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UNIVERSITY OF CALIFORNIA, SAN DIEGO

Elucidating How Heavy Substance Use Impacts Affect and Cognition of Adolescents

A dissertation submitted in partial satisfaction of the requirements for the degree
Doctor of Philosophy

in

Psychology

by

Jennifer Laven Winward

Committee in charge:

Professor Sandra A. Brown, Chair
Professor Stephan Anagnostaras
Professor Mark Appelbaum
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Professor Susan Tapert

2014

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The Dissertation of Jennifer Laven Winward is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chapter 1, in full, is a reprint of the material as it appears in Winward, J.L., Bekman, N.M., Hanson, K.L., Lejuez, C.W., & Brown S.A. Changes in emotional reactivity and distress tolerance among heavy drinking adolescents during sustained abstinence. *Alcoholism: Clinical & Experimental Research*. Manuscript accepted and in press. The dissertation author was the primary investigator and primary author of this paper.

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Chapter 3, in full, is a reprint of the material as it appears in Winward, J.L., Hanson, K.L., Tapert, S.F., & Brown, S.A. Heavy Alcohol Use, Marijuana Use, and Concomitant Use by Adolescents are Associated with Unique and Shared Cognitive Decrements. *Journal of the International Neuropsychological Society*. Manuscript was

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Winward, J.L., Hanson, K.L., Bekman, N.M., Tapert, S.F., & Brown, S.A. (2014). Adolescent heavy episodic drinking: Neurocognitive functioning during early abstinence. *Journal of the International Neuropsychological Society*, 20, 218-229.

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Meloy, M.J., Meloy J.R., Eyer, L.T., Tapert, S.F., **Winward**, J.L., Pulido, C., & Mano, Q.R. Reduced Implicit Emotional Processing as Measured by fMRI in Adolescent Psychopathy and its Relevance to Instrumental Violence. *Biological Psychiatry*. Manuscript UNDER REVIEW.

Bekman, N.M., **Winward**, J.L., Lau, L.L., Wagner, C.C., & Brown, S.A. (2013). The impact of adolescent binge drinking and sustained abstinence on affective state. *Alcoholism: Clinical & Experimental Research*, 37(8): 1432-1439.

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2002	Presidential Student Service Award for Outstanding Community Service
2002	California Governor's Scholarship Award
2002	Marin County School Administrator Association Award for Exemplary Academics
2002	California State Assembly Recognition for Extraordinary Community Service

ABSTRACT OF THE DISSERTATION

Elucidating How Heavy Substance Use Impacts Affect and Cognition of Adolescents

by

Jennifer Laven Winward

Doctor of Philosophy in Psychology

University of California, San Diego, 2014

Professor Sandra A. Brown, Chair

This body of research elucidates the complex relationship among premorbid functioning, brain development, and the effects of alcohol and marijuana use during adolescence. Given the high rates of alcohol and marijuana use among youth, these findings have far-reaching, important implications in academic, occupational, and personal settings.

Chapter 1 indicates that heavy drinking youth with recent alcohol exposure show much greater emotional responses and poorer distress tolerance to a challenging cognitive task. Importantly, their affective responses diminish with sustained abstinence. It is possible that the combination of elevated negative affect and low distress tolerance during early abstinence may heighten risk for progression to an alcohol use disorder or

result in return to use. The capacity to withstand aversive internal states is integral to daily functioning, so reductions in emotional reactivity with abstinence may contribute to academic and social improvements.

Chapter 2 identifies deficits among heavy drinking youth during early abstinence and following four weeks of abstention in prospective memory, cognitive switching, inhibition task accuracy, verbal memory, visuospatial construction, reading, and vocabulary. Given teens' comparable 5th grade math and language arts standardized test performance, the study suggests alcohol-related influences on several underlying brain systems that may (1) arise in heavy social drinkers prior to the onset of alcohol abuse or dependence or (2) take longer than four weeks to recover.

Chapter 3 extends the findings of Chapter 2 by introducing two more groups of adolescents: protracted marijuana users and those with concomitant use of both alcohol and marijuana. The study suggests that relative weakness in cognitive flexibility, verbal recall, semantic clustering, and reading skills may be related to heavy alcohol use during adolescence, whereas poorer task accuracy, verbal memory, and psychomotor speed may be associated with regular marijuana use. Further, working memory may be particularly impacted by concomitant use of marijuana and alcohol.

These studies contribute to methods for measuring changes on important affective and cognitive domains associated with heavy alcohol and/or marijuana use during adolescence. Possible decrements may significantly impact adolescents' daily experiences, and with knowledge of these deficits, educators, parents, and clinicians may be able to improve outcomes for these teens.

INTRODUCTION

Elucidating How Heavy Substance Use Impacts Affect and Cognition of Adolescents

Adolescent Brain Development: Overview

While development of overall brain size is largely complete by age five, specific structural and functional changes continue during adolescence and contribute to more efficient cognitive functioning (Durstun et al., 2001). During adolescence, the brain undergoes significant developmental changes, with the frontal lobe maturing in later adolescence and into early adulthood and both myelination and synaptic refinement continuing throughout adolescence (Giedd et al., 1999; Gogtay et al., 2004; Paus et al., 1999). Studies in typically developing teens without heavy alcohol or drug use demonstrate that white matter volumes increase throughout the brain with continued myelination during adolescence. Gray matter volumes peak around age 12 in males and age 11 in females and then decline as unnecessary neural connections are eliminated, resulting in a net volume loss during this time (Giedd et al., 1999). Increases in myelination, detected as increases in white matter volumes, and in pruning of gray matter, detected as decreases in cortical gray matter, facilitate more effective communication among neurons in the brain. These changes allow specialized cognitive processing required for optimal cognition and performance (Brown & Tapert, 2004). Neurotransmitter systems also mature during adolescence. Specific to marijuana, cannabinoid (CB)1 receptors are widely distributed throughout the brain, with high levels of density in the hippocampus, cerebellum, basal ganglia, and prefrontal cortex (Glass, Dragunow, & Faull, 1997; Herkenham et al., 1990). These CB1 receptors increase during adolescence, and, in doing so, both facilitate release of neurotransmitters and contribute

to genetic expression of neural development (Iversen, 2003; Rubino & Parolaro, 2008). Healthy adolescent brain development therefore progresses with increases in white matter and in CB1 receptor density and decreases in grey matter volumes. Therefore, the potential neurotoxic effects of alcohol and marijuana include disruptions to grey matter macrostructure, white matter microstructure, neurochemical communication, and genetic expression of neural development, all of which have widespread implications for cognitive functioning and success in daily functioning.

Adolescent Substance Use Research: Brief History

Most of what research has provided us in terms of understanding the impact of adolescent substance use on neuroanatomical and neurocognitive functioning has historically come from clinical populations of youth with substance use disorders and more recently from community samples of binge drinking and marijuana using youth. Understandably, many initial studies in this field utilized smaller, clinical samples of adolescents who frequently had comorbid conduct disorder, ADHD, depression, and substance use other than alcohol or marijuana. Despite their methodological limitations, these earlier clinical samples provided informative findings that shaped the direction and methodology of later research. Recent research in this field typically recruits community youth with heavy drinking experiences or protracted marijuana use and compensates them financially for abstaining prior to neuropsychological assessments or brain scans. Ideally, researchers should continue the practice of monitored abstinence and consider carefully the impact of recent alcohol and marijuana use on results if teens are not abstinent prior to assessments or test positively for any substance at the time of testing. Studies seeking to understand the impact of alcohol and marijuana would also carefully

consider potential confounding influences like gender, age, poor self regulation, family history of substance use, and comorbid Axis I disorders.

Current Rates of Adolescent Alcohol and Marijuana Use

Alcohol is the most commonly used illicit substance among adolescents. By the time students reach their senior year of high school, over 68% have consumed alcohol and over 54% have been drunk (Johnston et al., 2014). According to national data, 39% of high school seniors drank alcohol in the past 30 days, and 23% of high school seniors reported heavy episodic drinking (≥ 5 drinks in males or ≥ 4 drinks in females within a 2-hour period) in the prior two weeks (Johnston et al., 2014). The binge-type pattern of drinking (i.e., consuming 5 or more drinks in males or 4 or more drinks in females in fewer than two hours to achieve a high level of intoxication) prevalent among adolescents has been shown to be more harmful than the consumption of the same amount of alcohol consumed in moderation (1 or 2 drinks) every day (Tapert & Schweinsburg, 2005). This finding suggests that it is not the quantity of alcohol consumed that is concerning, but rather the combination of the quantity with the pattern of binge consumption common among teenagers. Imbibing greater quantities of alcohol in one sitting is concerning because heavy episodic alcohol consumption associates with high risk, life-threatening outcomes including motor vehicle accidents, alcohol poisoning, illegal activities, school failure, and risky sexual behavior (Hingson, Heeren, Winter, & Wechsler, 2005). Such heavy episodic drinking appears to alter developmental trajectories and may interfere with normal neurocognitive and neuroanatomical development (Brown et al., 2008; Brown & Tapert, 2004).

Similar to alcohol, marijuana has consistently been a widely used illegal drug among adolescents in the United States (Johnston et al., 2014). In 2013, 46% of high school seniors reported having tried marijuana, 22% used in the past month, and 7% endorsed daily use (Johnston et al., 2012). Of individuals who initiated marijuana use before 15 years of age, 14% went on to meet criteria for drug abuse or dependence during adulthood (Substance Abuse and Mental Health Services Administration, 2009). As mentioned previously, adolescence is a period of significant neurodevelopment (Giedd et al., 1996; Sowell, Trauner, Gamst, & Jernigan, 2002), so the potential neurocognitive effects of alcohol and marijuana use are a concern.

