Longitudinal Change in Cognition and White Matter Integrity in Young Adult Cannabis Users

A DISSERTATION
SUBMITTED TO THE FACULTY OF
UNIVERSITY OF MINNESOTA
BY

Mary P. Becker

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

Adviser: Monica Luciana, Ph.D.

September 2015

Acknowledgements

I'd like to extend my sincere thanks to my research advisor and mentor, Monica Luciana, for her support and guidance throughout graduate school and this research project. She has been instrumental in my development as an independent researcher. I would also like to thank Paul Collins for his assistance with the technical descriptions included in Study 2, as well as for his advice, feedback, and valuable discussions regarding interpretation. Thank you to all of the past and present members of the Luciana Lab for their contributions to data collection and management. Thank you also to my friend and colleague Snežana Urošević, for her encouragement and our valuable discussions about research methods.

This work was supported by the National Institute on Drug Abuse under Grant R01DA017843 awarded to M. Luciana, by the National Institute on Alcohol Abuse and Alcoholism under Grant R01AA020033 awarded to M. Luciana, by BTRC P41 EB015894 and P30 NS076408 grants awarded to the University of Minnesota's Center for Magnetic Resonance Research, by the University of Minnesota's Center for Neurobehavioral Development Seed Grant awarded to M. (Petrosko) Becker, and by the Minnesota Supercomputing Institute.

Finally, thank you to the research participants who volunteered their time and made this project possible.

Dedication

This is dedicated to my husband, Robert Becker, who provided unfailing support and encouragement at all points along this journey. Please let your brother know that I finally finished that paper.

Abstract

Cross-sectional research indicates that cannabis use is associated with cognitive and neuroanatomical damage, particularly when used regularly during development. The timing of use-related impacts on cognition and brain structure remains unclear. This dissertation includes two studies to characterize the longitudinal (1) neurocognitive profile and (2) white matter microstructure of young adult cannabis users who initiated use during adolescence. Cannabis users were assessed on a comprehensive neurocognitive battery and Diffusion Tensor Imaging (DTI) protocol at baseline and at a 2-year follow-up. In Study 1, cannabis users had stable deficits in verbal learning and memory as well as planning ability, and a stable relative strength in processing speed at baseline and follow-up. Deficits in spatial working memory and motivated decision-making observed at baseline recovered to control-level performance at follow-up. Heavier and earlier use of cannabis during adolescence was associated with decline in verbal learning and memory performance over time. In Study 2, change in white matter microstructure between time points was observed. Cannabis users exhibited reduced white matter microstructure organization in the central and parietal regions of the superior longitudinal fasciculus, left superior frontal gyrus, corticospinal tract, right anterior thalamic radiation, and in the posterior cingulum; cannabis users demonstrated increased white matter microstructure in the left anterior corpus callosum and left thalamic white matter. The findings suggest that continued heavy cannabis use during adolescence and young adulthood disrupts ongoing development of white matter microstructure. White matter microstructure changes were generally unrelated to

cognitive performance, and future research is needed to clarify their functional significance. Potential mechanisms and implications of the findings are discussed.

Table of Contents

List of Tables

List of Figures

General Introduction

Cannabis is experiencing its moment in the spotlight in the United States. At the time of this writing, 23 states and the District of Columbia have legalized cannabis use for medical use, and 4 states have legalized cannabis for both medical and recreational use. Political, social, and legal debates about cannabis's legal status continue (Volkow, Baler, Compton, & Weiss, 2014), and ongoing changes to its legal status across the United States are likely.

In the context of its uncertain and changing legal status, cannabis has consistently been the most commonly used "illicit" substance in the United States (Substance Abuse and Mental Health Services Administration, 2014). Among high school juniors and seniors reporting no problems associated with substance use, 14% of students said they had used cannabis during their lifetime (Falck, Nahhas, Li, & Carlson, 2012). Among 12^{th} grade students, 6.5% report daily cannabis use (Johnston et al., 2013).

Along with the high prevalence of cannabis use, adolescents and young adults report decreased perceived risk and disapproval of cannabis use (Johnston, Bachman, & Schulenberg, 2012; Johnston et al., 2013; Substance Abuse and Mental Health Services Administration, 2014). Historically, attitude change toward cannabis use has coincided with increased prevalence of use (Johnston et al., 2012). Higher levels of cannabis use in adolescents and young adults are associated with individuals' approval of cannabis use as well as the perception of approval among one's peers and parents (LaBrie, Hummer, & Lac, 2011; Wu, Swartz, Brady, & Hoyle, 2015). Medical and recreational cannabis laws are potential factors causing decreased perception of risk, which contributes to an

increase in cannabis use. Decreased perception of risk (Schuermeyer et al., 2014; Wall et al., 2011) and increased cannabis use (Cerdá, Wall, Keyes, Galea, & Hasin, 2012; Harper, Strumpf, & Kaufman, 2012) have been found in states with medical cannabis laws. However, establishing a causal link between newly enacted laws and shifts in perception and use requires further research (Wall et al., 2012).

Given attitude changes, changes in the legal status of cannabis, and cannabis's continued popularity, cannabis use among young people is likely to be an important and enduring public health concern. A growing body of research is dedicated to understanding possible long-term consequences of cannabis use during adolescence and young adulthood (Volkow, Baler, et al., 2014). Adolescence and young adulthood have been targeted because they are important periods of maturation and change in the brain, with reorganization of cortical connections, corticolimbic interactions, and neurotransmitter systems (Colby, Van Horn, & Sowell, 2011; Gogtay & Thompson, 2010; Gogtay et al., 2004; O'Hare & Sowell, 2008; Rice & Barone, 2000). Chronic cannabis use during adolescence has the potential to alter brain structure and function as well as cognitive performance through disruption of the endogenous cannabinoid system that is widely distributed throughout the brain.

The endocannabinoid system plays an important role in prenatal central nervous system development (Galve-Roperh, Palazuelos, Aguado, & Guzmán, 2009) and cortical development during adolescence, with peak endocannabinoid receptor expression and binding capacity in the striatum, limbic system, and ventral midbrain noted during adolescence (Rodriguez de Fonseca, Ramos, Bonnin, & Fernández-Ruiz, 1993). Cannabis

acts directly on the brain by binding to receptors in the endocannabinoid system. The endocannabinoid system broadly regulates synaptic transmission by inhibiting neurotransmitter release at axon terminals (Howlett et al., 2002; Szabo & Schlicker, 2005), causing both excitatory and inhibitory downstream effects relative to the function of the inhibited neurotransmitter (i.e., glutamate, GABA, dopamine, serotonin, acetylcholine; Freund, Katona, & Piomelli, 2003). The endocannabinoid system plays a large role in synaptic plasticity by promoting or inhibiting neurotransmission across a wide range of brain regions (Heifets & Castillo, 2009; Trezza et al., 2012), and altering its function during important windows of neural development could result in long-lasting changes in brain structure and function.

Endocannabinoid receptors are broadly distributed throughout the brain, in the prefrontal cortex, hippocampus, basal ganglia, thalamus, hypothalamus, and cerebellum (Freund et al., 2003; Herkenham et al., 1990; Viveros, Llorente, Moreno, & Marco, 2005). These regions contribute to a variety of cognitive functions, including behavioral inhibition, learning and memory, attention, planning, self-monitoring, decision-making, motor processes, as well as appetite and sleep regulation (Lezak, Howieson, & Loring, 2004; Spear, 2000; Viveros et al., 2005). Chronic cannabis use disrupts the endocannabinoid system through downregulation of endocannabinoid receptors in cortical brain regions (Hirvonen et al., 2012), and altering endocannabinoid-mediated synaptic transmission (Heifets & Castillo, 2009). Disruption of the endocannabinoid system during adolescence, as opposed to adulthood, is associated with long-term changes in brain structure, neurochemical signaling, and cognitive performance, both in

animal models (e.g., Bambico, Nguyen, Katz, & Gobbi, 2010; Gleason, Birnbaum, Shukla, & Ghose, 2012; Pistis et al., 2004; Raver, Haughwout, & Keller, 2013; Rubino et al., 2009; Schneider & Koch, 2003, 2007; Schneider, Schömig, & Leweke, 2008; Stopponi et al., 2014) and in humans (e.g., Battisti et al., 2010; Ehrenreich et al., 1999; Fontes et al., 2011; Lisdahl, Gilbart, Wright, & Shollenbarger, 2013; Meier et al., 2012; Pope et al., 2003; Solowij et al., 2012; Wagner, Becker, Gouzoulis-Mayfrank, & Daumann, 2010). The purported effects of endocannabinoid system disruption during adolescence and young adulthood include long-term changes in serotonin (Bambico et al., 2010; Best & Regehr, 2008) and dopamine (Kowal, Colzato, & Hommel, 2011; Pistis et al., 2004; Schneider & Koch, 2003) signaling, as well as changes in emotionality (Schneider & Koch, 2003; Trezza et al., 2012), IQ (Meier et al., 2012; Pope et al., 2003), memory and learning (Cha, White, Kuhn, Wilson, & Swartzwelder, 2006; Jager & Ramsey, 2008; Quinn et al., 2008; Realini, Rubino, & Parolaro, 2009; Schneider & Koch, 2003, 2007; Wagner et al., 2010), inhibitory control (Realini et al., 2009; Schneider & Koch, 2003), and executive functioning (Battisti, Roodenrys, Johnstone, Pesa, et al., 2010; Fontes et al., 2011; Solowij et al., 2012). Neuroplastic changes resulting from chronic cannabis use initiated in adolescence could drive long-term structural and functional organization of the brain in adulthood, affecting cognition, emotional functioning, and behavioral regulation beyond the period of acute intoxication.

The aims of this dissertation are to characterize the neurocognitive and neuroanatomical profiles associated with sustained cannabis use during adolescence and young adulthood. Two studies are presented. Study 1 characterizes the baseline profile

and longitudinal changes in neurocognitive functioning within a cohort of adolescent-onset cannabis users assessed at two time points during early adulthood. Study 2 characterizes the baseline profile and longitudinal changes in measures of brain white matter microstructure within this same group of cannabis users, and then explores associations between the neurocognitive and neuroanatomical profiles and longitudinal change within cannabis users.

By examining both cognitive performance and brain structure, the scientific community can reach a greater understanding about the cognitive and neurobiological vulnerabilities associated with adolescent-onset and young adult cannabis use. Consensus in the scientific community can help to inform the public debate about the legality of cannabis use, and more clearly define the actual risks associated with use.

1 Study 1: Longitudinal Neurocognitive Profile of Young Adult Cannabis Users

Cannabis use during adolescence and young adulthood is associated with disruptions in select cognitive domains outside of the time period of acute intoxication. Defining a cognitive profile among cannabis users outside of the period of acute intoxication, while still in the context of regular use, approximates how regular cannabis use impacts day-to-day cognitive function. The majority of research with adolescent and young adult cannabis users has employed cross-sectional research methods to assess regular cannabis users outside of the period of acute intoxication to characterize the relative strengths and weaknesses associated with regular cannabis use. An overview of this literature by cognitive domain is provided below. Fewer studies have used longitudinal methods, and a summary of this more limited literature is also provided.

Attention. Attention is a cognitive ability that underpins many skills, including various aspects of executive functioning, learning and memory, and processing speed. Attention is a complicated construct, but can be succinctly described as a process that relates to one's ability to perceive salient information in the environment, allocate attentional resources, and respond to the environment and feedback appropriately (Anderson, Laurent, & Yantis, 2011; Desimone & Duncan, 1995). Adolescent and young adult cannabis users have demonstrated poorer sustained attention and reduced accuracy during sustained attention conditions (Dougherty et al., 2013; Jacobsen, Mencl, Westerveld, & Pugh, 2004) compared to controls. Slowed reaction times on measures of sustained attention and mental tracking have been noted among earlier-onset cannabis

users (15-16 years old; Ehrenreich et al., 1999; Fontes et al., 2011), young adult cannabis users (Lisdahl & Price, 2012), and young adults with greater cannabis use (Bolla, Brown, Eldreth, Tate, & Cadet, 2002). Slowed reaction times during sustained attention tasks may represent deficits in processing speed or may reflect participants' greater efforts to maintain performance at high levels of accuracy.

Diminished performance on attentional tasks persists into periods of abstinence as well. After one month of abstinence, decreased attentional accuracy was assocated with increased cannabis use in young adult cannabis users (Bolla et al., 2002). However, the findings are equivocal when it comes to longer periods of abstinence. Reduced sustained attention accuracy has been noted in adolescent cannabis users compared to controls after three months of abstinence (Hanson et al., 2010), while no deficits were observed in another study among a different cohort of cannabis users after at least three months of abstinence (Fried, Watkinson, & Gray, 2005).

Processing speed. The domain of processing speed has considerable overlap with attentional ability. For the purposes of this overview, processing speed refers to quick mental manipulation and recruitment of effective strategies during task performance. Measures that are thought to reflect processing speed, at least in part, include sequencing tasks (e.g., Trail Making Test) and coding tasks (e.g., Digit Symbol Coding). This domain has also been termed "complex attention" by Tapert and colleagues (Hanson et al., 2010; Lisdahl & Price, 2012; Medina et al., 2007; Tapert, Granholm, Leedy, & Brown, 2002).

In the context of regular cannabis use, current users demonstrate slowed processing speed performance relative to controls (Fried et al., 2005), and greater slowing associated with greater cannabis use (Bolla et al., 2002; Lisdahl & Price, 2012; Medina et al., 2007). A longitudinal study that followed adolescents with substance use disorders over 8 years noted that greater cannabis use during the follow-up period was associated with poorer complex attention/processing speed performance at follow-up (Tapert et al., 2002). Evidence indicates that cannabis users demonstrate slowed and relatively less accurate processing speed performance during early abstinence periods of one week (Lisdahl & Price, 2012) and one month (Medina et al., 2007), but that these relative impairments are no longer evident after three months of abstinence (Fried et al., 2005).

Executive functioning. Executive functioning encompasses a range of cognitive abilities and skills, including cognitive inhibition, cognitive flexibility, verbal fluency, decision-making, planning, and self-organization.

Cognitive Inhibition. Cognitive inhibition refers to the capacity to rapidly inhibit prepotent or initiated responses when required to by the environment or a particular task's demands. Cognitive inhibition performance has been noted to be relatively impaired in cannabis using adolescents (Lisdahl & Price, 2012), young adults (Bolla et al., 2002; Gruber, Sagar, Dahlgren, Racine, & Lukas, 2012), young adult males (Pope & Yurgelun-Todd, 1996) and early-onset users (Battisti, Roodenrys, Johnstone, Pesa, et al., 2010; Fontes et al., 2011; Gruber, Sagar, et al., 2012). While many studies report cognitive inhibition impairment among cannabis users, other studies have failed to find

the relationship (J. E. Grant, Chamberlain, Schreiber, & Odlaug, 2012; Pope et al., 2003; Takagi, Lubman, et al., 2011).

Cognitive Flexibility. This cognitive domain refers to one's ability to flexibly shift between different cognitive sets and adapt performance based on feedback from the environment or changing task goals (e.g., Wisconsin Card Sort Test: WCST; Lezak et al., 2004). In the context of regular use, cannabis users demonstrate poorer overall set-shifting performance (Bolla et al., 2002; Gruber et al., 2012; Pope & Yurgelun-Todd, 1996). Cannabis users demonstrate a greater tendency to perseverate (Lane, Cherek, Tcheremissine, Steinberg, & Sharon, 2007; Pope & Yurgelun-Todd, 1996) and make more errors (Dougherty et al., 2013; Lane et al., 2007) in their test-taking approach. As has been described in other domains, early-onset use is associated with worse performance (Fontes et al., 2011; Gruber, Sagar, et al., 2012). However, no impairments in WCST performance were noted in adult early-onset users after 1 month of abstinence (Pope et al., 2003), suggesting that cognitive flexibility can recover after prolonged abstinence in early-onset user cannabis users, but is impaired in the context of regular use.

Verbal Fluency. Performance on measures of fluency, the ability to employ effective strategies to quickly generate words according to task rules, indicates that cannabis users typically do not show alterations (Lisdahl & Price, 2012; Pope et al., 2003). However, users may demonstrate impaired verbal fluency in the context of lower IQ estimates (Pope & Yurgelun-Todd, 1996).

Decision-Making. A variety of task paradigms measure different aspects of decision-making. This overview focuses on reward-related decision-making in the context of unknown contingencies that are learned from feedback on prior selections (e.g., Iowa Gambling Task, IGT; Bechara et al., 2001), reward-related decision-making with unknown outcomes (e.g., Cambridge Gambling Task, CGT; J. E. Grant et al., 2012), and impulsive decision-making (e.g., Two Choice Impulsivity Paradigm, TCIP, Information Sampling Test, IST; Dougherty et al., 2013; Solowij et al., 2012).

Decision-making has not been extensively assessed in adolescent and young adult cannabis users. Among adult cannabis users, poorer IGT decision-making performance is observed after both acute use and extended periods of abstinence (Bolla et al., 2002; Ernst et al., 2003; Verdejo-García, Rivas-Pérez, Vilar-López, & Pérez-García, 2007; Whitlow et al., 2004). In younger cannabis users, some evidence indicates that cannabis users are more prone to risky choices associated with greater likelihood of punishment on the CGT (J. E. Grant et al., 2012). However, other studies have not reported this pattern of findings with IGT performance (Dougherty et al., 2013; Gonzalez et al., 2012). While group differences are not always observed, poorer task performance on the IGT has been associated with increased cannabis substance use disorder symptoms (Gonzalez et al., 2012) and cannabis-related problems (Gonzalez, Schuster, Mermelstein, & Diviak, 2015). Findings among cannabis users reflect the decision-making deficits reported among other substance using populations (Fernández-Serrano, Pérez-García, & Verdejo-García, 2011; Goudriaan, Grekin, & Sher, 2007; Hanson, Luciana, & Sullwold, 2008; Verdejo-García, Rivas-Pérez, et al., 2007; Verdejo-García, Benbrook, et al., 2007).

Studies to dismantle the psychological processes underlying decision-making on the IGT, which includes a component of learning about reward contingencies from feedback about earlier choices, have indicated that adult cannabis users allocate more attention to gains and recent outcomes (Yechiam, Busemeyer, Stout, & Bechara, 2005) and demonstrate less consistency and are less sensitive to losses (Fridberg et al., 2010). Reliance on recent and salient reward information can contribute to poorer overall decision-making strategies on tasks where a more conservative strategy is advantageous. This hypothesis is supported by cannabis users' performance on tasks assessing impulsive decision-making. When given the choice between receiving smaller rewards after a 5-second wait or larger rewards after a 15-second wait, adolescent cannabis users exhibit preference for shorter reward delays over longer delay intervals (Dougherty et al., 2013). Cannabis users demonstrate faster and more impulsive decision-making relative to controls, a pattern of responding associated with poorer task performance overall (Clark, Roiser, Robbins, & Sahakian, 2009; Solowij et al., 2012). Longer duration of cannabis use and earlier age of cannabis use onset is associated with more impulsive decision-making (Solowij et al., 2012).

Planning and self-organization. Measures of planning and self-organization assess one's ability to develop effective strategies and to execute plans to accomplish a set goal (Fernández-Serrano et al., 2011; Luciana, Collins, Olson, & Schissel, 2009). This domain can be assessed with more traditional measures of planning, including Tower of London-like tasks that measure immediate planning ability, or with measures of prospective memory, assessing future planning ability. Few studies have investigated

immediate planning ability among cannabis users. Diminished planning on the Tower of London (TOL) has been observed among acutely intoxicated cannabis users (McClure, Stitzer, & Vandrey, 2012; Ramaekers et al., 2006), as well as non-acutely high current users (Epstein & Kumra, 2015; J. E. Grant et al., 2012). After a month of abstinence, however, planning performance was equivalent to that of controls (Medina et al., 2007).

Prospective memory refers to the memory processes employed in everyday contexts to remember to perform future actions or intentions (e.g., remembering to run errands after work; Bartholomew, Holroyd, & Heffernan, 2010; McHale & Hunt, 2008). Cannabis users demonstrate poorer prospective memory when compared to controls on measures of event-based prospective memory (i.e., when asked to complete a task after a specific event happens; Bartholomew et al., 2010; McHale & Hunt, 2008), and time-based prospective memory (i.e., when asked to remember to complete a task at a certain time; McHale & Hunt, 2008; Montgomery et al., 2012).

Spatial working memory. The short-term storage and manipulation of on-line visuospatial information is an important component of establishing new learning and memory (Jonides et al., 2008). No deficits have been noted among cannabis users, as compared to controls, on a spatial span test (Harvey, Sellman, Porter, & Frampton, 2007) or a visual n-back task (Ehrenreich et al., 1999). However, on a more complex spatial working memory task (CANTAB spatial working memory test), which requires individuals to search for tokens that are hidden within an array of boxes without returning to previously visited boxes, current regular cannabis users demonstrated poorer

performance than non-regular users (Harvey et al., 2007). Regular cannabis users have demonstrated poorer organization and less consistency than non-regular users.

Spatial memory. Visuospatial memory refers to the recall and reproduction of visual information after the information is off-line and not actively rehearsed in working memory. This is assessed after a delay period during which the information is consolidated then recalled from memory. One study with male young adult heavy cannabis users found that users demonstrated poorer delayed visuospatial memory relative to males who used less cannabis (Pope & Yurgelun-Todd, 1996). However, several studies have found no differences between cannabis users and controls on measures of visuospatial memory (Bolla et al., 2002; Macher & Earleywine, 2012; Mahmood, Jacobus, Bava, Scarlett, & Tapert, 2010; McHale & Hunt, 2008; Medina et al., 2007; Pope et al., 2003).

Verbal working memory. Verbal working memory is the verbal analog of spatial working memory, referring to the maintenance and manipulation of on-line information. This ability is commonly assessed by measuring the number of bits of information a person can hold in mind and repeat back (digits, letters). Limited evidence supports a disruption in verbal working memory processes in young adult cannabis users (Hanson et al., 2010; Medina et al., 2007), with the majority of evidence finding no disruption in cannabis using samples (Cuttler et al., 2012; Fried et al., 2005; Macher & Earleywine, 2012; Pope & Yurgelun-Todd, 1996).

Verbal memory. Verbal memory refers to the recall and recognition of previously presented verbal information after the information is not actively rehearsed

(Lezak et al., 2004). Research in cannabis users has commonly used list-learning measures to assess verbal learning and memory. These tests consist of a list of target words that are read to participants multiple times during a learning stage of testing. Recall of the target words is measured immediately after the participant recalls a distractor list of words as well as after a time delay, typically 20-30 minutes after the learning stage.

Performance during the learning/encoding stage has been reported to be impaired in cannabis-using adolescents (Harvey et al., 2007) and young adults (Gonzalez et al., 2012; Hanson et al., 2010; Pope & Yurgelun-Todd, 1996; Solowij et al., 2011). Harvey et al. (2007) found that greater cannabis use predicting worse performance on the learning trials of regular cannabis users. Many studies have reported that after a time delay, cannabis users demonstrate poorer performance under different abstinence conditions, including short-term abstinence (Cuttler et al., 2012; Gonzalez et al., 2012; Hanson et al., 2010; Pope & Yurgelun-Todd, 1996; Solowij, Jones, et al., 2011; Takagi, Yücel, et al., 2011), and periods of abstinence of at least 28 days (Bolla et al., 2002; Hanson et al., 2010). Learning deficits exhibited by users are subtle, with users typically producing 1-2 fewer words than controls. Similar to the findings with list learning, cannabis users demonstrate impairments in story learning and memory tasks after at least 3 weeks of abstinence (Medina et al., 2007; Schwartz, Gruenewald, Klitzner, & Fedio, 1989).

While this is a relatively robust finding in the literature, not all studies have reported deficits in list learning associated with cannabis use (Bava, Jacobus, Mahmood, Yang, & Tapert, 2010; Lisdahl & Price, 2012; Pope et al., 2003; Schwartz et al., 1989).

Further, motivation to perform well appears to play an important role in overall task performance within cannabis users but not controls, with increased motivation ameliorating performance deficits among cannabis users (Macher & Earleywine, 2012). A meta-analysis examining the cognitive effects of cannabis use specifically addressed these conflicting cognitive findings with respect to adult cannabis users (Grant et al., 2003). A reliable negative effect was observed in the domains of verbal learning, recognition, and recall among cannabis users (Cohen's d = -.21).

Poorer list-learning performance has been associated with a variety of cannabis use characteristics among users (Wagner et al., 2010). Poorer performance on learning trials was associated with higher lifetime doses of cannabis and longer durations of regular use. Performance on memory trials was associated with frequency of use, lifetime dose, and duration of use. Associations between cannabis use and performance, and the consistency of performance deficits noted, provide compelling evidence for disruptions in verbal memory in adolescent and young adult cannabis users.

Longitudinal Findings

Longitudinal methods have been less commonly used to examine the cognitive correlates of cannabis use. To determine if cognitive deficits persist into periods of abstinence, researchers have assessed cannabis users after up to 3 months of abstinence (Fried et al., 2005; Hanson et al., 2010; Medina et al., 2007). Only three longitudinal studies have assessed cannabis users at more than one time point over a period of years (Jacobus, Squeglia, Sorg, Nguyen-Louie, & Tapert, 2014; Meier et al., 2012; Tait, Mackinnon, & Christensen, 2011), and Meier et al. (2012) is the only study to

prospectively assess cannabis users prior to initiation of use. Given the limitations in the literature, the causal role of cannabis use in the development of cognitive deficits remains unclear. Prospective studies are needed to better approximate causal effects.

The only longitudinal study to assess cannabis users prior to initiation of cannabis use included participants from the Dunedin Multidisciplinary Health and Development Study, a birth cohort of 1,037 participants, who were assessed over 38 years on a range of health and cognitive measures (Meier et al., 2012). Participants completed IQ assessment prior to cannabis initiation for the majority of cannabis using subjects. At age 38, participants were re-assessed on measures of IQ, and also tested on measures of verbal learning and memory, sustained and divided attention, and processing speed. Participants who did not use cannabis demonstrated stable IQ estimates throughout their lives while those who developed cannabis dependence at any point prior to age 38 demonstrated a decrease in IQ by about 6 points. Similarly, participants who used cannabis regularly (at least 4 days per week) demonstrated IQ declines as well. Those who initiated cannabis use prior to age 18 demonstrated an apparently greater IQ decline than those who initiated use later in life (Meier et al., 2012). Furthermore, among early-onset former persistent cannabis users, reduction in cannabis use in the year prior to testing had no effect on the IQ decrease. In contrast, adult-onset persistent cannabis users demonstrated no IQ decline regardless of current use patterns. Thus, age of cannabis use onset primarily accounted for the IQ decline among cannabis dependent participants. Broader neuropsychological performance was not explored in relation to age of initiation. This

study is the strongest evidence to date that use initiated during adolescence is associated long-term cognitive decline.

Two other longitudinal studies assessed cannabis users after participants had already initiated use (Jacobus et al., 2015; Tait et al., 2011). Tait et al. (2011) followed a young adult cohort of cannabis users, aged 20-24 at baseline, at 4-year intervals for two follow-up assessments of verbal learning and memory, associative memory, working memory, and processing speed. Reported amount of cannabis use at baseline varied between abstinence and regular use. Cannabis users with different trajectories of use differed in their immediate free recall skills, with persistent heavy users (at least weekly use) demonstrating poorer immediate recall while former heavy and former light users demonstrated task performance equivalent to that of controls. There was also a trend for current light users (~monthly use) to demonstrate diminished immediate recall compared to former light users. Cannabis user and non-user groups' task performance was equivalent on other cognitive measures of associative memory, working memory, and processing speed. These results indicate that verbal memory is a select cognitive domain that is diminished in the context of regular use, but that performance in young adulthood may be improved after prolonged abstinence.

The second longitudinal study to assess users after initiation followed 16-19 year old adolescent alcohol+cannabis users over a follow-up interval of 3 years (Jacobus, Squeglia, Bava, & Tapert, 2013; Jacobus et al., 2015). Participants were assessed at 1.5-year intervals for 3 time points (i.e., assessment at baseline, 18 months, 3 years). Global neuropsychological performance, which was a calculated as a composite score of

attention, processing speed, verbal memory, visuospatial function, and executive function measures, was equivalent between the alcohol+cannabis users and non-substance using controls. Global neuropsychological performance was lower among alcohol+cannabis participants, relative to participants who only used alcohol, at the second assessment, but the group difference no longer remained at the third assessment (Jacobus, Squeglia, Bava, et al., 2013). A follow-up analysis explored performance differences between groups across the separate tasks that composed the global neuropsychological composite. Alcohol+cannabis users demonstrated poorer performance relative to controls in the domains of processing speed/complex attention, verbal working memory, verbal learning, verbal memory, and visuospatial functioning at the 1.5 year follow-up (Jacobus et al., 2015), though only deficits in verbal working memory, verbal learning, and verbal memory were noted at the 3-year follow-up assessment. Verbal working memory and memory deficits were noted at all 3 assessments, with only verbal learning emerging as an area of weakness over time. Of note, earlier age of cannabis use onset was associated with worsened performance on measures of processing speed and sequencing at the 3-year follow-up assessment.

Summary

In sum, adolescent and young adult cannabis users demonstrate impairment across a range of cognitive domains within cross-sectional studies. Subtle deficits in the domains of attention, processing speed, various aspects of executive functioning, and verbal memory are most consistently associated with cannabis use. Across cognitive domains, early age of cannabis use initiation is associated with poorer task performance.

The relationship between cannabis use and impairments in cognitive control, visuospatial memory, and verbal working memory is not a robust finding among adolescent and young adult cannabis users.

Few longitudinal studies have examined neurocognitive performance of cannabis users over time. Only one study to date has prospectively assessed cannabis users prior to cannabis use initiation (Meier et al., 2012). Global neuropsychological impairment among adult persistent cannabis users and IQ decline was associated with both persistent cannabis use as well as younger age of cannabis use initiation. This compelling research points to deficits by the age of 38, but does not address whether impairments are detectable at an earlier age. Two other longitudinal studies suggest subtle but detectable impairments evidenced at an earlier age in the domains of working memory and verbal memory, while other domains of cognitive function are spared (Jacobus et al., 2015; Tait et al., 2011). Cessation of use appears to be associated with recovery of cognitive performance among young adult users but not adult users (Meier et al., 2012). This may represent greater cognitive resilience among younger users, which becomes less robust as cannabis users age.

The present study builds on the limited longitudinal research within cannabis users to examine the association between cannabis use and cognition over time in order to clarify how use over time may influence cognitive performance. A sample of chronic daily adolescent-onset cannabis users was assessed on a comprehensive neuropsychological battery and their performance was compared to that of non-using controls. It should be stated at the outset that an interpretive difficulty is introduced by

the fact that the cannabis users were not substance naïve at baseline. The following hypotheses are examined:

1.1 Hypotheses

Baseline

It was predicted that cannabis users would exhibit diminished performance on measures of attention, processing speed, executive functioning, and verbal memory relative to non-cannabis using controls.

Follow-up

Cannabis users were expected to continue to exhibit the same deficits evident at baseline. Because cannabis use patterns were not expected to stay uniform within the cannabis user sample, it was predicted that those who continued to use cannabis most heavily and/or frequently would demonstrate greater cognitive deficits relative to those who decreased use during the follow-up interval. An earlier age of cannabis use initiation was expected to be associated with diminished cognitive performance at baseline and over time.

1.2 Methods

1.2.1 Sample

Forty cannabis users, ages 19-20, were initially recruited into this longitudinal study. Initial cannabis use onset was required to be prior to age 17 given that adolescent onset of use has been associated with greater functional impairments (Ehrenreich et al., 1999; Fontes et al., 2011; Gruber, Dahlgren, Sagar, Gönenç, & Lukas, 2014; Lisdahl et al.,

2013). Inclusion criteria specified that cannabis users reported using at least 5x/week. Two cannabis users reported use at a lower frequency (3-4x/week) and were allowed in the recruited sample by error. To maximize sample size, all participants in the recruited sample were included in the current analyses, with 90% of users reporting using 5+ times per week. Cannabis users were excluded if they reported daily cigarette use, or if alcohol use was reported to exceed 4 drinks for females and 5 drinks for males on more than 2 occasions per week. The current sample is a minor expansion of the cannabis user sample reported previously (Becker, Collins, & Luciana, 2014), including 1 cannabis user who met criteria for alcohol dependence. Alcohol use was examined in relation to cognitive performance for all participants.

Thirty-five non-drug using control participants were selected from a larger longitudinal study exploring adolescent brain development. At initial study recruitment, controls were excluded if they met current or past Axis I DSM-IV-TR (American Psychiatric Association, 2000) criteria for any psychiatric disorder. Therefore, additional exclusion criteria were applied. Controls were also excluded if they reported cannabis use more than once monthly, and/or if they endorsed any other illicit substance use.

General inclusion criteria for all participants included being a native English speaker, right-handed, with normal/corrected-to-normal vision and hearing. Exclusion criteria included any contraindicates to MRI scanning, any reported history of neurological problems or head injury, intellectual disability, or current pregnancy. All participants were recruited through university advertisements, and all were monetarily

compensated. Participants provided informed consent. The University of Minnesota's Institutional Review Board approved the protocol.

Of the 40 cannabis users initially screened for the study, 2 were excluded because their reported cannabis use was less than an average of 3x/week for the prior year. One cannabis user was excluded because of a reported history of seizures. Thirty-seven cannabis users completed the baseline assessment following screening. One cannabis user was excluded from the final sample due to missing data (see below). Table 1 reports sample characteristics for the cannabis user (n = 36) and control (n = 35) samples.

At baseline, cannabis user and control samples were matched for age, IQ, and demographic background. Because of sample inclusion requirements, controls exhibited no psychopathology at study initiation. Cannabis users exhibited minimal psychopathology outside of substance use disorders (Table 2). Within substance use disorders, cannabis users exhibited more symptoms related to problematic cannabis use than problematic alcohol use (Table 3), and self-reported substance use patterns indicate that cannabis was the primary drug used within the cannabis users (Table 4).

Of the 72 participants who initially participated in the study, 58 participants (27 cannabis users and 31 controls) returned for a two-year follow-up assessment. The retention rate of 80% for the follow-up sample is within the range of those reported among other longitudinal studies with cannabis users (89% for wave 2 reported in Tait et al., 2011; 64% for the final sample included in Jacobus et al., 2015, Jacobus, J, personal communication, August 5, 2015). Five cannabis users were not interested in participating, 2 could not be contacted, and 2 had moved and were unavailable for assessment. Of the

control participants, 1 was not interested in participating, 2 could not be contacted, 1 had moved, and 2 failed to return for unknown reasons. One cannabis user and 2 control participants were excluded from follow-up analyses due to missing alcohol use data. Table 1 reflects sample characteristics for included participants at follow-up. Participants returned after approximately a two-year interval (cannabis users M = 2.35 years, SD = 0.31; control M = 2.22 years, SD = 0.49), with no significant group difference in time interval to follow-up.

During both baseline and follow-up assessments, all participants, including cannabis users, were asked to refrain from drug use for at least 24 hours before testing so as not to be acutely high during the assessment, though participants who reported 12-to-24 hours of abstinence were accepted. Longer periods of abstinence were not required to avoid assessing individuals in the midst of drug withdrawal and because a goal of the study was to capture functional capacities in the context of active use. Formal drug testing was not implemented due to budgetary limitations and given that the study did not require long-term cannabis abstinence.

1.2.2 Procedure

At study enrollment, interested participants completed brief telephone interviews as a screen for study eligibility. Eligible participants were invited to complete a more in-depth in-person screening assessment to verify inclusion and exclusion criteria. Participants completed an in-person structured interview, the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL: Kaufman et al., 1997) to assess for recent and past histories of affective, psychotic,

childhood developmental, and behavioral disorders. The benefit of using the K-SADS to assess psychopathology in young adults is that it captures past histories of childhood disorders while also providing an in-depth assessment of DSM-IV-based adult psychopathology. Current (recent) ratings were based on the previous 2 months for non-substance use related disorders and the previous 6 months for substance use disorders. Intelligence was estimated using the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI: Wechsler, 1999). Participants completed detailed health and demographic questionnaires. Handedness was verified using the Edinburgh Handedness Inventory (Oldfield, 1971). Participants who met inclusion criteria returned for a second assessment, which included magnetic resonance imaging (MRI) scans as well as behavioral questionnaires and a comprehensive neurocognitive battery. The neurocognitive battery was designed to capture a broad array of functions in the domains of motor function, processing speed, attention, spatial and verbal memory, and executive functioning skills. Together, these measures took several hours to complete.

During the follow-up assessment, the same procedure was used. General health and IQ measures (K-SADS-PL, WASI, Health and demographic measures, Edinburgh Handedness Inventory) were collected at follow-up to measure change since initial enrollment. No participants were excluded after initial study enrollment. At follow-up, the K-SADS-PL assessed for symptom presence during the follow-up interval, and did not assess for lifetime presence of psychopathology.

1.2.3 Measures

1.2.3.1 Neurocognitive Battery

Motor Function

Finger Tapping Test (Lezak et al., 2004). This test measured bimanual motor speed. Participants tapped a key as many times as possible within a 10-second period. Three trials were administered for each hand, and the number of taps per trial was recorded. The average of all three trials per hand is reported.

Grooved Pegboard (Lafayette Instruments, 1989). This test measured psychomotor bimanual dexterity and speed. Participants were presented with a flat board containing rows of holes and small metal 'pegs' that fit into the holes on the board. The pegs were shaped so that one side is square. Each peg had to be correctly manipulated in order to fit the holes. Under timed conditions, participants used the pegs to fill the holes on the board using first the right (dominant) hand, then the left (non-dominant) hand. Accuracy and response time are reported.

Processing Speed

Digit Symbol (WAIS-III Digit Symbol; Wechsler, 1997). This test measured psychomotor speed, sustained attention, scanning ability, and the ability to quickly learn associations between numbers and symbols (Sattler & Ryan, 2009). This test was administered according to WAIS-III standardized procedures. Specifically, participants were presented with a piece of paper with rows containing blank squares below randomly assigned numbers from 1 to 9. Participants were asked to assign symbols to the spaces

below the numbered boxes according to a key that pairs each number with a unique symbol. The total score represents the total correct number of items completed within 120 seconds, out of a total possible score of 133.

Letter Cancellation Task (Lezak et al., 2004). This task measured immediate attention and vigilance under timed conditions. Participants viewed a piece of paper on which were printed rows of capitalized letters. They were instructed to work as quickly and as accurately as possible and to cross out all occurrences of the letters 'E' and 'C'. Time-to-completion and numbers of errors (commission and omission) are reported.

Verbal Fluency

Controlled Oral Word Association Test (COWAT; Delis, Kramer, Kaplan, & Ober, 2000; Lezak et al., 2004). The COWAT assessed expressive speech fluency as well as rule maintenance and response monitoring. Standardized administration procedures using the target letters F, A, and S were employed. The total score for each participant represents the total number of words generated across all three trials after deductions for rule violations, which include set-loss errors (i.e., words not beginning with target letters) and perseverations (i.e., saying the same word more than once). Total correct words and numbers of errors are reported.

Verbal Attention and Working Memory

Digit Span (WAIS–III Digit Span; Wechsler, 1997). This test measured immediate recall of auditory verbal information. Digit span forward and digit span backward conditions were administered according to WAIS-III standardized procedures. Participants were read sequences of digits, and were then asked to repeat the sequence as

presented (digits forward) or in the reverse order (digits backward). Participants were administered successively more difficult levels, with one digit added to the sequence at every level. The maximum number of digits correctly recalled is reported for both the digit span forward and backward conditions.

Verbal Learning and Memory

Rey Auditory Verbal Learning Test (RAVLT; Lezak et al., 2004; A. Rey, 1993). This test measured acquisition, storage, and retrieval of verbal information. During the learning phase, participants were first read and asked to recall a list of 15 words. This procedure was repeated four additional times to yield the number of items correctly recalled on trials 1-5. This learning phase assessed the participant's immediate learning and temporary storage of verbal information. Following the learning trials, participants were then read and asked to recall a new list of 15 words (interference trial). The interference trial assessed immediate learning of new information, and was presented only once. Following the interference trial, participants were then asked to freely recall as many words as they could from the first list (immediate recall) and again following a 30-minute delay (delayed recall). The immediate recall trial assessed learning recall when the items are not actively rehearsed in working memory. Performance on the delayed recall trial represented learning that has been consolidated into memory. The number of words recalled during the learning trials, interference trial, immediate recall, and delayed recall trials are reported. Intrusion (recall of non-list words) and perseverative (repeated responses) errors are also tabulated. These variables are standard for this task.

Additional learning and memory variables were calculated to characterize performance in a more nuanced manner. The amount of information recalled after consolidation was calculated as the percentage of words recalled during the 30-minute delay relative to the number of words recalled during the last of the five learning trials ([Trial 7/Trial 5] × 100; Takagi, Yücel, et al., 2011). Retroactive interference (trial 5 vs. immediate recall) and proactive interference (trial 1 vs. interference) were also examined (Takagi, Yücel, et al., 2011). Retroactive interference refers to later learning disrupting the recall of previously learned information, whereas proactive interference refers to earlier learning disrupting the recall of information learned later.

