at the annual International Neuropsychological Society conference in Boston, MA.
5. **Wright, N.E.** & Lisdahl, K.M. (November, 2015). *The potential influence of 5-HTTLPR Genotype, Gender and Ecstasy use on Depressive Symptoms in Adolescent and Emerging Adults.* Poster presented at the Society for Neuroscience conference in Chicago, Illinois.
6. **Wright, N.E**., Padula, C.B., Anthenelli, R.M., Nelson, E., Eliassen, J., Lisdahl, K.M. (June, 2015). *Amygdala hyperactivity and functional connectivity during a stress task in alcohol dependent individuals*. Poster presented at the Research Society on Alcoholism, San Antonio, Texas.
7. Maple, K.E., **Wright, N.E.**, & Lisdahl, K.M. (June, 2014). *Marijuana use and FAAH genotype predict sleep quality in adolescent and emerging adults*. Poster presented at the College on Problems of Drug Dependence, San Juan, Puerto Rico.
8. **Wright, N.E**., Shollenbarger, S.G., & Lisdahl, K.M. (June, 2013). *5-HTTLPR genotype, gender and ecstasy use interact to predict verbal memory in adolescent and emerging adults.* Presented at The International Women's and Children's Health and Gender Group, San Diego, CA.
9. Shollenbarger, S., **Wright, N.E.**, Browning, E., Lisdahl, K. (August, 2013). *Executive functioning in adolescent and emerging adult poly-substance users.* Poster presented at The American Psychological Association, Honolulu, HI.
10. Higley, A.E., **Wright, N.E.**, Tibbs, J.J., Quello, S., & Mason, B.J. (June, 2012). *Stress and craving: Predicting alcohol treatment outcomes using a human laboratory paradigm of interpersonal stress induction*. Presented at Research Society on Alcoholism, San Francisco, CA.
11. **Wright, N.E.** & Oakes Mueller, R. (April, 2012). *The role of disgust in predicting prosocial behavior*. Presented at Western Psychological Association, San Francisco, CA.

INVITED TALKS

1. **Wright, N.E.** (2016, March). *Clinical Cannabinoid Gems for the Practitioner from Research Data*. Invited talk to the pre-doctoral Psychology Interns and the Mental Health Department at the Zablocki VA Medical Center, Milwaukee, WI.
2. **Wright, N.E**. (2015, March). *Marijuana, Brain Development, and the University*. Invited talk to the undergraduate students at Mount Vernon Nazarene University, Mount Vernon, OH.

RESEARCH EXPERIENCE

2012-Present **Graduate Research Assistant**, Brain Imaging and Neuropsychology (BraIN) Lab, University of Wisconsin-Milwaukee, P.I.: Krista Medina Lisdahl, Ph.D.

(1) Assist in running a three-week study of the effects of marijuana use on adolescent and emerging adult brain development, as well as the potential influence of factors such as gender, alcohol use, life stress, and exercise. Additional longitudinal effects at 2-year follow-up are also being assessed.
Funding Source: **R01 DA030354**, NIDA; P.I.: Lisdahl, K.M.

(2) Integrate neuropsychological and psychosocial data across five sites (University of Wisconsin-Milwaukee, University of California San Diego, University of New Mexico, University of Texas Dallas, and Harvard University) for use in the Imaging Data in Emerging Adults with Addiction (IDEAA) Consortium.
Funding Source: **R01DA030354-03S1**, NIDA; P.I.s: Lisdahl, K.M., Gruber, S., Tapert, S., &
Filbey, F.

(3) Help run baseline data collection at the University of Wisconsin-Milwaukee site in the Adolescent Brain and Cognitive Development (ABCD) study, a 10-year longitudinal study recruiting 11,500 kids at approximately 20 sites across the country.
Funding Source: **DA041025-01U01**, NIDA; P.I.: Lisdahl, K.M.

2014-2017 **Research Consultant,** MAPPS Project, University of Wisconsin-Milwaukee, P.I.: Davies, W. Hobey Davies, Ph.D.

Consult on a project assessing the feasibility of a behavioral intervention parents can use to prevent the initiation of alcohol use by adolescents.

2016-2017 **Research Assistant,** Atwater Standing Desks Project, University of Wisconsin-Milwaukee, P.I.: Ann Swartz, Ph.D.

Assisted in a year-long study of in a community elementary school to determine possible outcomes of standing desks compared to sitting desks on executive function, learning, attention, postural stability, and physical activity levels.

Funding Source: **SAFCO Products Company**

2011-2012 **Research Intern**, Laboratory of Clinical Psychopharmacology, Committee on the Neurobiology of Addictive Disorders, The Pearson Center for Alcoholism and Addiction Research, The Scripps Research Institute, P.I.: Barbara Mason, Ph.D.

Assisted in conduction of 12-week long clinical trial for alcohol dependence, including neuropsychological assessment and a cue- and stress-induced craving paradigm.

Funding Source: **MERIT Award for Medication Development**, National Institutes of Health; P.I.: Mason, B.J., Ph.D.