Animal Research Suggests Heightened Vulnerability During Adolescence

Because of its rigorous experimental control, animal research is amenable to the examination of the neurotoxic effects of alcohol and marijuana on a developing adolescent brain. Animal research provides the ability to control premorbid and environmental factors as well as to administer directly ethanol and cannabinoids during a rodent's adolescence. In animals, postnatal days 28-49 correspond with human adolescent development, which can extend to days 21-59 to include early and late adolescence (Dinieri & Hurd, 2012). Animal studies involving exposure to ethanol and to cannabinoids during this postnatal time period evaluate cognitive functioning, behavior, emotions, and impact to specific brain structures.

Overall, animal research suggests that adolescent animals are more vulnerable than adults to ethanol-induced decrements in functioning, especially following chronic, intermittent exposure to high levels of ethanol, which is considered the analog of 'binge drinking' in humans (White, Ghia, Levin, & Swartzwelder, 2000). A growing number of

animal studies suggests that drinking alcohol during adolescence is particularly harmful to the brain and is associated with altered brain development (i.e., neuroanatomical consequences) and brain functioning (i.e., neurocognitive consequences). The effects of alcohol use in adolescence are similar to those in adulthood, except adolescents seem to experience (1) lower initial brain sensitivity to ethanol than adults (Roehrs, Beare, Zorick, & Roth, 1994; Silveri & Spear, 1998), (2) abnormal development of sensitivity to alcohol-induced motor impairments that typically occur between adolescence and adulthood (White et al., 2002), and (3) tolerance to alcohol's sedating effects with slower onset of sedation following alcohol exposure and smaller magnitude of sedation (Little, Kuhn, Wilson, & Swartzwelder, 1996; Silveri & Spear, 1998; Swartzwelder, Richardson, Markwiese-Foerch, Wilson, & Little, 1998). Adolescent rats also show more susceptibility to hippocampal injury (Nixon et al., 2002; Slawecki, Betancourt, Cole, & Ehlers, 2001; Ward et al., 2009) and to frontal-anterior cortical damage (Crews et al., 2000). These decrements that first present during adolescence extend into later time periods with rats exposed to alcohol during their adolescent years continuing to show structural and functional abnormalities into adulthood. These adult rats show continued alcohol-induced spatial memory impairments (White et al., 2000), lasting decreases in sensitivity to the sedative effects of ethanol (Slawecki, 2002), and enduring neurophysiological effects in the cortex and hippocampus (Slawecki & Roth, 2004). On a physiological level, alcohol exposure in adolescence has also been linked to long-term alterations in brain signaling involving the neurotransmitter serotonin (Obernier, White, Swartzwelder, & Crews, 2002), to GABA-A receptors that alter sensitivity to ethanol's aversive effects into adulthood (Graham & Diaz-Granados, 2006), and to inhibition or

deactivation of NMDA receptors, which likely contributes to reduced long term potentiation seen following alcohol exposure (Li, Wilson, & Swartzwelder, 2002; Schummers & Browning, 2001).

Similar to animal studies investigating the impact of ethanol, a large body of work can also be found on animal models with cannabis exposure. Of note, natural marijuana (smoked by humans) contains many cannabinoids. Although THC is the main active constituent in marijuana, it is possible THC interacts with other plant cannabinoids to produce unique effects in humans that cannot be replicated by isolated or synthetic cannabinoid used in rodent research. Despite this limitation, animal research offers evidence of unique cognitive effects of cannabinoid use in adolescents compared to adults. A series of studies has examined different aspects of learning after chronic administration of cannabinoids. Immature rats (i.e., day 40) treated with the synthetic cannabinoid agonist WIN 55, 212-2, compared to mature rats (i.e., day 70), showed (1) poorer performance on cognitive tasks including maze learning (Fehr, Kalant, & LeBlanc, 1976; Stiglick & Kalant, 1985), which suggests learning dysfunction associated with chronic marijuana administration; (2) more pronounced behavioral alterations and lasting deficits in social play and grooming behaviors (Schneider, Schomig, & Leweke, 2008); and (3) disrupted object recognition and reduced motivation (O'Shea, McGregor, & Mallet, 2006; O'Shea, Singh, McGregor, & Mallet, 2004; Schneider & Koch, 2003, 2005). Chronic WIN treatment has been found to result in both acute and long term effects in spatial memory, object recognition, and long term potentiation in areas like the nucleus accumbens (Abush & Akirav, 2012). Follow up investigations examining the influence of adolescent cannabinoid exposure on memory functioning revealed that THC-

exposed adolescent rats showed object recognition memory deficits, and their THC exposure was associated with hippocampal protein expression abnormalities (Quinn et al., 2007).

In sum, animal research suggests that adolescents, compared to adults, experience heightened neuroanatomical and neurocognitive responses to alcohol and to marijuana. Specific to ethanol exposure, adolescents show reduced sensitivity to alcohol-induced motor impairing and sedative effects, which likely leads to greater alcohol intake and the attainment of higher blood alcohol concentrations with less sedation than would be expected in adulthood. The concurrence of reduced susceptibility to the sedating and motor impairing effects of alcohol with an enhanced vulnerability to alcohol-induced neuroanatomical and neurocognitive deficits presents a concerning effect during adolescence. Specific to cannabinoid exposure, rodent studies provide evidence of both structural and behavioral vulnerability to cannabinoid-induced impairments, particularly in the areas of learning and memory and working memory.

Human Research Findings Coincide with Those of Animal Studies

Observations in human research are consistent with the animal literature and suggest that heavy alcohol and marijuana exposure in adolescence leads to structural and functional brain abnormalities. Since the brain undergoes such significant change during adolescence, it is not surprising that chronic, heavy alcohol use and protracted marijuana use in adolescence and into young adulthood have been linked to neuroanatomical consequences with structural and functional brain abnormalities and to neurocognitive consequences with decrements in neuropsychological and academic performance.

Neuroanatomical Consequences

Both the animal and human literature suggest that compared to adult brains, adolescent brains show differential sensitivity to alcohol-induced and marijuana-induced brain changes, most notably in the frontal cortex, corpus callosum, and hippocampus for both substances and in the cerebellum for marijuana.

Cortical Volume. Human studies utilizing magnetic resonance imaging, tomography, and post-mortem tissue analyses demonstrate that adult alcoholics, particularly females, experience reduction in white and gray matter (Hommer et al., 2001; Hommer et al., 1996) and enlarging of cerebral ventricles (Crews, 1999), which together suggest an overall reduction of adult alcoholics' brain mass. Adults with histories of alcohol withdrawal related seizures showed greater loss of white matter volume in temporal brain regions, relative to controls and to alcohol dependent adults without histories of alcohol-related seizures (Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1996). Animal studies have demonstrated that adolescent rats exposed to the same heavy dosage of ethanol as adult rats showed damage in the same olfactory mesocorticolimbic association and memory-consolidating brain regions as those found in adults; however, several regions that were spared in the adults were damaged in the adolescents, including the frontal cortical olfactory regions and the anterior perirhinal and piriform cortex (Crews et al., 2000).

Human adolescent studies have found similar results both for subclinical, binge drinking teens who do not meet criteria for alcohol abuse or dependence and for clinical populations of teens with alcohol use disorders (AUD). Results suggest reduced white matter integrity in frontal and parietal regions in subclinical teens (McQueeney et al., 2009), smaller prefrontal cortex (PFC) white matter volumes in adolescents with

comorbid alcohol use disorders and Axis I disorders compared to controls (De Bellis et al., 2005), and a unique gender effect with female adolescents with AUDs having smaller PFC volumes and male adolescents with AUDs having greater PFC volumes, relative to demographically-matched controls (Medina et al., 2008). The findings of Medina and colleagues (2008) do conflict with those of De Bellis and colleagues (2005) as the De Bellis group found smaller PFC volumes in both genders. However, the De Bellis study utilized a slightly older population (so pruning may have occurred in males) and one with a higher frequency of comorbidity with conduct disorder, ADHD, depression, and other substance use. These methodological inconsistencies could have impacted the findings about PFC volume in adolescent drinkers. Specific to marijuana use, adolescent cannabis users (ages 16-19) were found to have decreased right medial orbital prefrontal cortex volume compared to nonusing youth (Churchwell, Lopez-Larson, & Yurgelun-Todd, 2010). It appears that both alcohol and marijuana use during this time of development impact the volume and white matter integrity of the prefrontal cortex.

Hippocampus. Animal research also suggests that the hippocampus is especially sensitive both to acute and to chronic alcohol and marijuana exposure during adolescence. Acute alcohol exposure, even at low doses, has been shown to inhibit long-term potentiation in the rat hippocampus (Blitzer, Gil, & Landau, 1990). Nixon and Crews (2002) showed that ethanol inhibits neural progenitor cell proliferation and survival (i.e., reduced formation of new cells) in the rat hippocampus, which they believe contribute to alcohol-induced neuropathology and cognitive deficits. Compared to adult rodents, adolescent rodents were found to be more susceptible to hippocampal injury (Slawecki et al., 2001) and were found to have increased activation of microglia in the

hippocampus following binge-type alcohol exposure (Slawecki, 2002). A follow-up study found consistent findings and reported enhanced activation of excitatory amino acid glutamate and other phagocytic cells in the hippocampus of binge drinking adolescent mice, which could be an early indication of neurodegeneration in this brain region (Ward et al., 2009). Similarly, adolescent cannabis exposure has been associated with hippocampal protein expression abnormalities in adolescent rats (Quinn et al., 2007).