Spatial Memory

Spatial Working Memory (SWM CANTAB; Owen, Downes, Sahakian, Polkey, & Robbins, 1990). This test measured spatial working memory, self-monitoring, and behavioral self-organization. Using a computerized touch-screen, participants searched for tokens hidden inside an array of boxes. The task was organized into 4, 6 and 8 box problems, with increased box number corresponding to increased task difficulty. Participants viewed the array of boxes on the screen and were instructed that at any one time, there was a single token hidden inside one of the boxes. Their task was to search until they found it, at which point the next token was hidden. Once a given box yielded a token, that box was not used to hide the token again during the trial. Returning to a box after a token had already been found within it constituted an error. Every box was used once on every trial; thus, the total number of tokens to be found during each trial corresponded to the number of boxes on the screen. A "between-search" error was

recorded when participants returned to a box in which a token had already been found. A strategy score was also tabulated. The strategy score, based on responses to 6- and 8-item searches, reflected the participant's tendency to search through available locations in an organized manner (Owen et al., 1990). A high score represented poorer use of an organized search strategy. Total between-search error score (sum of errors on 4-, 6-, 8-move problems), as well as strategy scores, are the variables of interest.

Spatial Delayed Response Task (DRT; Luciana & Collins, 1997; Luciana, Collins, & Depue, 1998). This computerized task measured working memory for the locations of spatial targets. During the task, participants were seated with their head in a chin-forehead rest such that the computer monitor is 27 cm from their eyes. During each of 48 trials, the participants first observed a black "+" central fixation point on a computer monitor (0.63° × 0.63°) for 3 seconds. Next, a black "*" visual cue appeared in their peripheral vision, within a 360° circumference, for 200 ms. After the peripheral visual cue, the cue and fixation point disappeared, and the screen blackened for randomly interspersed delay intervals of 500 or 8,000 ms. After the delay interval, the participant indicated the remembered location of the cue by touching that area of the screen with a touch-pen device (FastPoint Technologies, Inc.). Visual cues were presented at 4 different locations in each of 4 quadrants for the 2 delay conditions. Visual cue eccentricities were 10° to minimize the use of edge or center cues and ensure cues did not fall within the participant's blind spot, and locations of 0°, 90°, 180°, and 270° were not included to minimize the use of spatial referencing to exact vertical and horizontal positions.

A block of 16 “no delay” trials (during which the target appeared but remained on-screen) was also administered prior to the delay trials to measure basic perceptual and visuomotor abilities independent of memory. Average accuracy (in millimeters) and response times (in milliseconds) are reported for each condition.

Planning

Tower of London (TOL CANTAB; Owen et al., 1990). This test measured planning ability. The task consisted of a problem-solving block and a yoked following block. During the problem-solving block, participants viewed two displays of colored balls, presented simultaneously, on a computer screen. One of these displays was the target, and the second was the participant’s workspace. Using a computerized touch-screen, participants moved the colored balls within their own workspace to match the target display (problem-solving block). Participants were told at the start of each problem-solving trial that the trial should be completed in *X* number of moves, where *X* was the minimum number of moves required to achieve a perfect solution. This instruction was provided to encourage participants to plan their moves to achieve perfect solutions. The total number of problems in which participants responded with the minimum number of moves is recorded and expressed as a proportion of total possible perfect solutions. Participants were instructed not to make the first move until they knew which balls to move and were encouraged to solve the problem correctly on the first try. The time from presentation of the problem to starting to solve the problem (planning time) is reported.

During the yoked following block, participants were instructed to repeat moves that were executed by the computer. Unbeknownst to the participant, the computer-generated moves on the yoked following block replicated the exact moves that the participant made during the problem-solving block trials. Participants' response times during yoked following trials provided measures of basic motor speed in the absence of planning and/or problem solving. For each trial, first move initiation (or planning) time was the time between the presentation of the problem and the execution of the first move minus the initiation time from the yoked following block trial. First move initiation time, percent perfect solutions, and average moves on 2-, 3-, 4-, and 5-move problems are examined.

The CANTAB battery, from which this task is derived, was updated in the course of the project. At their baseline assessment, controls completed a version of the task that contained problems that could be solved in 2-, 3-, 4-, and 5-moves, presented in that order. At follow-up, 27 controls completed the updated version of the task that contained 2-, 3-, 4-, 5- and 6-move problems, while 4 received the earlier version. Cannabis users completed the second updated version (2- to 6-move problems) at both time points. To harmonize scoring between the groups and assessment time points, only scores from the 2- to 5-move problems were included in the analyses.

Motivated Decision-Making

Iowa Gambling Task (IGT: Bechara, Damasio, Damasio, & Anderson, 1994). This task measured motivated decision-making ability. Participants completed a computerized version of the IGT during which they selected from among four decks of

cards varying in their amounts of monetary reward and punishment (Table 5; Bechara et al., 1994). Participants worked to earn real money (maximum of $5). For each selection from Decks 1 or 2 (the "disadvantageous/bad decks"), participants won $0.25 but also incurred losses so that over 20 selections from these decks, participants incurred a net loss of $1.25. Decks 1 and 2 differed in the frequency and magnitude of punishment: Deck 1 contained frequent (50% of cards) but smaller ($0.35-$0.90) punishments, whereas Deck 2 contained less frequent (10% of cards) but much larger ($3.00-$3.25) punishments. For each selection from Decks 3 or 4 (the "advantageous/good decks"), participants won either $0.10 or $0.15 and the losses were organized so that over 20 selections from these decks, participants accrued a net gain of $1.25. Similar to the disadvantageous decks, the two advantageous decks differed from each other in the frequency of punishment: Deck 3 contained frequent (50% of cards) but smaller ($0.05-$0.20) punishments, and Deck 4 contained less frequent (10% of cards) but larger punishments ($0.60-$0.65). The decks were presented in order from left to right on the computer screen at baseline, then the order of the decks was shuffled at the follow-up assessment to minimize practice effects.

For analysis, trials (n = 100) were divided into 5 blocks with 20 trials per block. For each block, the number of choices from disadvantageous decks was subtracted from number of choices from advantageous decks. Thus, values above "0" correspond to relatively advantageous choices. In addition, the actual numbers of selections made from each deck were tabulated across the full task to analyze choice preferences.

1.2.3.2 Substance Use

Amount and frequency of substance use were assessed with the K-SADS-PL interview at baseline and at follow-up for cannabis users and controls. Controls selected from the larger database were included in these analyses if they reported minimal cannabis use (no more than once monthly) and no other illicit substance use. Substance use patterns within the cannabis users were more variable, as inclusion criteria did not require abstinence from non-cannabis illicit substances. Therefore, multiple measures were employed to characterize substance use patterns in cannabis users.

An in-house interview questionnaire based on guidelines provided by the NIAAA was implemented at baseline and follow-up to assess detailed frequency and quantity of alcohol and cannabis use among cannabis users. This measure assessed frequency of use, typical number of hits per use occasion, and largest number of hits consumed in 24 hours, each of which was assessed for the prior 12 months and prior 30 days. Total number of hits within the last 12 months was calculated as a product of the number of occasions a participant used cannabis during the past year and the typical number of hits used per occasion, capturing both the frequency and quantity of cannabis use patterns.

At baseline and follow-up, cannabis users completed the Personal Experience Inventory (Henley & Winters, 1989) to assess other substance use. The PEI measures the frequency of substance use within the last 12 months on a 5-point scale (never, 1-5 times, 6-20 times, 21-49 times, 50-99 times, 100+ times). Non-cannabis drug use for the 12 months prior to each assessment was calculated by summing the frequency ratings across

illicit drug classes (psychedelics, cocaine, amphetamines, barbiturates, tranquilizers, heroin, narcotics, steroids, inhalants, and recreation use of prescription drugs).

All participants completed the Achenbach's Adult Self-Report (ASR; Achenbach & Rescorla, 2003) questionnaire, yielding substance use scales of self-reported daily tobacco use, number of days drunk, and days using drugs (other than alcohol or tobacco) for the previous 6 months.

1.2.4 Statistical Approach

Data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA), Windows version 20. Data were screened for outliers and influential data points. Distributions of all variables were examined and variables that did not meet the assumptions for parametric analysis were square root transformed, including error variables for the Letter Cancellation, RAVLT, and COWAT, substance use variables from the ASR, and total number of cannabis hits within the past year for cannabis users. Chi-square tests were used to compare nominal variables (i.e., sex) between cannabis users and controls. Mann-Whitney U analyses assessed for group differences in substance use characteristics given that variances were unequal between groups.

In order to characterize cognitive performance, both cognitive composite scores and separate task variables were examined. Composite scales were created in a two-step process by first selecting measures according to known cognitive domains (Lezak et al., 2004), then refining composites according to internal reliability analyses (Delis, Jacobson, Bondi, Hamilton, & Salmon, 2003). This method is consistent with several

other studies examining cognitive performance among adolescent and young adult substance users (Hanson & Luciana, 2010; Hanson et al., 2010; Jacobus et al., 2014; Medina et al., 2007, 2009). Individual neuropsychological test variables were converted to z-scores based on the whole sample of participants at both time points (n = 126). Z-scores were transformed such that higher scores represented better performance across all variables. Next, the individual test z-scores were averaged to form the final composite score for each cognitive domain. Internal consistencies of the composite scores were assessed using Cronbach's α coefficient.

Six cognitive composites were created: (1) *Processing speed* (α = 0.60; Letter Cancellation time, Digit Symbol total correct, COWAT total correct words); (2) *Verbal learning and memory* (α = 0.91; RAVLT trial 1-5 total words, RAVLT immediate recall, RAVLT delayed recall); (3) *Spatial working memory and planning* (α = 0.73; SWM strategy score, SWM total errors, TOL % perfect solutions, TOL total average moves); (4) *Motor speed* (α = 0.91; Finger Tapping dominant hand taps, Finger Tapping non-dominant hand taps); (5) *Motor dexterity* (α = 0.82; Grooved Pegboard dominant hand time, Grooved Pegboard non-dominant hand time).

For all reported analyses, alpha levels equal to or below 0.05 were considered statistically significant, and alpha levels at or below 0.10 were considered trend effects.

Baseline

Univariate and repeated measures analyses of variance (ANCOVA) assessed for group differences in the same way as the earlier report (Becker et al., 2014). The Greenhouse-Geisser method was used to adjust the degrees of freedom where appropriate

(Greenhouse & Geisser, 1959). Sex, IQ, and alcohol use were covaried in all group comparisons. Alcohol use was quantified as an average of two alcohol use variables that were z-scored across the whole sample (controls and cannabis users). The first alcohol use variable was calculated by multiplying the participants' self-reported average drinking occasions per week and the average number of alcoholic drinks per occasion for the previous 6 months, as assessed by direct K-SADS-PL interview (occasions per week × number of drinks); responses were coded on an ordinal scale for occasions per week (1 = 0 occasions, 2 = 1-2 occasions, 3 = 3+ occasions) and number of drinks (1 = 0 drinks, 2 = 1-2 drinks, 3 = 3+ drinks). Ordinal scaling was used because the responses were derived from ordinal ratings on the K-SADS-PL interview. The second alcohol use variable was the number of days that the participant reported being drunk in the last 6 months, as assessed by the ASR questionnaire.

Due to the study's inclusion criteria, controls had no history of tobacco use or non-alcohol-related drug use. For cannabis users, illicit drug use was calculated from responses on the PEI. Patterns of daily tobacco use were quantified by responses to questions from the ASR and K-SADS. Levels of alcohol, tobacco, and other drug use differed between groups, but alcohol use was the only variable that could be used in between-group analyses. The contributions of tobacco and other drug use to cognition in the cannabis users were examined within cannabis users using partial correlations to explore the extent to which other substance use contributed to performance where group differences were observed. Alcohol, tobacco, drug use, and cannabis use variables were

correlated with task performance in cannabis users, controlling for sex, IQ, and other substance use.

To ensure that the sample of participants who returned for follow-up assessment was equivalent to the full baseline sample, Univariate ANOVA and Mann-Whitney U analyses assessed for group differences between participants who returned for follow-up assessment and participants who were lost to follow-up. These analyses were conducted separately for control and cannabis user samples.

Follow-up

Repeated measures ANCOVA was used to characterize change between baseline and follow-up performance. This approach examined differences between groups on cognitive performance, as well as the group × time interaction effect. The Greenhouse-Geisser method was used to adjust the degrees of freedom where appropriate. Repeated measures ANCOVA is most appropriate when samples are well-balanced, have the same number of time points, and when time interval to follow-up time is generally consistent (Taris, 2000). Each of these conditions is satisfied in the current sample. Repeated measures ANCOVA was also used to be consistent with the limited existing literature characterizing change in cognitive performance in cannabis users given that others have used this approach (Hanson et al., 2010; Jacobus, Squeglia, Bava, et al., 2013; Jacobus, Squeglia, Infante, Bava, & Tapert, 2013; Jacobus et al., 2015, 2014; Tait et al., 2011). All repeated measures ANCOVAs covaried time interval to follow-up, sex, IQ, and average alcohol use during time interval to follow-up. Average alcohol use was quantified in the same manner as described above, as an average of two alcohol use variables (occasions

per week × number of drinks, number of days that the participant reported being drunk in the last 6 months) that were z-scored across the whole sample at baseline and follow-up (controls and cannabis users). The resulting estimates of average alcohol use at baseline and follow-up were averaged to create a measure of average alcohol use during baseline and follow-up. Estimates of average alcohol use did not change over time ($t(53) = -1.00$, $p = .321$).

Within the cannabis user group, hierarchical regression analyses, as described in the results section, explored whether cannabis use factors were associated with greater or less than predicted change in cognitive performance from baseline to follow-up.

1.3 Results

1.3.1 Baseline

1.3.1.1 Sample Characteristics

Demographic information and participant characteristics are presented in Table 1. Samples were matched on age, ethnicity/racial identity, educational attainment, and IQ. Both samples performed in the high average range of IQ performance, which is consistent with similar studies comparing non-substance users and substance users in a college population (Croft, Mackay, Mills, & Gruzelier, 2001; Hanson et al., 2008). There were significantly more males among cannabis users. This is consistent with the sex distribution of cannabis users in this age range (Substance Abuse and Mental Health Services Administration, 2013).

Given selection procedures, controls had no full-syndrome psychopathology at baseline. Outside of substance use disorders, cannabis users reported little psychopathology (Table 2). One cannabis user participant met criteria for current Bipolar Disorder NOS; another met criteria for past Bipolar Disorder NOS. Both disorders were diagnosed based on episodic hypomania. This finding is consistent with the reported comorbidity between substance use disorders and bipolar disorder (Perlis et al., 2004; Wilens et al., 2008). Other psychological disorders evident in cannabis users included past Oppositional Defiant Disorder (n = 2) and past Specific Phobia (n = 1). To assess if comorbid psychopathology contributed to the between groups findings, data were analyzed with and without inclusion of these individuals.

1.3.1.2 Substance Use Characteristics

Cannabis users had significantly higher average alcohol use ($p < .001$; Table 1). Further, as would be expected from national norms among cannabis users (Substance Abuse and Mental Health Services Administration, 2013), users had greater tobacco use, days drunk, and days using drugs in the last 6 months compared to controls. Despite differences from the control sample, cannabis users reported relatively little substance use outside of cannabis and alcohol. The majority of cannabis users had tried other drugs fewer than 5 times (See Table 4). As a result of exclusion criteria, controls reported no cannabis use beyond 1x/month. Cannabis users reported a mean age of initiation of regular cannabis use during mid-adolescence (M = 15.24, SD = 1.23) with a range from 13 to 18 years. Cannabis users reported nearly daily cannabis use during the past 30 days, with a self-reported average of 262.69 hits within the last 30 days; however, there was

considerable variability in the number of total hits, with a standard deviation of 200.41, and a range of 45-750.

DSM-IV-TR substance use disorder diagnostic characteristics. Almost all cannabis users met criteria for current and/or past cannabis substance use disorder (Table 2) and many met criteria for current and/or past alcohol abuse. Substance use symptom patterns were examined in detail to clarify symptom expression related to alcohol, cannabis, and other drug use (Table 3). Cannabis users exhibited fewer symptoms related to alcohol use (M = 0.97, SD = 1.24 current symptoms per person; M = 1.30, SD = 1.53 past symptoms per person) than related to cannabis use (M = 4.14, SD = 1.92 current symptoms per person, U = 125, $p < .001$; M = 4.35, SD = 1.83 past symptoms per person, U = 142.0, $p < .001$). No substance use disorder symptoms related to other drug use were expressed among cannabis users or controls. As a result of exclusion criteria, controls exhibited very few symptoms related to alcohol use (M = 0.11, SD = 0.32 current symptoms per person; M = 0.03, SD = 0.17 past symptoms per person), and no symptoms related to other drug use.

1.3.1.3 Baseline Group Differences in Neurocognitive Performance

Tables 6 and 7 present neurocognitive data for cognitive composites and specific task variables (marginal means and standard errors) as well as relevant statistics for each group. Major findings will be summarized here within the text.

Motor Function

Groups were equivalent on the motor speed and motor dexterity cognitive composites. No laterality differences emerged between groups (Group × Hand

interactions in repeated measures ANCOVA). When task variables were analyzed separately, there was a trend for cannabis users to demonstrate faster motor speed on dominant hand Finger Tapping. Groups had equivalent performance on non-dominant hand Finger Tapping and on the Grooved Pegboard.

Processing Speed

Cannabis users exhibited better performance on the processing speed composite relative to controls. Task by task analyses revealed that cannabis users exhibited faster Letter Cancellation completion times. Omission and commission errors were equivalent between groups, and completion times were uncorrelated with overall errors in both groups. Groups did not differ in their Digit Symbol performance. Cannabis users displayed greater verbal fluency than controls, producing more correct responses on the COWAT. Cannabis users also made greater set-loss errors than controls. A marginal positive partial correlation was observed between correct COWAT responses and set-loss errors among cannabis users ($r(31) = .293$, $p = .098$) but not controls ($r(30) = .018$, $p = .922$), controlling for sex, IQ, and alcohol use. No group difference was noted for perseverative errors.

Verbal Learning and Memory

The groups were equivalent on Digit Span forward performance. Cannabis users recalled marginally fewer digits on the digits backward condition of the task.

Controls performed better than cannabis users on the verbal learning and memory cognitive composite. A repeated measures ANCOVA was used to analyze all RAVLT trials, with RAVLT trial (learning trials 1-5, interference trial, immediate recall, and

delayed recall) as a within subjects factor and group as a between subjects factor. A main effect of time, $F(4.949, 326.62) = 2.861$, $p = .016$, $\eta_p^2 = .04$, group, $F(1, 66) = 6.25$, $p = .015$, $\eta_p^2 = .09$, and a Group × Trial interaction, $F(4.949, 326.62) = 2.375$, $p = .039$, $\eta_p^2 = .04$, emerged. Follow-up one-way ANCOVAs revealed that there was a trend for cannabis users to recall fewer words on trials 4 and 5. Cannabis users performed worse than controls on the interference trial. Following the interference trial, cannabis users demonstrated poorer immediate recall as well as poorer 30-minute delayed recall relative to controls. Cannabis users exhibited a lower percent of learning after consolidation, $F(1, 66) = 6.84$, $p = .011$, $\eta_p^2 = .09$ (cannabis user $M = 77.68\%$, $SE = 3.13$; control $M = 90.87\%$, $SE = 3.19$). There was a trend for cannabis users to show greater proactive interference than controls (Trial 1 vs. Interference Trial), Group × Trial interaction $F(1, 66) = 2.90$, $p = .093$, $\eta_p^2 = .04$. No Group × Trial interaction emerged for retroactive interference (Trial 5 vs. Immediate Recall).

There was a trend for cannabis users to produce more intrusion errors during learning trials. The number of perseverative errors during list learning was equivalent between groups.

Spatial Memory

Groups demonstrated equivalent performance on the spatial working memory and planning composite.

No significant group differences were evident on the SWM test in relation to memory errors or strategy score.

On the Spatial Delayed Response Task (DRT), groups were equivalent in their accuracies and response latencies for the no delay condition, indicating that the basic sensorimotor functions required for the task were similar between groups. Cannabis users demonstrated a trend toward decreased accuracy on the 500 ms delay condition, and a significant effect of decreased accuracy on the 8,000 ms delay condition. Cannabis users had significantly longer response latencies (slower performance) after both 500 ms and 8,000 ms delays. Accuracy and response latencies were uncorrelated in cannabis users and controls for the 500 ms (cannabis user $r(31) = -.176$, $p = .327$; control $r(30) = -.157$, $p = .390$) and 8,000 ms (cannabis user $r(31) = -.184$, $p = .305$; control $r(30) = -.109$, $p = .551$) delay conditions, controlling for sex, IQ, and alcohol use.

Planning

Cannabis users produced fewer perfect solutions on the Tower of London (TOL) task, indicating that they made more moves than necessary to achieve accurate performance. When task difficulty levels were examined, cannabis users made significantly more moves than controls to complete 3-move problems, which are considered to be relatively easy. Cannabis users had marginally slower initiation times during 2-move problems, and faster initiation times during 5-move problems.

Motivated Decision-Making

On the Iowa Gambling Task (IGT), total good minus bad choices over five blocks of the task were examined with block as the within subjects factor and group as the between subjects factor in a repeated measures ANCOVA. This approach is standard for the task (Bechara et al., 2001; Fridberg et al., 2010; Verdejo-García, Benbrook, et al.,

2007). A marginal Group × Block interaction, $F(3.08,200.19) = 2.214$, $p = 0.086$, $\eta_p^2 = 0.03$, and a significant main effect of group, $F(1,65) = 9.19$, $p = 0.003$, $\eta_p^2 = 0.12$, were observed. Across the task, cannabis users made fewer advantageous choices. Follow-up one-way ANCOVAs revealed a marginal group difference on Blocks 2 and 3, and a significant group difference on Blocks 4 and 5, with cannabis users making fewer advantageous deck selections on all blocks. Analyses of deck choices revealed that cannabis users made significantly more choices from disadvantageous Decks 1 and 2 than controls, and marginally fewer choices than controls from advantageous Decks 3 and 4 (deck contingencies described in Table 5).

1.3.1.4 Baseline Neurocognitive Performance and Substance Use

For all significant group effects described above, alcohol, tobacco, non-cannabis drug, and cannabis use measures were each separately examined for associations with task performance within cannabis users (Table 8). Substance use measures were uncorrelated with one another (Table 8).

Cannabis. Earlier age of cannabis use initiation was correlated with slower reaction time on the 500 ms and 8,000 ms delay conditions of the DRT, and greater average moves on 3-move problems for the TOL.

Greater use in the past year (total # hits) was correlated with greater errors on the 500 ms condition of the DRT and faster initiation times on 5-move TOL problems. Greater use was marginally correlated with recall of fewer words during the interference trial of the RAVLT. Other cannabis use variables, including number of days participants used cannabis in the past year and past 30 days, and total number of hits in the past 30

days, were not significantly correlated with the cognitive performance measures that distinguished cannabis users from controls.

Alcohol. For the verbal learning and memory composite, learning and recall measures of the RAVLT, errors made within the 8,000 ms delay condition of the delayed response task, and TOL average moves on 3-move problems, greater alcohol use was unexpectedly associated with *better* task performance in cannabis users. There was a trend for greater alcohol use to be associated with faster reaction times on the 8,000 ms delay condition of the DRT and higher percent perfect solutions on the TOL. Alcohol use was not significantly correlated with other task performance variables.

Tobacco. Cognitive performance was not significantly correlated with tobacco use within cannabis users.

Non-cannabis drug use. Greater non-cannabis drug use was unexpectedly correlated with a higher percentage of learned words recalled after a delay on the RAVLT as well as faster initiation times (decreased planning) on 5-move TOL problems. There was a trend for greater non-cannabis drug use to be correlated with poorer processing speed composite scores, fewer errors on the COWAT, and better performance on the delayed recall on the RAVLT.

Impact of Comorbid Psychopathology

Significant group differences as described above remained unchanged when cannabis users with psychopathology outside of SUDs (n = 5) were excluded.

1.3.1.5 Baseline Demographic Characteristics and Cognitive Performance in Follow-up sample

To ensure that the subset of participants who returned for follow-up was representative of the full sample assessed at baseline, demographic and substance use characteristics were compared between participants who returned for follow-up versus those who did not.

Follow-up Sample: Baseline Sample Characteristics (Table 9)

Participants who returned for follow-up assessment and participants who did not return were equivalent in age, ethnicity/racial identity, and IQ. Controls were equivalent in sex; among cannabis users, there was a trend for more males to be in the follow-up sample relative to those who did not return for follow-up. Cannabis users were matched on educational achievement, though there was a trend for controls who returned for follow-up assessment to have somewhat lower educational achievement at baseline, which was not fully accounted for by age ($F(1, 31) = 6.676$, $p = .015$, $\eta_p^2 = .18$, with age covaried).

The follow-up sample and participants lost to follow-up were equivalent on alcohol and tobacco use. In controls, both samples were equivalent on drug use. In the cannabis user sample, those who returned for follow-up assessment endorsed fewer occasions of drug use during the past 6 months (at baseline), and marginally fewer cannabis use occasions when compared to those who did not return for the follow-up assessment. Both samples reported equivalent age of cannabis use initiation, and total number of hits within the last 3 and 12 months.

Follow-up Sample: Baseline Neurocognitive Performance

Significant baseline group differences remained largely unchanged when the sample was reduced to participants who completed the follow-up assessment (see Table 11, which reports the baseline marginal mean and standard errors for task variables among the participants who returned for the follow-up assessment).

On the Finger Tapping Test, the trend for cannabis users to display a greater number of taps with the dominant hand became fully significant, $F(1, 50) = 4.17$, $p = .046$, $\eta_p^2 = .08$. There was no longer a significant or marginal group difference in spatial DRT errors made during the 500 ms ($p = .266$, $\eta_p^2 = .03$) or 8,000 ms ($p = .123$, $\eta_p^2 = .05$) delay conditions of the task. The trends for cannabis users to recall fewer words on the RAVLT Trial 4 ($p = .277$, $\eta_p^2 = .02$) and Trial 5 ($p = .193$, $\eta_p^2 = .03$) were no longer significant. On the Tower of London, the trend for cannabis users to display slower initiation time on 2-move problems became fully significant, $F(1, 50) = 5.253$, $p = .026$, $\eta_p^2 = .10$, and the finding that cannabis users had faster initiation times on 5-move problems was no longer significant ($p = .273$, $\eta_p^2 = .02$). The trend for cannabis users to have lower IGT good-bad choices during block 2 was no longer significant ($p = .110$, $\eta_p^2 = .05$). The trend for cannabis users to make fewer choices from Deck 3 became fully significant $F(1, 50) = 4.70$, $p = .035$, $\eta_p^2 = .09$.

Given the smaller sample size in these follow-up analyses, a reduction in power to detect group differences cannot be ruled out. Comparing baseline differences between groups within the full sample at baseline yields a power estimate of 0.54 to detect the medium effect size observed among significant and trend group differences at baseline

(average η_p^2 = 0.088 in whole sample), whereas the power estimate was reduced to 0.41 to detect a medium effect size in the reduced sample.

1.3.2 Follow-up

1.3.2.1 Sample Characteristics

Demographic information and participant characteristics at follow-up are presented in Table 1. Demographic characteristics mirrored those found at baseline.

1.3.2.2 Substance Use Characteristics

At follow-up, cannabis users continued to report significantly higher alcohol use, tobacco use, and days using drugs than controls (see Tables 1 and 4). Cannabis users continued to report relatively little substance use outside of cannabis and alcohol use, and control subjects reported minimal experimentation with cannabis and no other substance use (Table 4).

Increased occasions using alcohol per week (responses coded on an ordinal scale for occasions per week, 1 = 0 occasions, 2 = 1-2 occasions, 3 = 3+ occasions) were reported among controls, $t(28) = -3.087$, $p = .005$ (baseline $M = 1.72$, $SD = 0.53$, follow-up $M = 2.03$, $SD = 0.50$) and cannabis users, $t(25) = -6.325$, $p < .001$ (baseline $M = 2.19$, $SD = 0.49$; follow-up $M = 2.81$, $SD = 0.49$). Controls reported an increase in the quantity of alcohol consumed on a typical occasion of use (number of drinks, 1 = 0 drinks, 2 = 1-2 drinks, 3 = 3+ drinks), $t(28) = -3.087$, $p = .005$ (baseline $M = 2.17$, $SD = 0.89$, follow-up $M = 2.55$, $SD = 0.78$) and cannabis users reported no change in the typical quantity of alcohol consumed per use occasion. Alcohol use occasions per week × quantity of use

was marginally increased at follow-up among controls, $t(28) = -2.015$, $p = .054$ (baseline $M = 4.14$, $SD = 2.37$; follow-up $M = 5.14$, $SD = 2.37$), and cannabis users, $t(26) = -6.261$, $p < .001$ (baseline $M = 6.48$, $SD = 1.67$; follow-up $M = 8.35$, $SD = 1.92$). No significant change was reported on average days drunk in the past 6 months. Participants reported no significant change in tobacco use per day in the past 6 months.

Cannabis users reported a *decreased* number of days using cannabis in the past year, $t(25) = 3.266$, $p = .003$, and in the past 30 days, $t(25) = 4.133$, $p < .001$ at follow-up versus baseline (Table 1). Despite the decline in use, regular use continued to be reported by the majority of cannabis users (median use occasions in past year = 287.90 [range of 0-365], and past 30 days = 19.25 [range of 0-30]). The average number of hits per day did not change between time points, though considerable variability remained among participants. No significant change was noted in the typical number of cannabis hits per occasion used. Cannabis users reported a decrease in the number of days using drugs in the past 6 months, $t(23) = 2.167$, $p = .041$, while no significant change was noted in controls' reported days using drugs other than alcohol.

1.3.2.3 Group Differences in Neurocognitive Performance at Follow-Up (Tables 10 and 11)

Repeated measures ANCOVAs, with cognitive variables as a within subjects factor, group status as a between-subjects factor, and the covariates of IQ, sex, time interval to follow-up, and average alcohol use during baseline and follow-up, were used to measure change between baseline and follow-up for each of the cognitive measures. Main effects of group would suggest differences between groups, regardless of time

point. Main effects of time would suggest differences between time points, regardless of group. Group × Time interactions suggest that the groups differ either in their baseline or follow-up performance or in the magnitude of change over time. Significant and marginal interactions were followed-up with one- or two-way ANCOVAs, with the nuisance covariates of IQ, sex, time interval to follow-up, and average alcohol use within time point. All cognitive composite scores and task variables were analyzed to mirror the statistical approach at baseline. Only marginal and significant group or Group × Time interactions will be described below.

Motor Function

A marginal Group × Time interaction for the dominant hand completion time on the grooved pegboard task was found, but follow-up one-way ANCOVAs indicated that there were no significant group differences at both baseline, $F(1, 50) = 0.131$, $p = .719$, $\eta_p^2 < .00$, and follow-up, $F(1, 50) = 2.562$, $p = .116$, $\eta_p^2 = .05$. The effect size at follow up was higher than at baseline with findings approaching significance, which may account for the interaction. A main effect of time was not significant for controls ($p = .606$, $\eta_p^2 = .01$) or cannabis users ($p = .970$, $\eta_p^2 < .00$) when groups were analyzed separately.

Processing Speed

Cannabis users performed better relative to controls on the processing speed composite regardless of time point.

A main effect of group on Letter Cancellation completion time indicated that cannabis users demonstrated faster completion times than controls. A marginal Group ×

Time interaction on Letter Cancellation omission errors was found, but follow-up one-way ANCOVAs indicated that groups were equivalent at both baseline, $F(1, 50) = 0.085$, $p = .771$, $\eta_p^2 < .00$, and follow-up, $F(1, 50) = 1.300$, $p = .260$, $\eta_p^2 = .03$. A main effect of time was not significant for controls ($p = .697$, $\eta_p^2 = .01$) or cannabis users ($p = .225$, $\eta_p^2 = .06$) when groups were analyzed separately. A main effect of time point was observed for total correct words generated on the COWAT, $F(1, 49) = 4.202$, $p = .046$, $\eta_p^2 = .08$, with more words generated at follow-up than at baseline.

Verbal Learning and Memory

There was a marginal main effect of group on the verbal learning and memory composite, with cannabis users demonstrating poorer performance than controls regardless of time point (Figure 1).

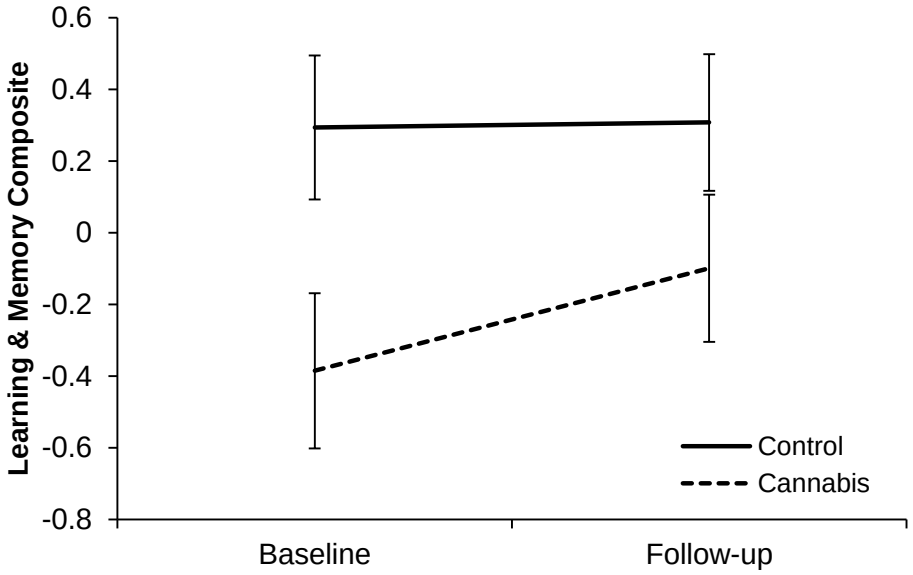

Figure 1. Learning and memory composite score change between baseline and follow-up. Error bars represent standard errors. Means reported are marginal means, controlling for interval, sex, IQ, and average alcohol use at baseline and follow-up.

Follow-up RAVLT task variables were examined using a repeated measures ANCOVA, with RAVLT trial (number of words recalled on learning trials 1-5, interference trial, immediate recall, and delayed recall) as a within subjects factor and group status as a between-subjects factor. This analysis includes interference trial performance, whereas the composite excludes that trial. At follow-up, main effects of RAVLT trial (p = .169, η_p^2 = .03), group (p = .632, η_p^2 = .01), and a Group × RAVLT trial interaction (p = .346, η_p^2 = 02) were all non-significant (Figure 2).

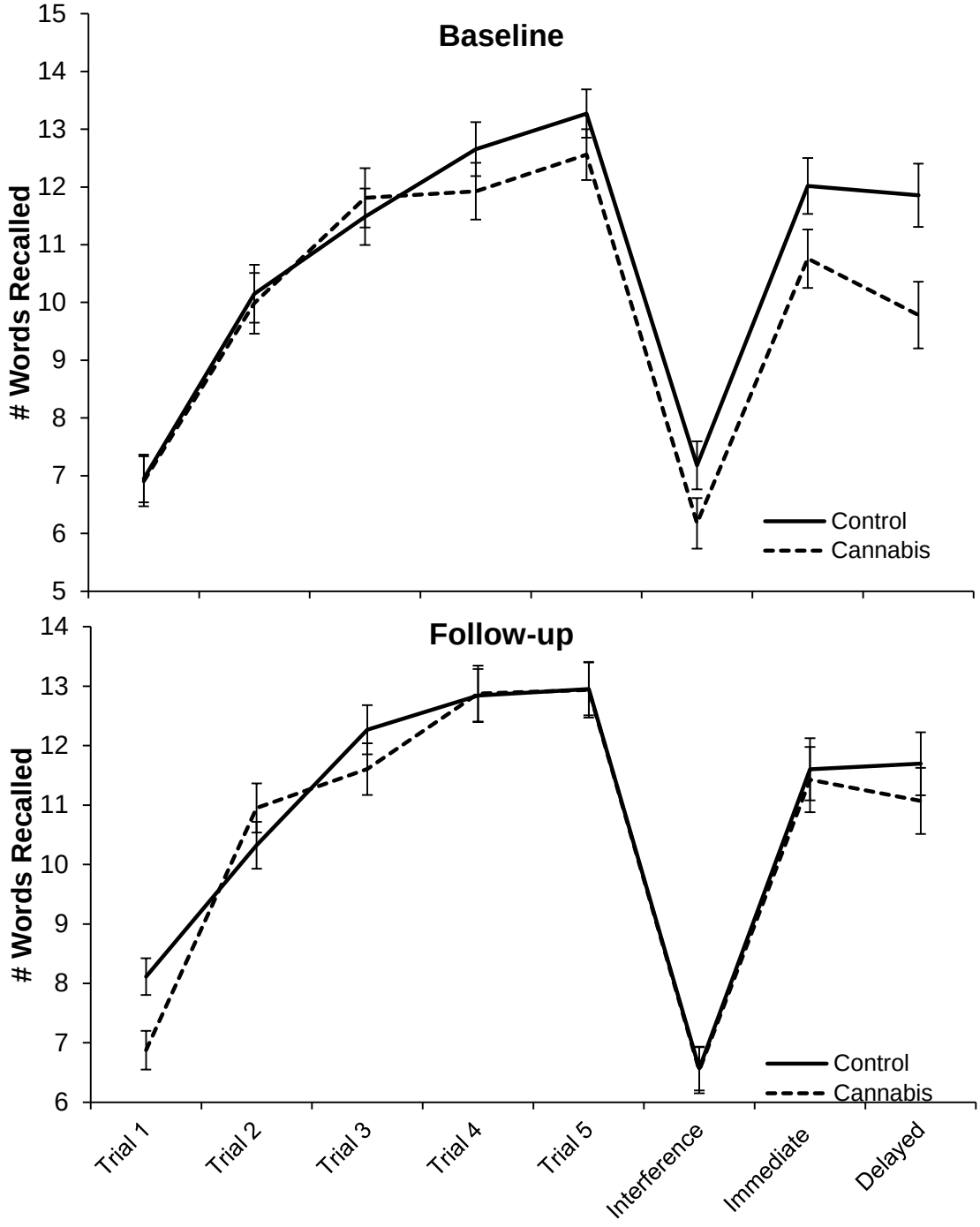

Figure 2. RAVLT performance across trials at baseline and follow-up for cannabis users and controls. Error bars represent standard errors. Means reported are marginal means, controlling for interval, sex, IQ, and average alcohol use at baseline and follow-up.

Post-hoc analyses examined individual RAVLT trials with a repeated measures ANCOVA, with time point as a within subjects variable and group as a between-subjects variable (main effects of group and Group × Time interactions are reported in Table 11). A marginal Group × Time interaction on Trial 1 was followed-up with one-way ANCOVAs to examine baseline and follow-up performance. Groups demonstrated equivalent performance at baseline, $F(1, 50) = 0.590$, $p = .446$, $\eta_p^2 = .01$, but were significantly different at follow-up, with cannabis users recalling fewer words than controls at follow-up, $F(1, 50) = 10.407$, $p = .002$, $\eta_p^2 = .17$ (Figure 3). A marginal main effect of time was observed within cannabis users ($p = .071$, $\eta_p^2 = .15$), but not controls ($p = .425$, $\eta_p^2 = .03$) when groups were analyzed separately.

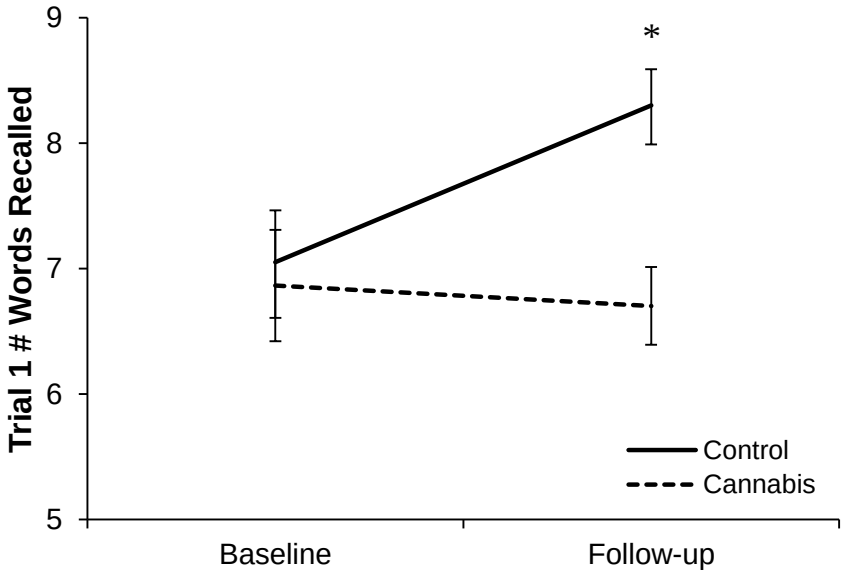

Figure 3. RAVLT Trial 1 words recalled change between baseline and follow-up. Error bars represent standard errors. Means reported are marginal means, controlling for interval, sex, IQ, and average alcohol use at baseline and follow-up.

A marginal main effect of group on immediate recall, and a significant main effect of group on delayed recall both indicated poorer performance among cannabis

users. A main effect of group was observed for total intrusions during learning trials was observed, with cannabis users making more errors.

Spatial Memory

There was a trend main effect of group on the spatial working memory and planning composite, with cannabis users demonstrating poorer performance than controls.

A main effect of time point was observed on the DRT for errors on the no delay condition, $F(1, 49) = 4.477$, $p = .039$, $\eta_p^2 = .08$, with more errors at follow-up than at baseline, though when groups were analyzed separately, this effect was only significant in cannabis users ($p = .025$, $\eta_p^2 = .21$) and not controls ($p = .819$, $\eta_p^2 < .00$). A main effect of group and a Group × Time interaction were observed for reaction time on the 500 and 8,000 ms delay conditions. Follow-up analyses indicated that cannabis users had greater reaction times than controls at baseline, 500 ms: $F(1, 50) = 14.16$, $p < .000$, $\eta_p^2 = .22$; 8,000 ms: $F(1, 50) = 12.722$, $p = .001$, $\eta_p^2 =. 20$, but had equivalent performance at follow-up, 500 ms: $F(1, 50) = .687$, $p = .411$, $\eta_p^2 = .01$; 8,000 ms: $F(1, 50) = 0.550$, $p = .462$, $\eta_p^2 = .01$ (**Figure 4**). Main effect of time was not significant for either group in both conditions when groups were analyzed separately.