TEACHING EXPERIENCE

Instructor

2015-2016 PSYCH433 Neuropsychology, University of Wisconsin—Milwaukee

Teaching Assistant

2014-2015 Graduate Clinical Assessment Practicum, University of Wisconsin—Milwaukee
2013-2014 *Psychology of Women* (PSYCH320), University of Wisconsin—Milwaukee
2012 *Introduction to Psychology* (PSYCH101), U-Pace Online Course, University of Wisconsin—Milwaukee

Guest Lecturer

2016 PSYCH912 Developmental Psychopathology (Graduate Level). *Substance Use Disorders*. University of Wisconsin-Milwaukee
2016 CON770 Psychopathology. *Dissociative Disorders*. Mount Mary University
2014 PYC3500 Abnormal Psychology. *Substance Use Disorders*. Carthage College
2013 PYC3500 Abnormal Psychology. *Substance Use Disorders*. Carthage College
2012-2013 PSYCH433 Neuropsychology. *Neurological Disorders.* University of Wisconsin—Milwaukee
2011 PSY308 Development Psychology. *Brain Development and Neuroplasticity*. Point Loma Nazarene University
2011 PSY301 Physiological and Neuropsychology. *Brain Plasticity and Recovery.* Point Loma Nazarene University

CLINICAL TRAINING AND EXPERIENCE

2017-Present **Psychology Intern**, VA Puget Sound American Lake

- Complete three 4-month rotations over the course of the year: (1) Mental Health Neuropsychology, with a CBT-Insomnia intervention minor; (2)

Geriatric Research, Education, and Clinical Care (GRECC); (3) Residential Substance Treatment.

In Mental Health Neuropsychology, conducted full neuropsychological evaluations, from interview through feedback and report, across the lifespan and med-neuro and psych-neuro referrals. Additionally, co-lead a CBT for Insomnia group.

Additional rotations have not yet begun (GRECC: December 18-April 6; Residential Substance Treatment: April 8-July 27).

2016-2017 **Practicum Student**, Medical College of Wisconsin Pediatric Neuropsychology Department

- Completed outpatient neuropsychological assessments with children between the ages of 6 and 17, including intake interview, testing, report writing, and feedback sessions.

2014-2017 **Practicum Student**, Therapy Practicum in the UWM Psychology Clinic

- Practice evidence-based outpatient treatments for couple's therapy (Integrative Behavioral Couples Therapy) and children's anxiety disorders (Coping Cat) with members of the community.

2015-2016 **Practicum Student**, Milwaukee VA Neuropsychology Department

- Completed full neuropsychological assessments, with one to two cases seen and reports written per week. Conducted brief cognitive screenings in the Neurology Clinic and participated in rounds with the Neurology team.

2014-2015 **Peer Supervisor**, Peer Supervision of Assessments in the UWM Psychology Clinic

- Live supervised child and adult learning disability assessment sessions for second year clinical psychology graduate students. Supervised first year clinical psychology graduate student's, observing clinical interviews, assessments, and teaching them the common factors of therapy.

2013-2014 **Practicum Student**, Assessment Practicum in the UWM Psychology Clinic

- Conducted learning disability and psychodiagnostic assessments using a range of cognitive, achievement, and neuropsychological measures, as well as symptom and behavioral questionnaires. Completed clinical interviews, reports, and feedback sessions.

ACADEMIC AWARDS AND HONORS

2016-2017 Distinguished Dissertation Fellowship, a competitive merit-based award from the University of Wisconsin-Milwaukee Graduate School

2016 Research Society on Alcoholism Student Merit Award, for the 2016 RSA Conference, funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA)

2015-2016	Distinguished Graduate Student Fellowship, a competitive merit-based award from the University of Wisconsin-Milwaukee Graduate School
2015	Research Society on Alcoholism Student Merit Award, for the 2015 RSA Conference, funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA)
2013	Division 40 (Clinical Neuropsychology) Student Poster Award, from APA Division 40 at the 2013 APA conference
2012-2014	Chancellor's Award, recipient of merit-based award from the University of Wisconsin-Milwaukee Graduate School

PROFESSIONAL AFFILIATIONS AND ADDITIONAL EXPERIENCE

Intern Liaison	Training Committee, VA Puget Sound American Lake, 2017-Present
Reviewer	*PLOSOne* APA Graduate Students Science Committee for Basic Research Science Grants, 2013-2014
Student Rep.	Clinical Training Committee, University of Wisconsin—Milwaukee, 2013-2015
AFNI Bootcamp	Week-long special training in Analysis of Functional Images (AFNI) at the National Institutes of Health, 2013
Professional Affiliations	Member of Associate of Graduate Students in Neuropsychology, UWM, 2014-2017 Student Member, Society for Neuroscience, 2015-2016 Student Member, Research Society on Alcoholism, 2015-2016 Student Affiliate of APA, 2013-2015 Student Affiliate of APA Division 40 (Clinical Neuropsychology), 2013-2015