Consistent with animal research, human studies have also shown heightened sensitivity in the hippocampus. Both the left and right hippocampi were found to be significantly smaller in adolescent AUD subjects than in control subjects (De Bellis et al., 2000). These findings were replicated in studies of adolescents with AUDs without significant histories of other substance use or psychiatric conditions. Specifically, left hippocampal volumes were smaller in teens with AUDs than in demographically-matched controls, and youth with greater severity of AUDs had the smallest left hippocampi (Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007; Nagel et al., 2005). In adolescent cannabis users, those abstinent for a month still showed smaller bilateral hippocampal volumes compared to controls, whereas no group effects were identified in amygdala volume (Ashtari et al., 2011). Furthermore, disruptions in hippocampal white matter integrity have also been identified with decreased fractional anisotropy in hippocampal projections of cannabis using youth (Yucel et al., 2010). The heavy drinking and marijuana use during adolescence that are linked to smaller hippocampi are concerning as the hippocampus is a brain structure critical for learning and memory function (Tapert & Schweinsburg, 2005).

Corpus Callosum. Human research about the effects of alcohol on the corpus callosum has demonstrated both macrostructural and microstructural abnormalities. While one study found that the corpus callosum is smaller in alcoholic women compared to non-alcoholic women of the same age (Hommer et al., 1996), another study found that gross area measures of the corpus callosum and its components were equivalent between groups; however more sensitive measurements by diffusion tensor imaging (DTI) of fractional anisotropy and intervoxel coherence showed alcohol related disruption of white matter fiber integrity in the genu of the corpus callosum and in the centrum semiovale (Pfefferbaum & Sullivan, 2002). Consistent with adult research, white matter microstructure abnormalities in the corpus callosum have also been shown in human adolescents with histories of alcohol abuse and dependence (Tapert & Schweinsburg, 2005; Tapert, Theilmann, Schweinsburg, Yafai, & Frank, 2003). Increased mean diffusivity of white matter tracts has also been identified in the prefrontal bundle fibers of the corpus callosum in heavy cannabis using adults (Arnone et al., 2008). The adolescent literature therefore suggests that both alcohol and marijuana use impact white matter integrity in the corpus callosum of substance using adolescents.

Cerebellum. In studies investigating differences in cerebellar volume between adolescent cannabis users and nonusing youth, adolescent marijuana users demonstrated larger cerebellar volumes (Cousijn et al., 2012; Medina, Nagel, & Tapert, 2010). Furthermore, larger cerebellar volumes were associated with poorer executive functioning (Medina, Nagel, & Tapert, 2010). The cerebellum may have a unique sensitivity to the neurotoxic effect of marijuana, which is understandable given its high density of cannabinoid receptors.

Summary of Neuroanatomical Group Effects

In sum, adolescents seem to show a heightened sensitivity to alcohol-induced and marijuana-induced neuroanatomical changes compared to adults. Consistent with adult and animal research, the human adolescent literature suggests that adolescent alcohol and marijuana use is linked to white matter microstructure and grey matter macrostructure abnormalities throughout their brains, particularly in their prefrontal cortex, hippocampus, corpus callosum, and, for marijuana users, the cerebellum. Taken in concert, these group findings suggest aberrant brain structure and function in adolescents with heavy drinking and marijuana-using histories.

Neurocognitive Consequences

In addition to possibly impairing the growth and integrity of certain brain structures, heavy drinking and marijuana use in adolescence has also been linked to poorer neuropsychological and academic performance. Neuropsychological studies of demographically matched, non-drinking teens and adolescents with AUDs or with subclinical, heavy drinking have consistently reported group differences in executive functioning, visuospatial abilities, learning and memory, processing speed and attention, and academic achievement. Further, heavy drinking during adolescence is associated with poorer neurocognitive functioning into adulthood, particularly in visuospatial abilities and attention (Tapert & Schweinsburg, 2005). Protracted marijuana use among adolescents has been linked to group differences across neuropsychological domains in executive functioning, attention, and processing speed, and most notably in learning and memory.

Executive Functioning. Studies on adolescents with AUDs have consistently found deficits in tests of planning and executive functioning (Giancola & Mezzich, 2000; Giancola & Moss, 1998; Giancola, Shoal, & Mezzich, 2001; Moss et al., 1994). Adolescents (age 15-16) with comorbid alcohol and substance use disorders committed commission errors twice as often when responding impulsively to a non-target stimulus (Tarter, Mezzich, Hsieh, & Parks, 1995). Binge drinkers (age 18-20) also showed less advantageous decision making on the Iowa Gambling Task (Goudriaan, Grekin, & Sher, 2007), and female, binge-drinking young adults (age 18-30) were less able to inhibit their response to an alerting stimulus during a vigilance task, suggesting that binge drinking may associate with deficits in inhibitory control (Townshend & Duka, 2005). Deficits in executive functioning and inhibition are particularly concerning given the slow rate of neurocognitive recovery in the frontal lobe from ethanol exposure (Fein et al., 1994). Executive functioning scores also predict age at first drink, with those students using alcohol prior to sixth grade having less well-developed decision making skills (Brown et al., 2009).

Studies on teens with marijuana use histories found worse performance on perseverative responding and flexible thinking compared to controls (Lane, Cherek, Tcheremissine, Steinberg, & Sharon, 2007). Poorer performance on executive functioning among adolescent marijuana users was related to more days of cannabis use in the prior month (Harvey, Sellman, Porter, & Frampton, 2007). In a recent, large-scale, longitudinal investigation, individuals with persistent cannabis dependence showed decline in their intelligence quotient with time, particularly in executive functioning (Meier et al., 2012).

Visuospatial Abilities. Reduced visuospatial performance seems particularly associated with alcohol exposure in adolescence (Garland, Parsons, & Nixon, 1993; Nichols & Martin, 1996; Sher, Martin, Wood, & Rutledge, 1997). Animal research suggests that the acquisition of spatial memory is impaired more in adolescent animals exposed to ethanol than in adult animals with the same quantity of exposure (Markwiese, Acheson, Levin, Wilson, & Swartzwelder, 1998). In general, adolescent rats exposed to alcohol experience heightened vulnerability to spatial impairments later in life (White et al., 2000). Adolescent and young adult heavy drinkers (age 13-24) perform more poorly on spatial operation assessments (Tapert & Brown, 1999; Tapert, Granholm, Leedy, & Brown, 2002) and block design tasks (Sher et al., 1997; Tapert et al., 2004). A study comparing detoxified, alcohol-dependent adolescents (age 15-16) to control teens found that aspects of visuospatial cognition were poor in the AUD adolescents (Brown, Tapert, Granholm, & Delis, 2000). Binge drinking teens and young adults (age 18-35) were found to perform worse than non-binge drinkers on spatial working memory and pattern recognition tasks (Weissenborn & Duka, 2003). Among female adolescents (age 12-18), increased drinking predicted greater reductions in visuospatial performance on a complex figure delay (Squeglia, Spadoni, Infante, Myers, & Tapert, 2009). Worse visuospatial ability continues in the decade following treatment for AUD youth (Hanson, Medina, Padula, Tapert, & Brown, 2011; Tapert & Brown, 1999; Tapert et al., 2002), with frequent drinkers performing more poorly on delayed recall complex figure tasks (Hanson et al., 2011). Similar to the adolescent literature, a study of male adults found deficits in spatial imagination among the alcoholics (Mann, Gunther, Stetter, & Ackermann, 1999). One study of 18- to 35-year-old alcoholics, with an average of six

years of excessive alcohol consumption, found their cognitive functioning to be within normal limits; however, the study did not utilize a control group for comparison and it did find that greater lifetime consumption and shorter periods of abstinence predicted lower scores (Eckardt et al., 1995).

Learning and Memory. Verbal and spatial working memory abilities improve throughout adolescence, with older teens responding more accurately and more quickly (Brown et al., 2009), and alcohol use and marijuana use during this time appear to interfere with those improvements. Animal literature suggests that adolescence is a time of enhanced sensitivity to memory attenuation by ethanol and cannabis, and studies on heavily drinking and marijuana using adolescent humans are largely consistent with these findings. Animal research suggests that adolescent rats show greater impairment than adult rats in acquisition of memory tasks following acute ethanol exposure (Markwiese et al., 1998). Longer lasting and heavier patterns of alcohol and marijuana use among adolescents are linked to disruptions in the hippocampus, a brain structure critical for learning and memory. As discussed previously, adolescent drinking and marijuana use are linked to smaller hippocampal volumes and disturbed hippocampal white matter integrity. Hence, it is not surprising that many studies have found impaired learning and memory function among adolescents with either protracted alcohol or marijuana exposure.

Neuropsychological studies of adolescents with AUDs demonstrate deficits in verbal and non-verbal memory (Brown et al., 2000; Tapert et al., 2001). Poorer verbal learning and recognition discriminability were identified among detoxified 15- to 16-year-old teens with protracted alcohol exposure (Brown et al., 2000), and female young

adult participants (age 18-25) with greater withdrawal history performed worse on verbal working memory tasks (Tapert et al., 2001). Another study among 13- to 18-year-old adolescents presented consistent findings and identified that heavy use of alcohol was related to impaired learning of verbal material and to poorer free recall after a short delay (Hanson et al., 2011). Studies have also found that alcohol dependent youth underutilized semantic learning strategies, which likely led to the poorer retention rates after a short delay (Brown et al., 2000; Hanson et al., 2011). AUD youth (age 15-17) made more perseveration errors when recalling recently learned words on the CVLT, a verbal learning task (Tapert et al., 2004). Consistent with adolescent memory literature, male adult drinkers' auditory verbal learning scores were worse than those of controls after six weeks of abstinence, and detoxified female adults were shown to have deficits in verbal working memory (Mann et al., 1999; Sullivan et al., 2002). Non-verbal memory deficits have also been identified among AUD youth (Brown et al., 2000). A study of detoxified teens (age 15-16) with AUD showed a ten percent deficit of AUD teens' ability to recall nonverbal information that had previously been presented to them: visual reproduction rates were significantly lower in the alcohol dependent teens than in the controls (Brown et al., 2000). Female young adults (ages 18-25) with greater withdrawal history performed worse on non-verbal, working memory tasks (Tapert et al., 2001). Interestingly, more self-reported alcohol withdrawal symptoms predicted poorer performance on learning and memory in a sample of teens with histories of heavy drinking (Mahmood, Jacobus, Bava, Scarlett, & Tapert, 2010).