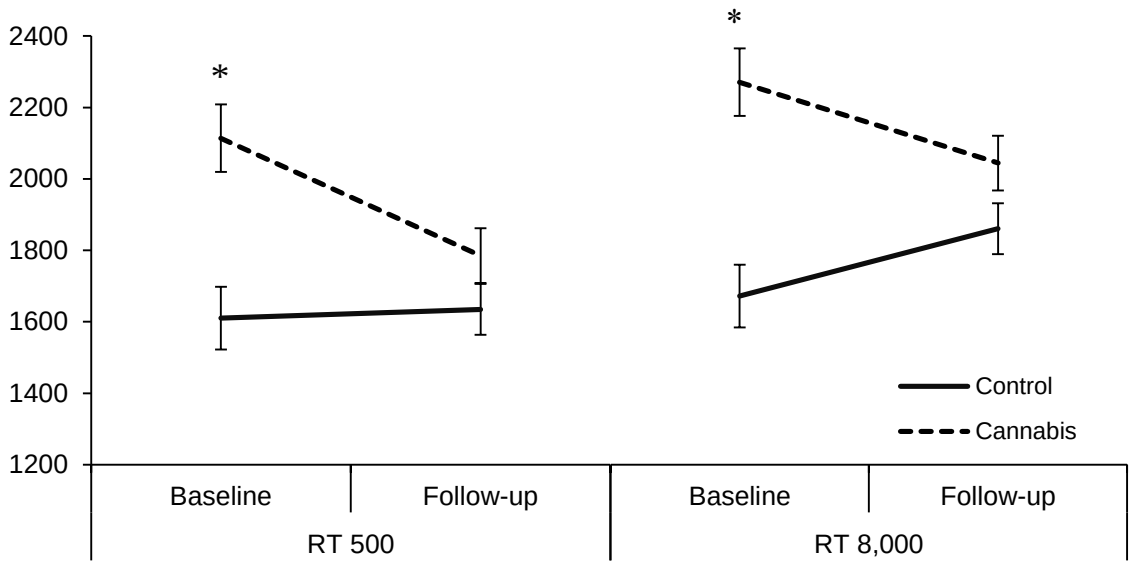

Figure 4. DRT reaction time on 500 ms 8,000 ms delay condition change between baseline and follow-up. Error bars represent standard errors. Means reported are marginal means, controlling for interval sex, IQ, and average alcohol use at baseline and follow-up.

Planning

A main effect of group was found for the TOL percent perfect solutions, with cannabis users performing worse than controls overall. Examination of separate difficulty levels of the TOL revealed a main effect of group and a significant Group × Time interaction for average moves to complete 3-move trials (Figure 5). Cannabis users required more moves to complete these trials accurately at baseline, $F(1, 49) = 6.074$, $p = .017$, $\eta_p^2 = .11$, and at follow-up, $F(1, 50) = 4.383$, $p = .041$, $\eta_p^2 < .08$. A main effect of time was not significant for either group when analyzed separately.

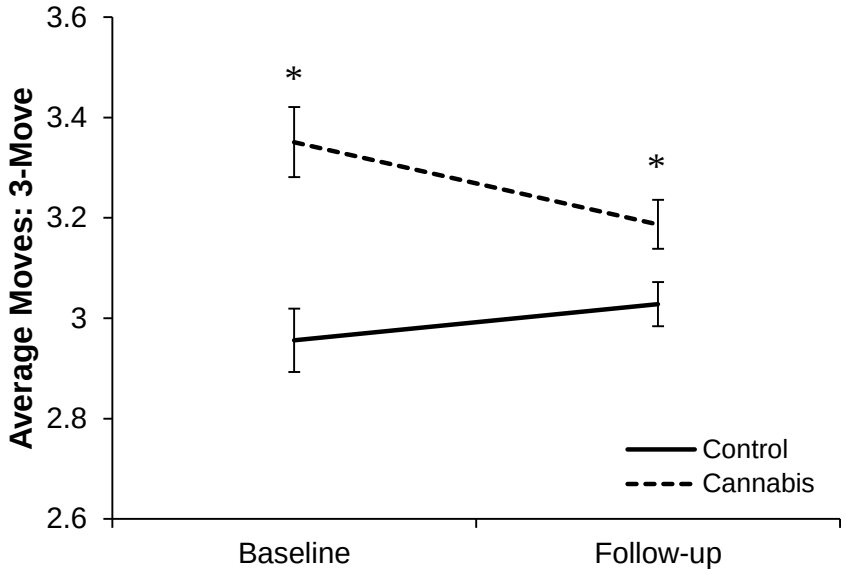

Figure 5. Average moves to complete 3-move trials change between baseline and follow-up. Error bars represent standard errors. Means reported are marginal means, controlling for interval, sex, IQ, and average alcohol use at baseline and follow-up.

A marginal Group × Time interaction on average moves for 5-move problems was observed. Groups did not significantly differ at baseline, $F(1, 49) = 2.304$, $p = .135$, $\eta_p^2 = .05$, or follow-up, $F(1, 50) = 0.236$, $p = .629$, $\eta_p^2 = .01$, though the effect size at baseline was higher than at follow-up with findings approaching significance, which may account for the interaction. Controls demonstrated a main effect of improvement over time ($p = .028$, $\eta_p^2 = .19$) but cannabis users did not ($p = .230$, $\eta_p^2 = .07$).

Examination of first move initiation time, or planning time prior to solving the problem, revealed significant main effects of time point for initiation times on 3-move problems, $F(1, 46) = 5.910$, $p = .019$, $\eta_p^2 = .11$, 4-move problems, $F(1, 46) = 4.943$, $p = .031$, $\eta_p^2 = .10$, and 5-move problems, $F(1, 46) = 4.897$, $p = .003$, $\eta_p^2 = .10$, and average initiation times across difficulty levels, $F(1, 46) = 6.344$, $p = .015$, $\eta_p^2 = .12$, with greater planning time observed at follow-up compared to baseline. A marginal Group × Time

interaction on first move initiation time was observed for 4-move problems. Groups did not significantly differ at baseline, $F(1, 49) = 1.077$, $p = .304$, $\eta_p^2 = .11$, but were significantly different at follow-up, $F(1, 48) = 4.332$, $p = .043$, $\eta_p^2 = .08$, with cannabis users demonstrating faster initiation times than controls (Figure 6).

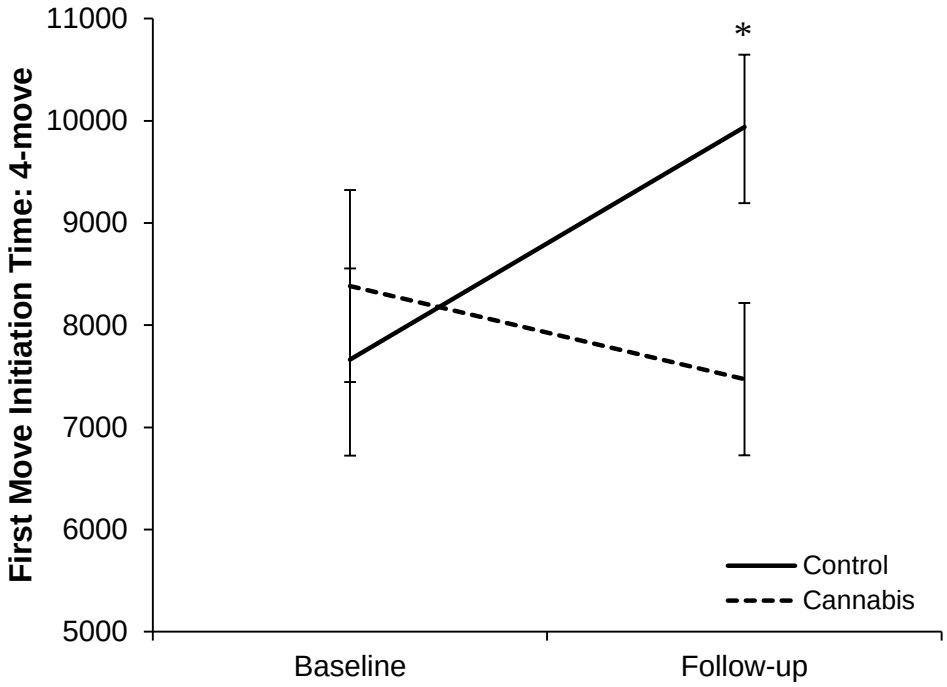

Figure 6. Change between baseline and follow-up on first move initiation time for 4-move problems. Error bars represent standard errors. Means reported are marginal means, controlling for interval, sex, IQ, and average alcohol use at baseline and follow-up.

Motivated Decision-Making

The IGT was examined using a repeated measures ANCOVA, with IGT block (total good minus bad choices over five blocks of the task) and time point (baseline and follow-up) as within subjects factors and group status as a between-subjects factor. A significant main effect of improvement over time, $F(1, 45) = 11.411$, $p = .002$, $\eta_p^2 = .20$, as well as a Group × Time interaction, $F(1, 45) = 9.788$, $p = .003$, $\eta_p^2 = .18$, and an IGT

Block × Group interaction, $F(2.80, 125.86) = 3.692$, $p = .016$, $\eta_p^2 = .08$, were observed, whereas main effects of IGT block or group, or Time × IGT block or Group × Time × IGT block interactions were not observed (Figure 7).

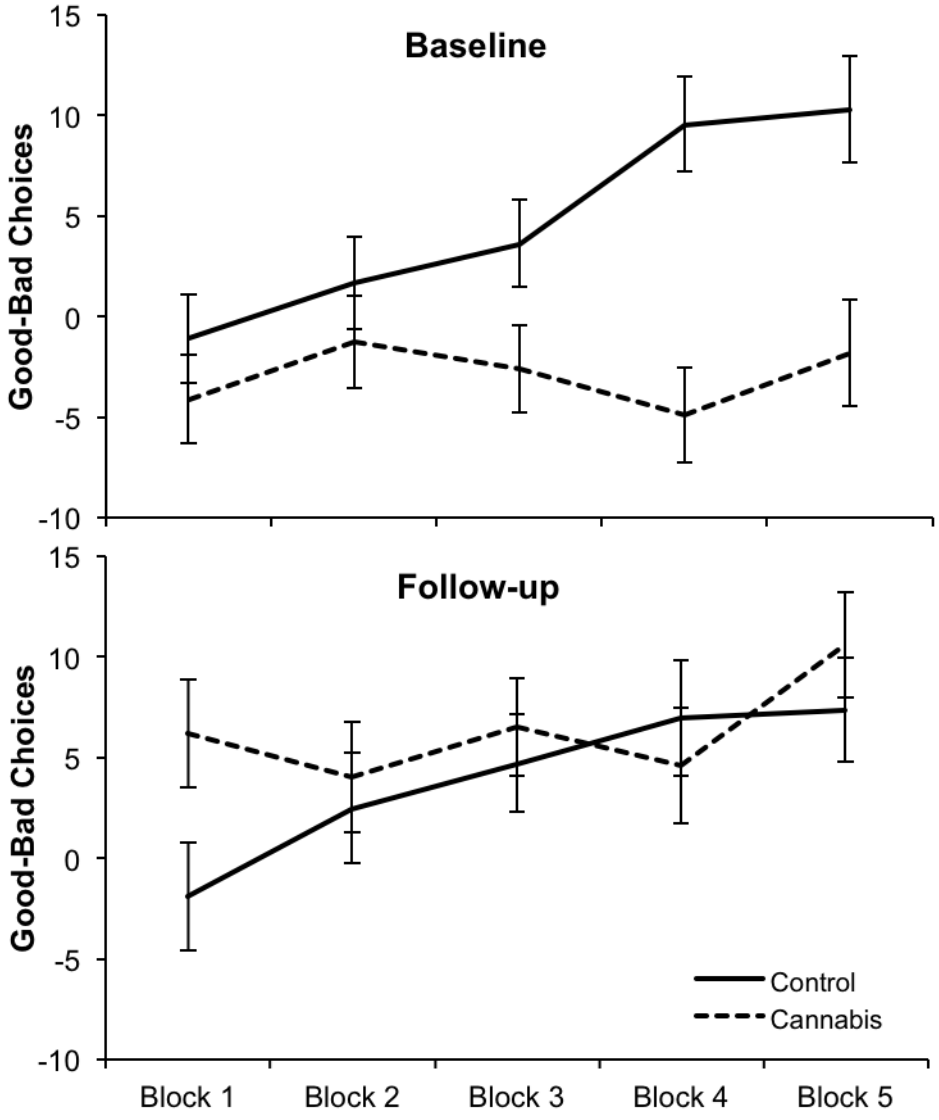

Figure 7. IGT good minus bad deck choices across blocks at baseline and follow-up. Error bars represent standard errors. Means reported are marginal means, controlling for interval, sex, IQ, and average alcohol use at baseline and follow-up.

To more fully understand the interactions, a repeated measures ANCOVA, with IGT block and time point as within subjects factors, was repeated for each group

separately. Both groups demonstrated a main effect of time (controls: $F(1, 20) = 5.165$, $p = .034$, $\eta_p^2 = .20$; cannabis users: $F(1, 21) = 6.396$, $p = .020$, $\eta_p^2 = .23$), demonstrating improvement between baseline and follow-up, and cannabis users demonstrated a Time Point × Interval interaction, $F(1, 21) = 8.621$, $p = .008$, $\eta_p^2 = .29$, whereas controls did not show this effect ($p = .789$, $\eta_p^2 < .00$). Greater advantageous choices at follow-up were associated with shorter time interval to follow-up only among cannabis users (cannabis $r_{partial} = -.595$, $p = .004$; controls $r_{partial} = -.178$, $p = .439$), controlling for IQ, sex, and average alcohol use.

To characterize group differences at follow-up, a repeated measures ANCOVA with IGT block as a within subjects factor and group status as a between-subjects variable. Main effects of IGT block ($p = .961$, $\eta_p^2 < .00$), group ($p = .409$, $\eta_p^2 = .02$), and a Group × IGT Block interaction ($p = .261$, $\eta_p^2 = .03$) were all non-significant. Groups differed at baseline but showed equivalent performance at follow-up.

To explore performance change between baseline and follow-up across blocks, repeated measures ANCOVAs were performed with time point (baseline and follow-up) as a within subjects factor and group as a between-subjects factors (main effects of group and Group × Time interactions are reported in Table 11). Significant and marginal main effects of time were observed for Block 1 $F(1,45) = 7.781$, $p = .008$, $\eta_p^2 = .15$, Block 2 $F(1,45) = 7.691$, $p = .008$, $\eta_p^2 = .15$, Block 3, $F(1,45) = 3.956$, $p = .053$, $\eta_p^2 = .08$, and Block 5, $F(1,45) = 6.859$, $p = .012$, $\eta_p^2 = .13$, all indicating better performance at follow-up relative to baseline. When groups were analyzed separately, only cannabis users demonstrated a main effect of time across the majority of blocks (cannabis user Block 1:

$p = .009$, $\eta_p^2 = .28$; Block 2: $p = .041$, $\eta_p^2 = .18$; Block 4: $p = .005$, $\eta_p^2 = .33$; Block 5: $p = .014$, $\eta_p^2 = .25$), and controls did not (control Block 1: $p = .814$, $\eta_p^2 < .00$; Block 2: $p = .122$, $\eta_p^2 = .12$; Block 4: $p = .182$, $\eta_p^2 = .09$; Block 5: $p = .121$, $\eta_p^2 = .12$). Cannabis users and controls had equivalent Block 1 performance at both baseline ($p = .693$, $\eta_p^2 < .00$) and follow-up ($p = .136$, $\eta_p^2 = .02$). On Blocks 4 and 5, cannabis users made fewer choices from good decks than controls at baseline, but cannabis users and controls had equivalent performance at follow-up, (Block 4: $p = .455$, $\eta_p^2 = .01$; Block 5: $p = .917$, $\eta_p^2 < .00$). Overall, analyses revealed that group differences at baseline accounted for the interactions observed in the omnibus repeated measures ANCOVA, and that groups had equivalent performance at follow-up. Cannabis users showed more improvement over time than controls.

Examination of specific deck selections (deck contingencies described in Table 5; main effects of group and Group × Time interactions reported in Table 11; Figure 8) revealed a main effect of time for choices from Deck 1, $F(1,45) = 6.663$, $p = .013$, $\eta_p^2 = .13$, and Deck 2, $F(1,45) = 7.920$, $p = .007$, $\eta_p^2 = .15$, indicating that participants made fewer choices from the two disadvantageous decks at follow-up compared to baseline. However, when groups were considered separately, only cannabis users had a main effect of time (cannabis user Deck 1: $p = .006$, $\eta_p^2 = .31$, Deck 2: $p = .026$, $\eta_p^2 = .22$; control Deck 1: $p = .733$, $\eta_p^2 < .00$; Deck 2: $p = .391$, $\eta_p^2 = .04$).

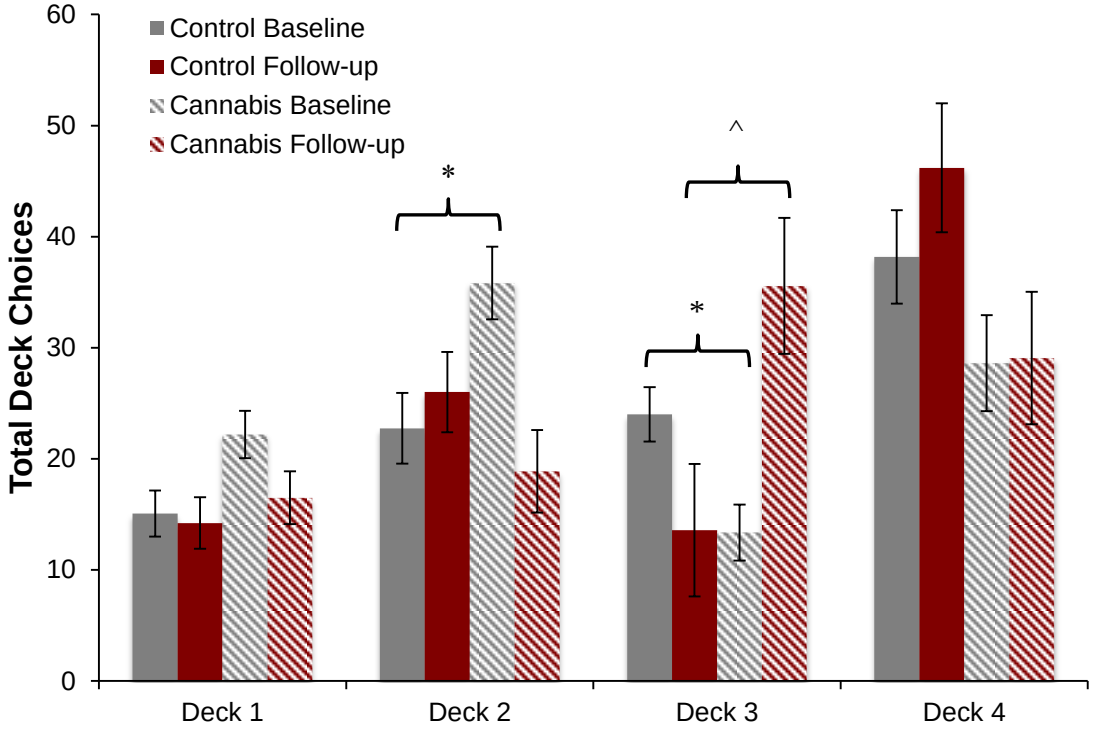

Figure 8. IGT Deck selections at baseline and follow-up for cannabis users and controls. Error bars represent standard errors. Means reported are marginal means, controlling for interval, sex, IQ, and average alcohol use at baseline and follow-up.

Significant Group × Time interactions for Decks 2 and 3 were followed-up with ANCOVAs to explore group differences at baseline and follow-up (Figure 8). Follow-up analyses of Deck 2 choices indicated that cannabis users made more selections from this disadvantageous deck at baseline, but that there were no group differences at follow-up (p = .362, η_p^2 = .02). For choices from Deck 3, cannabis users made fewer choices than controls from this advantageous deck at baseline, and there was a trend for cannabis users to make more deck 3 choices than controls at follow-up, $F(1,46) = 3.585$, p = .065, η_p^2 = .07. A main effect of group was observed for choices from Deck 4, with cannabis users making fewer sections than controls from this deck.

Influence of Abstinence or Reduced Use at Follow-up

While the majority of the cannabis user sample reported continued heavy cannabis use at follow-up, 2 cannabis users reported occasional use (< 20 hits in past year) and 1 user reported abstinence during the follow-up assessment. Significant findings from the repeated measures ANCOVAs remained largely unchanged when these cannabis users who reported markedly reduced cannabis use at follow-up (n = 3) were excluded. Marginal main effects of group on the verbal learning and memory composite, $F(1,46) = 4.316$, $p = .043$, $\eta_p^2 = .09$, and RAVLT Trial 1, $F(1,46) = 5.185$, $p = .027$, $\eta_p^2 = .10$, became fully significant, as did the Group × Time interactions for the average reaction time on the DRT 500 ms condition, $F(1,46) = 4.470$, $p = .040$, $\eta_p^2 = .09$, and total good deck selections on the IGT, $F(1,42) = 4.342$, $p = .043$, $\eta_p^2 = .09$. The main effect of group on IGT Deck 4 choices was reduced to a trend, $F(1,42) = 2.808$, $p = .100$, $\eta_p^2 = .06$. The direction of findings remained unchanged in all analyses.

1.3.2.4 Hierarchical Regression within Cannabis Users

Hierarchical regression analyses were conducted to examine the prediction of cognitive task performance at follow-up from cannabis use characteristics within the cannabis users, above and beyond what would be expected given their baseline performance. Baseline cognitive performance, time interval to follow-up, sex, IQ, and average alcohol use during baseline and follow-up were entered in the first step as nuisance variables. Cannabis use predictors of interest were entered in the second step, and included the total number of hits within the last 12 months and age of cannabis use onset. Both cannabis use variables are the most commonly reported in the adolescent and

young adult cannabis user literature. Change in R^2 at each step was explored to assess predictors' contribution to model fit. Separate regression analyses with the cognitive composites and all cognitive measure variables as dependent variables were conducted. Analyses in which cannabis use predictors contributed to a significant portion of the dependent variable's variance are described below. To represent the association between follow-up cognitive performance and cannabis use across the entire cognitive battery, partial correlations between all follow-up cognitive performance measures and the cannabis use variable of interest, controlling for the covariates described above, are reported in Table 12.

Baseline Cannabis Use Predicting Cognition at Follow-up

In this set of analyses, the cannabis use variable of interest was the total number of hits reported at baseline. The dependent variable was follow-up cognitive performance. Baseline cognitive performance, time interval to follow-up, sex, IQ, and average alcohol use during baseline and follow-up were entered in the first step as nuisance variables.

Verbal learning and memory. A higher number of total hits reported at baseline was significantly associated with fewer words recalled during the RAVLT learning trials at follow-up ($r_{partial}$ = -.514, p = .014; Figure 9; Table 13 provides full hierarchical regression model). A follow-up partial correlation analysis within the follow-up cannabis user sample found that baseline total number of hits within the last 12 months was not correlated with trial 1-5 total words recalled at baseline, with sex, IQ, and average alcohol use at baseline covaried ($r_{partial}$ = .055, p = .813).

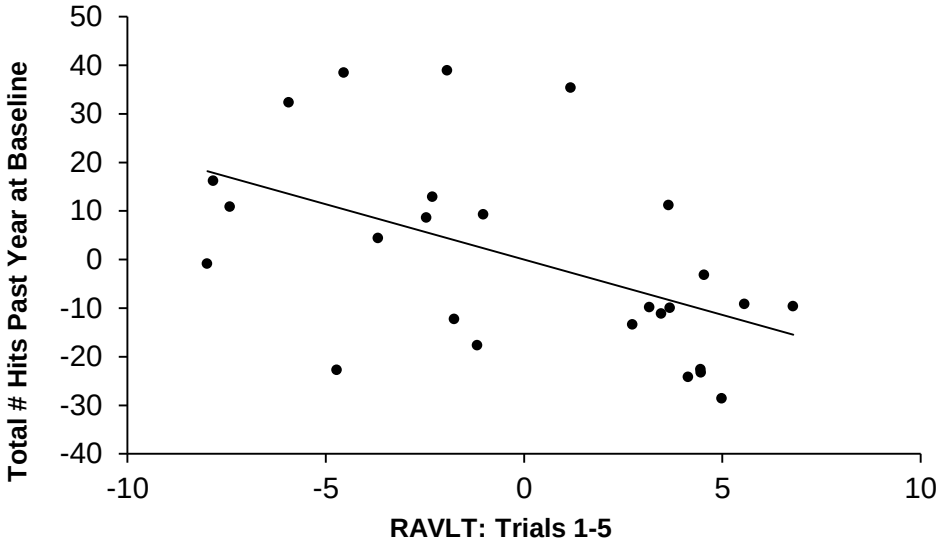

Figure 9. Scatterplot of follow-up RAVLT Trial 1-5 performance by baseline total hits in the past year. Partial regression plot controlling for baseline cognitive performance, interval, sex, IQ, and average alcohol use at baseline and follow-up.

Follow-up Cannabis Use Predicting Cognition at Follow-up

Next, the cannabis use variable of interest was the total number of hits reported at follow-up. Follow-up total number of hits within the last year was regressed on baseline total number of hits within the last year, and the unstandardized residuals from the model were saved and used as the cannabis use variable of interest representing the variance attributed to cannabis use at follow-up, controlling for baseline use. In the regression model predicting follow-up cognitive performance, baseline cognitive performance, interval between assessments, sex, IQ, and average alcohol use between baseline and follow-up were was entered in the first step, and the unstandardized residual of follow-up regressed on baseline total number of hits within the last year was entered in the second step.

Processing speed. Within the whole cannabis user group, a higher number of total hits reported at follow-up was significantly associated with better follow-up processing speed ($r_{partial}$ = .501, p = .021), and verbal fluency ($r_{partial}$ = .521, p = .016). However, these relationships were reduced to non-significance after removal of two influential data points (Table 12).

Age of Cannabis Use Onset Predicting Cognition at Follow-up

Next, the age of cannabis use onset was examined in relation to follow-up cognitive performance. For each task variable, follow-up cognitive performance was predicted, using hierarchical regression analyses, with baseline cognitive performance, time interval to follow-up, sex, IQ, and average alcohol use at baseline and follow-up entered in Step 1, and age of cannabis use onset entered in Step 2.

Verbal learning and memory. A later age of cannabis use onset was associated with better performance on forward digit span at follow-up ($r_{partial}$ = .479, p = .028; Figure 10; Table 14 for full regression model). A follow-up partial correlation analysis within the follow-up cannabis user sample found that age of regular cannabis use onset was not significantly associated with baseline forward digit span, with sex, IQ, and average alcohol use at baseline covaried ($r_{partial}$ = .126, p = .587).

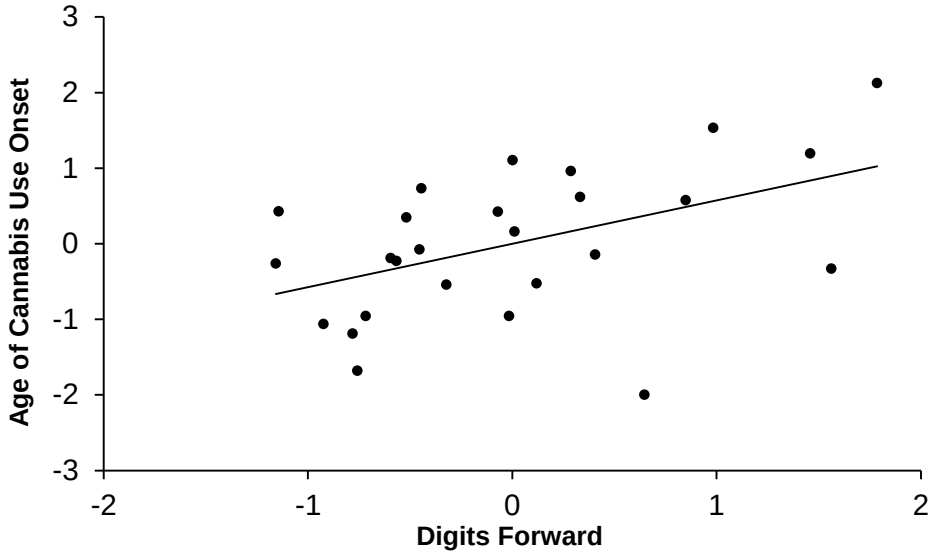

Figure 10. Scatterplot of follow-up Digit Span Forward performance by age of cannabis use onset. Partial regression plot controlling for baseline cognitive performance, interval, sex, IQ, and average alcohol use at baseline and follow-up.

A later age of cannabis use onset was also associated with better follow-up performance on the learning and memory composite ($r_{partial}$ = .507, p = .019; Table 15 for full regression model; Figure 11), and the alcohol use predictor was marginally associated with performance, such that higher alcohol use was associated with better performance (b* = .302, p = .057; Table 15). As reported in section 1.3.1.4 above, age of cannabis use onset was not significantly correlated with the learning and memory composite score at baseline in a partial correlation controlling for sex, IQ, alcohol, tobacco, and other drug use within the full cannabis user sample at baseline (Table 8).

Examination of RAVLT task variables revealed that a later age of onset was associated with better follow-up performance on the RAVLT for the sum of all learning trials, trials 1-5, ($r_{partial}$ = .530, p = .013), delayed recall ($r_{partial}$ = .560, p = .008), and percentage of learned words recalled after consolidation ($r_{partial}$ = .503, p = .020). See

Table 15 for full regression models and Figure 11. Higher alcohol use marginally predicted better delayed recall performance (b^* = .248, p = .086; Table 15). Within the full cannabis sample at baseline, age of cannabis use onset was not correlated with delayed recall performance or percentage of learned words recalled after consolidation (Table 8). A follow-up partial correlation within the follow-up cannabis user sample found that age of regular cannabis use onset was marginally associated with trial 1-5 total words at baseline, with sex, IQ, and average alcohol use at baseline covaried ($r_{partial}$ = .381, p = .089), showing the same directional relationship observed at follow-up.

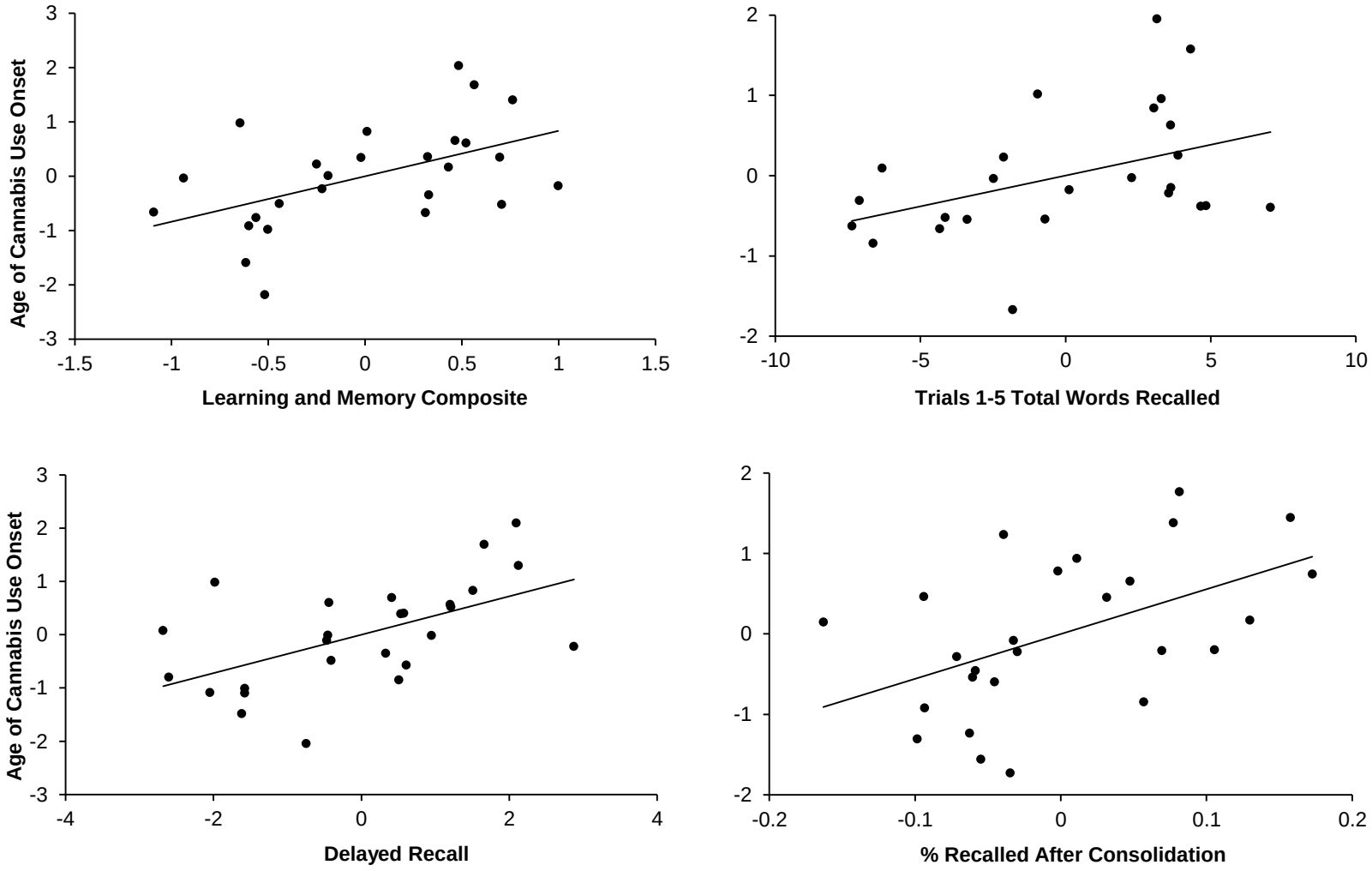

Figure 11. RAVLT scatterplots of follow-up performance by age of cannabis use onset. Partial regression plot controlling for baseline delayed recall performance, interval, sex, IQ, and average alcohol use at baseline and follow-up.

Planning. Within the whole cannabis user group, a later age of cannabis use onset was associated with a greater percentage of perfect solutions ($r_{partial}$ = .485, p = .030), and better performance on 5-move problems ($r_{partial}$ = -.450, p = .047). However, these relationships were reduced to non-significance after removal of an influential data point (Table 12).

Motivated decision-making. There was a trend association between an earlier age of onset and fewer choices from disadvantageous Deck 2 at follow-up ($r_{partial}$ = -.406, p = .076; Table 16; Figure 12). A follow-up partial correlation, controlling for sex, IQ, and average alcohol use at baseline, indicated that Deck 2 selections at baseline were not associated with age of cannabis use onset ($r_{partial}$ = -.026, p = .912).

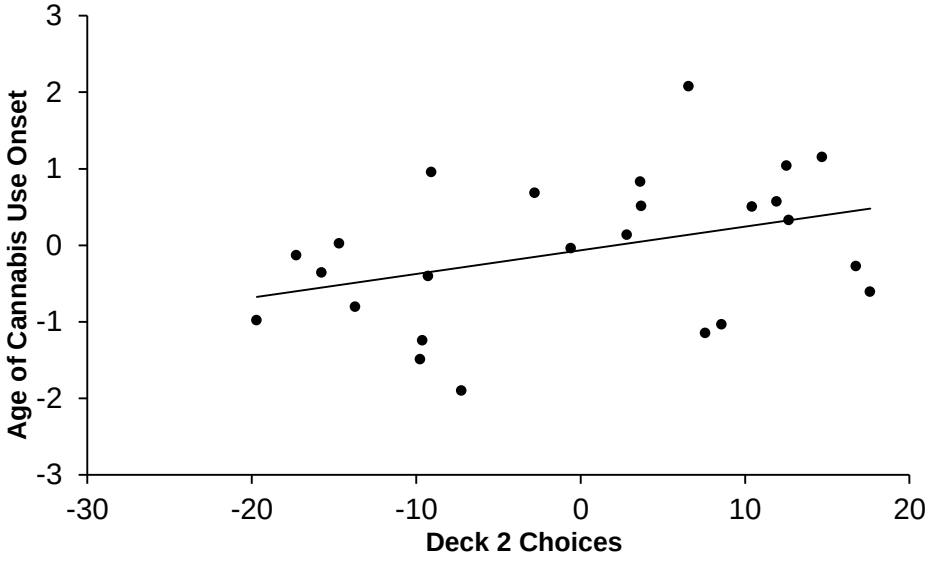

Figure 12. Scatterplot of follow-up IGT deck 2 choices by age of cannabis use onset. Partial regression plot controlling for baseline deck 2 choices, interval, sex, IQ, and average alcohol use at baseline and follow-up.

1.4 Discussion

This study assessed neuropsychological performance among a sample of young adult heavy cannabis users, then re-assessed neuropsychological performance after two years of continued heavy use within the majority of the sample. The study sample is largely overlapping with that used in a prior analysis of baseline neurocognitive performance (Becker et al., 2014), and the baseline results in the present analysis mirror those of the earlier paper. As predicted, cannabis users demonstrated relative weaknesses in the domains of verbal learning and memory, spatial working memory, spatial planning, and motivated decision-making at baseline when compared to non-using demographically-matched controls. These findings are consistent with cross-sectional studies that find deficits in the domains of abstract reasoning, decision-making, and verbal memory in young adult users (Bossong, Jager, Bhattacharyya, & Allen, 2014; Crean, Crane, & Mason, 2011; Lisdahl et al., 2013; Solowij & Battisti, 2008). Beyond cannabis user samples, neuropsychological impairments in episodic memory and decision-making are generally found among substance using samples, while more specific impairments are noted in the domains of planning and prospective memory among cannabis users (reviewed in Fernández-Serrano, Pérez-García, & Verdejo-García, 2011). The baseline cognitive profile of cannabis users shares many of the common deficits noted among substance using populations as well as the specific deficits more commonly found among cannabis users. Further, the relative deficits noted were not accounted for by the impact of other substance use, since alcohol use and non-cannabis

drug use were either unrelated to performance or associated with better performance on measures that distinguished the groups.

Unexpectedly, cannabis users exhibited a relative strength in the domains of verbal fluency and processing speed, strengths not typically noted among cannabis users. Processing speed/complex attention (Croft et al., 2001; Fried et al., 2005; Lisdahl & Price, 2012; Medina et al., 2007; Winward, Hanson, Tapert, & Brown, 2014) and verbal fluency (Fernández-Serrano et al., 2011) are among the domains commonly reported to be diminished among cannabis users, and are generally noted to be impaired among substance using populations. However, cannabis users in the current sample demonstrated high average IQs, which is a sample characteristic not typically noted among cannabis user samples that demonstrate lower processing speed performance (Fernández-Serrano et al., 2011; Lisdahl & Price, 2012; Medina et al., 2007). This difference in general intellectual ability may account for the discrepancy between the current findings and those reported in other cannabis user samples. The notable cognitive strengths displayed by the current sample make the findings of cognitive deficits relative to control participants all the more striking. Despite these strengths, selective impairments in important cognitive domains emerged among users.

At follow-up, cannabis users continued to report regular and heavy cannabis use in general. It was expected that the neuropsychological deficits observed at baseline would persist at follow-up given the continued high level of use among cannabis users. This hypothesis was only partially supported. As expected, the relative cognitive deficits observed in the domains of planning and delayed verbal memory remained stable at

follow-up, suggesting that these are stable cognitive vulnerabilities associated with continued cannabis use during young adulthood. When analyses were restricted to cannabis users who continued regular and heavy cannabis use, the group difference in verbal learning and memory became more pronounced. Poorer verbal memory performance is the most robust finding that characterizes non-acutely high cannabis users' neurocognitive profile both in the context of regular use and after periods of sustained abstinence (Bolla et al., 2002; Cuttler et al., 2012; Gonzalez et al., 2012; I. Grant et al., 2003; Hanson & Luciana, 2010; Hanson et al., 2010; Harvey et al., 2007; Jacobsen, Pugh, Constable, Westerveld, & Mencl, 2007; Medina et al., 2007; Pope & Yurgelun-Todd, 1996; Schwartz et al., 1989; Solowij, Jones, et al., 2011; Tait et al., 2011; Takagi, Yücel, et al., 2011; Wagner et al., 2010). The verbal learning and memory task is good measure of internal motivation and effortful performance. Participants must develop and use efficient strategies to facilitate learning and memory recall. A high level of cognitive control and self-organization that relies on coordinated frontal and medial temporal mechanisms is required for successful encoding and retrieval of information (Long, Oztekin, & Badre, 2010).While cannabis users in this study acquired learning at the same rate and magnitude as controls, they exhibited greater loss of information after learning consolidation at both time points. This pattern is consistent with the use of less efficient strategies rather than disruptions in consolidation.

Alterations in cognitive and neural efficiency could emerge from cannabinoid-mediated neuroplastic changes among chronic users. Chronic cannabinoid exposure induces a variety of changes in synaptic transmission across different neurotransmitters

and brain regions, notably within the prefrontal cortex and limbic system (Bossong et al., 2014; Heifets & Castillo, 2009; Lubman, Cheetham, & Yücel, 2015). Functionally, chronic cannabis use is associated with activation of alternative brain regions in the context of control-level task performance on fMRI and ERP studies (Battisti, Roodenrys, Johnstone, Respondek, et al., 2010; Harding et al., 2012; Tapert et al., 2007), with earlier age of onset associated with greater alterations. The finding that extent and age of cannabis use were associated with poorer verbal learning and memory performance over time provides further support for this interpretation. Recruitment of alternative pathways may provide compensatory, but less efficient, functional networks. Less efficient networks may be overly taxed during more complex and effortful tasks, producing poorer performance.