Similar to studies examining the impact of alcohol on learning and memory, multiple studies have shown similar deficits among cannabis using youth. In one of the

earliest investigations of the impact of marijuana on adolescent cognition, Schwartz and colleagues identified that short-term memory impairment persisted even after six weeks of abstinence in cannabis-dependent adolescents (ages 14-16) compared to matched controls (Schwartz et al., 1989). Studies in the past two decades have consistently identified deficits in immediate and delayed recall among adolescent and young adult (ages 13-24) cannabis users (Gonzalez et al., 2012; Harvey, Sellman, Porter, & Frampton, 2007; Takagi et al., 2011). In a study of adolescent marijuana users ages 16-18, marijuana users demonstrated poorer verbal learning and memory, even after one month of abstinence (Medina et al., 2007). Memory deficits identified among young adult (ages 20-24) cannabis users with recent use showed improvement with abstinence over the course of eight years (Tait, Mackinnon, & Christensen, 2011). Importantly, impaired performance on learning and recall among adolescent cannabis users has been linked to severity, frequency, and age of initiation of cannabis use (Solowij et al., 2011).

Processing Speed and Attention. Neuropsychological studies of adolescents with either alcohol use disorders or protracted marijuana exposure have consistently reported deficits in processing speed and attention. Alcohol dependent first year college undergraduates were found to have more impaired motor speed than alcohol abusing youth of a similar age, and both alcohol abusing and alcohol dependent youth showed worse attention scores than controls (Sher et al., 1997). In a longitudinal study of youth treated for alcohol and substance use disorders during adolescence, participants with continued alcohol use were found to develop deficits in attention in the decade following treatment (Hanson et al., 2011; Tapert & Brown, 1999; Tapert et al., 2002). Male adolescents (age 12-18) were found to have slower completion times on the Digit

Vigilance Test (DVT) while not showing impairments on DVT accuracy (Squeglia et al., 2009). Similar to those found in adolescent literature, decrements among male adult alcoholics were found in completion time of the DVT but not on other tasks for processing speed (i.e., Trails or Digit Symbol). This finding suggests alcohol-induced deficits in sustained attention and not simply in processing speed (Tedstone & Coyle, 2004).

In the marijuana literature, deficits in attention and processing speed have also been consistently identified. Adolescent marijuana users who smoke more than once per week were found to have worse performance on attention tasks (Harvey, Sellman, Porter, & Frampton, 2007). In a longitudinal study examining neuropsychological performance among heavy marijuana using youth compared to non-using youth, between-group differences in attention were identified at baseline and across 3 weeks of monitored abstinence, with attention differences persisting with time (Hanson et al., 2010). Slower processing speed has also been identified among heavy marijuana using youth (ages 16-18), even after one month of monitored abstinence (Medina et al., 2007).

Academic Achievement. Alcohol abusing adolescents have been shown to have significantly lower verbal and full scale IQ scores than controls (Brown et al., 2000; Giancola et al., 2001); lower academic achievement in math, reading, and spelling (Tarter et al., 1995); and lower age standardized scores on achievement tests of reading recognition, total reading, and spelling (Moss et al., 1994). Persistent cannabis dependence has also been associated with both full-scale and verbal IQ decline (Fried, Watkinson, James, & Gray, 2002; Meier et al., 2012).

Summary of Neurocognitive Group Effects

In sum, adolescents seem to show modest but significant deficits in cognition across multiple domains. In the area of executive functioning, adolescent drinkers show worse decision making and inhibitory control, whereas adolescent marijuana users show worse flexible thinking and more perseverative errors. The area of visuospatial functioning appears especially sensitive to heavy alcohol use as adolescent heavy drinkers show worse spatial operations, block design, complex figure copying, and pattern recognition. Both adolescent alcohol and marijuana users show similar deficits in verbal and nonverbal learning and memory, worse attention, slower psychomotor speed, and lower IQ. Taken in concert, these group findings suggest neuropsychological differences across multiple domains in both heavy alcohol and marijuana using adolescents. Potential limitations of this body of literature are examined later in this chapter.

Correlations to Alcohol and Marijuana Use Characteristics

Since much of what has been reviewed to this point discusses group findings in the animal and human literature, it is important to now consider what potential aspects of substance use (i.e., frequency of use, age of onset of use, cumulative exposure, or withdrawal experiences) may contribute most strongly to observed differences. Each substance use characteristic is examined and any association described in the extant literature between that characteristic and a group finding is provided.

Quantity and Frequency of Recent Substance Use. As binge drinking and heavy marijuana use are so prevalent among adolescents, it is important to consider studies' efforts to correlate observed impairments with recent exposure to high quantities of alcohol (i.e., drinks per month) or of marijuana (i.e., days smoking per month). Animal

research indicates that recent exposure to high doses of ethanol results in neurodegeneration of the corticolimbic circuit and more perseverative errors on a spatial learning task (Obernier et al., 2002). Studies have shown that recent consumption of large amounts of alcohol correlates with reduced white matter integrity in the splenium (Tapert et al., 2003). Among adolescents, more frequent consumption of alcohol correlates with poorer visuospatial task performance in complex figure delay for females (Squeglia et al., 2009) and in block design for all participants (Brown et al., 2000). Frequent, heavy use of alcohol was also related to neuropsychological performance over time, with more frequent drinking associated with worse visuospatial memory and verbal short-term memory task performance (Hanson et al., 2011). Similar to findings for alcohol, studies examining marijuana using youth also found correlations between greater frequency of marijuana use and worse performance on tasks of learning and memory (Solowij et al., 2011). Smaller right hippocampal volumes were also correlated with greater self-reported cannabis use (Ashtari et al., 2011) and with more weekly cannabis use (in grams) (Cousijn et al., 2012).

Age of Onset of Substance Use. Age of onset is an important correlate with alcohol-related outcomes as earlier age of drinking onset is associated with (1) greater likelihood of alcohol toxicity induced disruptions in developing brain regions, particularly the frontal lobe (Pishkin, Lovallo, & Bourne, 1985), (2) greater lifetime risk for developing alcohol dependence (Grant, 1998; McGue, Iacono, Legrand, & Elkins, 2001), and (3) elevated risk for myriad social and mental health problems (McGue et al., 2001). It is interesting to note that while earlier age of onset relates to long-term alcohol use disorders and worse outcomes, studies have not found consistent correlations between

age of onset of drinking and neuroanatomical and neurocognitive measures. An initial study found a positive correlation between age of onset and hippocampal volume (De Bellis et al., 2000), but a later study failed to replicate that finding (Nagel et al., 2005). One study found that participants who initiated binge drinking at an earlier age had worse decision making on a gambling task (Goudriaan et al., 2007).

Age of onset of marijuana use, however, appears strongly related to multiple findings. Age of initiation of marijuana use correlates positively with prefrontal cortex volume, with younger age of first use associating with reduced volume (Churchwell, Lopez-Larson, & Yurgelun, 2010). Alterations of cortical thickness are also related to younger age of initiation of cannabis (Lopez-Larson et al., 2011). Earlier age of onset of marijuana use has also been associated with worse visual scanning performance (Ehrenreich et al., 1999); decreases in verbal IQ, verbal recall, and use of semantic categories (Pope et al., 2003); and poorer performance on tasks of sustained attention, impulse control, and executive functioning (Fontes et al., 2011).

Cumulative Lifetime Exposure to the Substance. When examining the effects of a substance on a developing adolescent brain, it is important to consider the impact of cumulative exposure measured as either total lifetime episodes or years of abuse or dependence. Several studies have identified associations between lifetime drinking episodes and structural, functional, and neurocognitive outcomes. Among adolescents, longer duration of heavy drinking was related to decreased white matter integrity in the corpus callosum (Tapert et al., 2003), and those with longer lasting AUDs had smaller hippocampi (De Bellis et al., 2000). Lifetime drinking episodes have also been found to correlate with several neurocognitive outcomes. Among adolescents with AUD, greater

lifetime consumption correlated with increased perseveration errors on a verbal memory task (Tapert et al., 2004) and worse attention functioning (Tapert et al., 2002). Among marijuana using adolescents, severity of use has been linked to worse performance on tasks of learning and recall (Solowij et al., 2011).

Lifetime and Recent Withdrawal from the Substance. The correlations between withdrawal and neuroanatomical and neurocognitive outcomes have been examined most extensively in the adolescent alcohol literature. Acute effects of high dose alcohol exposure continue to be experienced in the day or two following alcohol consumption. In adolescents, these effects include headaches, muscle aches or weakness, feeling weak or faint when standing, heart racing, feeling depressed or irritable, nausea, vomiting, sweating, trouble sleeping, or tremor and shaking (Brown, Tapert, Tate, & Abrantes, 2000; Stewart & Brown, 1995; Tapert & Brown, 1999). Additionally, youth who develop physical addiction to alcohol can experience alcohol related seizures in the first few days of abstinence (Brown & Tapert, 2004). Hangover and withdrawal symptoms are very common following binge drinking and appear to be strongly related to cognitive impairments among teens who frequently binge drink (Tapert & Schweinsburg, 2005). A body of compelling evidence suggests that it is the repeated withdrawal from alcohol that may be responsible for many of the central nervous system effects of chronic alcohol exposure and that repeated withdrawal from alcohol provokes cognitive impairments (White & Swartzwelder, 2004). In animals, repeated withdrawal from alcohol resulted in higher rates of seizures during withdrawal than were observed after continuous exposure over the same duration, suggesting a strong association between repeated withdrawals and withdrawal seizure susceptibility (Becker & Hale, 1993).

Negative affective states - including hyperirritability, depression, and anxiety that commonly occur among those experiencing post alcohol effects and impact neurocognitive performance - seem to maintain alcohol consumption and promote relapse (Koob, 1996; Miller & Harris, 2000; Zywiak, Connors, Maisto, & Westerberg, 1996). The severity of withdrawal-like symptoms is an important indication of neuropsychological impairments in detoxified human adolescents and young adults, which makes the examination of withdrawal's relation to impairments warranted (Brown et al., 2000). Research needs to address whether impairments are likely caused by alcohol itself, by negative affective states provoked by alcohol, or by damage caused by repeated withdrawals.

The research is largely consistent in its findings about the relationship between lifetime withdrawal and neuroanatomical and neurocognitive outcomes. Withdrawal experience does not seem to correlate with reduced hippocampal volumes (De Bellis et al., 2000; Nagel et al., 2005), while it does correlate with reductions in white matter integrity and neuropsychological deficits.

Among youth with AUDs, reduced white matter integrity in the corpus callosum was significantly related to the number of alcohol withdrawal symptoms (Tapert et al., 2003). Among subclinical, binge drinking teens, those with more hangover symptoms showed more compromised white matter in the body and genu of the corpus callosum, frontal lobe projection fibers, and cerebellar tracts (McQueeney et al., 2009). Of note, among adult alcoholics, alcohol-related seizures were associated with smaller white matter volumes in the temporal lobe, suggesting cumulative effects of these withdrawal experiences (Sullivan et al., 1996).

Among adolescents with alcohol use disorders, those with more withdrawal symptoms performed worse on tasks of working memory (Tapert et al., 2001; Tapert & Brown, 1999), visuospatial functioning (Tapert et al., 2001; Tapert & Brown, 1999; Tapert et al., 2002), delayed verbal retention (Brown et al., 2000), and attention (Tapert & Brown, 1999). Lifetime withdrawal predicted attention and visuospatial functioning at year 8 of a longitudinal study (Tapert et al., 2002). Withdrawal scores also predicted slower DVT completion times for males, which suggests that withdrawal and hangover symptoms significantly predict deterioration of attention skills in boys who initiate heavy drinking (Squeglia et al., 2009).

Recent withdrawal is also important to consider as a potential contributor to brain changes and neuropsychological deficits. Associations between neuroanatomical and neurocognitive measures of interest and recent withdrawal (in the three months prior to testing) are consistent with findings for lifetime withdrawal. Among youth with AUDs, those who reported more withdrawal symptoms in the prior three months showed poorer visuospatial abilities, working memory, and attention - even after controlling for gender, history of head injury or learning disability, socioeconomic status (SES), and grades completed (Brown et al., 2000; Tapert & Brown, 1999). Similarly, the number of substance withdrawal symptoms in the three months prior to neuropsychological testing significantly predicted verbal learning, recall, and recognition with greater withdrawal negatively affecting immediate, delayed, and recognition memory performance among youth followed over a ten year period (Hanson et al., 2011).

Both lifetime and recent withdrawal showed relationships with poorer visuospatial functioning, memory, and attention. Lifetime withdrawal symptoms may

reflect distinct, negative effects on brain functioning, with a particular impact on white matter integrity and on memory and visuospatial functioning.

Summary of Associations Between Findings and Substance Use Characteristics

While correlations have been identified for both alcohol and marijuana across multiple measures, it appears that deficits seen in adolescent drinkers associate most strongly and most consistently with frequent and lifetime consumption and with recent and lifetime withdrawal. Deficits seen in marijuana using teens appear most strongly associated with age of onset of use and with the quantity and frequency of recent use.

Reflections on Extant Literature

It is important at this time to reflect on some of the methodological limitations of the aforementioned studies. As these studies were done on adolescents after their initiation of alcohol and/or marijuana use, it is not possible to determine if their substance use led to their neuroanatomical and neurocognitive deficits or if those with lower cognitive functioning (i.e., executive functioning, learning and memory, attention, or processing speed) have a propensity to drink alcohol or smoke marijuana. This issue emphasizes the need for studies to utilize prospective designs to collect data on participants in late childhood or early adolescence and follow them through adolescence. Alternatively, efforts to match groups on aspects of their premorbid functioning (i.e., standardized test scores that predate initiation of use) would also be warranted. Also of note, in both the adult and adolescent literature of neuroanatomical and neuropsychological outcomes, abstinence periods vary widely (from hours to months to years), thereby making direct comparisons challenging and leaving unclear the chronicity of cognitive changes among alcohol and marijuana using youth.

It is also important to consider differences between clinical and subclinical populations, as much of the original research in the field was conducted on teens in clinical settings. Those in treatment both for alcohol and for marijuana manifest more severe substance use disorders and tend to have poorer cognitive, behavioral, and social functioning (Tims et al., 2002). So while more recent efforts to recruit from the community may be more generalizable to the population of adolescent users, these youth may be higher functioning than those in treatment programs. In general, heavy users of alcohol and/or marijuana are also more likely to have other comorbid disorders, making it difficult to disentangle unique effects attributable to the substance distinct from mood, anxiety, or attentional features, unless specific efforts are made by researchers to consider such differences in analyses.

While multiple studies reviewed have reported neuroanatomical and neuropsychological differences in alcohol and marijuana using teens, even after one month of abstinence, another limitation across these studies is the high rate of comorbid substance use. Many alcohol-using populations have moderate to high levels of marijuana use; similarly, many marijuana-using teens have significant exposure to heavy drinking. Therefore, much of the existing literature cannot report confidently if cognitive decrements are primarily related to alcohol, marijuana, or to use of both substances. Until this point, studying users of mainly alcohol or mainly marijuana may have limited sample size in a population that is already difficult to recruit and study; so many users studied also have use of other substances. Additionally, the existing literature predominately compares (1) alcohol users to nonusers or (2) marijuana users to nonusers. Existing

investigations have not compared alcohol users and marijuana users directly to each other.

Importance of Current Investigations

This review inspired three investigations to address specific areas previously unexplored in the extant literature and/or limitations in the existing research.

The first study aimed to make a contribution to the literature on the affective vulnerability processes governing alcohol misuse among adolescents by investigating the rate and pattern of changes in emotional reactivity and distress tolerance during the initial days to weeks of abstinence from alcohol in heavy drinking youth. Adult research has demonstrated improvements in mood (Brown & Schuckit, 1988; Brown et al., 1995a; Brown et al., 1991; Liappas et al., 2002) with sustained abstinence that contribute to decreased emotional reactivity and improved distress tolerance, but this possibility had not yet been explored in adolescent populations. Many researchers have examined relapse phenomena via self-report outside of a relapse risk context, either using retrospective report of previous relapse events or in the context of longitudinal studies that utilize prospective reports (Maisto et al., 2002; Myers & Brown, 1990), yet without proximity to the additive impact of stress. This study introduced an objective stressor to examine affective response, cognitive performance, and distress tolerance in heavy episodic drinking and non-drinking adolescents and to assess potential group differences and determine whether affective reactivity, performance, and distress tolerance improve over a four-week period following cessation of substance use in the heavy drinking youth. The utilization of the PASAT-C task created an opportunity to test a negative reinforcement

model by employing a behavioral measure that provides measurable responses in close proximity to a stressor.

The second study hoped to fill a void in the existing literature by examining neuropsychological functioning during early abstinence in adolescents with histories of heavy episodic drinking as compared to well-matched controls. While many of the existing studies report deficits across several neurocognitive domains, no study had investigated the rate and pattern of neuropsychological recovery in heavy episodic drinking teens throughout the initial days to weeks of abstinence from alcohol (Brown et al., 2008). Further, to the best of our knowledge, no existing study had ensured groups' comparable academic functioning that predates initiation of substance use (e.g., standardized academic test scores), which limits the ability to make generalizations about the impact of alcohol as compared to preexisting differences. By ensuring comparable, premorbid academic functioning and by following adolescents over several weeks of abstinence, this study aimed to elucidate the pattern of neurocognitive recovery during early abstinence from heavy alcohol use.

The final study built on the existing literature in two ways: addressing the limitation of the high rates of comorbid substance use among adolescent samples and comparing directly substance using groups to each other instead of just to non-using youth. Given that many alcohol-using populations have moderate to high levels of marijuana use, and similarly, many marijuana-using teens have significant exposure to heavy drinking, it was important to design a study that (1) strictly defined the criteria of the groups to minimize substance use other than the one of interest, and (2) directly compared alcohol-using youth to marijuana-using youth to those who use both

substances. The study examined the effects of alcohol and marijuana use during adolescence in a sample of substance using teens and demographically-similar non-using teens using a neuropsychological battery after four weeks of monitored abstinence. Using strict criteria to differentiate groups, the study compared neuropsychological performance among (1) alcohol users, (2) marijuana users, (3) those who use both marijuana and alcohol, and (4) non-using controls. To the best of our knowledge, direct comparisons among these groups following four weeks of monitored abstinence have not been previously reported.

Overall, this body of literature aims to elucidate the pattern of recovery of emotional reactivity and neurocognitive functioning during early abstinence from alcohol among heavy adolescent drinkers. Such knowledge may have important implications for improving academic and social functioning and reducing relapse risk among users. Additionally, the body of work aimed to identify the unique contribution of alcohol and marijuana or concomitant use to neuropsychological outcomes following one month of abstinence. Possible decrements in functioning among adolescent substance users may have a significant impact on adolescents' daily experiences in academic, occupational, or personal settings. With knowledge of deficits, educators and parents may be able to improve outcomes for these teens by considering their cognitive abilities during instruction and employing strategies of repetition and active learning to more effectively engage and instruct a population of substance using youth.