While fewer studies have examined planning ability among cannabis users, a general trend has emerged that planning ability is diminished in the context of regular use (Epstein & Kumra, 2015; J. E. Grant et al., 2012; McHale & Hunt, 2008; Montgomery et al., 2012). Cannabis users' performance on the planning task was impaired only on the relatively easy 3-move problems. These problems are less complex than subsequent trials, and can be completed using perceptual rather than representational cues. Typically, less than optimal performance on relatively easy tasks in the context of normal performance on more challenging tasks is interpreted as a motivational deficit, (Lezak et al., 2004), where effort-based resources are more strongly allocated to more challenging relative to less challenging problems.

The finding that cannabis users' performance improved to control-level performance on measures of spatial working memory and motivated decision-making was unexpected. Baseline performance deficits noted among cannabis users in these domains were consistent with cross-sectional evidence of spatial working memory (Harvey et al., 2007) and motivated decision-making (Fridberg et al., 2010; Yechiam et al., 2005) deficits among cannabis users. However, this literature is limited by a total lack of longitudinal assessment of both domains. The current findings suggest that with repeated experience with both tasks, cannabis users' performance recovers to control-level performance, even in the context of continued cannabis use. Cannabis users continued regular use, but reported an overall decline in use from baseline to follow-up. It is possible that the reduction in use resulted in the improvements noted on these two tasks, though dose-dependent relationships between change in use and performance change were not observed at follow-up. Cross-sectional studies find that after reduction or cessation of use, some cognitive performance deficits in young adults resolve (Fried et al., 2005; Medina et al., 2007). Longitudinal evidence also supports some recovery of cognitive function in the context of continued use. A recently-reported longitudinal study that followed young adult alcohol+cannabis users, similar to the current study, found that along with reductions in cannabis use, deficits in processing speed/complex attention and visuospatial construction reported at a 1.5 year follow-up had resolved to control-level performance by the 3-year follow-up (Jacobus et al., 2015). Further longitudinal research is needed to replicate these findings and clarify if decreased use is the mechanism driving these findings.

Another possible mechanism accounting for the recovery in performance on certain cognitive tasks could be "behavioral tolerance" to the effects of cannabis with sustained use. In acute administrations, regular cannabis users display better performance relative to occasional cannabis users on measures of attention (Desrosiers, Ramaekers, Chauchard, Gorelick, & Huestis, 2015; Ramaekers, Kauert, Theunissen, Toennes, & Moeller, 2009; Theunissen et al., 2012), and measures of road-tracking control while driving (Bosker et al., 2012). As described above, chronic cannabis use is associated with activation of alternative functional networks during cognitive task performance. Alternative and compensatory networks may be sufficient to support performance when completing simpler tasks (Hart, Van Gorp, Haney, Foltin, & Fischman, 2001). More complex tasks that require more cognitive resources may remain vulnerable to the acute effects of cannabis, since performance on more complex and effortful tasks of executive functioning remains diminished among both regular and occasional users when acutely intoxicated (Ramaekers et al., 2009; Theunissen et al., 2012). The link between behavioral tolerance and recovery of cognitive performance on select measures reported in this study, including spatial working memory and motivated decision-making, is speculative and more longitudinal research is needed to examine this potential relationship.

Beyond observing stable deficits, I expected that continued and heavy cannabis use would be associated with cognitive decline over time. However, this relationship was not observed. Cannabis users demonstrated control-level performance during the follow-up assessment across many measures of the neurocognitive battery, and no new areas of

weakness emerged at follow-up. While these findings were unexpected, they are largely consistent with those reported by Jacobus and colleagues (2015), who found stable working memory and verbal memory deficits at all assessments, with only verbal learning performance worsening over time. Neither Jacobus et al. (2015) nor the current study support the hypothesis that widespread cognitive impairments develop over a 2-3 year period in the context of sustained cannabis use during early adulthood. Instead, select cognitive impairments in verbal learning and memory and executive functioning, noted at baseline, persist over the follow-up interval, while relative deficits in other cognitive domains improve to control-level performance by follow-up.

Examination of cannabis use patterns revealed that cannabis use during adolescence, rather than young adulthood, exerted an impact on neurocognitive performance at follow-up, specifically in the domain of verbal learning and memory. Extent of cannabis use at *baseline,* and not the time to follow-up interval, was associated with diminished follow-up verbal learning performance. Similarly, as expected, earlier age of regular cannabis use was associated with poorer verbal working memory and verbal learning and memory performance. Extent and age of regular use were not associated with these measures at baseline, with the exception of a marginal relationship between verbal working memory and age of use, and the majority of measures only emerged as predictors of performance decline over time. These findings support the current theory that the magnitude and timing of adolescent cannabis use plays an important role in the trajectory of neural development and cognitive performance over time, irrespective of continued use patterns during young adulthood (Lisdahl et al., 2013).

This theory has been supported by longitudinal evidence linking earlier cannabis use with poorer processing speed and sequencing ability during young adulthood (Jacobus et al., 2015) and greater IQ decline during adulthood (Meier et al., 2012), as well as cross-sectional evidence that earlier use is associated with poorer IQ (Pope et al., 2003), attention (Ehrenreich et al., 1999), visual search (Huestegge, Radach, & Kunert, 2009), verbal fluency (Gruber, Sagar, et al., 2012), and executive functioning performance (Battisti, Roodenrys, Johnstone, Pesa, et al., 2010; Fontes et al., 2011; Gruber, Dahlgren, Sagar, Gönenç, & Killgore, 2012; Gruber, Sagar, et al., 2012). While this association was expected, the current study is the first to document this finding longitudinally in the domain of verbal learning and memory. Given that learning and memory is the neurocognitive domain most commonly impaired among cannabis users, this is an important contribution to the current understanding of adolescent cannabis use.

Though the current study's findings are suggestive of selective patterns of impairment that emerge as a consequence of use and replicate findings reported in the literature, cause-effect associations cannot be determined because users were not assessed prior to initiation of use. It could be that premorbid levels of function were impaired in cannabis users prior to use onset. Cognitive vulnerabilities may contribute to early initiation and continued cannabis use, which then manifest in later testing (Iacono, Malone, & McGue, 2008). Parsing the causes from effects of substance use is very challenging, and further research is need to dismantle the general liabilities associated with substance use and the specific effects caused by regular use.

Important limitations must be noted for the current study. To provide a full view of the data and replicate other studies, the statistical comparisons in this study were not corrected for multiple comparisons. Many of the findings interpreted as significant in the present study would not remain if more rigorous statistical thresholding was employed.

Another limitation of the current study is the overrepresentation of males in the cannabis user sample, which is consistent with the sex distribution of cannabis users in the United States (Substance Abuse and Mental Health Services Administration, 2014). Sex was controlled in all statistical analyses; however, findings cannot be readily generalized to female marijuana users. A further limitation that it is difficult to quantify the precise level of cannabis exposure given that the potency of cannabis is not standard. While there was an attempt to quantify it by calculating number of hits, this measure does not address potency or the amount of drug ingested during a hit. Drug testing was not employed to quantify cannabis exposure at the time of testing or confirm levels of reported use. Multiple interview and self-report measures were used to assess substance use characteristics, and the level of detail that participants conveyed regarding their use patterns was convincing in terms of the likelihood that they were, indeed, heavy cannabis users, an assumption validated by their reports of symptoms of cannabis dependence. A related limitation is that the majority of the cannabis user sample demonstrated homogenous use patterns at both baseline and follow-up, reducing the ability to detect dose-response associations over time.

Additionally, while cannabis users were not acutely high during testing, the possibility that the cognitive differences observed in this sample are due to residual

effects of cannabis use cannot be ruled out. That said, given that performance was largely unimpaired, this potential limitation appears unlikely unless residual effects of cannabis confer cognitive advantages. The current assessment provides a comprehensive cognitive profile of otherwise high functioning individuals in the context of current cannabis use. This profile allows us to make real-world inferences about how regular and sustained cannabis use might impact cognition. In order to minimize potential confounds, high functioning individuals were recruited, with comparable education and IQ to other young adult controls, and a low level of psychopathology. While this feature of the study can be considered a strength since the sample of users represents college-aged individuals who heavily use the drug, it may limit generalizability to other cannabis-using samples who evidence more externalizing behavior, less education, and more psychopathology. The expectation is that they would show greater levels of impairment. Another possible concern is that cannabis users were in active states of withdrawal during testing, affecting the results. Cannabis users were asked to abstain for at least a 24 hours period prior to the assessment, but were accepted if they reported abstinence for at least 12 hours prior to assessment. This possibility appears unlikely given the normative psychomotor performance and relative strength in processing speed exhibited by cannabis users at both time points, which is inconsistent with behaviors that individuals in the midst of cannabis withdrawal demonstrate (Haney et al., 2001).

While these behavioral findings add to the growing corpus of longitudinal studies of cannabis-using individuals, they would be incomplete without consideration of how neural systems are impacted by use. The next study addresses this issue.

2 Study 2: Longitudinal Changes in White Matter Microstructure in Young Adult Cannabis Users

This chapter focuses on longitudinal changes in white matter microstructure in the sample of adolescent-onset young adult cannabis users discussed in the first study. White matter microstructure is important to examine in this sample because it is a measure of brain connectivity and organization, and disruptions in connectivity may underlie the behavioral deficits discussed in Study 1. Very few studies have examined the neurobiological underpinnings of behavioral deficits noted among cannabis users, and a clear biological mechanism driving the deficits is lacking in the literature. White matter is one potential mechanism driving these differences among adolescent-onset cannabis users.

Adolescence and young adulthood are critical periods of neural maturation, during which there is reorganization of cortical connections, an increase in the fidelity of corticolimbic interactions, and neurochemical changes that promote adaptive behavioral regulation (Colby et al., 2011; Giedd, 2004; O'Hare & Sowell, 2008; Wahlstrom, Collins, White, & Luciana, 2010). Grey matter develops along a nonlinear trajectory, with peak proliferation prior to puberty, then gradual grey matter decline and pruning during adolescence and young adulthood, extending into the 30s (Giedd, 2004; Giedd et al., 1999; Gogtay et al., 2004; Pfefferbaum et al., 1994; Sowell et al., 2003; Sowell, Thompson, Tessner, & Toga, 2001). In contrast, white matter volume develops linearly from childhood to adolescence (Giedd et al., 1999; Paus et al., 2001), following a posterior-inferior to anterior-superior developmental trajectory (Colby et al., 2011;

Sowell, Thompson, Holmes, Jernigan, & Toga, 1999) and does not reach its peak until adulthood, between the mid-30s and 40s (Bartzokis et al., 2001; Sowell et al., 2003; Westlye et al., 2010). White matter improves the efficiency of signal conduction between brain regions, and its development is associated with improved cognitive control and executive functioning performance during adolescence (Peters et al., 2014; Treit, Chen, Rasmussen, & Beaulieu, 2013).

Diffusion Tensor Imaging (DTI) is a sensitive neuroimaging technique that characterizes white matter microstructure, and yields measures of the directional organization of white matter (fractional anisotropy: FA), averaged water diffusion in all directions (mean diffusivity: MD), and water diffusion perpendicular to the primary fiber orientation (radial diffusivity: RD). In general, increases in FA and decreases in MD and RD are observed in major white matter fiber tracts throughout adolescence and extending into adulthood. Reduction in RD has been associated with increased myelination and axonal packing in animal models (Budde et al., 2007; Song et al., 2003, 2005), and age-related changes in FA in humans are often attributed to decreased RD (Giorgio et al., 2008; Lebel & Beaulieu, 2011; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). The biological mechanisms that drive MD changes are less clear.

Estimates of peak development of white matter microstructure vary between ages 20-42 (Kochunov et al., 2012; Lebel et al., 2012; Schmithorst & Yuan, 2010; Westlye et al., 2010). There is considerable regional variability in the maturational timing of white matter microstructure, with earlier maturation in commissural and projection white matter tracts, and later development during adolescence and young adulthood in the association

tracts (Ashtari et al., 2007; Kochunov et al., 2012; Lebel & Beaulieu, 2011; Lebel et al., 2008).

As is the case with other active periods of brain development (Fride, 2008; Huizink, 2014; Linnet et al., 2003), substance use during adolescence and young adulthood may interfere with normative development, altering the structural integrity and function of the adult brain. A growing literature suggests there are neurocognitive deficits and neuroanatomical alterations among adolescent and young adult cannabis users relative to non-users. Behaviorally, cannabis use in adolescence and young adulthood is most commonly associated with relative deficits in verbal learning and memory, decision-making, and executive functioning (reviewed in Study 1).

Neuroimaging studies find alterations in brain structure and function associated with use. Reduced hippocampal (Ashtari et al., 2011; Demirakca et al., 2011; Filbey, McQueeny, Kadamangudi, Bice, & Ketcherside, 2015; Lorenzetti et al., 2014; Schacht, Hutchison, & Filbey, 2012; Yücel et al., 2008), parahippocampal gyrus (Battistella et al., 2014; Matochik, Eldreth, Cadet, & Bolla, 2005), orbital frontal (Battistella et al., 2014; Churchwell, Lopez-Larson, & Yurgelun-Todd, 2010; Filbey et al., 2014), and increased cerebellum (Battistella et al., 2014; Cousijn et al., 2012; Medina, Nagel, & Tapert, 2010) gray matter volumes are among the more consistent findings within cannabis users. Alterations in amygdala gray matter are also reported, but the direction of alterations varies between reports (Gilman et al., 2014; Lorenzetti et al., 2014; Schacht et al., 2012; Yücel et al., 2008). The degree to which groups are matched on the potential confounds of sex, age, and other substance use varies between studies. One notable recent study

found no group differences between cannabis users and controls, who were matched on alcohol use, on measures of gray matter morphology in the nucleus accumbens, amygdala, hippocampus, and cerebellum, suggesting alcohol use or other confounds may significantly contribute to reported group differences (Weiland et al., 2015). Further, findings across studies suggest cannabis use likely exerts only a modest effect on gray matter volume, indicating that large sample sizes may be needed to detect a true effect (Weiland et al., 2015).

Among MRI and positron emission tomography (PET) studies of functional relationships among brain regions, cannabis users demonstrate altered patterns of brain activity when compared to non-using controls, particularly within the prefrontal cortex (Batalla et al., 2013), orbitofrontal network (Filbey et al., 2014), prefrontal and occipitoparietal cortex (Harding et al., 2012), and frontal-subcortical network (Filbey & Yezhuvath, 2013). A potential mechanism driving these differences may be disruption of white matter fiber tracts that support signaling between neurons within and across neural nodes. Cannabinoid receptors are widely distributed in white matter fiber tracts (Romero et al., 1997), and exhibit higher binding capacity in white matter structures during development as opposed to adulthood (Romero et al., 1997; Zalesky et al., 2012). Disruption of the endocannabinoid system during development could alter white matter development, and, in turn, the efficiency of neural signaling.

The direction of alterations in white matter volume in a variety of cortical and subcortical regions has been inconsistently reported in cannabis users, with one group finding increased density of white matter associated with the left parahippocampal and

fusiform gyri and lower density in left parietal lobe white matter (Matochik et al., 2005), and a second group noting cerebellar white matter volume reduction in cannabis users (Solowij, Yücel, et al., 2011). Other studies find no association between cannabis use and the extent or volume of white matter (Block et al., 2000; Cousijn et al., 2012; Jager et al., 2007), making it difficult to draw general conclusions from the existing studies. Measures of white matter volume or extent derived from T_1 weighted structural MRI scans may not be sufficiently sensitive to subtle alterations in white matter microstructure that impact information processing.

DTI has the potential to address this limitation given that white matter organization can be examined at the microstructural level. DTI studies indicate that cannabis users demonstrate altered white matter organization, although, again, there are inconsistencies across studies in the direction of MRI-measured changes. Most studies indicate that FA is lower in various white matter regions in cannabis users. Some DTI reports include findings of increased cannabis user RD and MD, also indicative of reduced white matter organization in cannabis users. DTI findings for cannabis users have involved widely scattered brain regions, including the superior longitudinal fasciculus (Ashtari et al., 2009; Bava et al., 2009; Thatcher, Pajtek, Chung, Terwilliger, & Clark, 2010; Yücel et al., 2010), arcuate fasciculus (Ashtari et al., 2009), frontal white matter adjacent to the anterior cingulate cortex (Gruber, Silveri, Dahlgren, & Yurgelun-Todd, 2011) and hippocampus (Zalesky et al., 2012), internal capsule (Gruber et al., 2014), and the rostrum (Arnone et al., 2008), genu (Gruber et al., 2014), and splenium (Zalesky et al., 2012) of the corpus callosum. Cannabis use may disrupt the

developmental trajectory of white matter organization since lower FA levels have been associated with an earlier age of cannabis use onset (Gruber et al., 2014, 2011).

Not all DTI studies have found evidence for lower FA and/or greater RD and MD in cannabis users. Greater FA and lower RD have been reported in the forceps minor of the corpus callosum, a tract that connects the orbitofrontal cortices (Filbey et al., 2014), although years of use within the cannabis user group showed a curvilinear (quadratic) association with declining FA levels and rising RD levels. One early study found increased FA in cannabis users in white matter associated with medial frontal, cingulate, precentral, and parietal cortex, as well as decreased MD in cingulate and medial frontal white matter (Delisi et al., 2006).

Though findings are compelling, this literature is comprised of cross-sectional designs, limiting interpretation of group-based differences. Longitudinal research may clarify some interpretative complexities, by assessing neural changes over time in relation to ongoing substance use. Recent longitudinal studies have explored white matter development associated with alcohol initiation (Luciana, Collins, Muetzel, & Lim, 2013), binge alcohol use with comorbid cannabis use (Jacobus, Squeglia, Bava, et al., 2013), and polysubstance use (Bava, Jacobus, Thayer, & Tapert, 2013). No longitudinal study to date has explored white matter microstructure specifically related to sustained cannabis use during young adulthood.

This study examines change in measures of white matter microstructure across time as a function of cannabis use and in relation to substance use patterns and cognitive

performance. Young adult, regular cannabis users and control participants were assessed at two time points, with a two-year time interval between assessments.

2.1 Hypotheses

It was predicted that white matter organization, as measured by FA and RD, would be relatively diminished among cannabis users after multiple years of chronic use. Given the broadly distributed DTI findings to date, alterations were expected in frontal white matter as well as fiber tracts connecting frontal and posterior regions; hippocampal white matter; the corpus callosum; and cortical-subcortical projection fibers such as the corticospinal tract. Alterations in white matter organization were predicted to be correlated with amount of cannabis use in the follow-up interval within the cannabis user group.

Correlation with Behavior

Clusters that emerged as significantly different between groups are expected to correlate with cognitive performance within cannabis users, with better performance associated with greater white matter organization. I also expected that substance use patterns would be associated with white matter organization such that earlier use onset and greater use would be associated with poorer white matter organization.

2.2 Methods

2.2.1 Sample

The sample of cannabis users included in this study is a reduced sample of the cannabis users included in Study 1 and included only those participants who completed

both baseline and follow-up assessments (Table 17). Thirty-seven cannabis users, ages 19-20, were initially recruited into this longitudinal study. At study enrollment, cannabis users were recruited if they reported using cannabis at least 5 times per week for at least 1 year; 1 cannabis user reported use at a lower rate (3-4 times per week, on average, during the prior year), but was retained in the sample. Initial cannabis use onset was required to prior to age 17. Cannabis users were excluded if they were daily cigarette smokers, or if alcohol use exceeded 4 drinks for females and 5 drinks for males on more than 2 occasions per week.

Of the cannabis users initially recruited into this longitudinal study, 27 cannabis users returned for follow-up assessment after a two-year interval. To maximize homogeneity of use patterns within users, 2 cannabis users were excluded from the current analysis because they reported cannabis use patterns markedly lower than the majority of the cannabis user sample ($\leq$ 5 times in past 12 months). Twenty-three of the remaining 25 subjects (16 males, 7 females), aged 18 to 20 years (M = 19.45, SD = 0.66) generated artifact-free scanning data and comprised the final sample included in this study.

The control sample differs from the control sample included in Study 1. Within the larger longitudinal study, all cannabis users were initially recruited and completed their baseline assessment during the controls' third follow-up assessment wave (Time 3) and completed their follow-up assessment during the controls' fourth assessment wave (Time 4). The cognitive comparisons reported above used the controls' initial (baseline, Time 1) assessment and their first follow-up (Time 2) so that the groups would be

matched on task experience. There was an MRI scanner upgrade during the second assessment wave (Time 2) of the larger longitudinal study, confounding comparison of MRI data collected before and after the scanner upgrade. Controls' baseline assessment (Time 1) was completed prior to the scanner upgrade, whereas cannabis users' assessment was completed after the upgrade (Time 3). To eliminate this confound for the analysis of imaging data, controls who were scanned after the scanner upgrade were selected from follow-up assessment waves (Time 2-Time 4) of the longitudinal study for the following analyses. For the purposes of reporting, the controls' assessments in the analyses are referred to as "baseline" and "follow-up," respectively. Twenty-three control participants (16 males, 7 females) were selected from the larger longitudinal study of adolescent brain development. Controls were selected to match the cannabis users on sex, to reduce this potential confound when analyzing MRI data. This selection procedure required inclusion of participants from a wider age range (15-23 years old; M = 19.19, SD = 2.31), though the mean of age was equivalent between groups. Given this difference between groups, age was statistically controlled in all analyses. Controls were excluded from analyses if they endorsed more than minimal experimentation with cannabis at baseline (> 5 use occasions during their lifetime). All control participants who met these selection criteria were included in the sample.

General inclusion criteria for all participants included being a native English speaker, right-handed, and with normal/corrected-to-normal vision and hearing. Exclusion criteria included any contraindications to MRI scanning, a reported history of neurological problems or significant head injury, intellectual disability, or current

pregnancy. Adult participants and parents of minors provided informed consent, and minors (those under age 18) assented to participate in the study. All participants were monetarily compensated. The University of Minnesota's Institutional Review Board approved the protocol.

During both baseline and follow-up assessments, all participants, were asked to refrain from drug use for at least 24 hours before testing so as not to be acutely high during the assessment, though participants who reported 12 hours of abstinence were accepted. Longer periods of abstinence were not required to avoid assessing individuals in the midst of drug withdrawal and because a goal of the study was to capture functional capacities in the context of active use. Formal drug testing was not implemented due to budgetary limitations and given that the study did not require long-term cannabis abstinence.

2.2.2 Procedure

The procedure for assessment and study inclusion is detailed in Study 1 above (section 1.2.2). Inclusion criteria were verified during an initial visit by a demographic and health interview questionnaire, the Edinburgh Handedness Inventory (Oldfield, 1971), the Wechsler Abbreviated Scale of Intelligence (WASI: Wechsler, 1999), and by structured diagnostic interviews (the Kiddie Schedule for Affective Disorders and Schizophrenia; Kaufman et al., 1997) administered to the participant as well as (for those under age 18) a parent. Participants who met inclusion criteria at study enrollment returned for a second assessment, which included MRI scans as well as a battery of neurocognitive tasks. The neurocognitive battery was designed to capture a broad array

of functions in the domains of motor function, processing speed, attention, spatial and verbal memory, and executive functioning skills. Together, these measures took several hours to complete.

2.2.3 Measures

2.2.3.1 Neurocognitive Battery

The neurocognitive battery described in Study 1 (1.2.3.1) was employed for this study. Neurocognitive measures assessed the domains of motor function (Finger Tapping Test, Grooved Pegboard), processing speed (Digit Symbol, Letter Cancellation Task), verbal fluency (COWAT: Controlled Oral Word Association Test), verbal attention and working memory (Digit Span), verbal learning and memory (RAVLT: Rey Auditory Verbal Learning Test), spatial memory (SWM: Spatial Working Memory, DRT: Spatial Delayed Response Task), planning (TOL: Tower of London), and motivated decision-making (IGT: Iowa Gambling Task). Please see section 1.2.3.1 above for full task descriptions.

2.2.3.2 Substance Use

At baseline and follow-up within the full sample, the frequency of substance use was assessed with the Personal Experience Inventory (Henley & Winters, 1989). The PEI measures the frequency of substance use within the last 12 months on a 5-point scale (never, 1-5 times, 6-20 times, 21-49 times, 50-99 times, 100+ times). Participants rated the frequency of substance use separately for each drug class (alcohol, cannabis, psychedelics, cocaine, amphetamines, barbiturates, tranquilizers, heroin, narcotics,

steroids, inhalants, and recreation use of prescription drugs). Non-cannabis drug use for the 12 months prior to each assessment was calculated by summing the frequency ratings across illicit drug classes. Controls selected from the larger database were included in these analyses if they reported minimal cannabis use (> 5 occasions of use) and no other illicit substance use.

Participants older than 18 years of age completed Achenbach's Adult Self-Report (ASR; Achenbach & Rescorla, 2003) questionnaire, which yields substance use scales that consist of self-reported daily tobacco use, number of days drunk, and days using drugs (other than alcohol or tobacco) during the previous 6 months. Control participants younger than 18 years old completed the Youth Self-Report (YSR; Achenbach, 1991) questionnaire, which does not include substance use scales. All participants who completed the YSR reported no tobacco, alcohol, or other drug use during the K-SADS-PL interview or the PEI.

An in-house interview questionnaire based on guidelines provided by the NIAAA was implemented at baseline and follow-up to assess detailed frequency and quantity of alcohol and cannabis use among cannabis users.

2.2.4 MRI Data Acquisition and Processing

MRI data were collected on a Siemens 3T Tim Trio scanner (Siemens Medical Systems, Erlangen, Germany) using a twelve-channel array head coil at the University of Minnesota Center for Magnetic Resonance Research. The scanner and all scanning parameters were similar for both the control and cannabis-using samples at both time points reported here. Diffusion weighted data were acquired in the axial plane using a

dual spin echo, single-shot, pulsed-gradient, echo-planar imaging (EPI) sequence (TR = 8500 msec., TE = 90 ms, 64 slices, no gap, FOV = 256 mm, voxel size = 2.0 × 2.0 × 2.0 mm, b value = 1000 sec/mm2, GRAPPA iPAT = 2). The acquisition box was positioned to cover the cerebrum and as much of the cerebellum as possible. Thirty-six volumes were acquired in the diffusion scan: 6 non-diffusion-weighted volumes (b = 0) and 30 diffusion-weighted volumes (b = 1000 sec/mm^2), using gradient vectors distributed uniformly in 3-dimensional space according to an electrostatic repulsion algorithm (i.e., the "Jones30"; Jones, Horsfield, & Simmons, 1999). For off-line EPI geometric distortion correction, b0 field maps were constructed from gradient-echo images acquired using different echo times (TE = 4.62 ms and 7.08 ms; TR = 700 ms, flip angle = 90°, 64 slices, no gap, voxel size = 2.0 × 2.0 × 2.0 mm, FOV = 256 mm).

Diffusion MRI data were processed using the FDT and TBSS packages in FSL (FMRIB Software Library v4.0.1, http://www.fmrib.ox.ac.uk/fsl, Smith et al., 2004). Each diffusion-weighted volume was corrected for head motion and eddy current distortions using an affine registration to the first b0 reference volume. The diffusion series was corrected for geometric distortion caused by magnetic field inhomogeneity using PRELUDE (Phase Region Expanding Labeler for Unwrapping Discrete Estimates) and FUGUE (FMRIB's Utility for geometrically Unwarping EPIs) in conjunction with the b0 field maps. Brain tissue was extracted using BET (Brain Extraction Tool). The diffusion tensor was fit at each voxel by submitting the preprocessed data from the b0 reference volume and the 30 diffusion-weighted volumes to FSL's DTIFIT. Diagonalization yields the eigenvectors (V1, V2, V3) and corresponding eigenvalues (L1,

L2, L3) of the diffusion tensor, which describe the directions and apparent magnitudes of water diffusion within each voxel. Three scalar variables were computed from these tensor components: mean diffusivity (MD), which is the average of L1, L2, and L3, and reflects average total diffusion; radial diffusivity (RD), which is the average of L2 and L3 and reflects the magnitude of diffusion perpendicular to white matter tracts; and fractional anisotropy (FA), a variance measure that reflects how strongly water diffusion is restricted to the principle eigenvector and ranges from 0 (equivalent diffusion along V1, V2, and V3) to 1 (no diffusion along V2 and V3).

Tract-Based Spatial Statistics (TBSS; Smith et al., 2006) was used to align the DTI scalar volumes so that voxelwise statistical analysis could be performed across participants and between time points. All FA volumes were aligned to a common space template using the nonlinear registration IRTK (Rueckert et al., 1999; www.doc.ic.ac.uk/~dr/software). The template was an average FA volume constructed from 72 participants drawn from the full research sample, aligned to 2 mm isotropic MNI voxel space (Luciana et al., 2013; Olson et al., 2009). MD and RD volumes were aligned to common space by applying the transformation matrices previously computed during the FA volume alignments. FA volumes were masked at a threshold of FA $\geq$ .15 to reduce partial volume effects, and the same voxel masks were applied to MD and RD volumes. FA, RD, and MD volumes were smoothed at 4 mm FWHM prior to statistical analysis.

2.2.5 Statistical Approach

Data were analyzed using the Statistical Package for the Social Sciences (SPSS

Inc., Chicago, IL, USA), Windows version 20. Scatterplots of residuals were examined to assess for normal distributions, and data were screened for outliers and influential data points. Distributions of all variables were examined. The total number of cannabis hits within the past year did not meet the assumptions for parametric analysis and was square root transformed. Chi-square tests were used to compare nominal variables (i.e., sex) between cannabis users and controls. Mann-Whitney U analyses assessed for group differences in substance use characteristics, in which variances were unequal between groups.

To assess changes over time, common space DTI scalar volumes at follow-up were regressed on baseline volumes, yielding follow-up vs. baseline regression residuals for FA, RD, and MD. Preliminary analyses revealed that MD clusters had substantial overlap with RD clusters and did not identify unique areas of differential growth between groups. Given the substantial overlap between the two scalars, and that RD is more directly related to the maturational processes of interest in this study, including myelination, axonal packing, and age-related changes in FA (Budde et al., 2007; Giorgio et al., 2008; Lebel & Beaulieu, 2011; Lebel et al., 2008; Song et al., 2003, 2005), RD and FA were selected as the scalars of interest to reduce the number of statistical comparisons.

SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8) was used to perform voxelwise multiple regression analysis of the FA and RD follow-up vs. baseline residuals. Predictors in the multiple regression equations included group, sex, age at baseline, time interval between baseline and follow-up assessments, and average alcohol use (the mean

of baseline and follow-up PEI ratings for use in the past 12 months). Preliminary analyses were conducted using both baseline and follow-up PEI ratings for alcohol use in the past 12 months, but no supra-threshold clusters were produced for the alcohol predictors. Accordingly, the final regression models were simplified to include a single alcohol covariate averaged across baseline and follow-up.

To assess group differences at baseline, multiple regressions were performed on baseline FA and RD volumes with group, sex, age at baseline, and alcohol use at baseline (past 12 months) as predictors in the model.

All regression analyses used an input voxelwise height threshold of $p < .01$ and cluster-level statistical thresholding at $p \leq .05$ after family-wise error correction for multiple comparisons, as derived from random field theory (Worsley, Evans, Marrett, & Neelin, 1992).

Correlation Between White Matter Microstructure and Substance Use Variables

Mean FA within clusters was computed for the clusters that emerged in the baseline FA group difference and baseline to follow-up FA-change analyses. The mean FA cluster values at baseline were computed from the multiple regression analyses, which included the predictors of group, sex, age at baseline, and alcohol use during the past year at baseline. The mean FA-change cluster values were computed similarly from the multiple regression analyses, which included the predictors of group, sex, age at baseline, time interval between baseline and follow-up assessments, and average alcohol use at baseline and follow-up.

Mean FA cluster values were correlated with cannabis use variables within the cannabis user group, while controlling for variables of no interest. Cannabis use variables of interest were the age of regular cannabis use and total number of cannabis hits for past year. Cannabis use measures at baseline were regressed on sex and alcohol use during the past year. Residuals from these regressions were used as the outcome use variables and were correlated with the mean FA cluster values at baseline. Follow-up cannabis use measures were regressed on baseline cannabis use measures, sex, time interval between baseline and follow-up assessments, and average alcohol use in the past year. Residuals from these regressions were used as the outcome use variables and were correlated with the mean FA-change cluster values.

For comparison, correlations were performed on follow-up measures of alcohol use (i.e., total number of drinks, controlling for interval time and sex as described above) and tobacco use, controlling for sex, time interval between baseline and follow-up, and average 12-month alcohol use.

Correlation Between White Matter Microstructure and Cognitive Performance

To determine the association between cognitive performance and the white matter findings, mean FA cluster values for the clusters that distinguished groups were correlated with cognitive performance within the cannabis user sample. Because the control sample was selected from later waves of the larger longitudinal study, controls and cannabis users differed in their prior exposure to the neurocognitive battery. For example, a control subject in this study may have completed the neurocognitive battery 1-2 times prior to the “baseline” MRI assessment examined in these analyses, whereas the

cannabis users' baseline MRI assessment corresponds to their first neurocognitive assessment. Controls and cannabis users had different levels of experience with the tasks; therefore, a direct comparison between groups on task performance would have been confounded by different practice effects between groups.

To reduce the number of statistical comparisons, cognitive composite scores were used to characterize cognitive performance. The 6 cognitive composites that were developed with the hybrid method described in 1.2.4, with scales first theoretically-defined then refined with reliability analyses, were used for these analyses, specifically, (1) Processing speed (Letter Cancellation time, Digit Symbol total correct, COWAT total correct words); (2) Verbal learning and memory (RAVLT Trial 1-5 total words, RAVLT immediate recall, RAVLT delayed recall); (3) Spatial working memory and planning (SWM strategy score, SWM total errors, TOL % perfect solutions, Tower of London total average moves); (4) Motor speed (Finger Tapping dominant hand taps, Finger Tapping non-dominant hand taps); (5) Motor dexterity (Grooved Pegboard dominant hand time, Grooved Pegboard non-dominant hand time). Individual neuropsychological test variables were converted to z-scores based on the cannabis user sample participants included in this study's imaging analyses at both time points (n = 46). Z-scores were transformed such that higher scores represented better performance across all variables. The individual test z-scores were averaged to form the final composite score for each cognitive domain. Because the Iowa Gambling Task is not included in any of the cognitive composites, the separate task variables of deck choices and total good choices were examined as well.

Similar to the substance use correlations described above, mean FA cluster values were correlated with cognitive variables within the cannabis user group, while controlling for other predictors of no interest. For the baseline assessment, baseline cognitive performance was regressed on sex and alcohol use during the past year. Residuals from these regressions were used as the outcome use variables and were correlated with the mean FA cluster values at baseline. Follow-up cognitive performance was regressed on baseline cognitive performance, sex, time interval between baseline and follow-up assessments, and average alcohol use in the past year. Residuals from these regressions were used as the outcome use variables and were correlated with the mean FA-change cluster values.

2.3 Results

2.3.1 Sample Characteristics

Demographic information and participant characteristics are presented in Table 17. Groups were matched on sex distribution, ethnicity/racial identity, years of education, and estimated IQ. The study participants were largely Caucasian and had above average IQ estimates. Groups were matched in terms of mean age, though a larger age range characterized the control sample to balance the sex distribution across both groups. Time to follow-up assessment was equivalent between groups, with an overall mean interval of 2.23 years (*SD* = 0.52).

Minimal psychopathology was expressed within the sample. Among controls, 2 participants reported past major depressive disorder at baseline and follow-up, 1

participant reported social phobia at follow-up, and 1 participant met criteria for alcohol abuse at follow-up (Table 18). Among cannabis users, 1 participant met criteria for bipolar disorder NOS at baseline and follow-up. Both disorders were diagnosed based on episodic hypomania. Other psychological disorders evident in cannabis users included past specific phobia at baseline (n = 1), past major depressive disorder at follow-up (n = 1), and past generalized anxiety disorder at follow-up (n = 1). The majority of cannabis users met criteria for a cannabis use disorder at baseline and follow-up (Table 18), and a large portion of users met criteria for an alcohol use disorder, though alcohol abuse was more common than alcohol dependence, and symptom expression was lower for alcohol use disorders.

2.3.2 Substance Use Characteristics

All cannabis users reported consistent cannabis use prior to both the Time 1 and Time 2 assessments (see Table 17) Given the high prevalence of cannabis use in the general population, controls who had minimally experimented with cannabis use were included. Minimal experimentation with cannabis use was reported by 2 controls at the Time 1 assessment (*both* reported using cannabis 1-5 times in the past 12 months); at Time 2, n = 7 reported using 1-5 times in the past 12 months, n = 2 reported having transitioned into using 6-20 times in the past 12 months. Additionally, cannabis users reported greater alcohol use (Time 1 & Time 2 cannabis user *Mdn* use = 50-99 times in past 12 months) than controls (Time 1 *Mdn* use = never in the past 12 months; Time 2 *Mdn* use = 21-49 times in past 12 months). Minimal non-cannabis drug use was reported

among cannabis users at baseline and follow-up (use ≤ 20) and controls (Time 1: no reported use; Time 2: ≤ 5 times; see Table 19).

Cannabis users in this sample reported a mean age of initiation of regular cannabis use during mid-adolescence (M = 15.35, SD = 1.16). At baseline, cannabis users reported nearly daily cannabis use during the past 30 days. Cannabis use occasions had declined by follow-up, with cannabis users reporting fewer occasions of use in the past year ($t(21) = 2.650$, $p = .015$) and past month ($t(21) = 3.626$, $p = .002$). The total number of hits reported did not significantly differ between assessments.

2.3.3 Baseline Differences in White Matter Microstructure Between Groups (Table 20)

Analysis of FA group differences at baseline yielded one significant voxel cluster (2584 mm^3), in which FA levels were unexpectedly greater for cannabis users than controls. This cluster covered the right side of the genu of the corpus callosum (CC), crossing over the CC midline to extend into the inferior part of the left genu. In terms of fiber tracts, the cluster overlapped the caudal forceps minor, with a much greater extension into the right hemisphere than the left (Figure 13, cluster color coded blue).

Analysis of RD group differences at baseline yielded one trend-level voxel cluster (1640 mm^3; trend level at clusterwise FWE $p = .10$), in which RD levels were unexpectedly greater for controls than cannabis users. The controls > cannabis users baseline RD cluster was located in the same corpus callosum region as the controls < cannabis users baseline FA cluster, but was smaller in size (Figure 13), cluster color coded yellow). No other significant group differences emerged as baseline.

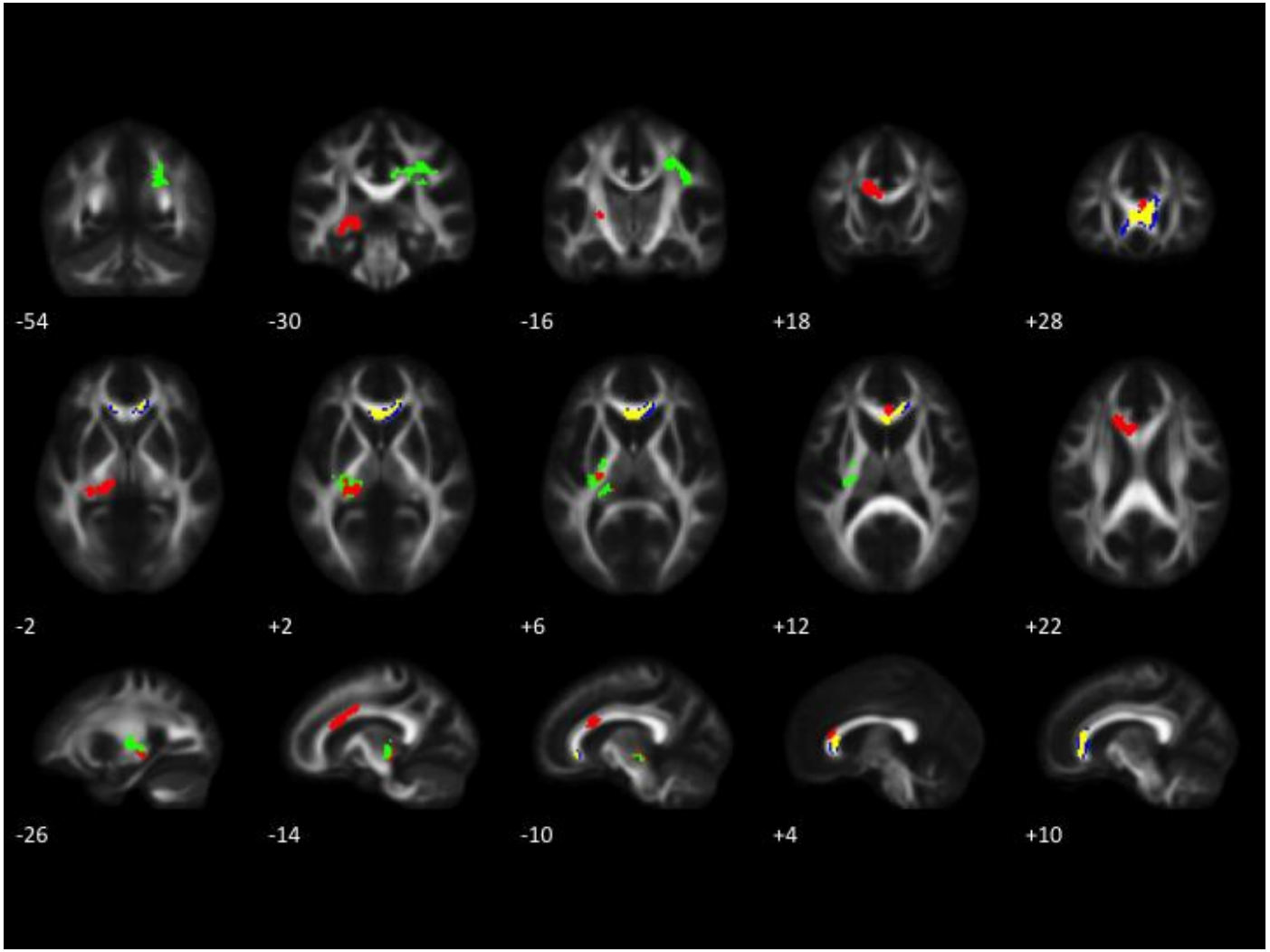

Figure 13. Cannabis user > Control FA, Control > Cannabis user RD. Voxelwise analysis of baseline group difference and 2-year change in fractional anisotropy and radial diffusivity. Multiple regression analyses controlled for covariates. Color coding indicates contrasts for multiple regression effects: blue = baseline FA, cannabis users > controls; yellow = baseline RD, cannabis users < controls; red = FA, cannabis users > controls; green = RD, cannabis users < controls.