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CHAPTER 1. CHANGES IN EMOTIONAL REACTIVITY AND DISTRESS
TOLERANCE AMONG HEAVY DRINKING ADOLESCENTS DURING
SUSTAINED ABSTINENCE

Abstract

Introduction: Negative affect and low distress tolerance have been associated with increased likelihood of alcohol consumption and relapse. This study utilized the Paced Auditory Serial Attention Test (PASAT-C) Computer Version to examine affective reactivity, cognitive performance, and distress tolerance during early abstinence among heavy drinking adolescents.

Method: Participants, ages 16-18 (50% female), were 23 heavy episodic drinking youth (HED) and 23 demographically-matched, non-drinking teens (CON). Both groups were drawn from the same schools and assessed at three time points: HED were first studied within 10 days ($M = 4.26$, $SD = 4.4$) of heavy episodic drinking and then at two 2-week intervals over four subsequent weeks of monitored abstinence. CON were studied at the same 2-week intervals.

Results: Findings indicate that HED responded with greater emotional response to the PASAT-C (i.e., greater increases in frustration and irritability and greater decreases in happiness) at the initial assessment, but their affective responses diminished with sustained abstinence. CON and HED task performance did not differ at the initial assessment or across time. HED showed faster task discontinuation times to the PASAT-C at the first assessment, and both groups reduced task persistence across testings. Among HED, greater lifetime and recent alcohol consumption, alcohol-induced blackouts, and withdrawal symptoms were associated with increases in negative affect with PASAT-C exposure. Earlier age of onset of alcohol use was linked to poorer performance.

Discussion: Heavy episodic drinking adolescents demonstrated heightened emotional reactivity and poorer distress tolerance to a cognitively challenging task during early abstinence. The combination of elevated negative affect and low distress tolerance may place adolescents at a heightened risk for escalations in or return to alcohol involvement.

Introduction

Current theoretical models of abuse and dependence posit that a propensity for stronger negative affect magnifies risk for progression to alcohol dependence (Abrantes et al., 2008; Tate et al., 2005) and that a stressor provokes additive risk for return to use among adults who recently completed treatment (Tate et al., 2005). In adults with substance use disorders, low tolerance for distress is predictive of treatment dropout (Daughters et al., 2005a) and shorter abstinence attempts (Daughters et al., 2005b). This progression from heightened negative affect and low distress tolerance to relapse may be due to expectations of both negative (i.e., reductions in negative mood) and positive (i.e., mood enhancement) reinforcement from substance intake (e.g., Koob and Le Moal, 2008; Wills et al., 1995; Witkiewitz & Marlatt, 2007). Such decisions to return to use or to continue to use are influenced by rational cognitive processes as well as by negative emotions that further direct behavior (Bechara & Martin, 2004). Furthermore, individuals with low distress tolerance may have difficulty persisting in a task when experiencing negative emotions and rely on disengaging from the stressful activity to provide relief (Daughters et al., 2009). The prefrontal cortex, which is involved in decision-making and impulse control, undergoes continued development during adolescence and young adulthood (Giedd, 2004). Therefore, the risk for impulsive decision-making associated with negative affective states and low distress tolerance is elevated in youth (Ernst & Fudge, 2009), especially among teens who misuse alcohol or drugs (Clark et al., 2008).

Among adolescents with histories of alcohol problems, negative affect and low distress tolerance are associated with increased probability of alcohol use (Daughters et al., 2009). These factors are also considered risk factors for relapse among youth with

alcohol use disorders (Ramo et al., 2012), especially during early abstinence when affective disruption is most pronounced (Brown et al., 1989a). Furthermore, protracted heavy drinking may provoke negative affect (Brown et al., 1995b; Liappas et al., 2002) and diminish problem-solving abilities (Brown et al. 2000; Goudriaan et al., 2007), thereby compromising distress tolerance and decision-making skills during this critical time. In the context of ongoing neurodevelopment, the combination of low distress tolerance, elevated negative affect, and a tendency towards negative reinforcement or reward-dependence may place abstaining adolescents at particularly heightened risk for return to problematic drinking.

Adult research has demonstrated that improvements in mood (Brown & Schuckit, 1988; Brown et al., 1995a; Brown et al., 1991; Liappas et al., 2002) after sustained abstinence may contribute to decreased emotional reactivity and improved distress tolerance, but this possibility has not yet been explored in adolescent populations. To date, no study has investigated the rate and pattern of changes in emotional reactivity and distress tolerance during the initial days to weeks of abstinence from alcohol in heavy drinking youth (Brown et al., 2008). Elucidating the features of emotional improvements during early abstinence may have important implications for improvements in academic and social functioning among nonclinical heavy drinking youth, prevention, early intervention tailored to different stages of use and recovery, and reduction of problematic use among youth with alcohol use disorders.

Present Study

Many researchers have examined relapse phenomena via self-report outside of a relapse risk context, either using retrospective report of previous relapse events or in the

context of longitudinal studies that utilize prospective reports (Maisto et al., 2002; Myers & Brown, 1990), yet without proximity to the additive impact of stress. This study introduced an objective stressor to examine affective response, cognitive performance, and distress tolerance in heavy episodic drinking and non-drinking adolescents and to assess potential group differences and determine whether affective reactivity, performance, and distress tolerance improve over a four-week period following cessation of substance use in the heavy drinking youth. This study utilized a modified version of the Paced Auditory Serial Addition Test (PASAT-C; Lejuez et al., 2003) to provide a challenging cognitive task that assessed cognition (i.e., task performance) and generated negative affect in the context of an objective stressor to measure emotional reactivity (i.e., self-reported difference in affect after exposure to the challenging task). During the final stage of the PASAT-C, participants were provided the opportunity to persist in the task in the presence of negative affect or terminate the source of negative affect by quitting the task (i.e., task discontinuation). The PASAT-C created an opportunity to test a negative reinforcement model by employing a behavioral measure that provides measurable responses in close proximity to a stressor.

We expected that both heavy episodic drinkers and nondrinkers would evidence negative affect in response to the task; however, we hypothesized that heavy episodic drinkers with limited abstinence would show more pronounced affective responses that would improve as length of abstinence increased. We also predicted that heavy episodic drinking youth would show impacted cognition (i.e., worse task performance) and impulsive decision-making (i.e., quitting the task sooner), and that task performance as well as behavioral persistence would improve with extended periods of abstinence.

Relations between emotional reactivity, task performance, distress tolerance, and alcohol use history were also explored.

Method

Participants

We were interested in studying youth with recent and frequent heavy episodic drinking who experienced recent withdrawal symptoms and had limited experiences with marijuana and other drugs. Heavy episodic drinking was defined as ≥ 5 drinks in males or ≥ 4 drinks in females within a 2-hour period (NIAAA, 2002). We examined 23 heavy episodic drinking adolescents (HED; ≥ 100 lifetime drinking episodes, > 3 past month heavy episodic drinking episodes, > 1 recent alcohol withdrawal symptom, < 50 lifetime marijuana episodes, and < 15 lifetime experiences with other drugs) and 23 control teens (CON; < 5 drinking episodes, no history of heavy drinking or alcohol withdrawal symptoms, no previous marijuana or other drug use). HED and CON, ages 16-18, were drawn from the same schools and matched on socio-demographic factors including age, gender (50% female), ethnicity (74% Caucasian), grades completed, recent grade point average, socioeconomic status (Hollingshead 1965), and family history of depression and of alcohol dependence in a first degree relative (Table 1.1). In accordance with the University of California, San Diego (UCSD) Institutional Review Board, written informed assent (for adolescents under 18) and consent (parent/legal guardian and teens 18 or older) were obtained prior to participation.

[INSERT TABLE 1.1 HERE]

Recruitment and Eligibility Screening

Participants were recruited from local high schools, colleges, and community settings via mailings and fliers (Brown et al., 2005; Tapert et al., 2003). No information regarding alcohol or drug use criteria was described in the fliers or discussed prior to screening. Interested students responding by phone were independently screened to determine eligibility. All interested teens and their parents underwent a subsequent, detailed phone interview to confirm eligibility. To ensure findings were due to heavy drinking and not impacted by other factors shown to influence cognitive performance, emotional reactivity, or distress tolerance among youth, exclusionary criteria included history of alcohol dependence, non-alcohol related DSM-IV Axis I or II psychiatric disorder; extensive or recent drug use other than alcohol (i.e., not consistent with inclusionary criteria listed above); neurological dysfunction/trauma; serious medical illness; prenatal alcohol/drug exposure; sensory problems; and use of psychoactive medications.

Measures

Structured Clinical Interview and Substance Use History. Adolescent participants and their parents independently completed structured interviews to assess demographics, social and academic functioning (Brown et al., 1989b), family history of alcohol or psychiatric disorders (Family History Assessment Module Screener; Rice et al., 1995), and personal history of Axis I psychiatric disorders (Diagnostic Interview Schedule for Children; DISC; Shaffer et al., 2000). The Customary Drinking and Drug Use Record (CDDR; Brown et al., 1998) and modified Time Line Follow Back (TLFB; Sobell & Sobell, 1992) documented teen substance use history, including lifetime and recent

tobacco, alcohol, and drug use (12 types), withdrawal symptoms, DSM-IV abuse and dependence criteria, and other alcohol-related social and physiological problems.

Baseline Affect. To assess baseline mood state prior to PASAT-C testing, all participants completed the 20-item Positive and Negative Affect Scale (PANAS; Watson et al., 1988), a reliable measure of affective states with each rated from 1 (low) to 5 (high).

Paced Auditory Serial Addition Test - Computerized Version (PASAT-C).