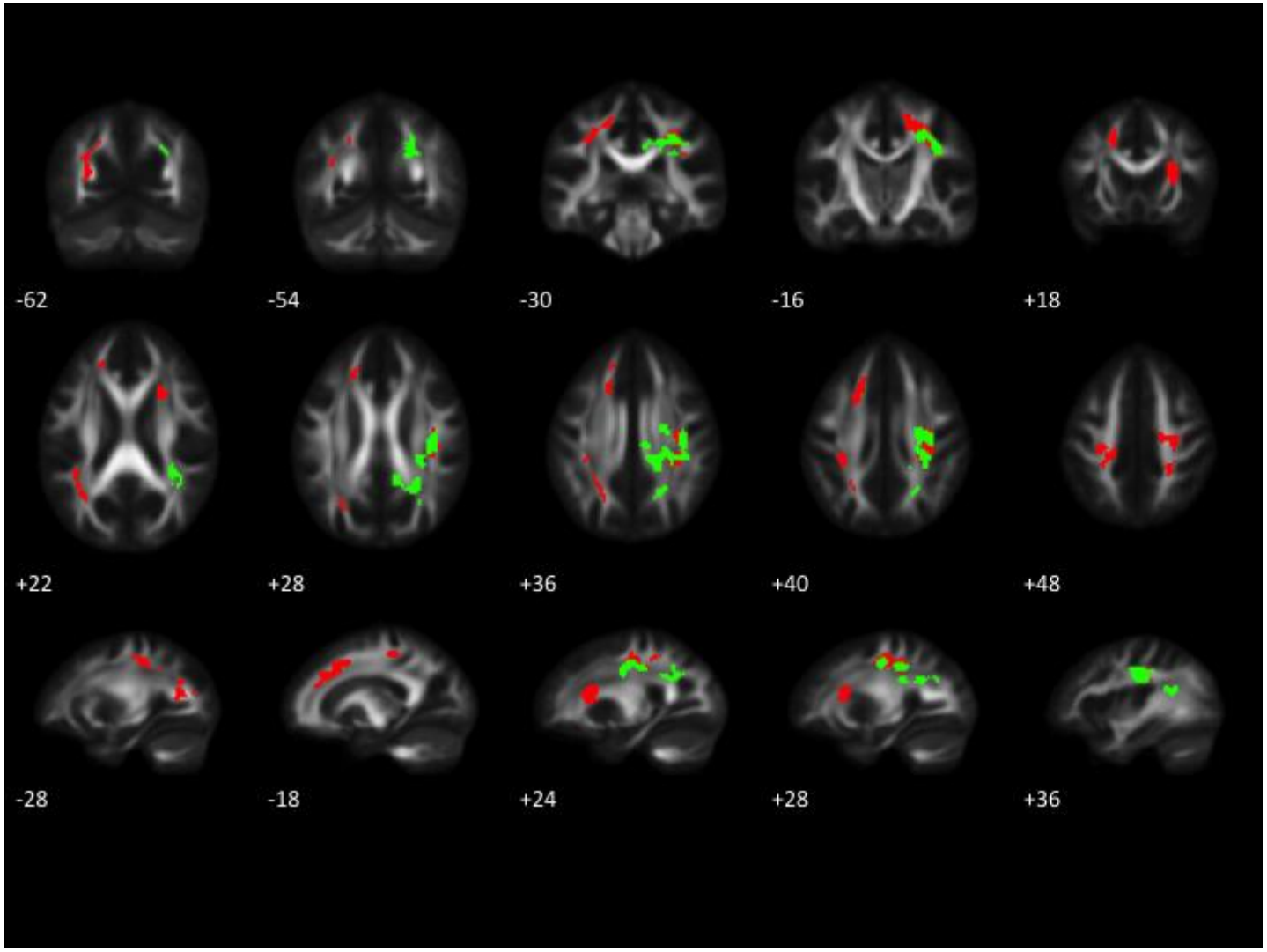

Figure 14. Control > Cannabis user FA, Cannabis user > Control RD. Voxelwise analysis of 2-year change in fractional anisotropy and radial diffusivity. Multiple regression analyses controlled for age, sex, interval between baseline and follow-up, average alcohol use at baseline and follow-up. Color coding indicates contrasts for multiple regression effects: red = FA, controls > cannabis users; green = RD, controls < cannabis users.

2.3.4 Baseline White Matter Microstructure Behavioral Correlates

Substance Use

Greater FA in the cannabis user > controls right genu/forceps minor CC cluster was associated with fewer total drinks in the past year in cannabis users (Table 21; Figure 15).

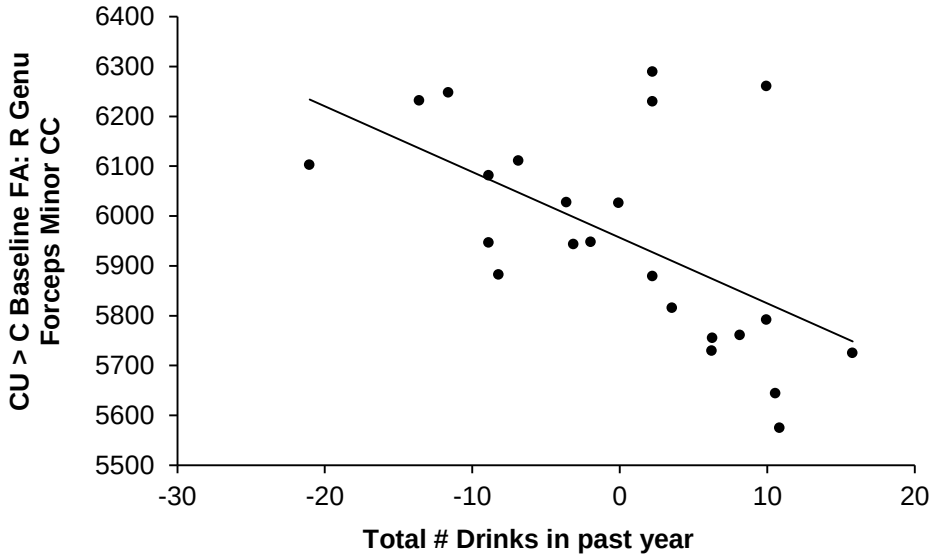

Figure 15. Scatterplot of baseline total # of drinks in the past year by mean FA in cannabis users > controls baseline cluster in the right genu and forceps minor of the CC, controlling for sex and average alcohol use at baseline.

This cluster was uncorrelated with measures of cannabis use or tobacco use.

Neurocognitive Performance

Motivated decision-making. Higher mean cluster FA was associated with fewer choices from the disadvantageous Deck 2 (Table 21; Figure 16).

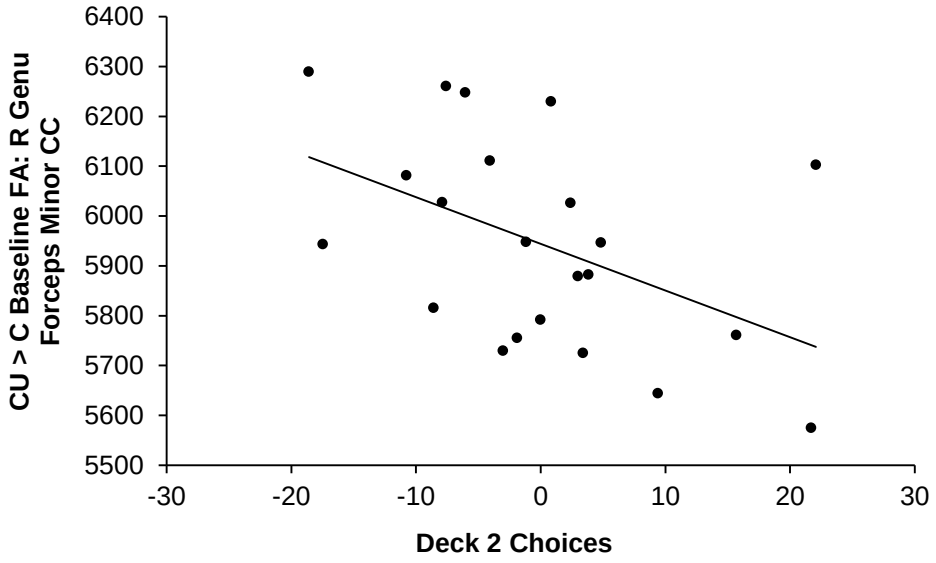

Figure 16. Scatterplot of baseline IGT disadvantageous Deck 2 choices by mean FA in cannabis users > controls baseline cluster in the right genu and forceps minor of the CC, controlling for sex and alcohol use at baseline.

Mean FA in the right genu and forceps minor of the CC was not correlated with other measures of the IGT or the cognitive composites.

2.3.5 Follow-up Differences in White Matter Microstructure Between Groups

Significant differences in two-year FA change between cannabis users and non-using controls were identified in seven voxel clusters (see Table 22). In five of the clusters, the controls had more positive FA change than cannabis users over the two-year follow-up interval, which was the expected direction of effects (Figure 14), while the cannabis users had more positive FA change than controls for the remaining two clusters (Figure 13). The largest controls > cannabis user FA-change cluster (3864 mm^3) was located in the right hemisphere primarily along the superior longitudinal fasciculus (SLF) adjacent to the precentral and postcentral gyri. It extended anteriorly into the junction

between the SLF and the corticospinal tract (CST). The next largest FA cluster (1632 mm^3) had its peak adjacent to the parietal operculum in the left hemisphere. The cluster followed the SLF adjacent to the supramarginal and angular gyri, extending into the forceps major of the CC near the anterior portion of the lateral occipital cortex; above the forceps major, it overlapped a caudodorsal portion of the inferior longitudinal fasciculus (ILF). The posterior portion of the third FA cluster (1464 mm^3) was located in the white matter of the middle region of the superior frontal gyrus in the left hemisphere, while the anterior portion extended into the lateral anterior cingulum and anterior thalamic radiation (ATR) adjacent to the anterior superior frontal gyrus. Most of the fourth FA cluster (1232 mm^3; trend level at clusterwise FWE $p = .065$) was located within the CST adjacent to the precentral and postcentral gyri in the left hemisphere, with the lateral aspect of the cluster extending into the SLF. The fifth controls > cannabis user FA-change cluster (1208 mm^3; trend level at clusterwise FWE $p = .071$) was adjacent to the inferior frontal gyrus (specifically, the frontal operculum) in the right hemisphere, with the medial aspect of the cluster overlapping the anterior thalamic radiation and the lateral aspect extending into the superior portion of the fronto-occipital fasciculus (FOF).

More positive two-year FA change was observed for cannabis users than Controls within two clusters in the left hemisphere. One cluster (1808 mm^3) was located primarily in anterior corpus callosum (posterior genu, rostral body), with a small overlap into the caudal anterior cingulum. The other cluster (1696 mm^3) was located in posterior thalamus white matter. The medial aspect of this cluster overlapped the CST and the ATR, while the lateral aspect extended into the acoustic and optic radiations.

Radial Diffusivity

In addition to the FA results, significant differences in two-year DTI change between cannabis users and Controls were identified in the analysis of RD data. It was generally expected that RD would decrease over time. RD change was more positive for cannabis users than Controls in a very large voxel cluster (6848 mm^3) that extended over the posterior two-thirds of the right hemisphere, in white matter adjacent to precentral, postcentral, supramarginal, inferior parietal, precuneus, and posterior cingulate cortex. The cluster peak was located in the medial aspect of the cluster, which overlapped the posterior cingulum. The middle section of the cluster overlapped the CST, while the lateral aspect overlapped the SLF. Both of these cluster segments had substantial overlap with a similarly located controls > cannabis user FA-change cluster (note that increased FA often is accompanied by decreased RD; see Figure 14). RD change was more positive for controls than cannabis users in a left hemisphere voxel cluster (2368 mm^3) located along the CST, with a peak in the posterior limb of the internal capsule.

2.3.6 Follow-up White Matter Microstructure Behavioral Correlates

Substance Use (Table 23)

The number of cannabis hits in the past year during follow-up was negatively associated with the control > cannabis user mean FA-change clusters in the left SLF/CC forceps major (Figure 17) and left CST (Figure 18) within cannabis users, indicating that higher levels of reported cannabis use were associated with lower magnitudes of FA change over time.

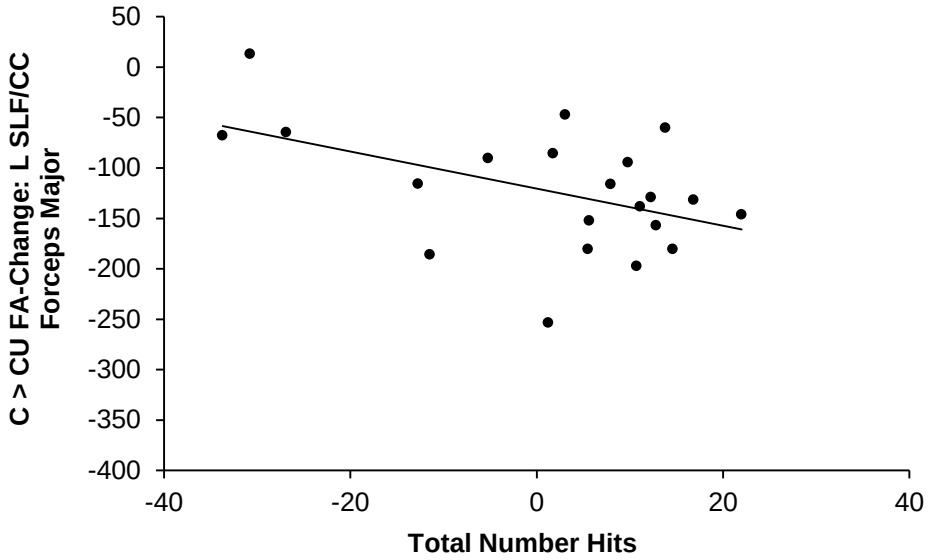

Figure 17. Scatterplot of total number of hits at follow-up, controlling for baseline hits, by mean FA-change in controls > cannabis users cluster in the left SLF/CC forceps major. Analysis controlled for sex, interval between baseline and follow-up, and average baseline and follow-up alcohol use.

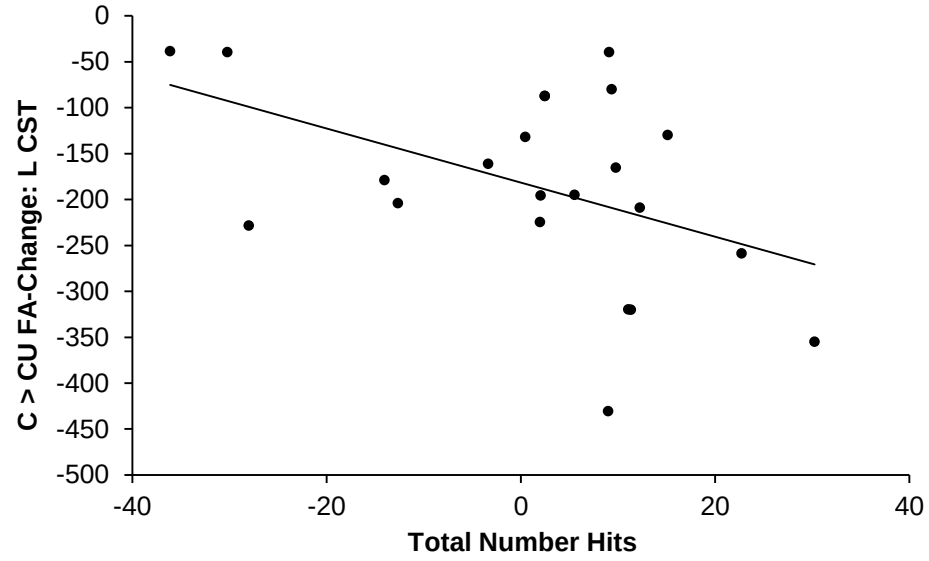

Figure 18. Scatterplot of total number of hits at follow-up, controlling for baseline hits, by mean FA-change in controls > cannabis users cluster in the left CST. Analysis controlled for sex, interval between baseline and follow-up, and average baseline and follow-up alcohol use.

Age of cannabis use onset was not significantly correlated with cluster mean FA-change values. Total number of alcoholic drinks consumed in the past year and tobacco use measures were not correlated with any of the significant FA-change clusters.

A secondary analysis explored the association between FA-change values and baseline number of hits, controlling for sex, interval, and average alcohol use (Table 23). A trend emerged for greater hits at baseline correlating with increased FA change in the right ATR controls > cannabis users cluster. No significant associations were noted.

Neurocognitive Performance

Motor speed. Better performance on the motor speed composite was positively correlated with increased FA-change within the control > cannabis user right ATR cluster (Figure 19).

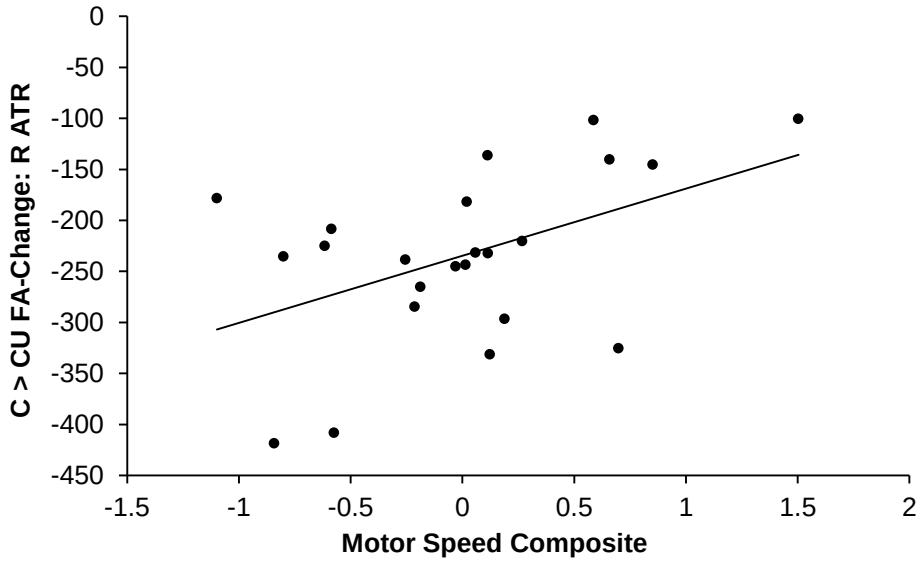

Figure 19. Scatterplot of motor speed composite scores, controlling for baseline motor speed performance, by mean FA-change in controls > cannabis users cluster in the right ATR. Analysis controlled for sex, interval between baseline and follow-up, and average baseline and follow-up alcohol use.

Motivated decision-making. Counter to prediction, increased FA-change was associated with fewer selections from advantageous decks on the IGT (Figure 20, Figure 21), and more choices from the disadvantageous deck 1 (Figure 22).

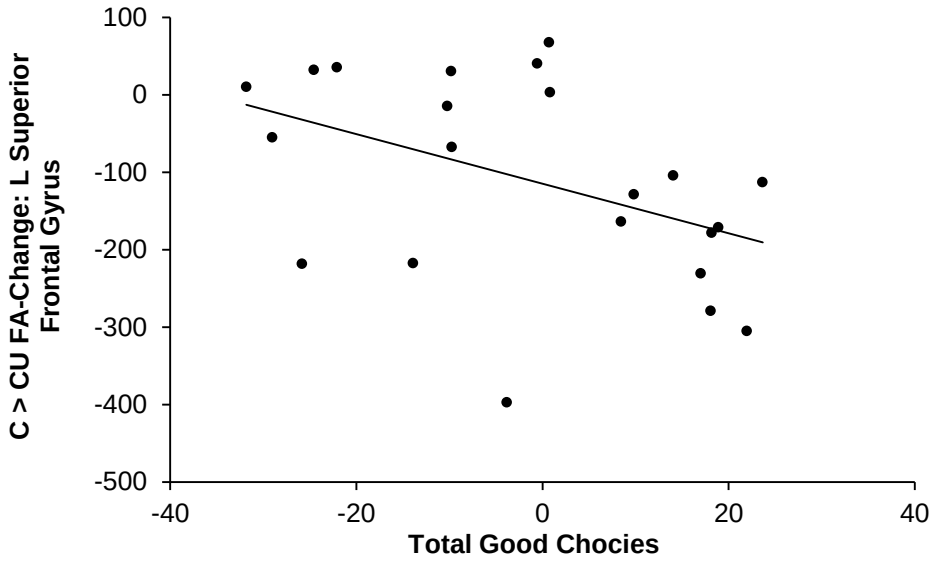

Figure 20. Scatterplot of IGT total good choices, controlling for baseline total good choices, by mean FA-change in controls > cannabis users cluster in the left SFG white matter. Analysis controlled for sex, interval between baseline and follow-up, and average baseline and follow-up alcohol use.

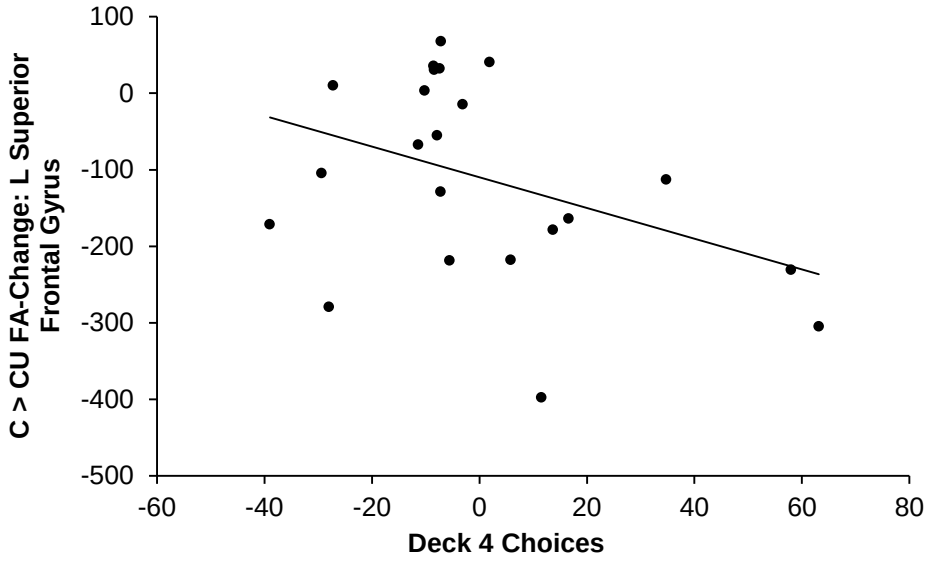

Figure 21. Scatterplot of IGT advantageous Deck 4 choices, controlling for baseline Deck 4 choices, by mean FA-change in controls > cannabis users cluster in the left SFG white matter. Analysis controlled for sex, interval between baseline and follow-up, and average baseline and follow-up alcohol use. Trend association, $p = .069$.

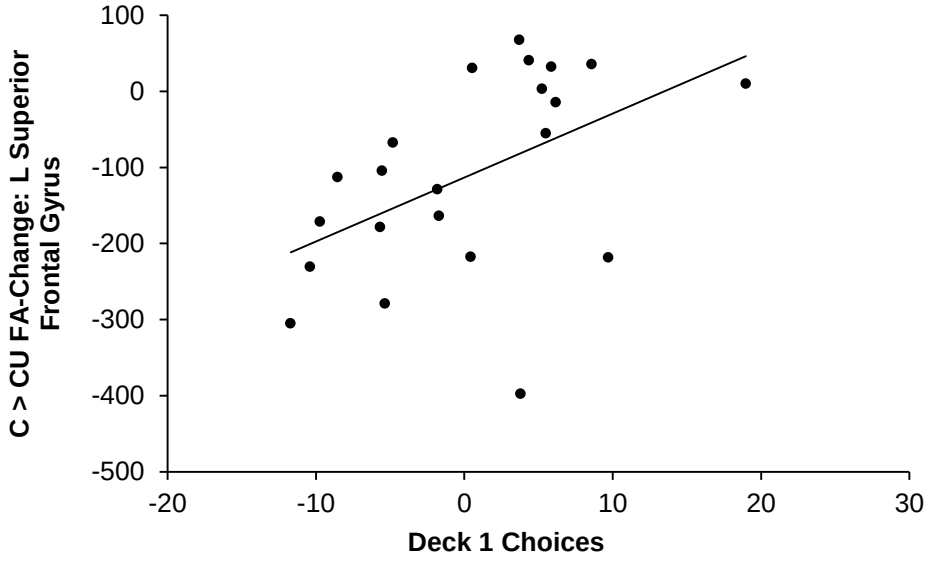

Figure 22. Scatterplot of IGT disadvantageous deck choices, controlling for baseline total good choices, by mean FA-change in controls > cannabis users cluster in the left SFG white matter. Analysis controlled for sex, interval between baseline and follow-up, and average baseline and follow-up alcohol use.

FA-change clusters were not correlated with the motor dexterity, processing speed, verbal learning and memory, or spatial working memory cognitive composites.

2.4 Discussion

This study assessed changes in white matter microstructure over a 2-year period of continued heavy cannabis use in young adults who initiated use during adolescence. White matter microstructure is known to show continued developmental changes during this age period (Lebel et al., 2012). As predicted, FA-change was generally lower and RD-change was generally higher for cannabis users as compared to controls. Specifically, cannabis users showed less FA change in the central and parietal regions of the right and left SLF (extending into the temporal/parietal/occipital white matter junction region on the left), in white matter adjacent to the left superior frontal gyrus, in the left CST just medial to the SLF, and in the right anterior thalamic radiation lateral to the genu of the corpus callosum. A corresponding finding of more RD change for cannabis users overlapped the FA cluster in the right SLF, but encompassed a much larger white matter region that included adjacent medial structures such as the CST and posterior cingulum. These results were not accounted for by group differences at baseline.

These deviations in the development of white matter microstructure were observed primarily in widely distributed cortical association fibers, which is consistent with findings from functional MRI and behavioral studies of cannabis users. Cognitive studies consistently find diminished cannabis user performance on tasks that require more effortful performance, such as were found for verbal memory in Study 1. In functional MRI studies, cannabis users tend to show a broader pattern of cortical activation,

recruiting alternative brain networks during task performance, as compared to non-using controls (Block et al., 2002; Chang et al., 2006; Harding et al., 2012; Jacobsen et al., 2004; Kanayama et al., 2004; Padula et al., 2007; Schweinsburg et al., 2010; Tapert et al., 2007). Increased activation and recruitment of alternative information processing pathways by cannabis users may reflect imperfect functional compensation for subtle degradations in structural connectivity, such as those reported here.

The hypothesis that white matter changes would be associated with substance use characteristics was partially supported. Decreased FA change in the left SLF (-38, -44, 24) and CST (-16, -28, 50) clusters was associated with greater cannabis use hits during the follow-up period. Similar measures of alcohol and tobacco use did not correlate with FA change. Increased alcohol use at baseline was associated with the decreased FA in the right genu (4, 26, 4) cluster that distinguished between groups at baseline, but was not associated with FA-change over time. Thus, although the cannabis user group used more alcohol and tobacco than controls, only their cannabis use was associated in a continuous quantitative manner with FA change, thereby strengthening the inference that cannabis use itself was a primary factor underlying the observed group differences at follow-up. This finding contradicts the majority of existing longitudinal DTI studies that have not documented changes over time attributable to amount of cannabis use. Bava et al. (2013) reported a large number of DTI voxel clusters differentiating alcohol and cannabis users from non-users but found that results were driven by alcohol use over the 18-month follow-up period rather than cannabis use. Similarly, Jacobus et al. (2013) found that over a 3-year interval, a group of binge alcohol users and a group of combined binge alcohol and cannabis users differed from non-using controls in 15 voxel clusters, but with only

one exception, the clusters did not differentiate the two user groups. However, a smaller longitudinal DTI study (n = 16) on the initiation (rather than continuation) of heavy alcohol and cannabis use reported 20 clusters distributed throughout the brain that differentiated participants who initiated combined alcohol and cannabis use vs. alcohol use alone, with decreased FA shown almost exclusively by the combined alcohol and cannabis users over the 3-year follow-up period (Jacobus, Squeglia, Infante, et al., 2013). The current results are consistent with Jacobus, Squeglia, Infante, et al. (2013) in suggesting that brain white matter changes driven by heavy cannabis use during late adolescence and early adulthood can be detected by DTI despite the presence of concurrent heavy alcohol use. This is an important empirical demonstration, given that white matter development extends into the third decade of life (e.g., Lebel et al., 2012) and that cannabis use during adolescence and early adulthood has been found to have long-term impacts on cognitive functioning and brain structure and organization, both in animal models (e.g., Bambico, Nguyen, Katz, & Gobbi, 2010; Gleason, Birnbaum, Shukla, & Ghose, 2012; Pistis et al., 2004; Raver, Haughwout, & Keller, 2013; Rubino et al., 2009; Schneider & Koch, 2003, 2007; Schneider, Schömig, & Leweke, 2008; Stopponi et al., 2014) and in humans (e.g., Battisti et al., 2010; Ehrenreich et al., 1999; Fontes et al., 2011; Lisdahl, Gilbart, Wright, & Shollenbarger, 2013; Meier et al., 2012; Pope et al., 2003; Solowij et al., 2012; Wagner, Becker, Gouzoulis-Mayfrank, & Daumann, 2010).

Contrary to predictions, several findings for the cannabis user group involved DTI changes generally associated with better white matter organization, i.e., increased FA and decreased RD. In the left hemisphere, more positive FA change was observed for

cannabis users in the anterior CC (posterior genu, rostral body) and posterior thalamic white matter. A corresponding decreased-RD cluster overlapped the posterior thalamic area and also extended medially into the CST. In analyses of baseline data, the medial CC genu region (caudal forceps minor tract) showed higher FA values and lower RD values in the cannabis user group. Filbey et al. (2014) also reported higher FA and lower RD for cannabis users in the forceps minor of the CC, and more generally an early study reported a similar pattern in several regions including the medial frontal white matter (Delisi et al., 2006). Differences observed at baseline may reflect areas of compensation and relative strength in the cannabis user group, as higher FA in the region at baseline was associated with better task strategy on a measure of motivated decision-making.

Interpretation of the functional relevance of FA increases and RD decreases in the cannabis user group over the 2-year follow-up period is complex. It was expected that FA-changes would map onto neurocognitive performance over time, such that increased FA would be associated with improved task performance. However, this association was only observed between the right ATR cluster and the motor speed composite. In contrast, advantageous IGT performance was negatively associated with increased FA-change in the left SFG white matter cluster. Other cognitive domains were unrelated to average FA-change in the areas that distinguished groups. The overall pattern of findings did not support a strong association between cognitive performance and FA-change over time. This may be due to limitations inherent in the study design. The association between cognitive performance and white matter integrity was investigated only in those regions that distinguished between groups, and task performance was not analyzed in relation to whole-brain white matter integrity within cannabis users. It is possible that the regions

that differed between groups support cognitive functions not assessed in the cognitive battery employed, or that the behavioral alterations that are associated with these regions may emerge over time but are not detectable yet. As magnitude of cannabis use was associated with greater alterations, it is expected that continued use would lead to the emergence of these associations over time.

In the absence of strong behavioral correlates, it is difficult to interpret the significance of the white matter deviations. This is a problem that is widespread in the cannabis user neuroimaging literature. Alterations (reductions *or* increases) are interpreted as negative when observed among cannabis users, yet few studies have been linked to behavioral correlates that substantiate those interpretations (Weiland et al., 2015). Further research is needed to establish meaningful behavioral links with the observed alterations.

Notably, the study findings are informative regarding the timing of use-related impacts on brain structure. At baseline, cannabis users had been heavily using cannabis for an average of two years. Group differences evident at the follow-up assessment were detectable after four or more years of continued heavy use.

Unlike previous cross-sectional studies, no DTI differences were found between cannabis users and non-using controls in white matter tracts associated with core limbic structures such as the hippocampus (e.g., fimbria; Zalesky et al., 2012; Yücel et al., 2012) and amygdala (e.g., uncinate fasciculus; Jacobus, Squeglia, Infante, et al., 2013; Jacobus, Squeglia, Bava, et al., 2013; Shollenbarger, Price, Wieser, & Lisdahl, 2015), either at baseline or follow-up. These limbic structures are rich in endocannabinoid receptors, and cannabis exposure has been linked with hippocampal damage in animal models (Rubino

et al., 2009). Other studies may have had greater sensitivity to detect effects in these smaller tortuous white matter tracts due to the use of fiber tractography (Shollenbarger et al., 2015; Zalesky et al., 2012) and incorporation of substantially lower cluster-size thresholds in voxel-based analysis (Jacobus, Squeglia, Bava, et al., 2013; Jacobus, Squeglia, Infante, et al., 2013).

Limitations of this study must be noted. The sample was relatively small and was comprised mostly of Caucasian participants. While the DTI results reported here were similar to those reported in other samples, additional research is needed among more racially and ethnically diverse samples to improve generalizability of the findings. Similarly, this sample of cannabis users is characterized by high average IQ estimates, which again limits the generalizability of findings and perhaps skews overall FA levels toward higher values (Navas-Sánchez et al., 2014). That said, these findings are sobering regarding potential impacts of chronic cannabis use across late adolescent development in an otherwise low-risk sample. An additional limitation with the sample is the greater range of ages in the control group relative to cannabis users. Groups were matched on mean age, and age was statistically controlled in analyses to mitigate potential confounding by age variance. Baseline age did not produce supra-threshold clusters in analyses of FA and RD change over the two-year follow-up period, which indicated that the group-wise DTI findings were not confounded significantly by the age range difference between groups.

Perhaps more importantly, cannabis users and controls differed substantially in alcohol use, which is commonly observed in studies of adolescent and young adult cannabis users (e.g., Arnone et al., 2008; Bava et al., 2009, 2013; Gruber et al., 2014;

Jacobus, Squeglia, Infante, et al., 2013; Jacobus, Squeglia, Bava, et al., 2013; Shollenbarger et al., 2015; Thatcher, Pajtek, Chung, Terwilliger, & Clark, 2010b). To assess this sampling confound, past 12-month alcohol use at both baseline and follow-up were included in preliminary analyses of FA and RD change, which produced no supra-threshold clusters for the two alcohol use variables. To provide statistical control for sub-threshold differences, the average of the baseline and follow-up alcohol use variables were included in the final DTI analyses. The dose-dependent findings also indicated that cannabis use was the primary factor in the DTI cluster results, as mean values from several of the FA change clusters correlated with past 12-month cannabis use but not alcohol use. Nevertheless, the optimal design to detect and isolate longitudinal cannabis effects would employ contrasting groups that used alcohol at equivalent levels.

As noted in Study 1, participants were asked be free of substance use for at least 24 hours prior scanning, drug testing was not employed to verify reported levels of cannabis and other substance use among cannabis users and controls. Cannabis user and control participants completed multiple self-report and interview measures of substance use, and responses across measures were compared for reliability of information. While it is possible that participants endorsed false use levels, this appears unlikely given consistency of reports across measures within time points and across the follow-up interval. Further, cannabis users' self-reported level of cannabis use was supported by evidence of DSM-IV cannabis dependence in the sample as well as the neurocognitive impairments noted at baseline for these participants.

Finally, while reports have described alterations in cerebellar white matter in cannabis users, the field-of-view placement did not allow for equivalent examination of

this region across participants. Therefore, the current study could not address the impact of cannabis use on cerebellar white matter development.

3 General Conclusions and Future Directions

The two studies presented aimed to characterize the neurocognitive and neuroanatomical profiles associated with sustained cannabis use during adolescence and young adulthood in comparison to non-using controls. Cannabis is among the most commonly used drugs by adolescents and young adults, yet its effects in the developing brain are not well understood. It is important to better understand the cognitive and neurobiological vulnerabilities associated with cannabis use during the sensitive period of neurobehavioral development in adolescence. As the legal status of cannabis use continues to change, this research will ideally help to inform policy that can improve the public health of adolescents and young adults.

In Study 1, the neurocognitive profile associated with cannabis use at baseline and follow-up was examined. Cannabis users demonstrated more widespread cognitive deficits at baseline than at follow-up in the domains of verbal learning and memory, spatial working memory, planning, and motivated decision-making. Continued cannabis use over the follow-up interval was not associated with a decline in cognitive performance over time. Instead, stable cognitive deficits remained in the domains of verbal learning and memory and planning ability, whereas performance on spatial working memory and motivated decision-making tasks recovered to control-level performance, and processing speed performance continued to be a relative strength within cannabis users.

The overall profile of deficits that emerged at both time points indicates that motivation and effort may be mechanisms contributing to the cognitive vulnerabilities observed. Poorer performance on a relatively easy trial of the planning task, in the

context of normal performance on harder trials, suggests that diminished motivation may contribute to the cognitive profile of cannabis users. Cannabis users' neurocognitive performance can be enhanced with the use of motivational cues prior to task completion, whereas controls do not show this association (Macher & Earleywine, 2012), suggesting that internal motivation to sustain effortful performance is less robust among cannabis users. Increased internal motivation is needed to sustain effortful performance when there is no extrinsic reinforcement or reward (Ryan & Deci, 2000). Internal motivation relies on the subjective valuation of achieving success on a given task (Murayama, Matsumoto, Izuma, & Matsumoto, 2010), which is modulated by activity in the dopaminergic reward network, including endocannabinoid receptor-rich brain regions of the ventral tegmental area, nucleus accumbens, striatum, hippocampus, amygdala, and prefrontal cortex (Kable & Glimcher, 2007; Levy & Glimcher, 2011). Dopamine is hypothesized to be the primary transmitter that modulates the activity of the reward network, adapting and driving the relationship between motivation and behavior (Depue & Collins, 1999; Luciana, Wahlstrom, Porter, & Collins, 2012; Wahlstrom et al., 2010). Preclinical data indicate that the cannabinoid exposure may alter dopamine activity in the reward network, resulting in decreased motivation. Acute administration of cannabis increases dopamine release in the reward network (Tanda & Goldberg, 2003), while chronic administration produces a blunted dopamine response in the midbrain (Pistis et al., 2004). In humans, a pattern of chronic cannabis use is associated with reduced striatal dopamine synthesis and reactivity (Bloomfield, Morgan, Egerton, et al., 2014; Volkow, Wang, et al., 2014), with reduced striatal dopamine receptor binding associated with an earlier age of cannabis use initiation (Urban et al., 2012). Importantly, striatal dopamine synthesis capacity has been

inversely associated with apathy and amotivation among cannabis users (Bloomfield, Morgan, Kapur, Curran, & Howes, 2014). Together, the neurobiological alterations associated with chronic cannabinoid exposure likely contribute to diminished motivation for complex cognitive tasks. Diminished motivation could have drastic impacts on cannabis users' behavior, and may be important moderators of the deficits commonly observed. More research is needed to clarify the role of motivation in cognitive performance among cannabis users.

Deficits in verbal learning and memory may be accounted for, in part, by lower motivation among users. It is also plausible that neural inefficiency is a mechanism driving poorer performance on more complex tasks. Cannabinoid-mediated neuroplastic changes in the context of chronic use (Heifets & Castillo, 2009) is associated with the recruitment of alternative and less efficient neural pathways (Harding et al., 2012). Less efficient pathways may be sufficient to compensate for cognitive deficits on simpler tasks, but be overly taxed on more complex tasks. Neural inefficiency may manifest behaviorally in poorer performance on more effortful tasks, corresponding to the robust finding of verbal learning and memory deficits among cannabis users.

The deficits in verbal learning and memory and planning noted in this study represent more stable features associated with continued use. Subtle but significant deficits were observed in these domains at both time points. Cannabis use characteristics of early and heavy use initiation during adolescence were associated with greater performance impairments among cannabis users at follow-up. The relationship emerged despite the cognitive strengths of users and general homogeneity of use characteristics in the cannabis user sample. This is consistent with theories that the timing and magnitude

of use during adolescence has far-reaching impacts on cognition throughout life (Lisdahl et al., 2013; Meier et al., 2012). The study extended the existing literature by documenting the emergence of these use characteristics' contributions to poorer learning and memory performance in a young adult sample.

Unfortunately, this study does not resolve questions about the timing of the development of cognitive deficits in this sample, as select deficits were noted at baseline and persisted at follow-up. Notably, cannabis users in this sample had already initiated use at least a year prior to the baseline assessment, and premorbid differences between samples cannot be ruled out. More prospective research is needed to clarify the causal role of cannabis in cognitive deficits noted.

The lack of more widespread cognitive deficits, or decline in cognitive performance between assessments, may be accounted for by the greater cognitive reserve in younger cannabis users as opposed to older users. As cannabis use extends into adulthood, underlying cognitive vulnerabilities may emerge among those with earlier and greater cannabis use during adolescence, and performance deficits in affected cognitive domains could become more striking. The declines that have been reported in the context of other longitudinal studies might be observed in this sample of cannabis users were assessed after a longer time period to follow-up. Future longitudinal research that follows users during emerging adulthood and indexes cognitive performance as a function of amount and age of cannabis use in adolescence would address this outstanding question.

In Study 2, the underlying neuroanatomical profile of white matter microstructure was assessed at baseline and over the follow-up interval. The findings were consistent with cross-sectional DTI research indicating that heavy cannabis use is associated with

deleterious alterations in white matter microstructure within major fiber tracts, such as the superior longitudinal fasciculus, corticospinal tract, and corpus callosum. The deleterious alterations were not accounted for by baseline differences between groups and only emerged over the follow-up interval. The longitudinal study design extended the existing literature by assessing white matter microstructural change in the context of continuing regular cannabis use by high-functioning young adults. This design distinguished a small number of baseline DTI differences between cannabis users and non-using controls from a larger number of group differences in FA and RD change over time. The differences found suggest aberrant patterns of neurodevelopment as a consequence of heavy cannabis use.

It was expected that the cognitive vulnerabilities noted in Study 1 would be associated with the FA-change clusters in Study 2, providing a link between the behavioral and neurobiological alterations. However, this direct association was largely not observed, and FA-change was associated with few behavioral correlates. Overall, the functional significance of the white matter microstructure differences between groups was not detected with the neurocognitive battery employed. Behavioral manifestations of disrupted white matter microstructure may manifest in subtler ways than would be detected by task performance at this time, but this underlying vulnerability may emerge in more pronounced cognitive deficits over time. By assessing young adult cannabis users, this study captures cannabis' impact in the context of ongoing refinement and remodeling of neural connections across broad association areas of the brain (Lebel et al., 2012). As that maturational process slows and plateaus, cognitive processing efficiency may decline at a faster rate than in those with normative brain development. On the other

hand, the brain changes observed may represent neuroplastic changes that result in compensatory alternative brain organization, which ultimately yield equivalent task performance. Both possibilities are purely speculative at this point, and would require longer-term longitudinal studies to assess users over a longer time span, after brain development plateaus.

Similarly, identifying the neurobiological underpinnings of the cognitive deficits observed in Study 1 also remains an outstanding research question. I expected that white matter microstructure disruptions would underlie the cognitive deficits typically noted in cannabis users, but this was not supported by the current studies. Given the lack of correlation between white matter microstructure and behavioral alterations noted in this study, I suggest that future research should employ different imaging methods to determine the link between the biological and behavioral findings. More inclusive methods assessing white matter across the whole brain of cannabis users, rather than within clusters that distinguished cannabis users from controls, may detect this association.

It is also possible that neurobiological alterations not indexed with DTI underlie the cognitive alterations noted, such as molecular changes in neurotransmitter signaling. These more fine-grained alterations may not manifest in a broad index of white matter integrity, but are more likely to be detected with different imagining techniques that assess the chemical composition within brain regions (i.e., MRI spectroscopy: Muetzel et al., 2013). Each imaging technique has costs and benefits. The methods employed in the current studies allowed for comparison of white matter integrity between groups across the whole brain, whereas MRI spectroscopy assesses only a small portion of the brain.

However, the current results suggest more fine-grained imagining may be useful. A review of 8 MRI spectroscopy studies among cannabis users suggested that chronic cannabis use is associated with decreased neuronal viability and cannabinoid-mediated immunosuppression, supporting the hypothesis that exogenous cannabinoids are neurotoxic (Sneider, Mashhoon, & Silveri, 2013). However, *in vitro* and *in vivo* preclinical data support both a neuroprotective and neurotoxic profile of cannabinoids, (Sarne, Asaf, Fishbein, Gafni, & Keren, 2011). Further basic research is needed to clarify the complex role of the endocannabinoid system in the brain in general, during development, and how it can be disrupted through chronic cannabis use.

This dissertation replicated findings that both cognitive and neurobiological alterations characterized young adult chronic cannabis users. Cognitive abilities are not expressed in a vacuum, and it is important to consider the larger implications of these findings. Cognitive abilities are expressed through complex, multidimensional, and interactive environments in daily life. Regardless of underlying mechanisms driving the alterations, subtle deficits in the domains of planning and verbal memory have the potential to have far-reaching effects on daily life, given that these cognitive domains support goal-attainment and new learning. Alterations in these abilities are likely to impact performance in a variety of real-world situations, including educational and workplace settings.

One excellent illustration of how these cognitive deficits manifest in real-world settings was provided by Montgomery and colleagues (2012), who assessed young adult cannabis users and non-users as they played the role of an office worker in a non-immersive virtual reality task. Participants completed tasks that approximated duties one

might perform in an office, providing a glimpse into the functional capabilities of participants in a cognitively demanding setting. Cannabis users performed worse overall, and their performance was most impaired on measures of planning (i.e., write a plan of action for a list of tasks one needed to accomplish in a logical order) and prospective memory (i.e., update a log for the outgoing mail, remember to turn off the coffee maker when someone arrived for a meeting). Logical organization and successful completion of tasks are important skills for success in all types of occupations, as well as countless valued activities in everyday life (e.g., volunteer activities, sports, hobbies, relationships, parenting). Further, even subtle deficits in learning and memory could impact users' ability to apprehend new information, build on existing knowledge bases, and advance their learning and education in school and the workplace. It is likely that the cognitive performance deficits that characterize cannabis users are reflected in a broad range of diminished real world achievement and functioning.

Indeed, cannabis use is associated with lower educational achievement (Horwood et al., 2010; Medina et al., 2007) as well as poor psychosocial adjustment across a range of domains, including decreased life satisfaction, negative physical health consequences, and increased self-report of depression and anxiety, (Arseneault, Cannon, Witton, & Murray, 2004; Hall & Degenhardt, 2009; Hayatbakhsh et al., 2007; Patton et al., 2002; Rey et al., 2002). Ongoing research indicates that a broad range of risk factors predispose adolescents to initiate cannabis use, (Hayatbakhsh, Williams, Bor, & Najman, 2012), though, once initiated, cannabis use contributes to negative mental health and other poor psychosocial outcomes (Lynskey et al., 2003; Mcgee, Williams, Poulton, & Moffitt, 2000; Patton et al., 2002). While the mechanisms driving the correlates with use are not

fully understood, altered cognitive abilities may be one contributor to overall diminished functioning and negative health outcomes.

As legality questions are at the forefront in United States' political discussion, it is important to consider the actual risks that appear to be associated with cannabis use. The existing literature and, in part, this dissertation indicate that early and heavy use of cannabis is associated with a range of cognitive, neurobiological, and psychosocial risks. Thus, I support Krista Lisdahl's suggestion that young people "dare to delay" cannabis use during adolescence (Lisdahl et al., 2013), and wait until the window of increased developmental vulnerability closes to initiate use, if they choose to use at all. Crafting laws that reduce cannabis use during adolescence will be an important safeguard to mitigate the risks that are associated with that pattern of use. Further, focusing efforts and resources on early prevention of use and increased education to parents and adolescents about the risks associated with use are important steps to bridge the gap between the scientific community and those negatively impacted by use.

4 Tables

Table 1. *Study 1 Demographic and substance use characteristics of cannabis users and controls at baseline and follow-up*

Variable	Control	Cannabis User	*F, U,* χ^2	*p*
Baseline characteristics				
n	35	36		
Age	19.40 (0.93)	19.51 (0.61)	0.37	0.55
#Male/#Female	13/22	22/14	$\chi^2 = 4.08$	0.04*
#Caucasian/#Other Ethnicity	27/8	31/5	$\chi^2 = 0.95$	0.33
Years of education	13.26 (1.24)	13.26 (0.95)	< 0.00	0.98
Estimated Full Scale IQ[a]	114.85 (1.70)	114.40 (1.65)	0.03	0.86
Vocabulary T-Score	62.16 (1.29)	60.71 (1.26)	0.62	0.44
Matrix reasoning T-Score	54.56 (0.99)	55.65 (0.96)	0.60	0.44
Alcohol use average	-0.59 (0.69)	0.59 (0.75)	48.22*	< 0.00**
ASR substance use				
Past 6 months: Tobacco use per day	0.00 (0.00)	0.92 (1.53)	*U* = 385.0	< 0.00**
Past 6 months: Days drunk	5.37 (9.24)	25.21 (18.14)	*U* = 143.5	< 0.00**
Past 6 months: Days using drugs	0.14 (0.49)	145.20 (40.21)	*U* = 0.00	< 0.00**
Cannabis use[b]				
Age first used (years)	–	15.24 (1.23)		
Past year: Days used	–	333.86 (45.29)		
Past 30 days: Days used	–	27.50 (3.88)		
Past year: Total # hits	–	3256.97 (2307.04)		
Past 30 days: Total # hits	–	262.69 (200.41)		
Follow-up characteristics				
n	29	26		
Years between assessments	2.22 (0.49)	2.36 (0.31)	1.60	0.21
Age at follow-up	21.52 (0.90)	21.82 (0.76)	1.77	0.19
#Male/#Female	10/19	19/7	χ^2 =8.19	< 0.00**
#Caucasian/#Other Ethnicity	23/6	22/4	$\chi^2 = 0.26$	0.61

Variable	Control	Cannabis User	F, U, χ^2	p
Years of education	15.14 (1.13)	15.16 (2.72)	< 0.00	0.97
Estimated Full Scale IQ[a]	118.84 (1.54)	117.11 (1.63)	0.55	0.46
Vocabulary T-Score	62.25 (1.25)	61.38 (1.33)	0.21	0.65
Matrix reasoning T-Score	58.83 (0.90)	58.11 (0.96)	0.28	0.60
Alcohol use average	-0.51 (0.52)	0.58 (0.76)	39.57	< 0.00**
ASR substance use				
Past 6 months: Tobacco use per day	0.00 (0.00)	2.03 (3.10)	U = 130.5	< 0.00**
Past 6 months: Days drunk	6.90 (9.84)	27.65 (22.56)	U = 110.5	< 0.00**
Past 6 months: Days using drugs	0.45 (0.91)	93.71 (67.37)	U = 18.0	< 0.00**
Cannabis use[b,c]				
Past year: Days used	–	245.02 (134.92)		
Past 30 days: Days used	–	18.28 (11.96)		
Past year: Total # hits	–	2561.90 (2396.39)		
Past 30 days: Total # hits	–	184.41 (204.75)		

Notes. Values represent means and standard deviation units, unless otherwise specified. Group comparisons using chi-square, Mann-Whitney U, or one-way analysis of variance are reported. ASR = Adult Self-Report. [a]Marginal means and standard errors are presented, controlling for sex. [b]Variables only included for cannabis users. [c]Data unavailable for 1 cannabis user (n = 25).
*$p \leq$ .05. **$p \leq$ .01.

Table 2. *DSM-IV-TR Diagnoses at study initiation and follow-up, as assessed by the K-SADS-PL. The number of participants who met criteria for each disorder is reported.*

	Control						Cannabis					
	Baseline (*n* = 35)			Follow-up (*n* = 29)			Baseline (*n* = 36)			Follow-up (*n* = 26)		
Diagnosis	Current	Partial Remission	Past	Current	Partial Remission	Past	Current	Partial Remission	Past	Current	Partial Remission	Past
Cannabis Dependence	0	0	-	0	0	-	19	1	-	15	5	-
Cannabis Abuse	0	-	0	0	-	0	12	-	14	2	-	5
Alcohol Dependence	0	0	-	0	1	-	1	0	-	3	1	-
Alcohol Abuse	0	-	0	1	-	2	11	-	16	4	-	8
Major Depressive Disorder	0	-	0	0	-	0	0	-	0	0	-	2
Bipolar NOS	0	-	0	0	-	0	1	-	1	1	-	1
Oppositional Defiant Disorder	0	-	0	0	-	0	0	-	2	NA	-	NA
Specific Phobia	0	-	0	0	-	0	0	-	1	0	-	0
Generalized Anxiety Disorder	0	-	0	0	-	0	0	-	0	1	-	2

Notes. NA = not assessed at follow-up. Current ratings are based on previous 6 months for substance use disorders, and on the previous 2 months for other diagnoses. At baseline, past ratings are based on lifetime symptom expression. At follow-up, past ratings are based on symptoms during follow-up interval

Table 3. *Substance Use Disorder Symptoms baseline and follow-up. The number of participants who reported each symptom is reported.*

	Control				Cannabis User			
	Baseline		Follow-up		Baseline		Follow-up	
Symptom	Current	Past	Current	Past	Current	Past	Current	Past
Alcohol								
Uses more than planned	0	0	1	2	0	1	7	7
Recurrent negative physical consequences	3	1	5	9	17	19	5	15
Recurrent use in dangerous situations	0	0	0	0	5	7	5	9
Recurrent negative psychological consequences	0	0	1	1	2	3	1	1
Recurrent negative occupational consequences	0	0	0	0	1	1	2	2
Recurrent negative social consequences	0	0	1	1	2	5	2	2
Recurrent negative legal consequences	0	0	0	1	0	1	0	0
Recurrent failure to fulfill major role	0	0	0	0	0	2	2	3
Important activities reduced for use	0	0	0	0	1	1	1	2
Time consuming	0	0	0	0	2	1	5	5
Tolerance	1	0	0	1	6	6	6	7
Repeated attempts to quit	0	0	0	0	0	0	0	0
Withdrawal	0	0	0	1	0	0	0	0
Alcohol consumed to alleviate withdrawal	0	0	0	0	0	0	0	0
Cannabis								
Uses more than planned	0	0	0	0	11	12	8	11
Recurrent negative physical consequences	0	0	0	0	1	1	3	3
Recurrent use in dangerous situations	0	0	0	0	24	26	18	19
Recurrent negative psychological consequences	0	0	0	0	3	2	2	3
Recurrent negative occupational consequences	0	0	0	0	13	13	4	4
Recurrent negative social consequences	0	0	0	0	3	5	2	3
Recurrent negative legal consequences	0	0	0	0	0	0	0	0
Recurrent failure to fulfill major role	0	0	0	0	17	18	10	17
Important activities reduced for use	0	0	0	0	7	9	4	5
Time consuming	0	0	0	0	34	34	20	24
Tolerance	0	0	0	0	20	19	18	21

	Control				Cannabis User			
	Baseline		Follow-up		Baseline		Follow-up	
Symptom	Current	Past	Current	Past	Current	Past	Current	Past
Repeated attempts to quit	0	0	0	0	6	7	4	5
Withdrawal	0	0	0	0	8	9	6	11
Cannabis consumed to alleviate withdrawal	0	0	0	0	1	1	0	2

Note. Current ratings are based on previous 6 months. At baseline, past ratings are based on lifetime symptom expression. At follow-up, past ratings are based on symptoms during follow-up interval.

Table 4. *Lifetime other drug usage in cannabis users and controls at baseline and follow-up. Number of participants who used each drug at different usage levels. Count includes lifetime use at baseline, and use in past 12 months at follow-up*

	Control		Cannabis	
	Baseline	Follow-up	Baseline	Follow-up
	n = 35	*n* = 29	*n* = 36	*n* = 26
Cannabis				
No use	24	20	-	1
1-5 times	10	5	-	-
6-20 times	1	4	-	1
21-49 times	-	-	-	1
50-99 times	-	-	-	6
100+ times	-	-	37	17
Psychedelics				
No use	35	28	18	9
1-5 times	-	1	16	14
6-20 times	-	-	2	2
100+ times	-	-	-	1
Cocaine				
No use	35	29	33	17
1-5 times	-	-	2	9
6-20 times	-	-	1	-
Amphetamines				
No use	35	29	29	20
1-5 times	-	-	5	2
6-20 times	-	-	1	4
21-49 times	-	-	1	-
Barbiturates				
No use	35	29	31	25
1-5 times	-	-	5	1
Tranquilizers				
No use	35	29	29	26
1-5 times	-	-	7	-
Heroin				
No use	35	29	36	26
Other narcotics				
No use	35	29	23	20
1-5 times	-	-	12	6
21-49 times	-	-	1	-
Steroids				
No use	35	29	36	26
Inhalants				
No use	35	29	35	26
1-5 times	-	-	1	-
Prescription drugs				
No use	35	28	27	21
1-5 times	-	1	9	4
6-20 times	-	-	-	1

Table 5. *Iowa Gabling Task (IGT) deck contingencies*.

	Deck 1	Deck 2	Deck 3	Deck 4
Win Amount	$0.25	$0.25	$0.10 or $0.15	$0.10 or $0.15
% of losses	50%	10%	50%	10%
Range of losses	$0.35 - $0.90	$3.00 - $3.25	$0.05 - $0.20	$0.60 - $0.65
Net winnings after 20 choices	-$1.25	-$1.25	+1.25	+1.25
Good vs. Bad	Bad	Bad	Good	Good
Punishment	Frequent	Infrequent	Frequent	Infrequent

Table 6. *Baseline neuropsychological cognitive composite scores. Cognitive composite scores represent average z-scores from component test variables. Higher performance indicates better performance. Means reported are marginal means, controlling for sex, IQ, and alcohol use.*

Cognitive Composite	Cronbach's α	Control *M (SE)*	Cannabis user *M (SE)*	*F*	*p*	η_p^2
Motor Speed	0.91	-0.317 (0.20)	0.197 (0.20)	2.614	.111	.04
Motor Dexterity	0.82	-0.225 (0.17)	-0.046 (0.17)	0.440	.510	.01
Processing Speed	0.60	-0.361 (0.13)	0.213 (0.13)	7.470	.008**	.10
Verbal Learning and Memory	0.91	0.231 (0.16)	-0.446 (0.16)	7.313	.009**	.10
Spatial Working Memory and Planning	0.73	0.002 (0.13)	-0.236 (0.13)	1.333	.253	.02

**$p \leq .01$.

Table 7. *Baseline neuropsychological battery scores. Means reported are marginal means, controlling for sex, IQ, and alcohol use.*

Cognitive Measure	Control (n = 35) *M (SE)*	Cannabis user (n = 36) *M (SE)*	*F*	*p*	η_p^2
Finger Tapping Test					
Dominant hand (# taps)	42.11 (1.71)	46.98 (1.68)	3.25	.076^	.05
Non-dominant hand (# taps)	41.92 (1.50)	44.85 (1.48)	1.52	.222	.02
Grooved Pegboard					
Dominant hand time (s)	65.48 (1.44)	63.83 (1.42)	0.52	.473	.01
Non-dominant hand time (s)[b]	72.86 (2.00)	71.40 (2.00)	0.21	.650	<.00
Digit Symbol					
Total correct	87.61 (2.64)	89.33 (2.60)	0.17	.682	<.00
Letter Cancellation					
Time (s)	112.09 (3.45)	96.33 (3.39)	8.31	.005**	.11
Total omissions[a]	1.49 (0.15)	1.53 (0.14)	0.02	.881	<.00
Total commissions[a]	0.81 (0.04)	0.72 (0.04)	1.61	.209	.02
COWAT					
Total correct words generated	43.09 (1.80)	50.66 (1.77)	7.07	.010**	.10
Total set-loss errors[a]	0.82 (0.08)	1.10 (0.08)	4.16	.045*	.06
Total perseverative errors[a]	1.03 (0.08)	0.96 (0.08)	0.28	.602	<.00
Digit Span					
Digits forward (# recalled)	7.66 (0.22)	7.16 (0.21)	2.14	.148	.03
Digits backward (# recalled)	5.94 (0.26)	5.25 (0.25)	2.84	.097	.04
RAVLT					
Trial 1	7.07 (0.34)	6.62 (0.33)	0.72	.401	.01
Trial 2	9.92 (0.43)	9.72 (0.42)	0.09	.764	<.00
Trial 3	11.78 (0.38)	11.33 (0.37)	0.57	.451	.01
Trial 4	12.75 (0.4)	11.69 (0.39)	2.78	.100^	.04
Trial 5	13.38 (0.36)	12.36 (0.35)	3.25	.076^	.05
Total words: Trial 1-5	54.90 (1.46)	51.71 (1.43)	1.92	.171	.03
Trial 1-5 total intrusions[a]	1.02 (0.11)	1.32 (0.11)	2.77	.100^	.04
Trial 1-5 total perseverative errors[a]	1.94 (0.18)	1.85 (0.18)	0.10	.752	<.00
Total words: Interference trial list	7.37 (0.33)	5.92 (0.32)	7.74	.007**	.10

Cognitive Measure	Control (n = 35) *M (SE)*	Cannabis user (n = 36) *M (SE)*	*F*	*p*	η_p^2
Total words: Immediate recall	12.22 (0.41)	10.54 (0.40)	6.87	.011*	.09
Total words: Delayed recall	12.01 (0.45)	9.68 (0.44)	10.61	.002**	.14
Spatial Working Memory[b]					
Total between search errors	13.65 (1.93)	12.40 (1.93)	0.16	.686	<.00
Strategy Score: 6-8	30.30 (1.05)	28.90 (1.05)	0.69	.410	.01
Spatial Delayed Response Task	*2.45 (0.16)*	*2.53 (0.16)*			
Error: No delay (mm)	6.45 (0.44)	7.71 (0.43)	0.10	.752	<.00
Error: 500 ms delay (mm)	9.89 (0.60)	11.92 (0.59)	3.29	.074^	.05
Error: 8,000 ms delay (mm)	1816.66 (100.77)	1981.98 (98.98)	4.61	.036*	.07
Mean reaction time: No delay	1653.57 (74.05)	2070.81 (72.73)	1.08	.304	.02
Mean reaction time: 500 ms delay	1723.02 (82.39)	2268.63 (80.93)	12.69	.001**	.16
Mean reaction time: 8,000 ms delay			17.52	<.000**	.21
Tower of London[b]					
% Perfect Solutions	83.47 (0.03)	74.15 (0.03)	5.11	.027*	.07
Average moves: 2-move	2.00 (0.00)	2.00 (0.00)			
Average moves: 3-move	3.00 (0.06)	3.29 (0.06)	9.34	.003*	.13
Average moves: 4-move	4.93 (0.18)	5.16 (0.18)	0.64	.428	.01
Average moves: 5-move	5.67 (0.21)	6.20 (0.21)	2.54	.116	.04
First move initiation time: 2-move	3180.33 (195.14)	3704.75 (195.14)	2.85	.096^	.04
First move initiation time: 3-move	5508.33 (414.31)	5504.90 (414.31)	< 0.00	.996	<.00
First move initiation time: 4-move	8269.05 (845.16)	8518.35 (845.16)	0.03	.854	<.00
First move initiation time: 5-move	12989.62 (1185.74)	8930.44 (1185.74)	4.62	.035*	.07
First move initiation time: Average	7486.83 (586.33)	6664.61 (586.33)	0.78	.382	.01
Iowa Gambling Task[c]					
Good Choices-Bad Choices: Block 1	-1.25 (1.69)	-3.37 (1.63)	0.64	.426	.01
Good Choices-Bad Choices: Block 2	3.01 (1.75)	-1.78 (1.69)	3.06	.085^	.05
Good Choices-Bad Choices: Block 3	3.59 (1.83)	-1.39 (1.77)	3.02	.087^	.04
Good Choices-Bad Choices: Block 4	9.41 (1.92)	-1.00 (1.85)	11.98	.001**	.16
Good Choices-Bad Choices: Block 5	9.47 (2.05)	0.45 (1.97)	7.93	.006**	.11
Deck 1 choices	15.51 (1.62)	21.49 (1.56)	5.607	.021*	.08

Cognitive Measure	Control (n = 35) *M (SE)*	Cannabis user (n = 36) *M (SE)*	*F*	*p*	η_p^2
Deck 2 choices	22.38 (2.31)	32.06 (2.23)	7.183	.009**	.10
Deck 3 choices	22.73 (2.06)	17.28 (1.98)	2.872	.095^	.04
Deck 4 choices	39.38 (3.48)	29.17 (3.36)	3.507	.066^	.05

[a]Square root transformed. [b]Data unavailable for 1 cannabis user (n = 35). [c]Data unavailable for 1 control (n = 34).
^$p \leq .1$. *$p \leq .05$. **$p \leq .01$.

Table 8. *Partial correlations between baseline cognitive performance and substance use variables in cannabis users (n = 36).*

	Age of regular cannabis use	Past Year: Total # hits	Alcohol use	Tobacco use	Non-cannabis drug use
Substance Use Measures[a]					
Age of regular cannabis use	–	-.100	-.055	-.111	-.221
Past Year: Total # hits		–	.030	-.074	.164
Alcohol use			–	.126	.208
Tobacco use				–	-.073
Non-cannabis drug use					–
Cognitive Measures[b]	Age of regular cannabis use[c]	Past Year: Total # hits[c]	Alcohol use[d]	Tobacco use[e]	Non-cannabis drug use[f]
Processing Speed Composite	-.040	-.050	-.002	.121	-.299^
Verbal Learning and Memory Composite	.030	.136	.504**	-.185	.143
Letter Cancellation					
Time	.278	.153	.104	-.112	.290
COWAT – Verbal Fluency					
Total words	-.043	.226	-.128	-.157	.020
Total set-loss errors[g]	-.295	-.014	-.173	-.050	-.318^
RAVLT					
Total words: Interference trial list	.147	-.338^	.455**	.102	.009
Total words: Immediate recall	-.162	.118	.551**	-.208	.028
Total words: Delayed recall	-.060	.268	.457**	-.131	.326^
% Recalled after consolidation	-.279	.153	.242	-.100	.457**
Spatial Delayed Response Task					
Error: 8,000 ms delay	-.177	.426*	-.390*	.073	.180
Mean reaction time: 500 ms delay	-.429*	.018	-.293	-.272	.054
Mean reaction time: 8,000 ms delay	-.453*	.004	-.308^	-.192	.039
Tower of London[g]					
% Perfect Solutions	.026	.113	.344^	.033	.013
Average moves: 3-move	-.414*	.028	-.390*	-.301	-.200
First move initiation time: 5-move	.089	-.387*	.215	-.205	-.375*
Iowa Gambling Task					
Good Choices-Bad Choices: Block 2	.024	-.155	-.015	-.135	-.095
Good Choices-Bad Choices: Block 4	-.182	-.137	.194	.061	-.072
Good Choices-Bad Choices: Block 5	-.287	-.100	-.053	.099	-.141

Deck 1 choices	.013	.159	.087	-.056	-.027
Deck 2 choices	.297	-.058	-.198	-.011	.210

Notes. Tobacco use, non-cannabis drug use, past year: total # hits, and COWAT total set-loss errors were square root transformed. [a]Partial correlations with sex controlled. [b]Partial Correlations with sex and IQ controlled. [c]Also controlled for alcohol, tobacco, and non-cannabis drug use. [d]Controlling for tobacco and non-cannabis drug use. [e]Controlling for alcohol and non-cannabis drug use. [f]Controlling for alcohol and tobacco use. [g]Data unavailable for 1 participant (n = 35). ^$p \leq .1$. *$p \leq .05$. **$p \leq .01$.

Table 9. *Baseline demographic and substance use characteristics between participants who returned for follow-up assessment and those who dropped out of the study at follow-up, separated by controls and cannabis users.*

	Control *M* (*SD*)			Cannabis User *M* (*SD*)		
Variable	Follow-up Sample	Lost to Follow-up	*F* or χ^2	Follow-up Sample	Lost to Follow-up	*F* or χ^2
n	29	6		26	10	
Age	19.29 (0.93)	19.93 (0.80)	2.412	19.43 (0.65)	19.73 (0.44)	1.820
#Male/#Female	10/19	3/3	$\chi^2 = 0.513$	19/7	6/4	$\chi^2 = 3.425$^
#Caucasian/#Other Ethnicity	23/6	4/2	$\chi^2 = 0.451$	22/4	9/1	$\chi^2 = 0.175$
Years of education	13.00 (1.19)	14.50 (0.55)	9.007**	13.28 (0.98)	13.20 (0.92)	0.049
Estimated Full Scale IQ	114.79 (9.57)	114.17 (9.37)	0.021	114.77 (10.41)	114.00 (11.15)	0.038
Vocabulary T-Score	62.10 (6.93)	60.50 (6.92)	0.267	61.38 (8.21)	60.10 (9.12)	0.167
Matrix reasoning T-Score	54.52 (6.09)	55.67 (5.89)	0.179	55.38 (5.74)	55.80 (5.35)	0.039
Alcohol use average	-.58 (0.74)	-0.65 (0.35)	0.044	0.71 (0.76)	0.30 (0.68)	2.217
ASR substance use						
Past 6 months: Tobacco use per day	0.00 (0.00)	0.00 (0.00)	–	1.02 (1.62)	0.60 (1.58)	0.487
Past 6 months: Days drunk	5.28 (9.44)	5.83 (9.00)	0.018	28.58 (19.83)	21.30 (16.16)	1.068
Past 6 months: Days using drugs	0.10 (0.41)	0.33 (0.82)	1.081	136.20 (43.44)	174.70 (10.26)	7.558**
Cannabis use[b]						
Age first used (years)				15.42 (1.15)	14.75 (1.36)	2.259
Past year: Days used	–	–	–	324.9 (48.48)	357.18 (24.73)	3.983^
Past 30 days: Days used	–	–	–	26.79 (4.21)	29.36 (2.02)	3.384^
Past year: Total # hits	–	–	–	3234.65 (2482.38)	3314.99 (1891)	0.009
Past 30 days: Total # hits	–	–	–	257.19 (211.02)	276.98 (179.39)	0.069

Notes. Group comparisons using chi-square or one-way analysis of variance are reported. ASR = Adult Self-Report. [a]Variables only included for cannabis users. ^$p \leq$ .10. **$p \leq$ .01.

Table 10. *Baseline and follow-up neuropsychological cognitive composite scores for participants who completed the follow-up assessment (controls n = 29) and (cannabis users n = 26). Cognitive composite scores are average z-scores from component test variables with higher performance indicating better performance. Means reported are marginal means, controlling for sex, IQ, and average alcohol use within time point. Marginal means calculated for each time point separately.*

Cognitive Composite	Baseline		Follow-up		Repeated Measures ANCOVA	
	Control (n = 29) *M (SE)*	Cannabis user (*n* = 26) *M (SE)*	Control (n = 29) *M (SE)*	Cannabis user (*n* = 26) *M (SE)*	Group *F (p)/* η_p^2	Group × Time *F (p)/* η_p^2
Motor Speed	-0.441 (0.230)	0.285 (0.253)	0.004 (0.177)	0.131 (0.191)	0.63 (.430)/.013	0.49 (.487)/.010
Motor Dexterity	-0.249 (0.202)	-0.091 (0.223)	0.259 (0.185)	0.051 (0.199)	0.13 (.723)/.003	0.67 (.416)/.014
Processing Speed	-0.411 (0.148)	0.316 (0.163)	-0.136 (0.155)	0.355 (0.167)	**5.88 (.019*)/.107**	1.67 (.202)/.033
Verbal Learning and Memory	0.242 (0.183)	-0.408 (0.202)	0.304 (0.191)	-0.094 (0.206)	3.41 (.071^)/.065	0.67 (.416)/.014
Spatial Working Memory & Planning	0.032 (0.145)	-0.324 (0.160)	0.302 (0.175)	0.049 (0.189)	3.09 (.085^)/.060	1.64 (.207)/.033

*$p \leq .05$.

Table 11. *Baseline and Follow-up neuropsychological battery scores for participants who completed the follow-up assessment (controls n = 29) and (cannabis users n = 26). Means reported are marginal means, controlling for sex, IQ, and average alcohol use within time point. Marginal means calculated for each time point separately.*

Cognitive Measure	Baseline		Follow-up		Repeated Measures ANCOVA	
	Control (n = 29) *M (SE)*	Cannabis user (n = 26) *M (SE)*	Control (n = 29) *M (SE)*	Cannabis user (n = 26) *M (SE)*	Group *F (p)/* η_p^2	Group × Time *F (p)/* η_p^2
Finger Tapping Test						
Dominant hand (# taps)	41.03 (1.96)	47.80 (2.11)	44.68 (1.52)	47.22 (1.64)	1.54 (.22)/.031	0.21 (.648)/.004
Non-dominant hand (# taps)	41.14 (1.75)	45.44 (1.88)	43.94 (1.33)	43.49 (1.44)	0.09 (.768)/.002	0.77 (.385)/.015
Grooved Pegboard						
Dominant hand time (s)	65.42 (1.70)	64.38 (1.83)	59.86 (1.49)	63.96 (1.60)	0.60 (.442)/.012	2.94 (.093^)/.057
Non-dominant hand time (s)	73.46 (2.38)	71.67 (2.56)	70.54 (2.31)	69.32 (2.50)	0.01 (.913)/<.000	0.10 (.758)/.002
Digit Symbol						
Total correct	86.44 (3.07)	91.28 (3.31)	91.52 (2.98)	95.57 (3.21)	1.15 (.289)/.023	0.12 (.733)/.002
Letter Cancellation						
Time (s)	113.27 (3.66)	93.13 (3.94)	109.19 (4.09)	95.82 (4.41)	**7.72 (.008**)/.136**	1.85 (.180)/.036
Total omissions[a]	1.44 (0.15)	1.52 (0.16)	1.56 (0.15)	1.27 (0.16)	0.02 (.897)/ < .000	2.86 (.097^)/.055
Total commissions[a]	0.81 (0.05)	0.73 (0.06)	0.73 (0.04)	0.80 (0.04)	0.08 (.775)/.002	1.63 (.208)/.032
COWAT						
Total correct words generated	42.99 (2.14)	50.47 (2.30)	45.69 (2.33)	50.27 (2.51)	2.03 (.161)/0.04	0.28 (.597)/.006
Total set-loss errors[a]	0.85 (0.08)	1.03 (0.09)	1.11 (0.10)	1.01 (0.10)	0.01 (.939)/ < 0.000	0.49 (.486)/.010
Total perseverative errors[a]	1.08 (0.08)	0.82 (0.08)	1.04 (0.11)	1.11 (0.12)	0.12 (.733)/0.002	1.80 (.186)/.035
Digit Span[c]						
Digits forward (# recalled)	7.67 (0.23)	7.21 (0.25)	7.46 (0.24)	7.20 (0.25)	1.45 (.235)/0.029	0.46 (.503)/.009
Digits backward (# recalled)	5.89 (0.30)	5.20 (0.32)	5.64 (0.30)	5.81 (0.31)	0.34 (.560)/0.007	2.59 (.114)/.051
RAVLT						
Total words: Trial 1	7.13 (0.38)	6.63 (0.41)	8.30 (0.29)	6.70 (0.31)	3.69 (.060^)/.070	3.13 (.083^)/.060
Total words: Trial 2	10.22 (0.48)	9.91 (0.52)	10.50 (0.38)	10.75 (0.41)	0.01 (.905)/ < .000	0.82 (.370)/.016
Total words: Trial 3	11.68 (0.47)	11.59 (0.50)	12.40 (0.41)	11.44 (0.44)	0.34 (.565)/.007	1.92 (.172)/.038
Total words: Trial 4	12.73 (0.46)	11.88 (0.50)	13.03 (0.43)	12.62 (0.47)	1.17 (.285)/.023	0.35 (.558)/.007
Total words: Trial 5	13.40 (0.39)	12.52 (0.42)	13.13 (0.43)	12.70 (0.47)	1.38 (.246)/.027	0.40 (.529)/.008
Total words: Trial 1-5	55.15 (1.72)	52.53 (1.85)	57.36 (1.45)	54.21 (1.56)	1.20 (.278)/.024	0.11 (.744)/.002
Trial 1-5 total intrusions[a]	1.06 (0.10)	1.18 (0.11)	0.73 (0.11)	1.33 (0.11)	**11.05 (.002**)/.184**	1.80 (.186)/.035
Trial 1-5 total perseverations[a]	2.04 (0.21)	1.88 (0.22)	1.77 (0.22)	2.00 (0.24)	0.14 (.714)/.003	0.20 (.659)/.004

Cognitive Measure	Baseline		Follow-up		Repeated Measures ANCOVA	
	Control (n = 29) *M (SE)*	Cannabis user (n = 26) *M (SE)*	Control (n = 29) *M (SE)*	Cannabis user (n = 26) *M (SE)*	Group *F (p)/* η_p^2	Group × Time *F (p)/* η_p^2
Total words: Interference trial	7.39 (0.38)	5.88 (0.41)	6.73 (0.38)	6.46 (0.41)	2.67 (.109)/.052	1.43 (.238)/.028
Total words: Immediate recall	12.22 (0.45)	10.64 (0.49)	11.81 (0.51)	11.10 (0.55)	3.17 (.081^)/.061	1.11 (.298)/.022
Total words: Delayed recall	12.05 (0.52)	9.64 (0.56)	11.92 (0.53)	10.74 (0.57)	**5.21 (.027*)/.096**	1.85 (.180)/.036
Spatial Working Memory[b,c]						
Total between search errors[a]	13.03 (2.10)	13.05 (2.31)	9.09 (2.58)	11.82 (2.71)	0.46 (.502)/.010	< 0.00 (.988)/ < .000
Strategy Score: 6-8	30.49 (1.13)	29.96 (1.25)	27.5 (1.28)	27.38 (1.35)	< 0.00 (.989)/ < .000	0.03 (.855)/.001
Spatial Delayed Response Task						
Error: No delay (mm)	2.33 (0.14)	2.46 (0.15)	2.24 (0.25)	2.69 (0.27)	1.20 (.278)/.024	0.45 (.505)/.009
Error: 500 ms delay (mm)	6.60 (0.50)	7.55 (0.54)	7.79 (0.59)	6.85 (0.63)	0.01 (.941)/ < .000	2.27 (.138)/.044
Error: 8,000 ms delay (mm)	10.17 (0.70)	12.04 (0.76)	11.43 (0.91)	12.50 (0.99)	1.71 (.196)/.034	0.62 (.437)/.012
Mean reaction time: No delay	1876.57 (109.45)	1977.55 (117.64)	1919.95 (135.20)	1965.74 (145.74)	0.09 (.765)/.002	< 0.00 (.978)/ < .000
Mean reaction time: 500 ms delay	1623.18 (79.43)	2127.61 (85.37)	1634.68 (70.50)	1784.82 (75.99)	**8.94 (.004**)/.015**	**4.46 (.040*)/.08**
Mean reaction time: 8,000 ms delay	1701.68 (94.14)	2268.38 (101.19)	1862.74 (93.03)	2041.93 (100.28)	**7.85 (.007**)/.138**	**5.30 (.026*)/.098**
Tower of London[b]						
% Perfect Solutions[d]	84.79 (2.89)	72.98 (3.19)	87.07 (3.3)	79.45 (3.38)	**7.43 (.009**)/.139**	1.72 (.197)/.036
Average moves 2-move	2.00 (0.00)	2.00 (0.00)	2.00 (0.00)	2.00 (0.00)	-	-
Average moves 3-move	3.02 (0.06)	3.28 (0.07)	3.03 (0.04)	3.18 (0.05)	**11.75 (.001**)/.197**	**5.58 (.022*)/.104**
Average moves 4-move	4.96 (0.21)	5.17 (0.23)	4.59 (0.20)	4.94 (0.21)	1.95 (.169)/.039	0.02 (.891)/ < .000
Average moves 5-move	5.62 (0.23)	6.22 (0.26)	5.98 (0.24)	5.83 (0.26)	0.74 (.393)/.015	3.02 (.089^)/.059
First move initiation time 2-move[d]	3047.22 (188.46)	3783.47 (207.75)	3766.62 (246.93)	3884.28 (253.35)	1.76 (.191)/.037	1.78 (.189)/.037
First move initiation time 3-move[d]	5188.61 (466.35)	5618.77 (514.08)	6767.39 (696.40)	5608.14 (714.51)	0.18 (.672)/.004	1.67 (.202)/.035
First move initiation time 4-move[d]	7494.03 (814.22)	8890.52 (897.57)	9979.34 (703.40)	7533.22 (721.69)	0.65 (.426)/.014	3.83 (.056^)/.077
First move initiation time 5-move[d]	12119.97 (1219.36)	9817.20 (1344.18)	14868.04 (2090.80)	10742.39 (2145.16)	2.54 (.118)/.052	0.10 (.757)/.002
First move initiation time: Average[d]	6962.46 (584.97)	7027.49 (644.84)	8845.35 (777.26)	6942.01 (797.47)	1.24 (.272)/.026	1.30 (.260)/.028

Cognitive Measure	Baseline		Follow-up		Repeated Measures ANCOVA	
	Control (n = 29) *M (SE)*	Cannabis user (n = 26) *M (SE)*	Control (n = 29) *M (SE)*	Cannabis user (n = 26) *M (SE)*	Group *F (p)/* η_p^2	Group × Time *F (p)/* η_p^2
Iowa Gambling Task[e]						
Good-Bad Choices: Block 1	-2.02 (1.91)	-3.52 (2.05)	-1.51 (2.61)	5.17 (2.69)	0.74 (.395)/.016	**4.53 (.039)/.091**
Good-Bad Choices: Block 2	3.49 (2.02)	-2.05 (2.17)	2.77 (2.63)	3.04 (2.70)	< 0.00 (.978)/ < .000	1.57 (.216)/.034
Good-Bad Choices: Block 3	4.24 (1.95)	-1.65 (2.1)	5.04 (2.35)	5.56 (2.41)	0.48 (.494)/.010	2.66 (.110)/.056
Good-Bad Choices: Block 4	9.82 (2.11)	-3.80 (2.26)	7.37 (2.82)	3.78 (2.90)	**5.38 (.025*)/.107**	**6.00 (.018*)/.118**
Good-Bad Choices: Block 5	10.83 (2.3)	-0.62 (2.47)	8.51 (2.72)	8.99 (2.79)	1.65 (.206)/.035	**11.01 (.002**)/.197**
Deck 1 choices	15.39 (1.83)	21.49 (1.97)	13.66 (2.32)	17.08 (2.38)	2.43 (.126)/.051	2.081 (.156)/.044
Deck 2 choices	21.44 (2.57)	34.32 (2.76)	25.26 (3.60)	19.65 (3.70)	0.84 (.773)/.002	**10.90 (.002**)/.195**
Deck 3 choices	23.12 (2.23)	14.95 (2.40)	15.01 (5.97)	34.07 (6.13)	1.36 (.250)/.029	**10.90 (.002**)/.195**
Deck 4 choices	40.06 (3.78)	29.24 (4.07)	46.08 (5.68)	29.20 (5.84)	**4.12 (.048*)/.084**	0.34 (.565)/.007

Notes. Baseline and follow-up statistics for the follow-up sample (control n = 29, cannabis user n = 26). Marginal means and standard errors are presented for the, controlling for time to follow-up interval, sex, IQ, and average alcohol use during baseline and follow-up. [a]Square root transformed [b]Data unavailable for 1 cannabis user (n = 25) at baseline. [c]Data unavailable for 1 control at follow-up (n = 28). [d]Data unavailable for 2 controls (n = 27) at follow-up. [e]Data unavailable for 1 cannabis user (n = 25) and 3 controls (n = 26) at follow-up

^$p \leq .1$. *$p \leq .05$. **$p \leq .01$.