Participants completed the PASAT-C task (Lejuez et al., 2003) on three occasions at two 2-week intervals following cessation of alcohol use. During PASAT-C administration, numbers were presented on a computer screen, and participants were asked to add the number that was most recently presented with the number that appeared prior to it. The PASAT-C task presented three stages with varying latency between number presentation to (a) measure performance on a challenging neuropsychological test that involves working memory, attention, and arithmetic capabilities, and (b) introduce a cognitive stressor to assess negative emotional reactivity and distress tolerance. Prior to initiating the task and at the completion of the second stage, subjects were asked to rate their negative (anxiety, frustration, and irritability) and positive (happiness) emotional states on a visual analog scale ranging from 0 (none) to 100 (extreme) (Lejuez et al., 2003). Differences in those ratings were used to assess emotional reactivity.

During the initial ‘performance’ stage, numbers were presented in 3-second intervals to assess a participant’s ability to complete the task. During the second ‘negative affect induction’ stage, the latency period was decreased to 2 seconds to decrease participants’ success rates and provoke negative affect. Finally, during the third ‘distress

tolerance' stage, the latency period was further decreased to a 1-second interval and participants were offered the opportunity to persist with the task in the presence of negative affect or terminate the source of negative affect by discontinuing the task. In line with published work (e.g., Brown et al., 2002), *performance* was measured by the number of correct responses on the first stage, *emotional reactivity* was measured as the difference between pre-test affect and affect following the second stage, and *distress tolerance* was measured as time to discontinue the third stage as it indicated how long (in seconds) they were willing to persist in the presence of a cognitive stressor.

Assessment Timing and Abstinence Monitoring

HED and CON were assessed at three time points. HED were first studied within ten days of heavy episodic drinking ($M = 4.26$ days since last heavy episodic drinking episode, $SD = 4.43$) and then at two 2-week intervals over four subsequent weeks of monitored abstinence (2nd testing session: $M = 18.77$ days since last heavy episodic drinking episode, $SD = 4.96$; 3rd testing session: $M = 32.12$ days since last heavy episodic drinking episode, $SD = 4.55$). CON were studied at the same 2-week intervals.

Abstinence was monitored thrice weekly via ETG/ETS alcohol metabolite (Wurst et al. 2006) and 10-panel drug urine testing, randomly determined breath samples (Intoximeter, St. Louis, MO), and self-report. Standardized sample collection procedures minimized the likelihood of participant tampering, and samples were analyzed by Redwood Toxicology (Santa Rosa, CA) using cloned enzyme donor immunoassay (CEDIA) kits. Abstinence was also facilitated using a standardized Motivational Interviewing protocol (Miller and Rollnick, 1991) demonstrated to encourage the maintenance of abstinence for adolescents in prior research (Brown et al., 2005; Schweinsburg et al., 2005).

Participants were compensated for their time and abstention throughout the four weeks to maintain commitment and reward sustained abstinence, with a bonus for study completion to encourage continuation. Four HED drank alcohol between sessions 1 and 2 (detected via toxicology screen and confirmed with self-report) and data collected after their alcohol use were excluded from the present analyses. To minimize the impact of study participation on subjects' daily lives, research staff worked closely with enrolled youth to select a one month period that did not conflict with birthdays, school events, or breaks. As this was not a treatment seeking sample, eligibility was not contingent upon a teen's expressed desire to quit drinking. Instead, participants were motivated by financial compensation and the opportunity to contribute to research.

Statistical Analytic Plan

Comparison of socio-demographic characteristics between groups was conducted on distributions, means, and standard deviations using chi-square tests for categorical variables and t-tests for continuous variables.

Primary analyses were carried out with linear mixed model analyses of repeated measures, with participants entered as a random term, time point (as a category), and an interaction between time point and group. This approach is used in similar situations as a repeated measures ANCOVA, except that the linear mixed model allows us to retain data for the four participants who dropped the study and had only one valid data point. The mixed model analysis provided a convenient way to model error structures among repeated dependent variables; we modeled the structure of the means using fixed effects, specified a covariance structure for both between and within subjects, and fit the means model accounting for specified covariates (Gelman & Hill, 2007; Rabe-Hesketh &

Skrondal, 2005; Singer & Willett, 2003). Interactions were evaluated with likelihood ratio (LR) tests for the comparison of nested models. In this study, models with and without the interaction terms were evaluated with the LR tests whose sampling distribution approximates a chi-square distribution with degrees of freedom equal to the difference in degrees of freedom between the two models (Frees, 2004). To be consistent with prior research (e.g., Brown et al., 2002) and to limit the impact of skill or affective responding in the analyses, we took a conservative approach and covaried for baseline mood state (PANAS) and task performance in the linear mixed models examining affective reactivity and distress tolerance. Because performance may be influenced by pre-task mood states, we included pre-task mood in analysis of the performance stage.

Secondary analyses examined the associations between alcohol use characteristics and affective reactivity, task performance, and time (in seconds) to discontinue the task in the distress tolerance stage. Due to non-normal distribution of alcohol use characteristics and task discontinuation times, Spearman's correlations were calculated to describe these relationships.

Results

Affective response and changes with abstinence

Initial analyses examined baseline mood states of HED and CON and although positive and negative mood varied across individuals (positive: 1.1 - 4.6; negative: 1.0 - 2.3), groups did not differ in pre-test mood states at any of the three testing time points (p 's > .16). As designed, the negative affect induction stage of the PASAT-C task provoked negative affect beyond baseline mood in both CON and HED with feelings of frustration, irritability, and anxiety increasing and the positive feeling of happiness

decreasing from the onset of the performance stage to our assessment time point following the negative affect induction stage (p 's < .003).

Linear mixed models, controlling for self-reported pre-task mood states (PANAS) and task performance (Stage 1), tested the primary hypothesis that adolescent, heavy episodic drinkers would have more pronounced affective response to the stressor at the initial assessment but that their affective response would reduce with sustained abstinence. LRTs were used to evaluate whether inclusion of the interaction term improved overall model fit; the LR (approximates chi square) was statistically significant for frustration ($\chi^2(2, N = 46) = 6.73, p = .035$), irritability ($\chi^2(2, N = 46) = 9.84, p = .007$), and happiness ($\chi^2(2, N = 46) = 5.99, p = .050$), as described in more detail below. However, differences in anxiety between HED and CON at time point one and across time did not reach statistical significance (p 's > .055). Raw data for all four affective measure difference scores are shown in Table 1.2; marginal means estimates are used for the three statistically significant affective measures in Figure 1.1.

[INSERT TABLE 1.2 HERE]

Frustration. Both groups evidenced an increase in frustration when completing the PASAT-C. HED showed a 81% greater increase in frustration from pre- to post-testing than CON at time point one, when controlling for task performance and baseline negative mood ($b(SE) = 24.54 (7.48), z = 3.28, p = .001, 95\% CI: [9.88, 39.21]$). HED reduced the intensity of their frustration response from the task across testing with a trend at time point two ($b(SE) = -14.22 (7.74), z = -1.84, p = .066, 95\% CI: [-29.40, 0.94]$) and a statistically significant interaction at time point three ($b(SE) = -19.95 (7.81), z = -2.56, p = .011, 95\% CI: [-35.25, -4.65]$). While frustration reactivity of CON also decreased with

time, CON did not show a statistically significant change over testing session in their frustration response to the task at time point two ($b(SE) = -8.32 (6.04)$, $z = -1.38$, $p = .169$, 95% CI: [-20.18, 3.54]) or at time point three ($b(SE) = -11.60 (6.53)$, $z = -1.78$, $p = .076$, 95% CI: [-24.39, 1.19]). Using the marginal means estimates from the model, HED showed a 61% reduction in the intensity of their frustration response to the task from the initial to the final testing, while CON showed a 40% reduction in their emotional response (Figure 1.1).

[INSERT FIGURE 1.1 HERE]

Irritability. Similar group and group x time point effects were evident for intensity of and change in irritability across testing sessions, while controlling for task performance and baseline negative mood. Both groups showed an increase in irritability following the PASAT-C task; however, HED showed a 86% greater increase in irritability in response to the task compared to CON at time point one ($b(SE) = 13.95 (6.28)$, $z = 2.22$, $p = .026$, 95% CI: [1.63, 26.27]). HED reduced the intensity of their irritability reactions with a trend at the second time point ($b(SE) = -12.00 (6.40)$, $z = -1.88$, $p = .061$, 95% CI: [-24.53, 0.54]) and a statistically significant interaction at the third testing session ($b(SE) = -20.64 (6.45)$, $z = -3.20$, $p = .001$, 95% CI: [-33.30, -8.00]). CON did not show a statistically significant change over testing session in their irritability to the task at time point two ($b(SE) = -0.46 (5.02)$, $z = -0.09$, $p = .927$, 95% CI: [-10.29, 9.37]) or at time point three ($b(SE) = -0.88 (5.49)$, $z = -0.16$, $p = .873$, 95% CI: [-11.65, 9.89]). Abstaining HED showed a 71% reduction in irritability in response to the PASAT-C from the initial to the final testing session, whereas CON showed a 5% reduction in their irritability across testing sessions (Figure 1.1).