Table 12. *Partial correlations between follow-up cognitive performance and cannabis use measures in cognitive measures in cannabis users(n = 26). Partial correlations controlling for baseline cognitive performance, time to follow-up interval, sex, IQ, and average alcohol use during baseline and follow-up.*

Cognitive Measures	Baseline Past Year Total # hits	Past Year: Total # hits	Age of regular cannabis use
Cognitive Composites			
Motor Speed	-.277	-.174	.237
Motor Dexterity	-.017	.276	.155
Processing Speed	-.310	.328	-.154
Verbal Learning and Memory	-.326	-.083	.507*
Spatial Working Memory & Planning	-.077	.259	.334
Finger Tapping Test			
Dominant hand (# taps)	-.210	-.243	.158
Non-dominant hand (# taps)	-.327	-.066	.295
Grooved Pegboard			
Dominant hand time (s)	-.096	-.168	-.274
Non-dominant hand time (s)	.120	-.279	-.038
Digit Symbol			
Total correct	-.113	.274	-.274
Letter Cancellation			
Time (s)	.350	-.268	.158
COWAT			
Total correct words generated	-.190	.357	.158
Digit Span			
Digits forward (# recalled)	-.183	.072	.479*
Digits backward (# recalled)	.325	.089	-.218
RAVLT			
Total words: Trial 1-5	-.514*	-.101	.530*
Total words: Interference trial	.152	-.153	.061
Total words: Immediate recall	-.210	-.053	.344
Total words: Delayed recall	-.186	-.063	.560**
% Recalled after consolidation	-.088	-.021	.503*
Spatial Working Memory[a]			
Total between search errors	-.211	-.347	-.065
Strategy Score: 6-8	-.125	-.197	.145
Spatial Delayed Response Task			
Error: No delay (mm)	-.150	.028	-.071
Error: 500 ms delay (mm)	.033	-.230	.141
Error: 8,000 ms delay (mm)	.127	.042	.273
Mean reaction time: No delay	-.016	.067	.006
Mean reaction time: 500 ms delay	-.040	-.035	-.081
Mean reaction time: 8,000 ms delay	-.128	-.228	-.050
Tower of London[a]			
% Perfect Solutions	-.218	-.121	.366
Average moves 3-move	.032	-.311	.317
Average moves 4-move	.182	.004	-.346
Average moves 5-move	.269	-.162	-.313
First move initiation time 2-move[d]	-.158	.117	.287
First move initiation time 3-move[d]	.363	-.347	.175
First move initiation time 4-move[d]	.360	.094	-.130

Cognitive Measures	Baseline Past Year Total # hits	Past Year: Total # hits	Age of regular cannabis use
First move initiation time 5-move[d]	-.121	.192	.014
Iowa Gambling Task[b]			
Total Good-Bad Choices	.053	.263	-.351
Deck 1 choices	-.064	-.411	.126
Deck 2 choices	-.051	-.072	.406^
Deck 3 choices	-.083	.010	-.324
Deck 4 choices	.14y6	.045	.217

Notes Total # hits square root transformed. [a]Data unavailable for 1 cannabis user (n = 25) at baseline. [b]Data unavailable for 1 cannabis user (n = 25) at follow-up
^$p \leq .1$. *$p \leq .05$. **$p \leq .01$.

Table 13. *Hierarchical multiple regression analyses: Cannabis use at baseline assessment predicting follow-up RAVLT Trial 1-5 performance within cannabis users.*

Model	*Adj. R^2*	*F*	*p*	*b**	*t*	*p*
Dependent variable: RAVLT Trial 1-5						
Step/Model 1	.349	3.786	.013*			
Baseline Trials 1-5 Words				.476	2.894	.009**
Interval				.220	1.387	.180
Sex				-.064	-0.393	.698
IQ				.273	1.706	.103
Alcohol use				.234	1.427	.168
Step/Model 2	.497	5.278	.002**			
Baseline Trials 1-5 Words				.487	3.369	.003**
Interval				.281	1.990	.060^
Sex				-.149	-1.022	.319
IQ				.312	2.209	.039*
Alcohol use				.208	1.440	.165
Baseline Past Year Total # Hits				-.389	-2.678	.014*

Table 14. *Hierarchical multiple regression analyses: Age of cannabis use initiation predicting follow-up forward digit span performance within cannabis users.*

Model	*Adj. R^2*	*F*	*p*	*b**	*t*	*p*
Dependent variable: Digit Span Digits forward (# recalled)						
Step/Model 1	.133	1.765	.166			
Baseline Digits forward				.287	1.513	.146
Interval				.179	0.960	.348
Sex				-.239	-1.266	.220
IQ				.315	1.673	.110
Alcohol use				.153	0.798	.434
Step/Model 2	.297	2.760	.042*			
Baseline Digits forward				.242	1.405	.176
Interval				.034	0.189	.852
Sex				-.326	-1.875	.076^
IQ				.304	1.792	.089^
Alcohol use				.147	0.848	.407
Age cannabis use initiated				.438	2.381	.028*

^$p \leq .1$. *$p \leq .05$.

Table 15. *Hierarchical multiple regression analyses: Age of cannabis use initiation predicting learning and memory performance within cannabis users.*

Model	*Adj. R^2*	*F*	*p*	*b**	*t*	*p*
Dependent variable: Verbal Learning and Memory composite						
Step/Model 1	.506	4.094	.010**			
Baseline Verbal learning and memory				.438	2.514	.021*
Interval				.201	1.274	.217
Sex				.086	0.538	.597
IQ				.183	1.105	.282
Alcohol use				.285	1.689	.107
Step/Model 2	.633	5.462	.002**			
Baseline Verbal learning and memory				.337	2.122	.047*
Interval				.060	0.402	.692
Sex				.005	0.036	.972
IQ				.198	1.352	.192
Alcohol use				.302	2.028	.057^
Age cannabis use initiated				.401	2.566	.019*
Dependent variable: RAVLT Trial 1-5 total words						
Step/Model 1	.452	4.964	.004**			
Baseline Trial 1-5 words				.506	3.071	.006**
Interval				.250	1.579	.130
Sex				-.047	-0.290	.775
IQ				.267	1.675	.109
Alcohol use				.208	1.266	.220
Step/Model 2	.523	5.386	.002**			
Baseline Trial 1-5 words				.361	2.360	.029*
Interval				.098	0.662	.516
Sex				-.116	-0.814	.426
IQ				.259	1.862	.078^
Alcohol use				.228	1.588	.129
Age cannabis use initiated				.435	2.723	.013*
Dependent variable: RAVLT Delayed Recall						
Step/Model 1	.470	5.437	.003**			
Baseline Trial 7				.504	2.946	.008**
Interval				.206	1.397	.178
Sex				.080	0.537	.597
IQ				.205	1.306	.206
Alcohol use				.243	1.505	.148
Step/Model 2	.617	7.716	< .000**			
Baseline Trial 7				.454	3.099	.006**
Interval				.067	0.497	.625
Sex				-.004	-0.028	.978
IQ				.210	1.574	.132
Alcohol use				.248	1.808	.086^
Age cannabis use initiated				.400	2.946	.008**

Model	*Adj. R^2*	*F*	*p*	*b**	*t*	*p*
Dependent variable: RAVLT % Recalled after consolidation						
Step/Model 1	.286	3.004	.035*			
Baseline % after consol.				.381	1.874	.076^
Interval				-.004	-0.023	.982
Sex				.050	0.276	.785
IQ				.301	1.639	.117
Alcohol use				.222	1.203	.243
Step/Model 2	.438	4.253	.007**			
Baseline % after consol.				.505	2.706	.014*
Interval				-.125	-0.778	.446
Sex				.002	0.012	.991
IQ				.248	1.507	.148
Alcohol use				.165	1.001	.329
Age cannabis use initiated				.430	2.535	.020*

^$p \leq .1$. *$p \leq .05$. **$p \leq .01$.

Table 16. *Hierarchical multiple regression analyses: Age of cannabis use initiation predicting Iowa Gambling Task performance within cannabis users.*

Model	*Adj. R^2*	*F*	*p*	*b**	*t*	*p*
Dependent variable: IGT Deck 2 Choices						
Step/Model 1	.224	2.387	.077^			
Baseline Deck 2 choices				.141	0.729	.475
Interval				.532	2.870	.010*
Sex				-.113	-0.620	.543
IQ				-.252	-1.324	.201
Alcohol use				.250	1.336	.197
Step/Model 2	.487	2.848	.040*			
Baseline Deck 2 choices				.102	0.556	.585
Interval				.528	3.030	.007**
Sex				-.212	-1.180	.253
IQ				-.303	-1.676	.111
Alcohol use				.203	1.147	.266
Age cannabis use initiated				.342	1.884	.076^

^$p \leq .1$. *$p \leq .05$. **$p \leq .01$.

Table 17. *Study 2: Demographic and substance use characteristics of cannabis users and controls at baseline and follow-up.*

Variable	Control	Cannabis User	F, U, χ^2	p
n	23	23		
T1: Baseline characteristics				
Age	19.19 (2.31)	19.45 (0.66)	0.27	.61
#Male/#Female	16/7	16/7	$\chi^2 = 0.00$	1.00
#Caucasian/#Other Ethnicity	21/2	19/4	$\chi^2 = 0.77$	.38
Years of education	13.09 (2.07)	13.26 (0.92)	0.14	.71
Estimated Full Scale IQ	115.65 (9.46)	115.17 (11.02)	0.03	.88
Vocabulary T-Score	62.09 (5.43)	61.83 (8.34)	0.02	.90
Matrix reasoning T-Score	55.65 (7.06)	55.35 (5.58)	0.03	.87
Alcohol use, past 12 months *(Mdn PEI rating)*	1	4	$U = 54.00$	< .00**
0: Never (*n*)	9	1	–	–
1: 1-5 times (*n*)	7	0	–	–
2: 6-20 times (*n*)	3	3	–	–
3: 21-49 times (*n*)	3	6	–	–
4: 50-99 times (*n*)	1	8	–	–
5: 100+ times (*n*)	0	5	–	–
Cannabis use, past 12 months *(Mdn PEI rating)*	0	5	$U = 0.00$	< .00**
0: Never (*n*)	21	0	–	–
1: 1-5 times (*n*)	2	0	–	–
2: 6-20 times (*n*)	0	0	–	–
3: 21-49 times (*n*)	0	0	–	–
4: 50-99 times (*n*)	0	0	–	–
5: 100+ times (*n*)	0	23	–	–
Age of regular cannabis use onset[a]	–	15.35 (1.16)	–	–
Past year: Days used[a]		323.07 (49.55)		
Past 30 days: Days used[a]		26.37 (4.31)		
Past year: Total # hits[a]		3032.55 (2395.31)		
Past 30 days: Total # hits[a]	–	241.17 (209.71)	–	–
T2: Follow-up characteristics				
Years between assessments	2.12 (0.66)	2.34 (0.31)	2.18	.15
Age at follow-up	21.31 (2.43)	21.79 (0.82)	0.82	.37

Variable	Control	Cannabis User	*F, U,* χ^2	*p*
Age range at follow-up	17.2 – 26.0	20.6 – 23.3	–	–
Alcohol use, past 12 months *(Mdn PEI rating)*	3	4	*U* = 84.5	< .00**
0: Never (*n*)	2	1	–	–
1: 1-5 times (*n*)	3	0	–	–
2: 6-20 times (*n*)	6	1	–	–
3: 21-49 times (*n*)	8	2	–	–
4: 50-99 times (*n*)	3	11	–	–
5: 100+ times (*n*)	1	8	–	–
Cannabis use, past 12 months *(Mdn PEI rating)*	0	5	*U* = 0.00	< .00**
0: Never (*n*)	14	0	–	–
1: 1-5 times (*n*)	7	0	–	–
2: 6-20 times (*n*)	2	0	–	–
3: 21-49 times (*n*)	0	1	–	–
4: 50-99 times (*n*)	0	6	–	–
5: 100+ times (*n*)	0	16	–	–
Past year: Days used[a]		253.94 (118.69)		
Past 30 days: Days used[a]		18.73 (11.04)		
Past year: Total # hits[a]		2637.92 (2203.77)		
Past 30 days: Total # hits[a]	–	183.15 (190.88)	–	–

Notes. Values represent means and standard deviation units, unless otherwise specified. Group comparisons were conducted using chi-square, Mann-Whitney U, and one-way analysis of variance. PEI = personal Experience Inventory. [a]Variables only included for cannabis users.
*$p \leq$ .05. **$p \leq$ .01.

Table 18. *DSM-IV-TR Diagnoses at baseline and follow-up, as assessed by the K-SADS-PL. The number of participants who met criteria for each disorder is reported.*

	Control						Cannabis					
	Baseline (*n* = 23)			Follow-up (*n* = 23)			Baseline (*n* = 23)			Follow-up (*n* = 23)		
	Current	Partial Remission	Past	Current	Partial Remission	Past	Current	Partial Remission	Past	Current	Partial Remission	Past
Cannabis Dependence	0	0	-	0	0	-	13	0	-	15	3	-
Cannabis Abuse	0	-	0	0	-	0	7	-	8	2	-	5
Alcohol Dependence	0	0	-	0	0	-	2	0	-	3	1	-
Alcohol Abuse	0	-	0	0	-	1	5	-	8	4	-	7
Major Depressive Disorder	0	-	2	0	-	2	0	-	0	0	-	1
Bipolar NOS	0	-	0	0	-	0	1	-	0	1	-	1
Social Phobia	0	-	0	1	-	1	0	-	0	0	-	0
Specific Phobia	0	-	0	0	-	0	0	-	1	0	-	0
Generalized Anxiety Disorder	0	-	0	0	-	0	0	-	0	0	-	1

Notes. NA = not assessed at follow-up. Current ratings are based on previous 6 months for substance use disorders, and on the previous 2 months for other diagnoses. At baseline, past ratings are based on lifetime symptom expression for cannabis users. At baseline for controls and follow-up for controls and cannabis users, past ratings are based on symptoms during follow-up interval.

Table 19. *Other drug usage in cannabis users and controls at baseline and follow-up. Number of participants who used each drug at different usage levels. Count includes use in past 12 months at baseline and follow-up*

	Control		Cannabis	
	Baseline	Follow-up	Baseline	Follow-up
	n = 23	*n* = 23	*n* = 23	*n* = 23
Psychedelics				
No use	23	22	12	8
1-5 times	-	1	10	13
6-20 times	-	-	1	2
Cocaine				
No use	23	22	22	15
1-5 times	-	1	1	8
Amphetamines				
No use	23	23	19	17
1-5 times	-	-	3	1
6-20 times	-	-	1	5
Barbiturates				
No use	23	23	21	23
1-5 times	-	-	2	-
Tranquilizers				
No use	23	23	20	23
1-5 times	-	-	3	-
Heroin				
No use	23	23	23	23
Other narcotics				
No use	23	23	18	19
1-5 times	-	-	5	4
Steroids				
No use	23	23	23	23
Inhalants				
No use	23	23	23	23
Prescription drugs				
No use	23	22	18	20
1-5 times	-	1	5	3

Table 20. *Baseline group differences in fractional anisotropy (FA) and radial diffusivity (RD).*

Measure	**Contrast**	**Max Z-stat**	**Cluster Size (mm^3)**	**CWP**	**X**	**Y**	**Z**	**Hemisphere**	**Anatomical Region**
FA	Controls < CU	4.18	2584	0.012	4	26	4	Right	Genu, forceps minor of CC
RD	Controls > CU	3.86	1640	0.102	2	26	6	Right	Genu, forceps minor of CC

Notes. Results from voxelwise multiple regression analyses of FA and RD at baseline. Multiple regression covariates were group, sex, age, and baseline alcohol use. Cluster-level statistical thresholding was p<e.05 after family-wise error correction for multiple comparisons; trend-level results (FWE $p \leq .10$) are included as well. CC = corpus callosum.

Table 21. *Partial correlations between cognitive and substance use variables and mean FA in cannabis users > controls baseline cluster.*

Measure	R Genu, Forceps minor CC (4, 26, 4)
Past Year: total# hits[a]	-.152
Age first regular cannabis use[a]	-.070
Past Year: total # drinks[b]	-.577**
Tobacco use[a]	-.017
Cognitive Composites[a]	
Motor Speed	.291
Motor Dexterity	.282
Processing Speed	.299
Verbal Learning and Memory	.054
Spatial Working Memory & Planning	.042
Iowa Gambling Task[a]	
Deck 1 choices	-.155
Deck 2 choices	-.477*
Deck 3 choices	-.239
Deck 4 choices	.194
Good deck choices	.258

Notes. Past year: total # hits, past year: total # drinks, and tobacco use were square root transformed. [a]Controlling for sex and baseline alcohol use. [b]Controlling for sex.
^$p \leq .1$. *$p \leq .05$. **$p \leq .01$.

Table 22. *Analysis of 2-year change in fractional anisotropy and radial diffusivity.*

Measure	Contrast	Max Z-stat	Cluster Size (mm^3)	CWP	X	Y	Z	Hemisphere	Anatomical Region
Fractional Anisotropy	Controls > Cannabis	5.80	3864	0.001	32	-32	40	Right	SLF, extending to junction with CST
Fractional Anisotropy	Controls > Cannabis	4.12	1632	0.017	-38	-44	24	Left	SLF, extending to CC forceps major
Fractional Anisotropy	Controls > Cannabis	3.88	1464	0.030	-18	16	42	Left	White matter adjacent to superior frontal gyrus
Fractional Anisotropy	Controls > Cannabis	4.46	1232	0.065	-16	-28	50	Left	CST, adjacent to pre- and postcentral gyri
Fractional Anisotropy	Controls > Cannabis	4.25	1208	0.071	26	16	12	Right	ATR; superior FOF; adjacent to frontal operculum
Fractional Anisotropy	Cannabis > Controls	4.49	1808	0.010	-14	16	26	Left	Anterior CC
Fractional Anisotropy	Cannabis > Controls	3.75	1696	0.014	-10	-24	-6	Left	White matter adjacent to posterior thalamus
Radial Diffusivity	Controls < Cannabis	4.54	6848	0.001	16	-36	38	Right	CST; SLF; posterior cingulum
Radial Diffusivity	Controls > Cannabis	3.97	2368	0.006	-24	-18	4	Left	CST

Notes. Results from voxelwise multiple regression analysis of FA and RD 2-year change values (i.e., residuals from regression of each participant's follow-up FA or RD volume on the corresponding baseline FA or RD volume). Multiple regression covariates were group, sex, age at baseline, time interval between baseline and follow-up assessments, and average alcohol use. Cluster-level statistical thresholding was $p < .05$ after family-wise error correction for multiple comparisons; trend-level results (FWE $p < .10$) are included as well. ATR = anterior thalamic radiation; CC = corpus callosum; CST = corticospinal tract; FOF = fronto-occipital fasciculus; SLF = superior longitudinal fasciculus

Table 23. *Correlations between cognitive and substance use variables and mean FA-change cluster values.*

	Control > CU					Cannabis > Control	
	R SLF/CST (32, -32, 40)	L SLF/CC forceps major (-38, -44, 24)	L SFG WM (-18, 16, 42)	L CST (-16, -28, 50)	R ATR (26, 16, 12)	L Ant CC (-14, 16, 26)	L Thalamic WM (-10, -24, -6)
BL Past Year: total # hits[a]	.246	-.081	.218	-.127	.400^	-.189	-.054
Past Year: total# hits[a]	-.083	-.479*	-.290	-.461*	-.149	.276	.092
Age first regular cannabis use[a]	.245	-.018	.012	-.007	-.008	-.253	-.024
Past Year: total # drinks[b]	.039	.167	.239	-.019	-.095	.114	-.074
Tobacco use[a]	-.129	.120	.249	-.043	.021	-.286	.125
Cognitive Composites[a]							
Motor Speed	.039	.139	.126	.151	.473*	.138	.316
Motor Dexterity	.046	-.066	.263	.224	-.084	-.003	.061
Processing Speed	-.040	-.310	-.323	-.123	-.320	.142	-.083
Verbal Learning and Memory	-.094	.123	-.078	-.064	-.306	-.321	-.073
Spatial Working Memory & Planning	.038	-.187	-.094	-.074	-.204	.072	-.141
Iowa Gambling Task[a]							
Deck 1 choices	.211	.189	.496*	.207	.181	.126	-.005
Deck 2 choices	.128	.110	.348	.167	-.139	-.010	.125
Deck 3 choices	-.322	.161	.078	.352	.150	-.101	-.095
Deck 4 choices[c]	.085	-.252	-.394^	.136	-.116	.071	.040
Good deck choices	-.174	-.150	-.443*	-.198	.018	-.046	-.080

Notes. Past year: total # hits, past year: total # drinks, and tobacco use were square root transformed. [a]Controlling for baseline value, sex, interval between assessments, and average alcohol use at baseline and follow-up. [b]Controlling for baseline value, sex, and interval between assessments.
^$p \leq .1$. *$p \leq .05$. **$p \leq .01$.

5 References

Achenbach, T. M. (1991). *Manual for the Child Behavior Checklist/4-18 and 1991 Profile*. Burlington, VT: University of Vermont Department of Psychiatry.

Achenbach, T. M., & Rescorla, L. A. (2003). *Manual for the ASEBA Adult Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Anderson, B. A., Laurent, P. A., & Yantis, S. (2011). Value-driven attentional capture. *Proceedings of the National Academy of Sciences*, *108*(25), 10367–10371.

Arnone, D., Barrick, T. R., Chengappa, S., Mackay, C. E., Clark, C. A., & Abou-Saleh, M. T. (2008). Corpus callosum damage in heavy marijuana use: Preliminary evidence from diffusion tensor tractography and tract-based spatial statistics. *NeuroImage*, *41*(3), 1067–1074. doi:10.1016/j.neuroimage.2008.02.064

Arseneault, L., Cannon, M., Witton, J., & Murray, R. M. (2004). Causal association between cannabis and psychosis: Examination of the evidence. *The British Journal of Psychiatry*, *184*(2), 110–117. doi:10.1192/bjp.184.2.110

Ashtari, M., Avants, B., Cyckowski, L., Cervellione, K. L., Roofeh, D., Cook, P., … Kumra, S. (2011). Medial temporal structures and memory functions in adolescents with heavy cannabis use. *Journal of Psychiatric Research*, *45*(8), 1055–1066. doi:10.1016/j.jpsychires.2011.01.004

Ashtari, M., Cervellione, K., Cottone, J., Ardekani, B. A., Sevy, S., & Kumra, S. (2009). Diffusion abnormalities in adolescents and young adults with a history of heavy cannabis use. *Journal of Psychiatric Research*, *43*(3), 189–204. doi:10.1016/j.jpsychires.2008.12.002

Ashtari, M., Cervellione, K. L., Hasan, K. M., Wu, J., McIlree, C., Kester, H., … Kumra, S. (2007). White matter development during late adolescence in healthy males: A cross-sectional diffusion tensor imaging study. *NeuroImage*, *35*(2), 501–510. doi:10.1016/j.neuroimage.2006.10.047

Bambico, F. R., Nguyen, N. T., Katz, N., & Gobbi, G. (2010). Chronic exposure to cannabinoids during adolescence but not during adulthood impairs emotional behaviour and monoaminergic neurotransmission. *Neurobiology of Disease*, *37*(3), 641–655.

Bartholomew, J., Holroyd, S., & Heffernan, T. M. (2010). Does cannabis use affect prospective memory in young adults? *Journal of Psychopharmacology*, *24*(2), 241–246. doi:10.1177/0269881109106909

Bartzokis, G., Beckson, M., Lu, P. H., Nuechterlein, K. H., Edwards, N., & Mintz, J. (2001). Age-related changes in frontal and temporal lobe volumes in men: A magnetic resonance imaging study. *Archives of General Psychiatry*, *58*(May 2001), 461–465.

Batalla, A., Bhattacharyya, S., Yücel, M., Fusar-poli, P., Crippa, J. A., Nogué, S., … Yu, M. (2013). Structural and functional imaging studies in chronic cannabis users: A systematic review of adolescent and adult findings. *PloS One*, *8*(2), e55821. doi:10.1371/journal.pone.0055821

Battistella, G., Fornari, E., Annoni, J.-M., Chtioui, H., Dao, K., Fabritius, M., … Giroud, C. (2014). Long-Term Effects of Cannabis on Brain Structure. *Neuropsychopharmacology*, 1–8. doi:10.1038/npp.2014.67

Battisti, R. A., Roodenrys, S., Johnstone, S. J., Pesa, N., Hermens, D. F., & Solowij, N. (2010). Chronic cannabis users show altered neurophysiological functioning on Stroop task conflict resolution. *Psychopharmacology*, *212*(4), 613–624. doi:10.1007/s00213-010-1988-3

Battisti, R. A., Roodenrys, S., Johnstone, S. J., Respondek, C., Hermens, D. F., & Solowij, N. (2010). Chronic use of cannabis and poor neural efficiency in verbal memory ability. *Psychopharmacology*, *209*(4), 319–330. doi:10.1007/s00213-010-1800-4

Bava, S., Frank, L. R., McQueeny, T., Schweinsburg, B. C., Schweinsburg, A. D., & Tapert, S. F. (2009). Altered white matter microstructure in adolescent substance users. *Psychiatry Research: Neuroimaging*, *173*(3), 228–237. doi:10.1016/j.pscychresns.2009.04.005

Bava, S., Jacobus, J., Mahmood, O. M., Yang, T. T., & Tapert, S. F. (2010). Neurocognitive correlates of white matter quality in adolescent substance users. *Brain and Cognition*, *72*(3), 347–354. doi:10.1016/j.bandc.2009.10.012

Bava, S., Jacobus, J., Thayer, R. E., & Tapert, S. F. (2013). Longitudinal changes in white matter integrity among adolescent substance users. *Alcoholism: Clinical and Experimental Research*, *37*(S1), E181–E189. doi:10.1111/j.1530-0277.2012.01920.x

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, *50*(1-3), 7–15.

Bechara, A., Dolan, S., Denburg, N., Hindes, A., Anderson, S. W., & Nathan, P. E. (2001). Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia*, *39*(4), 376–389.

Becker, M. P., Collins, P. F., & Luciana, M. (2014). Neurocognition in college-aged daily marijuana users. *Journal of Clinical and Experimental Neuropsychology*, *36*(4), 379–98. doi:10.1080/13803395.2014.893996

Best, A. R., & Regehr, W. G. (2008). Serotonin evokes endocannabinoid release and retrogradely suppresses excitatory synapses. *Journal of Neuroscience*, *28*(25), 6508–6515.

Block, R. I., O'Leary, D. S., Ehrhardt, J. C., Augustinack, J. C., Ghoneim, M. M., Arndt, S., & Hall, J. A. (2000). Effects of frequent marijuana use on brain tissue volume and composition. *Neuroreport*, *11*(3), 491–6.

Block, R. I., O'Leary, D. S., Hichwa, R. D., Augustinack, J. C., Boles Ponto, L. L., Ghoneim, M. M., … Andreasen, N. C. (2002). Effects of frequent marijuana use on memory-related regional cerebral blood flow. *Pharmacology, Biochemistry, and Behavior*, *72*, 237–250.

Bloomfield, M. A. P., Morgan, C. J. A., Egerton, A., Kapur, S., Curran, H. V., & Howes, O. D. (2014). Dopaminergic function in cannabis users and its relationship to cannabis-induced psychotic symptoms. *Biological Psychiatry*, *75*(6), 470–8. doi:10.1016/j.biopsych.2013.05.027

Bloomfield, M. A. P., Morgan, C. J. A., Kapur, S., Curran, H. V., & Howes, O. D. (2014). The link between dopamine function and apathy in cannabis users: An [18F]-DOPA PET imaging study. *Psychopharmacology*, *231*(11), 2251–2259. doi:10.1007/s00213-014-3523-4

Bolla, K. I., Brown, K., Eldreth, D., Tate, K., & Cadet, J.-L. (2002). Dose-related neurocognitive effects of marijuana use. *Neurology*, *59*(9), 1337–1343.

Bosker, W. M., Kuypers, K. P. C., Theunissen, E. L., Surinx, A., Blankespoor, R. J., Skopp, G., … Ramaekers, J. G. (2012). Medicinal Δ(9) -tetrahydrocannabinol (dronabinol) impairs on-the-road driving performance of occasional and heavy cannabis users but is not detected in Standard Field Sobriety Tests. *Addiction*, *107*(10), 1837–1844. doi:10.1111/j.1360-0443.2012.03928.x

Bossong, M. G., Jager, G., Bhattacharyya, S., & Allen, P. (2014). Acute and non-acute effects of cannabis on human memory function: A critical review of neuroimaging studies. *Current Pharmaceutical Design*, *20*, 2114–25. doi:10.2174/13816128113199990436

Budde, M. D., Kim, J. H., Liang, H.-F., Schmidt, R. E., Russell, J. H., Cross, A. H., & Song, S.-K. (2007). Toward accurate diagnosis of white matter pathology using diffusion tensor imaging. *Magnetic Resonance in Medicine*, *57*(4), 688–695. doi:10.1002/mrm.21200

Cerdá, M., Wall, M. M., Keyes, K. M., Galea, S., & Hasin, D. S. (2012). Medical marijuana laws in 50 states: Investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. *Drug and Alcohol Dependence*, *120*, 22–27. doi:10.1016/j.drugalcdep.2011.06.011

Cha, Y. M., White, A. M., Kuhn, C. M., Wilson, W. A., & Swartzwelder, H. S. (2006). Differential effects of delta9-THC on learning in adolescent and adult rats. *Pharmacology, Biochemistry, and Behavior*, *83*(3), 448–55. doi:10.1016/j.pbb.2006.03.006

Chang, L., Yakupov, R., Cloak, C., & Ernst, T. (2006). Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. *Brain*, *129*, 1096–112. doi:10.1093/brain/awl064

Churchwell, J. C., Lopez-Larson, M. P., & Yurgelun-Todd, D. A. (2010). Altered frontal cortical volume and decision making in adolescent cannabis users. *Frontiers in Psychology*, *1*(December), 225. doi:10.3389/fpsyg.2010.00225

Clark, L., Roiser, J. P., Robbins, T. W., & Sahakian, B. J. (2009). Disrupted "reflection" impulsivity in cannabis users but not current or former ecstasy users. *Journal of Psychopharmacology*, *23*, 14–22. doi:10.1177/0269881108089587

Colby, J. B., Van Horn, J. D., & Sowell, E. R. (2011). Quantitative in vivo evidence for broad regional gradients in the timing of white matter maturation during adolescence. *NeuroImage*, *54*, 25–31. doi:10.1016/j.neuroimage.2010.08.014

Cousijn, J., Wiers, R. W., Ridderinkhof, K. R., van den Brink, W., Veltman, D. J., & Goudriaan, A. E. (2012). Grey matter alterations associated with cannabis use: Results of a VBM study in heavy cannabis users and healthy controls. *NeuroImage*, *59*(4), 3845–3851. doi:10.1016/j.neuroimage.2011.09.046

Crean, R. D., Crane, N. A., & Mason, B. J. (2011). An evidence-based review of acute and long-term effects of cannabis use on executive cognitive functions. *Journal of Addiction Medicine*, *5*(1), 1–8.

Croft, R. J., Mackay, A. J., Mills, A. T. D., & Gruzelier, J. G. H. (2001). The relative contributions of ecstasy and cannabis to cognitive impairment. *Psychopharmacology*, *153*(3), 373–379.

Cuttler, C., McLaughlin, R. J., & Graf, P. (2012). Mechanisms underlying the link between cannabis use and prospective memory. *PloS One*, *7*(5), e36820. doi:10.1371/journal.pone.0036820

Delis, D. C., Jacobson, M., Bondi, M. W., Hamilton, J. M., & Salmon, D. P. (2003). The myth of testing construct validity using factor analysis or correlations with normal or mixed clinical populations: Lessons from memory assessment. *Journal of the International Neuropsychological Society*, *9*(6), 936–946. doi:10.1017/S1355617703960139

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). *California Verbal Learning Test - Second Edition*. (Psychological Corporation, Ed.). San Antonio, Texas.

Delisi, L. E., Bertisch, H. C., Szulc, K. U., Majcher, M., Brown, K., Bappal, A., & Ardekani, B. A. (2006). A preliminary DTI study showing no brain structural change associated with adolescent cannabis use. *Harm Reduction Journal*, *3*, 17. doi:10.1186/1477-7517-3-17

Demirakca, T., Sartorius, A., Ende, G., Meyer, N., Welzel, H., Skopp, G., … Hermann, D. (2011). Diminished gray matter in the hippocampus of cannabis users: Possible protective effects of cannabidiol. *Drug and Alcohol Dependence*, *114*(2-3), 242–245. doi:10.1016/j.drugalcdep.2010.09.020

Depue, R. A., & Collins, P. F. (1999). Neurobiology of the structure of personality: Dopamine, facilitation of incentive motivation, and extraversion. *The Behavioral and Brain Sciences*, *22*(3), 491–569. doi:10.1017/S0140525X99002046

Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annual Review of Neuroscience*, *18*, 193–222. doi:10.1146/annurev.ne.18.030195.001205

Desrosiers, N. A., Ramaekers, J. G., Chauchard, E., Gorelick, D. A., & Huestis, M. A. (2015). Smoked cannabis' psychomotor and neurocognitive effects in occasional and frequent smokers. *Journal of Analytical Toxicology*, *39*(4), 251–61. doi:10.1093/jat/bkv012

Dougherty, D. M., Mathias, C. W., Dawes, M. A., Furr, R. M., Charles, N. E., Liguori, A., … Acheson, A. (2013). Impulsivity, attention, memory, and decision-making among adolescent marijuana users. *Psychopharmacology*, *226*, 307–319. doi:10.1007/s00213-012-2908-5

Ehrenreich, H., Rinn, T., Kunert, H. J., Moeller, M. R., Poser, W., Schilling, L., … Hoehe, M. R. (1999). Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology*, *142*(3), 295–301.

Epstein, K. A., & Kumra, S. (2015). Altered cortical maturation in adolescent cannabis users with and without schizophrenia. *Schizophrenia Research*, *162*(1-3), 143–152. doi:10.1016/j.schres.2014.11.029

Ernst, M., Grant, S. J., London, E. D., Contoreggi, C. S., Kimes, A. S., & Spurgeon, L. (2003). Decision making in adolescents with behavior disorders and adults with substance abuse. *The American Journal of Psychiatry*, *160*(1), 33–40.

Falck, R. S., Nahhas, R. W., Li, L., & Carlson, R. G. (2012). Surveying teens in school to assess the prevalence of problematic drug use. *Journal of School Health*, *82*(5), 217–224.

Fernández-Serrano, M. J., Pérez-García, M., & Verdejo-García, A. (2011). What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance? *Neuroscience and Biobehavioral Reviews*, *35*(3), 377–406. doi:10.1016/j.neubiorev.2010.04.008

Filbey, F. M., Aslan, S., Calhoun, V. D., Spence, J. S., Damaraju, E., Caprihan, A., & Segall, J. (2014). Long-term effects of marijuana use on the brain. *Proceedings of the National Academy of Sciences*, 1–6. doi:10.1073/pnas.1415297111

Filbey, F. M., McQueeny, T., Kadamangudi, S., Bice, C., & Ketcherside, A. (2015). Combined effects of marijuana and nicotine on memory performance and hippocampal volume. *Behavioural Brain Research*, *293*, 46–53. doi:10.1016/j.bbr.2015.07.029

Filbey, F. M., & Yezhuvath, U. (2013). Functional connectivity in inhibitory control networks and severity of cannabis use disorder. *The American Journal of Drug and Alcohol Abuse*, *39*(6), 382–91. doi:10.3109/00952990.2013.841710

Fontes, M. A., Bolla, K. I., Cunha, P. J., Almeida, P. P., Jungerman, F., Laranjeira, R. R., … Lacerda, A. L. T. (2011). Cannabis use before age 15 and subsequent executive functioning. *The British Journal of Psychiatry*, *198*(6), 442–447. doi:10.1192/bjp.bp.110.077479

Freund, T. F., Katona, I., & Piomelli, D. (2003). Role of endogenous cannabinoids in synaptic signaling. *Physiological Review*, *83*, 1017–1066.

Fridberg, D. J., Queller, S., Ahn, W.-Y., Kim, W., Bishara, A. J., Busemeyer, J. R., … Stout, J. C. (2010). Cognitive mechanisms underlying risky decision-making in chronic cannabis users. *Journal of Mathematical Psychology*, *54*, 28–38. doi:10.1016/j.jmp.2009.10.002.Cognitive

Fride, E. (2008). Multiple roles for the endocannabinoid system during the earliest stages of life: Pre- and postnatal development. *Journal of Neuroendocrinology*, *20*, 75–81. doi:10.1111/j.1365-2826.2008.01670.x

Fried, P. A., Watkinson, B., & Gray, R. (2005). Neurocognitive consequences of marihuana – A comparison with pre-drug performance. *Neurotoxicology and Teratology*, *27*(2), 231–239. doi:10.1016/j.ntt.2004.11.003

Galve-Roperh, I., Palazuelos, J., Aguado, T., & Guzmán, M. (2009). The endocannabinoid system and the regulation of neural development: Potential implications in psychiatric disorders. *European Archives of Psychiatry and Clinical Neuroscience*, *259*(7), 371–382. doi:10.1007/s00406-009-0028-y

Giedd, J. N. (2004). Stuctural magnetic resonance imaging of the adolescent brain. *Annals of the New York Academy of Sciences*, *1021*, 77–85.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., … Rapoport, J. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*, *2*(10), 861–3. doi:10.1038/13158

Gilman, J. M., Kuster, J. K., Lee, S., Lee, M. J., Kim, B. W., Makris, N., … Breiter, H. C. (2014). Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. *The Journal of Neuroscience*, *34*(16), 5529–38. doi:10.1523/JNEUROSCI.4745-13.2014

Giorgio, A., Watkins, K. E., Douaud, G., James, A. C., James, S., De Stefano, N., … Johansen-Berg, H. (2008). Changes in white matter microstructure during adolescence. *NeuroImage*, *39*(1), 52–61. doi:10.1016/j.neuroimage.2007.07.043

Gleason, K. A., Birnbaum, S. G., Shukla, A., & Ghose, S. (2012). Susceptibility of the adolescent brain to cannabinoids: Long-term hippocampal effects and relevance to schizophrenia. *Translational Psychiatry*, *2*(11), e199. doi:10.1038/tp.2012.122

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., … Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences*, *101*(21), 8174–9. doi:10.1073/pnas.0402680101

Gogtay, N., & Thompson, P. M. (2010). Mapping gray matter development: Implications for typical development and vulnerability to psychopathology. *Brain and Cognition*, *72*, 6–15. doi:10.1016/j.bandc.2009.08.009

Gonzalez, R., Schuster, R. M., Mermelstein, R. J., Vassileva, J., Martin, E. M., & Diviak, K. R. (2012). Performance of young adult cannabis users on neurocognitive measures of impulsive behavior and their relationship to symptoms of cannabis use disorders. *Journal of Clinical and Experimental Neuropsychology*, *34*(9), 962–976. doi:10.1080/13803395.2012.703642

Gonzalez, R., Schuster, R. M., Mermelstein, R. M., & Diviak, K. R. (2015). The role of decision-making in cannabis-related problems among young adults. *Drug and Alcohol Dependence*, *154*, 214–221. doi:10.1016/j.drugalcdep.2015.06.046

Goudriaan, A. E., Grekin, E. R., & Sher, K. J. (2007). Decision making and binge drinking: A longitudinal study. *Alcoholism: Clinical and Experimental Research*, *31*(6), 928–38. doi:10.1111/j.1530-0277.2007.00378.x

Grant, I., Gonzalez, R., Carey, C. L., Natarajan, L., & Wolfson, T. (2003). Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study. *Journal of the International Neuropsychological Society*, *9*(5), 679–689. doi:10.1017/S1355617703950016

Grant, J. E., Chamberlain, S. R., Schreiber, L. R. N., & Odlaug, B. L. (2012). Neuropsychological deficits associated with cannabis use in young adults. *Drug and Alcohol Dependence*, *121*, 159–162. doi:10.1016/j.drugalcdep.2011.08.015

Greenhouse, S. W., & Geisser, S. (1959). On methods in the analysis of profile data. *Psychometrika*, *24*(2), 95–112. doi:10.1007/BF02289823

Gruber, S. A., Dahlgren, M. K., Sagar, K. A., Gönenç, A., & Killgore, W. D. S. (2012). Age of onset of marijuana use impacts inhibitory processing. *Neuroscience Letters*, *511*(2), 89–94. doi:10.1016/j.neulet.2012.01.039

Gruber, S. A., Dahlgren, M. K., Sagar, K. A., Gönenç, A., & Lukas, S. E. (2014). Worth the wait: Effects of age of onset of marijuana use on white matter and impulsivity. *Psychopharmacology*, *231*(8), 1455–65. doi:10.1007/s00213-013-3326-z

Gruber, S. A., Sagar, K. A., Dahlgren, M. K., Racine, M. T., & Lukas, S. E. (2012). Age of onset of marijuana use and executive function. *Psychology of Addictive Behaviors*, *26*(3), 496–506. doi:10.1037/a0026269

Gruber, S. A., Silveri, M. M., Dahlgren, M. K., & Yurgelun-Todd, D. A. (2011). Why so impulsive? White matter alterations are associated with impulsivity in chronic marijuana smokers. *Experimental and Clinical Psychopharmacology*, *19*(3), 231–242. doi:10.1037/a0023034

Hall, W. D., & Degenhardt, L. (2009). Adverse health effects of non-medical cannabis use. *The Lancet*, *374*, 1383–1391.

Haney, M., Ward, A. S., Comer, S. D., Hart, C. L., Foltin, R. W., & Fischman, M. (2001). Bupropion SR worsens mood during marijuana withdrawal in humans. *Psychopharmacology*, *155*(2), 171–179. doi:10.1007/s002130000657

Hanson, K. L., & Luciana, M. (2010). Neurocognitive impairments in MDMA and other drug users: MDMA alone may not be a cognitive risk factor. *Journal of Clinical and Experimental Neuropsychology*, *32*(4), 337–349. doi:10.1080/13803390903042361

Hanson, K. L., Luciana, M., & Sullwold, K. (2008). Reward-related decision-making deficits and elevated impulsivity among MDMA and other drug users. *Drug and Alcohol Dependence*, *96*, 99–110. doi:10.1016/j.drugalcdep.2008.02.003

Hanson, K. L., Winward, J. L., Schweinsburg, A. D., Medina, K. L., Brown, S. A., & Tapert, S. F. (2010). Longitudinal study of cognition among adolescent marijuana users over three weeks of abstinence. *Addictive Behaviors*, *35*(11), 970–976. doi:10.1016/j.addbeh.2010.06.012

Harding, I. H., Solowij, N., Harrison, B. J., Takagi, M. J., Lorenzetti, V., Lubman, D. I., … Yücel, M. (2012). Functional connectivity in brain networks underlying cognitive control in chronic cannabis users. *Neuropsychopharmacology*, *37*(8), 1923–1933. doi:10.1038/npp.2012.39

Harper, S., Strumpf, E. C., & Kaufman, J. S. (2012). Do Medical Marijuana Laws Increase Marijuana Use? Replication Study and Extension. *Annals of Epidemiology*, *22*(3), 207–212. doi:10.1016/j.annepidem.2011.12.002

Hart, C. L., Van Gorp, W., Haney, M., Foltin, R. W., & Fischman, M. W. (2001). Effects of acute smoked marijuana on complex cognitive performance. *Neuropsychopharmacology*, *25*(5), 757–765. doi:10.1016/S0893-133X(01)00273-1

Harvey, M. A., Sellman, J. D., Porter, R. J., & Frampton, C. M. (2007). The relationship between non-acute adolescent cannabis use and cognition. *Drug and Alcohol Review*, *26*(3), 309–319. doi:10.1080/09595230701247772

Hayatbakhsh, M. R., Najman, J. M., Jamrozik, K., Mamun, A. A., Alati, R., & Bor, W. (2007). Cannabis and anxiety and depression in young adults: A large prospective study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*(3), 408–417. doi:10.1097/CHI.0b013e31802dc54d

Hayatbakhsh, M. R., Williams, G. M., Bor, W., & Najman, J. M. (2012). Early childhood predictors of age of initiation to use of cannabis: A birth prospective study. *Drug and Alcohol Review*, *32*(3), 232–240. doi:10.1111/j.1465-3362.2012.00520.x

Heifets, B. D., & Castillo, P. E. (2009). Endocannabinoid signaling and long-term synaptic plasticity. *Annual Review of Physiology*, *71*, 283–306. doi:10.1146/annurev.physiol.010908.163149

Henley, G. A., & Winters, K. C. (1989). Development of psychosocial scales for the assessment of adolescents involved with alcohol and drugs. *International Journal of Addictions*, *24*, 973–1001.

Herkenham, M., Lynn, A. B., Little, M. D., Johnson, M. R., Melvin, L. S., de Costa, B. R., & Rice, K. C. (1990). Cannabinoid receptor localization in brain. *Proceedings of the National Academy of Sciences*, *87*(5), 1932–1936.

Hirvonen, J., Goodwin, R. S., Li, C.-T., Terry, G. E., Zoghbi, S. S., Morse, C., … Innis, R. B. (2012). Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Molecular Psychiatry*, *17*, 642–649. doi:10.1038/mp.2011.82

Horwood, L. J., Fergusson, D. M., Hayatbakhsh, M. R., Najman, J. M., Coffey, C., Patton, G. C., … Hutchinson, D. M. (2010). Cannabis use and educational achievement: Findings from three Australasian cohort studies. *Drug and Alcohol Dependence*, *110*(3), 247–253. doi:10.1016/j.drugalcdep.2010.03.008

Howlett, A. C., Barth, F., Bonner, T. I., Cabral, G., Casellas, P., Devane, W. A., … Pertwee, R. G. (2002). International union of pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacological Reviews*, *54*(2), 161–202.

Huestegge, L., Radach, R., & Kunert, H. J. (2009). Long-term effects of cannabis on oculomotor function in humans. *Journal of Psychopharmacology*, *23*(6), 714–722. doi:10.1177/0269881108091601

Huizink, A. C. (2014). Prenatal cannabis exposure and infant outcomes: Overview of studies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *52*, 45–52. doi:10.1016/j.pnpbp.2013.09.014

Iacono, W. G., Malone, S. M., & McGue, M. (2008). Behavioral disinhibition and the development of early-onset addiction: Common and specific influences. *Annual Review of Clinical Psychology*, *4*, 325–348. doi:10.1146/annurev.clinpsy.4.022007.141157

Jacobsen, L. K., Mencl, W. E., Westerveld, M., & Pugh, K. R. (2004). Impact of cannabis use on brain function in adolescents. *Annals of the New York Academy of Sciences*, *1021*, 384–390. doi:10.1196/annals.1308.053

Jacobsen, L. K., Pugh, K. R., Constable, R. T., Westerveld, M., & Mencl, W. E. (2007). Functional correlates of verbal memory deficits emerging during nicotine withdrawal in abstinent adolescent cannabis users. *Biological Psychiatry*, *61*, 31–40. doi:10.1016/j.biopsych.2006.02.014

Jacobus, J., Squeglia, L. M., Bava, S., & Tapert, S. F. (2013). White matter characterization of adolescent binge drinking with and without co-occurring marijuana use: A 3-year investigation. *Psychiatry Research: Neuroimaging*, *214*(3), 374–81. doi:10.1016/j.pscychresns.2013.07.014

Jacobus, J., Squeglia, L. M., Infante, M. A., Bava, S., & Tapert, S. F. (2013). White matter integrity pre- and post marijuana and alcohol initiation in adolescence. *Brain Sciences*, *3*(1), 396–414. doi:10.3390/brainsci3010396

Jacobus, J., Squeglia, L. M., Infante, M. A., Castro, N., Brumback, T., Meruelo, A. D., … Meruelo, A. D. (2015). Neuropsychological performance in adolescent marijuana users with co-occurring alcohol use: A three-year longitudinal study. *Neuropsychology*, Advance online publication.

Jacobus, J., Squeglia, L. M., Sorg, S. F., Nguyen-Louie, T. T., & Tapert, S. F. (2014). Cortical thickness and neurocognition in adolescent marijuana and alcohol users following 28 days of monitored abstinence. *Journal of Studies on Alcohol and Drugs*.

Jager, G., & Ramsey, N. F. (2008). Long-term consequences of adolescent cannabis exposure on the development of cognition, brain structure and function: An overview of animal and human research. *Current Drug Abuse Reviews*, *1*(2), 114–123.

Jager, G., van Hell, H. H., De Win, M. M. L., Kahn, R. S., Van Den Brink, W., Van Ree, J. M., & Ramsey, N. F. (2007). Effects of frequent cannabis use on hippocampal activity during an associative memory task. *European Neuropsychopharmacology*, *17*(4), 289–297. doi:10.1016/j.euroneuro.2006.10.003

Johnston, L. D., Bachman, J. G., & Schulenberg, J. E. (2012). *Monitoring the Future national survey results on drug use, 1975–2011: Volume II, College students and adults ages 19–50*. Ann Arbor: Institute for Social Research, The University of Michigan.

Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (2013). *Monitoring the Future national results on drug use: 2012 Overview, Key Findings on Adolescent Drug Use.* Ann Arbor: Institute for Social Research, The University of Michigan.

Jones, D. K., Horsfield, M. A., & Simmons, A. (1999). Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging. *Magnetic Resonance in Medicine*, *42*(3), 515–525.

Jonides, J., Lewis, R. L., Nee, D. E., Lustig, C. A., Berman, M. G., & Moore, K. S. (2008). The mind and brain of short-term memory. *Annual Review of Psychology*, *59*, 193–224. doi:10.1146/annurev.psych.59.103006.093615

Kable, J. W., & Glimcher, P. W. (2007). The neural correlates of subjective value during intertemporal choice. *Nature Neuroscience*, *10*(12), 1625–33. doi:10.1038/nn2007

Kanayama, G., Rogowska, J., Pope, H. G., Gruber, S. A., & Yurgelun-Todd, D. A. (2004). Spatial working memory in heavy cannabis users: A functional magnetic resonance imaging study. *Psychopharmacology*, *176*, 239–247. doi:10.1007/s00213-004-1885-8

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., … Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*(7), 980–988. doi:10.1097/00004583-199707000-00021

Kochunov, P., Williamson, D. E., Lancaster, J., Fox, P., Cornell, J., Blangero, J., & Glahn, D. C. (2012). Fractional anisotropy of water diffusion in cerebral white matter across the lifespan. *Neurobiology of Aging*, *33*(1), 9–20. doi:10.1016/j.neurobiolaging.2010.01.014

Kowal, M. A., Colzato, L. S., & Hommel, B. (2011). Decreased spontaneous eye blink rates in chronic cannabis users: Evidence for striatal cannabinoid-dopamine interactions. *PloS One*, *6*(11), e26662. doi:10.1371/journal.pone.0026662

LaBrie, J. W., Hummer, J. F., & Lac, A. (2011). Comparing injunctive marijuana use norms of salient reference groups among college student marijuana users and nonusers. *Addictive Behaviors*, *36*(7), 717–720. doi:10.1016/j.addbeh.2011.02.004

Lafayette Instruments. (1989). *Instruction manual for the 32025 Grooved Pegboard Test*. Lafayette, IN: Author.

Lane, S. D., Cherek, D. R., Tcheremissine, O. V, Steinberg, J. L., & Sharon, J. L. (2007). Response perseveration and adaptation in heavy marijuana-smoking adolescents. *Addictive Behaviors*, *32*(5), 977–990. doi:10.1016/j.addbeh.2006.07.007

Lebel, C., & Beaulieu, C. (2011). Longitudinal development of human brain wiring continues from childhood into adulthood. *The Journal of Neuroscience*, *31*(30), 10937–47. doi:10.1523/JNEUROSCI.5302-10.2011

Lebel, C., Gee, M., Camicioli, R., Wieler, M., Martin, W., & Beaulieu, C. (2012). Diffusion tensor imaging of white matter tract evolution over the lifespan. *NeuroImage*, *60*, 340–352. doi:10.1016/j.neuroimage.2011.11.094

Lebel, C., Walker, L., Leemans, A., Phillips, L., & Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *NeuroImage*, *40*(3), 1044–1055. doi:10.1016/j.neuroimage.2007.12.053

Levy, D. J., & Glimcher, P. W. (2011). Comparing apples and oranges: Using reward-specific and reward-general subjective value representation in the brain. *The Journal of Neuroscience*, *31*(41), 14693–707. doi:10.1523/JNEUROSCI.2218-11.2011

Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). *Neuropsychological assessment* (4th ed.). New York: Oxford University Press.

Linnet, K. M., Dalsgaard, S., Obel, C., Wisborg, K., Henriksen, T. B., Rodriguez, A., … Jarvelin, M.-R. (2003). Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: Review of the current evidence. *The American Journal of Psychiatry*, *160*(6), 1028–1040. doi:10.1176/appi.ajp.160.6.1028

Lisdahl, K. M., Gilbart, E. R., Wright, N. E., & Shollenbarger, S. G. (2013). Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function. *Frontiers in Psychiatry*, *4*, 53. doi:10.3389/fpsyt.2013.00053

Lisdahl, K. M., & Price, J. S. (2012). Increased marijuana use and gender predict poorer cognitive functioning in adolescents and emerging adults. *Journal of the International Neuropsychological Society*, *18*(4), 678–688. doi:10.1017/S1355617712000276

Long, N. M., Oztekin, I., & Badre, D. (2010). Separable prefrontal cortex contributions to free recall. *The Journal of Neuroscience*, *30*(33), 10967–76. doi:10.1523/JNEUROSCI.2611-10.2010

Lorenzetti, V., Solowij, N., Whittle, S., Fornito, A., Lubman, D. I., Pantelis, C., & Yücel, M. (2014). Gross morphological brain changes with chronic, heavy cannabis use. *The British Journal of Psychiatry*, *206*(1), 77–8. doi:10.1192/bjp.bp.114.151407

Lubman, D. I., Cheetham, A., & Yücel, M. (2015). Cannabis and adolescent brain development. *Pharmacology & Therapeutics*, *148*, 1–16.

Luciana, M., & Collins, P. F. (1997). Dopaminergic modulation of working memory for spatial but not object cues in normal humans. *Journal of Cognitive Neuroscience*, *9*(3), 330–347. doi:10.1162/jocn.1997.9.3.330

Luciana, M., Collins, P. F., & Depue, R. A. (1998). Opposing roles for dopamine and serotonin in the modulation of human spatial working memory functions. *Cerebral Cortex*, *8*(3), 218–226.

Luciana, M., Collins, P. F., Muetzel, R. L., & Lim, K. O. (2013). Effects of alcohol use initiation on brain structure in typically developing adolescents. *The American Journal of Drug and Alcohol Abuse*, *39*(6), 345–55. doi:10.3109/00952990.2013.837057

Luciana, M., Collins, P. F., Olson, E. A., & Schissel, A. M. (2009). Tower of London performance in healthy adolescents: The development of planning skills and associations with self-reported inattention and impulsivity. *Developmental Neuropsychology*, *34*(4), 461–75. doi:10.1080/87565640902964540

Luciana, M., Wahlstrom, D., Porter, J. N., & Collins, P. F. (2012). Dopaminergic modulation of incentive motivation in adolescence: Age-related changes in signaling, individual differences, and implications for the development of self-regulation. *Developmental Psychology*, *48*(3), 844–861. doi:10.1037/a0027432

Lynskey, M. T., Heath, A. C., Bucholz, K. K., Slutske, W. S., Madden, P. A. F., Nelson, E. C., … Martin, N. G. (2003). Escalation of drug use in early-onset cannabis users vs co-twin controls. *JAMA*, *289*(4), 427–433.

Macher, R. B., & Earleywine, M. (2012). Enhancing neuropsychological performance in chronic cannabis users: The role of motivation. *Journal of Clinical and Experimental Neuropsychology*, *34*(4), 405–415. doi:10.1080/13803395.2011.646957

Mahmood, O. M., Jacobus, J., Bava, S., Scarlett, A., & Tapert, S. F. (2010). Learning and memory performances in adolescent users of alcohol and marijuana: Interactive effects. *Journal of Studies on Alcohol and Drugs*, *71*(6), 885–94.

Matochik, J. A., Eldreth, D. A., Cadet, J.-L., & Bolla, K. I. (2005). Altered brain tissue composition in heavy marijuana users. *Drug and Alcohol Dependence*, *77*, 23–30. doi:10.1016/j.drugalcdep.2004.06.011

McClure, E. A., Stitzer, M. L., & Vandrey, R. (2012). Characterizing smoking topography of cannabis in heavy users. *Psychopharmacology*, *220*(2), 309–318. doi:10.1007/s00213-011-2480-4

Mcgee, R., Williams, S., Poulton, R., & Moffitt, T. E. (2000). A longitudinal study of cannabis use and mental health from adolescence to early adulthood. *Addiction*, *95*(4), 491–503.

McHale, S., & Hunt, N. (2008). Executive function deficits in short-term abstinent cannabis users. *Human Psychopharmacology*, *23*(5), 409–415. doi:10.1002/hup.941

Medina, K. L., Hanson, K. L., Schweinsburg, A. D., Cohen-Zion, M., Nagel, B. J., & Tapert, S. F. (2007). Neuropsychological functioning in adolescent marijuana users: Subtle deficits detectable after a month of abstinence. *Journal of the International Neuropsychological Society*, *13*(5), 807–820. doi:10.1017/S1355617707071032

Medina, K. L., McQueeny, T., Nagel, B. J., Hanson, K. L., Yang, T. T., & Tapert, S. F. (2009). Prefrontal cortex morphometry in abstinent adolescent marijuana users:

Subtle gender effects. *Addiction Biology*, *14*(4), 457–468. doi:10.1111/j.1369-1600.2009.00166.x

Medina, K. L., Nagel, B. J., & Tapert, S. F. (2010). Abnormal cerebellar morphometry in abstinent adolescent marijuana users. *Psychiatry Research: Neuroimaging*, *182*(2), 152–9. doi:10.1016/j.pscychresns.2009.12.004

Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S. E., … Moffitt, T. E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences*, *109*(40), E2657–E2664. doi:10.1073/pnas.1206820109

Montgomery, C., Seddon, A. L., Fisk, J. E., Murphy, P. N., & Jansari, A. (2012). Cannabis-related deficits in real-world memory. *Human Psychopharmacology*, *27*, 217–225. doi:10.1002/hup.1273

Muetzel, R. L., Marjańska, M., Collins, P. F., Becker, M. P., Valabrègue, R., Auerbach, E. J., … Luciana, M. (2013). In vivo 1H magnetic resonance spectroscopy in young-adult daily marijuana users. *NeuroImage: Clinical*, *2*, 581–589. doi:10.1016/j.nicl.2013.04.011

Murayama, K., Matsumoto, M., Izuma, K., & Matsumoto, K. (2010). Neural basis of the undermining effect of monetary reward on intrinsic motivation. *Proceedings of the National Academy of Sciences*, *107*(49), 20911–6. doi:10.1073/pnas.1013305107

Navas-Sánchez, F. J., Alemán-Gómez, Y., Sánchez-Gonzalez, J., Guzmán-De-Villoria, J. A., Franco, C., Robles, O., … Desco, M. (2014). White matter microstructure correlates of mathematical giftedness and intelligence quotient. *Human Brain Mapping*, *35*(6), 2619–2631. doi:10.1002/hbm.22355

O'Hare, E. D., & Sowell, E. R. (2008). Imaging developmental changes in gray and white matter in the human brain. In C. A. Nelson & M. Luciana (Eds.), *Handbook of Developmental Cognitive Neuroscience* (2nd ed., pp. 23–38). Cambridge, MA: MIT Press.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia*, *9*, 97–113.

Olson, E. A., Collins, P. F., Hooper, C. J., Muetzel, R. L., Lim, K. O., & Luciana, M. (2009). White matter integrity predicts delay discounting behavior in 9- to 23-year-olds: A diffusion tensor imaging study. *Journal of Cognitive Neuroscience*, *21*(7), 1406–1421. doi:10.1162/jocn.2009.21107

Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia*, *28*(10), 1021–1034.

Padula, C. B., Schweinsburg, A. D., & Tapert, S. F. (2007). Spatial working memory performance and fMRI activation interaction in abstinent adolescent marijuana users. *Psychology of Addictive Behaviors*, *21*(4), 478–487. doi:10.1037/0893-164X.21.4.478

Patton, G. C., Coffey, C., Carlin, J. B., Degenhardt, L., Lynskey, M. T., & Hall, W. D. (2002). Cannabis use and mental health in young people: Cohort study. *The British Medical Journal*, *325*, 1195–1198.

Paus, T., Collins, D. L., Evans, A. C., Leonard, G., Pike, B., & Zijdenbos, A. (2001). Maturation of white matter in the human brain: A review of magnetic resonance

studies. *Brain Research Bulletin*, *54*(3), 255–266. doi:10.1016/S0361-9230(00)00434-2

Peters, B. D., Ikuta, T., Derosse, P., John, M., Burdick, K. E., Gruner, P., … Malhotra, A. K. (2014). Age-related differences in white matter tract microstructure are associated with cognitive performance from childhood to adulthood. *Biological Psychiatry*, *75*(3), 248–256. doi:10.1016/j.biopsych.2013.05.020

Pfefferbaum, A., Mathalon, D. H., Sullivan, E. V, Rawles, J. M., Zipursky, R. B., & Lim, K. O. (1994). A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Archives of Neurology*, *51*(9), 874–87.

Pistis, M., Perra, S., Pillolla, G., Melis, M., Muntoni, A. L., & Gessa, G. L. (2004). Adolescent exposure to cannabinoids induces long-lasting changes in the response to drugs of abuse of rat midbrain dopamine neurons. *Biological Psychiatry*, *56*, 86–94.

Pope, H. G., Gruber, A. J., Hudson, J. I., Cohane, G., Huestis, M. A., & Yurgelun-Todd, D. A. (2003). Early-onset cannabis use and cognitive deficits: What is the nature of the association? *Drug and Alcohol Dependence*, *69*(3), 303–310.

Pope, H. G., & Yurgelun-Todd, D. A. (1996). The residual cognitive effects of heavy marijuana use in college students. *JAMA*, *275*(7), 521–527.

Quinn, H. R., Matsumoto, I., Callaghan, P. D., Long, L. E., Arnold, J. C., Gunasekaran, N., … McGregor, I. S. (2008). Adolescent rats find repeated Delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. *Neuropsychopharmacology*, *33*(5), 1113–26. doi:10.1038/sj.npp.1301475

Ramaekers, J. G., Kauert, G. F., van Ruitenbeek, P., Theunissen, E. L., Schneider, E., & Moeller, M. R. (2006). High-potency marijuana impairs executive function and inhibitory motor control. *Neuropsychopharmacology*, *31*(10), 2296–2303. doi:10.1038/sj.npp.1301068

Ramaekers, J. G., Kauert, G., Theunissen, E. L., Toennes, S. W., & Moeller, M. R. (2009). Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. *Journal of Psychopharmacology*, *23*(3), 266–277. doi:10.1177/0269881108092393

Raver, S. M., Haughwout, S. P., & Keller, A. (2013). Adolescent Cannabinoid Exposure Permanently Suppresses Cortical Oscillations in Adult Mice. *Neuropsychopharmacology*, *38*(12), 2338–2347. doi:10.1038/npp.2013.164

Realini, N., Rubino, T., & Parolaro, D. (2009). Neurobiological alterations at adult age triggered by adolescent exposure to cannabinoids. *Pharmacological Research*, *60*(2), 132–138. doi:10.1016/j.phrs.2009.03.006

Rey, A. (1993). Psychological examination of traumatic encephalopathy [originally published in Archives de Psychologie 1941; 28: 286340; translated by Corwin J, Bylsma F.]. *Clinical Neuropsychologist*, *7*(1), 3–21.

Rey, J. M., Sawyer, M. G., Raphael, B., Patton, G. C., & Lynskey, M. T. (2002). Mental health of teenagers who use cannabis: Results of an Australian survey. *The British Journal of Psychiatry*, *180*(3), 216–221. doi:10.1192/bjp.180.3.216

Rice, D., & Barone, S. (2000). Critical periods of vulnerability for the developing nervous system: Evidence from human and animal models. *Environmental Health Perspectives*, *108*(Supplement 3), 511–33.

Rodriguez de Fonseca, F., Ramos, J. A., Bonnin, A., & Fernández-Ruiz, J. J. (1993). Presence of cannabinoid binding sites in the brain from early postnatal ages. *Neuroreport*, *4*(2), 135–138.

Romero, J., Garcia-Palomero, E., Berrendero, F., Garcia-Gil, L., Hernandez, M. L., Ramos, J. A., & Fernández-Ruiz, J. J. (1997). Atypical location of cannabinoid receptors in white matter areas during rat brain development. *Synapse*, *26*(3), 317–323. doi:10.1002/(SICI)1098-2396(199707)26:3<317::AID-SYN12>3.0.CO;2-S

Rubino, T., Realini, N., Braida, D., Guidi, S., Capurro, V., Vigano, D., … Parolaro, D. (2009). Changes in hippocampal morphology and neuroplasticity induced by adolescent THC treatment are associated with cognitive impairment in adulthood. *Hippocampus*, *19*(8), 763–772. doi:10.1002/hipo.20554

Rueckert, D., Sonoda, L. I., Hayes, C., Hill, D. L., Leach, M. O., & Hawkes, D. J. (1999). Nonrigid registration using free-form deformations: Application to breast MR images. *IEEE Transactions on Medical Imaging*, *18*(8), 712–721. doi:10.1109/42.796284

Ryan, R. M., & Deci, E. L. (2000). Intrinsic and extrinsic motivations: Classic definitions and new directions. *Contemporary Educational Psychology*, *25*(1), 54–67. doi:10.1006/ceps.1999.1020

Sarne, Y., Asaf, F., Fishbein, M., Gafni, M., & Keren, O. (2011). The dual neuroprotective-neurotoxic profile of cannabinoid drugs. *British Journal of Pharmacology*, *163*(7), 1391–1401. doi:10.1111/bph.2011.163

Sattler, J. M., & Ryan, J. J. (2009). *Assessment with the WAIS-IV*. San Diego, CA: Jerome M. Sattler.

Schacht, J. P., Hutchison, K. E., & Filbey, F. M. (2012). Associations between cannabinoid receptor-1 (CNR1) variation and hippocampus and amygdala volumes in heavy cannabis users. *Neuropsychopharmacology*, *37*(11), 2368–2376. doi:10.1038/npp.2012.92

Schmithorst, V. J., & Yuan, W. (2010). White matter development during adolescence as shown by diffusion MRI. *Brain and Cognition*, *72*(1), 16–25. doi:10.1016/j.bandc.2009.06.005

Schneider, M., & Koch, M. (2003). Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. *Neuropsychopharmacology*, *28*(10), 1760–1769. doi:10.1038/sj.npp.1300225

Schneider, M., & Koch, M. (2007). The effect of chronic peripubertal cannabinoid treatment on deficient object recognition memory in rats after neonatal mPFC lesion. *European Neuropsychopharmacology*, *17*(3), 180–186. doi:10.1016/j.euroneuro.2006.03.009

Schneider, M., Schömig, E., & Leweke, F. M. (2008). Acute and chronic cannabinoid treatment differentially affects recognition memory and social behavior in pubertal and adult rats. *Addiction Biology*, *13*(3-4), 345–57. doi:10.1111/j.1369-1600.2008.00117.x

Schuermeyer, J., Salomonsen-Sautel, S., Price, R. K., Balan, S., Thurstone, C., Min, S. J., & Sakai, J. T. (2014). Temporal trends in marijuana attitudes, availability and use in

Colorado compared to non-medical marijuana states: 2003-11. *Drug and Alcohol Dependence*, *140*, 145–155. doi:10.1016/j.drugalcdep.2014.04.016
Schwartz, R. H., Gruenewald, P. J., Klitzner, M., & Fedio, P. (1989). Short-term memory impairment in cannabis-dependent adolescents. *American Journal of Diseases of Children*, *143*(10), 1214–1219.
Schweinsburg, A. D., Schweinsburg, B. C., Medina, K. L., McQueeny, T., Brown, S. A., & Tapert, S. F. (2010). The influence of recency of use on fMRI response during spatial working memory in adolescent marijuana users. *Journal of Psychoactive Drugs*, *42*(3), 401–412.
Shollenbarger, S. G., Price, J. S., Wieser, J., & Lisdahl, K. (2015). Poorer frontolimbic white matter integrity is associated with chronic cannabis use, FAAH genotype, and increased depressive and apathy symptoms in adolescents and young adults. *NeuroImage: Clinical*, *8*, 117–125. doi:10.1016/j.nicl.2015.03.024
Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., … Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, *31*(4), 1487–505. doi:10.1016/j.neuroimage.2006.02.024
Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*, 208–219. doi:10.1016/j.neuroimage.2004.07.051
Sneider, J. T., Mashhoon, Y., & Silveri, M. M. (2013). A review of magnetic resonance spectroscopy studies in marijuana using adolescents and adults. *Journal of Addiction Research & Therapy*, *Suppl 4*, S4: 010. doi:10.4172/2155-6105.S4-010
Solowij, N., & Battisti, R. A. (2008). The chonic effects of cannabis on memory in humans: A review. *Current Drug Abuse Reviews*, *1*, 81–98.
Solowij, N., Jones, K. A., Rozman, M. E., Davis, S. M., Ciarrochi, J., Heaven, P. C. L., … Yücel, M. (2011). Verbal learning and memory in adolescent cannabis users, alcohol users and non-users. *Psychopharmacology*, *216*(1), 131–44. doi:10.1007/s00213-011-2203-x
Solowij, N., Jones, K. A., Rozman, M. E., Davis, S. M., Ciarrochi, J., Heaven, P. C. L., … Yücel, M. (2012). Reflection impulsivity in adolescent cannabis users: A comparison with alcohol-using and non-substance-using adolescents. *Psychopharmacology*, *219*(2), 575–586. doi:10.1007/s00213-011-2486-y
Solowij, N., Yücel, M., Respondek, C., Whittle, S., Lindsay, E., Pantelis, C., & Lubman, D. I. (2011). Cerebellar white-matter changes in cannabis users with and without schizophrenia. *Psychological Medicine*, *41*(11), 2349–2359. doi:10.1017/S003329171100050X
Song, S.-K., Sun, S. W., Ju, W. K., Lin, S. J., Cross, A. H., & Neufeld, A. H. (2003). Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *NeuroImage*, *20*(3), 1714–1722. doi:10.1016/j.neuroimage.2003.07.005
Song, S.-K., Yoshino, J., Le, T. Q., Lin, S. J., Sun, S. W., Cross, A. H., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage*, *26*(1), 132–140. doi:10.1016/j.neuroimage.2005.01.028

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience*, *6*(3), 309–315. doi:10.1038/nn1008

Sowell, E. R., Thompson, P. M., Holmes, C. J., Jernigan, T. L., & Toga, A. W. (1999). In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nature Neuroscience*, *2*(10), 859–861. doi:10.1038/13154

Sowell, E. R., Thompson, P. M., Tessner, K. D., & Toga, A. W. (2001). Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: Inverse relationships during postadolescent brain maturation. *The Journal of Neuroscience*, *21*(22), 8819–29.

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience and Biobehavioral Reviews*, *24*(4), 417–463.

Stopponi, S., Soverchia, L., Ubaldi, M., Cippitelli, A., Serpelloni, G., & Ciccocioppo, R. (2014). Chronic THC during adolescence increases the vulnerability to stress-induced relapse to heroin seeking in adult rats. *European Neuropsychopharmacology*, *24*(7), 1037–45. doi:10.1016/j.euroneuro.2013.12.012

Substance Abuse and Mental Health Services Administration. (2013). *Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-46, HHS Publication No. (SMA) 13-4795*. Rockville, MD.

Substance Abuse and Mental Health Services Administration. (2014). *Results from the 2013 National Survey on Drug Use and Health : Summary of National Findings, NSDUH Series H-48, HHS Publication No. (SMA) 14-4863*. Rockville, MD. doi:NSDUH Series H-41, HHS Publication No. (SMA) 11-4658

Szabo, B., & Schlicker, E. (2005). Effects of cannabinoids on neurotransmission. *Handbook of Experimental Pharmacology*, (168), 327–65.

Tait, R. J., Mackinnon, A., & Christensen, H. (2011). Cannabis use and cognitive function: 8-year trajectory in a young adult cohort. *Addiction*, *106*(12), 2195–203. doi:10.1111/j.1360-0443.2011.03574.x

Takagi, M. J., Lubman, D. I., Cotton, S. M., Fornito, A., Baliz, Y., Tucker, A., & Yücel, M. (2011). Executive control among adolescent inhalant and cannabis users. *Drug and Alcohol Review*, *30*(6), 629–637. doi:10.1111/j.1465-3362.2010.00256.x

Takagi, M. J., Yücel, M., Cotton, S. M., Baliz, Y., Tucker, A., Elkins, K., & Lubman, D. I. (2011). Verbal memory, learning, and executive functioning among adolescent inhalant and cannabis users. *Journal of Studies on Alcohol and Drugs*, *72*(1), 96–105.

Tanda, G., & Goldberg, S. R. (2003). Cannabinoids: Reward, dependence, and underlying neurochemical mechanisms - A review of recent preclinical data. *Psychopharmacology*, *169*(2), 115–134. doi:10.1007/s00213-003-1485-z

Tapert, S. F., Granholm, E., Leedy, N. G., & Brown, S. A. (2002). Substance use and withdrawal: neuropsychological functioning over 8 years in youth. *Journal of the International Neuropsychological Society*, *8*(7), 873–83.

Tapert, S. F., Schweinsburg, A. D., Drummond, S. P. A., Paulus, M. P., Brown, S. A., Yang, T. T., & Frank, L. R. (2007). Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology*, *194*(2), 173–183. doi:10.1007/s00213-007-0823-y

Taris, T. W. (2000). *A Primer in longitudinal data analysis*. London: SAGE Publications.
Thatcher, D. L., Pajtek, S., Chung, T., Terwilliger, R. A., & Clark, D. B. (2010). Gender differences in the relationship between white matter organization and adolescent substance use disorders. *Drug and Alcohol Dependence*, *110*(1-2), 55–61. doi:10.1016/j.drugalcdep.2010.02.004
Theunissen, E. L., Kauert, G. F., Toennes, S. W., Moeller, M. R., Sambeth, A., Blanchard, M. M., & Ramaekers, J. G. (2012). Neurophysiological functioning of occasional and heavy cannabis users during THC intoxication. *Psychopharmacology*, *220*(2), 341–350. doi:10.1007/s00213-011-2479-x
Treit, S., Chen, Z., Rasmussen, C., & Beaulieu, C. (2013). White matter correlates of cognitive inhibition during development: A diffusion tensor imaging study. *Neuroscience*, *276*, 87–97. doi:10.1016/j.neuroscience.2013.12.019
Trezza, V., Campolongo, P., Manduca, A., Morena, M., Palmery, M., Vanderschuren, L. J. M. J., & Cuomo, V. (2012). Altering endocannabinoid neurotransmission at critical developmental ages: Impact on rodent emotionality and cognitive performance. *Frontiers in Behavioral Neuroscience*, *6*(January), 1–12. doi:10.3389/fnbeh.2012.00002
Urban, N. B. L., Slifstein, M., Thompson, J. L., Xu, X., Girgis, R. R., Raheja, S., … Abi-Dargham, A. (2012). Dopamine release in chronic cannabis users: A [11c]raclopride positron emission tomography study. *Biological Psychiatry*, *71*(8), 677–83. doi:10.1016/j.biopsych.2011.12.018
Verdejo-García, A., Benbrook, A., Funderburk, F., David, P., Cadet, J.-L., & Bolla, K. I. (2007). The differential relationship between cocaine use and marijuana use on decision-making performance over repeat testing with the Iowa Gambling Task. *Drug and Alcohol Dependence*, *90*, 2–11. doi:10.1016/j.drugalcdep.2007.02.004
Verdejo-García, A., Rivas-Pérez, C., Vilar-López, R., & Pérez-García, M. (2007). Strategic self-regulation, decision-making and emotion processing in poly-substance abusers in their first year of abstinence. *Drug and Alcohol Dependence*, *86*, 139–146. doi:10.1016/j.drugalcdep.2006.05.024
Viveros, M.-P., Llorente, R., Moreno, E., & Marco, E. M. (2005). Behavioural and neuroendocrine effects of cannabinoids in critical developmental periods. *Behavioural Pharmacology*, *16*, 353–362.
Volkow, N. D., Baler, R. D., Compton, W. M., & Weiss, S. R. B. (2014). Adverse health effects of marijuana use. *The New England Journal of Medicine*, *370*, 2219–27. doi:10.1056/NEJMra1402309
Volkow, N. D., Wang, G.-J., Telang, F., Fowler, J. S., Alexoff, D., Logan, J., … Tomasi, D. (2014). Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. *Proceedings of the National Academy of Sciences*, 1–8. doi:10.1073/pnas.1411228111
Wagner, D., Becker, B., Gouzoulis-Mayfrank, E., & Daumann, J. (2010). Interactions between specific parameters of cannabis use and verbal memory. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *34*(6), 871–876. doi:10.1016/j.pnpbp.2010.04.004
Wahlstrom, D., Collins, P. F., White, T., & Luciana, M. (2010). Developmental changes in dopamine neurotransmission in adolescence: Behavioral implications and issues

in assessment. *Brain and Cognition*, *72*(1), 146–159. doi:10.1016/j.bandc.2009.10.013

Wall, M. M., Poh, E., Cerdá, M., Keyes, K. M., Galea, S., & Hasin, D. S. (2011). Adolescent marijuana use from 2002 to 2008: Higher in states with medical marijuana laws, cause still unclear. *Annals of Epidemiology*, *21*(9), 714–6. doi:10.1016/j.annepidem.2011.06.001

Wall, M. M., Poh, E., Cerdá, M., Keyes, K. M., Galea, S., & Hasin, D. S. (2012). Commentary on Harper S, Strumpf EC, Kaufman JS. Do Medical marijuana laws increase marijuana use? Replication study and extension. *Annals of Epidemiology*, *22*(7), 536–537. doi:10.1016/j.annepidem.2012.03.003.Commentary

Wechsler, D. (1997). *Manual for the Wechsler Adult Intelligence Scale - Third Revision*. San Antonio, Texas: The Psychological Corporation.

Wechsler, D. (1999). *Manual for the Weschler Abbreviated Scale of Intelligence*. San Antonio, Texas: The Psychological Corporation.

Weiland, B. J., Thayer, R. E., Depue, B. E., Sabbineni, A., Bryan, A. D., & Hutchison, K. E. (2015). Daily Marijuana Use Is Not Associated with Brain Morphometric Measures in Adolescents or Adults. *The Journal of Neuroscience*, *35*(4), 1505–1512. doi:10.1523/JNEUROSCI.2946-14.2015

Westlye, L. T., Walhovd, K. B., Dale, A. M., Bjørnerud, A., Due-Tønnessen, P., Engvig, A., … Fjell, A. M. (2010). Life-span changes of the human brain white matter: Diffusion tensor imaging (DTI) and volumetry. *Cerebral Cortex*, *20*(9), 2055–2068. doi:10.1093/cercor/bhp280

Whitlow, C. T., Liguori, A., Livengood, L. B., Hart, S. L., Mussat-Whitlow, B. J., Lamborn, C. M., … Porrino, L. J. (2004). Long-term heavy marijuana users make costly decisions on a gambling task. *Drug and Alcohol Dependence*, *76*(1), 107–111. doi:10.1016/j.drugalcdep.2004.04.009

Winward, J. L., Hanson, K. L., Tapert, S. F., & Brown, S. A. (2014). Heavy alcohol use, marijuana use, and concomitant use by adolescents are associated with unique and shared cognitive decrements. *Journal of the International Neuropsychological Society*, *20*(8), 784–95. doi:10.1017/S1355617714000666

Worsley, K. J., Evans, A. C., Marrett, S., & Neelin, P. (1992). A three-dimensional statistical analysis for CBF activation studies in human brain. *Journal of Cerebral Blood Flow and Metabolism*, *12*(6), 900–918. doi:10.1038/jcbfm.1992.127

Wu, L.-T., Swartz, M. S., Brady, K. T., & Hoyle, R. H. (2015). Perceived cannabis use norms and cannabis use among adolescents in the United States. *Journal of Psychiatric Research*, *64*, 79–87. doi:10.1016/j.jpsychires.2015.02.022

Yechiam, E., Busemeyer, J. R., Stout, J. C., & Bechara, A. (2005). Using cognitive models to map relations between neuropsychological disorders and human decision-making deficits. *Psychological Science*, *16*(12), 973–978.

Yücel, M., Solowij, N., Respondek, C., Whittle, S., Fornito, A., Pantelis, C., & Lubman, D. I. (2008). Regional brain abnormalities associated with long-term heavy cannabis use. *Archives of General Psychiatry*, *65*(6), 694–701. doi:10.1001/archpsyc.65.6.694

Yücel, M., Zalesky, A., Takagi, M. J., Bora, E., Fornito, A., Ditchfield, M., … Lubman, D. I. (2010). White-matter abnormalities in adolescents with long-term inhalant and

cannabis use: A diffusion magnetic resonance imaging study. *Journal of Psychiatry Neuroscience, 35*(6), 409–412.

Zalesky, A., Solowij, N., Yücel, M., Lubman, D. I., Takagi, M. J., Harding, I. H., … Seal, M. L. (2012). Effect of long-term cannabis use on axonal fibre connectivity. *Brain, 135*, 2245–2255. doi:10.1093/brain/aws136