Happiness. Both groups demonstrated a decrease in happiness following PASAT-C exposure when controlling for task performance and baseline positive mood; however, a main effect for group was identified with HED evidencing 320% greater reductions in the change in happiness scores at time point one ($b(SE) = -24.65 (5.95)$, $z = -4.14$, $p < .001$, 95% CI: [-36.31, -12.98]). HED continued to display a more pronounced decrease in happiness at each testing, but the intensity of their affective response diminished at time point two ($b(SE) = 10.36 (6.75)$, $z = 1.54$, $p = .125$, 95% CI: [-2.86, 23.59]) and at time point three ($b(SE) = 16.78 (6.82)$, $z = 2.46$, $p = .014$, 95% CI: [3.42, 30.14]). CON did not significantly change their happiness ratings over subsequent testing sessions at time point two ($b(SE) = -0.49 (5.21)$, $z = -0.09$, $p = .926$, 95% CI: [-10.69, 9.72]) or at time point three ($b(SE) = -2.66 (5.53)$, $z = 0.48$, $p = .630$, 95% CI: [-8.17, 13.49]). HED showed a 60% reduction in the intensity of their response to the task from the initial to the final testing, while CON showed a 35% reduction in their emotional response across testings (Figure 1.1).

PASAT-C performance

Linear mixed models controlled for baseline mood when examining whether HED would obtain lower performance scores than CON on the PASAT-C (Stage 1) and demonstrate greater improvement in task performance over testing session. CON and HED showed a trend for an initial group difference ($p = .066$) with HED performing worse on the task. Contrary to the hypothesis, no group x time point interactions were statistically significant (p 's $> .327$; Table 1.3).

[INSERT TABLE 1.3 HERE]

PASAT-C time to task discontinuation

To examine tolerance for distress, linear mixed models controlling for performance and baseline mood assessed PASAT-C distress tolerance stage discontinuation times to determine initial distress tolerance and possible increases in task persistence with extended abstinence of HED. All participants' Stage 3 duration times were included in the analyses. Five CON participants persisted for the full 600 seconds of Stage 3 at all three time points; two HED completed the full task at time point one and one HED completed the full task at time points two and three. Consistent with the hypothesis that HED would quit faster, HED showed shorter time to quit than CON on the distress tolerance stage at the first testing ($b(SE) = -108.28 (60.74)$, $z = -2.11$, $p = .035$). Of note, no significant group x time point interaction was observed for HED and CON Stage 3 discontinuation times at the second or third testing sessions (p 's $> .101$). At the initial time point, when participants first experienced the high level of difficulty of the distress tolerance stage, CON persisted 53% longer than HED. Both adolescent groups displayed a pattern of quitting the task more quickly across testing sessions ($p < .01$; Table 1.3). No participants quit the task prior to Stage 3.

Alcohol characteristics and affect, performance, and task discontinuation times among drinking youth

The relationship of HED youth family history of alcohol dependence and alcohol use characteristics to PASAT-C affective responses, performance, and persistence were examined using Spearman's correlations. While family history of alcohol dependence did not differ between groups and was not related to the dependent measures ($-.06 < rho$'s $< .12$, p 's $> .329$), alcohol use characteristics were related to PASAT-C response measures

during early abstinence (Initial Testing) and with sustained abstinence (Final Testing). Given our sample of 23 HED, these correlations should be considered preliminary.

Initial Testing. At initial measurement, both the number of lifetime drinking episodes and number of heavy episodic drinking episodes were positively correlated with level of induction of negative affect on the PASAT-C task. For example, drinkers with greater lifetime exposure to alcohol showed larger increases in frustration ($\rho = .55, p = .006$) and reductions in happiness ($\rho = -.56, p = .006$) following exposure to the task. More frequent recent drinking (i.e., 45 days prior to starting study) was positively correlated with induction of anxiety in the task ($\rho = .55, p = .006$). Greater frequency of blackouts from alcohol in the three months prior to starting the study was correlated with larger increases in frustration ($\rho = .47, p = .030$) and irritability during the task ($\rho = .46, p = .038$). At initial testing, PASAT-C measures of affect, performance, and task discontinuation times were not associated with days since use, age of onset, recent or lifetime withdrawal symptoms, or the highest quantity of alcohol consumed among HED.

Final Testing. At the third testing session, when the average length of abstinence was just over one month, HED with greater lifetime alcohol exposure still showed greater increases in frustration to the task ($\rho = .54, p = .016$). Significant correlations also emerged for age of onset of regular alcohol use and recent withdrawals from alcohol in the week prior to starting the study. HED with earlier ages of onset of drinking showed worse task performance ($\rho = .55, p = .021$), and HED with more recent alcohol withdrawal symptoms exhibited greater increases in frustration to the task at the third testing time point ($\rho = .63, p = .007$).

Discussion

Although preliminary, the present findings suggest that compared to nondrinking peers, adolescents with recent heavy episodic drinking (1) display greater negative affect responses and poorer distress tolerance in cognitively challenging situations during early abstinence and (2) become less emotionally reactive as abstinence continues. Recent heavy episodic drinking of these adolescents was associated with greater emotional reactivity to an externally produced stressful situation. Specifically, heavy episodic drinkers' affective responses to a cognitive stressor, with respect to frustration, irritability, and happiness, were initially more pronounced than those of peers with limited alcohol exposure, but the emotional reactivity of heavy drinkers diminished with continued abstinence. These findings suggest that heavy episodic drinking adolescents experience more emotional reactivity during early abstinence and appear to become less reactive within 4-6 weeks of abstinence. These findings could reflect a return to functioning that existed prior to onset of heavy drinking, an experience of short-term positive responses to encouraging life events (e.g., end of transient withdrawal symptoms or positive reinforcement for behavior change), or other factors related to recent abstinence.

Heavy episodic drinking teens with greater lifetime and recent alcohol consumption as well as a greater frequency of recent alcohol-induced blackouts and withdrawal symptoms showed greater increases in frustration, irritability, and anxiety from the task compared to youth without drinking experiences. Even when the groups reacted with similar levels of frustration following one month of abstinence, teens with greater lifetime exposure to alcohol and with more recent withdrawal symptoms still showed a greater induction of frustration to the task. Thus, among adolescents, recent

heavy drinking may be related to negative affect, and greater lifetime severity of alcohol involvement and withdrawal symptoms may relate to persistence of negative emotional states.

Contrary to our hypothesis, youth with and without histories of heavy episodic drinking did not differ significantly in their performance on the PASAT-C task at the initial session or across testing sessions, although drinkers consistently performed slightly worse than non-drinkers across time points. While the groups did not differ statistically in performance, teens who initiated regular alcohol use at an earlier age continued to show worse task performance even with sustained abstinence.

Lower distress tolerance was most evident during early abstinence for youth with a heavy drinking history. In the first week of abstinence, heavy episodic drinking adolescents quit the distress tolerance stage of the task an average of approximately 90 seconds earlier than nondrinking peers. The drinkers' behavioral response of quitting the task more quickly is consistent with prior adult and adolescent research showing that duration of recent abstinence is related to the ability to persist when facing a psychological stressor (Daughters et al., 2005b). These results suggest that youth with less than two weeks of abstinence may experience stronger emotional responses in challenging situations and that youth with low distress tolerance may have difficulty persisting in productive behavior when experiencing negative emotions and may rely on negative reinforcement (i.e., disengaging from stressful activities by quitting the task) to provide relief (Daughters et al., 2009). It is possible that heavy episodic drinking adolescents may focus on immediate gains (e.g., relief from negative affect by getting drunk) and attend less to the potential negative consequences of their behavior, which

may be an important vulnerability factor in progression to or persistence of alcohol involvement (Ramo et al., 2012).

Interestingly, at the initial testing session, heavy episodic drinking teens with recent alcohol exposure showed poorer tolerance of distress, but they showed a different pattern than predicted at subsequent assessments. Contrary to the hypothesis, both groups of participants, regardless of drinking history, quit the task sooner with subsequent administration, and in fact may be learning that quitting earlier is more adaptive in this stage. The difficulty level of the distress tolerance stage, with one second inter-stimulus intervals, is very high and with repeated exposure youth may learn that this stage is unlikely to result in significant point increases. Thus, while the initial administration of the PASAT-C may indicate poorer distress tolerance among recent heavy episodic drinkers, repeated administration of the PASAT-C may reflect youth expectations of the quit option, rather than distress tolerance alone.

This study is the first to examine changes in emotional reactivity and distress tolerance in relation to length of abstinence among heavy episodic drinking youth. The groups were comparable on demographic and family history of alcoholism dimensions, and the heavy drinking teens were studied prior to onset of alcohol dependence. The study also considered both affective and behavioral responses to a stressful situation. Nevertheless, these findings should be considered tentative as the sample size was modest, limiting generalizability and resulting in lower power to examine gender or ethnic differences. Replication of these findings with a larger sample would substantiate and strengthen these preliminary findings. The PASAT-C was designed to measure performance, change in affect, and distress tolerance in specific stages of the task (Lejuez

et al., 2003), but participants may not have responded to the task as designed over repeated testings. There is a need for further research to distinguish the contributing factors in adolescent responses to the PASAT-C over repeated administration. Future studies might also consider including youth who continue to engage in heavy drinking (i.e., no abstinence protocol) but follow the same testing schedule, allowing a more direct test of the effects of abstinence on youth functioning and enabling a better understanding of the practice effects with this task.

The existing literature examining substance use and dependence suggests that intolerance of emotional and somatic sensations is a key mechanism driving continued use (Brown et al., 2002). While the effects are modest, this study is the first to illustrate heightened emotional reactivity and poorer distress tolerance to a cognitively challenging task in heavy drinking adolescents in early periods of abstinence. It is possible that the combination of elevated negative affect and low distress tolerance during early abstinence may be a mechanism whereby heavy episodic drinking heightens risk for progression to an alcohol use disorder or results in a return to use following periods of abstinence. This information may also be relevant for teachers, parents, and counselors to understand that youth with recent heavy alcohol exposure may show heightened emotional reactivity and poorer tolerance of distress. Students and young adults frequently encounter academically challenging or socially demanding situations, and those with recent heavy drinking may have more difficulty due to their reduced ability to manage their emotional reactivity and tolerate negative affect, which can also lead to disrupted interpersonal relations or heightened risk for impulsive decision making (Clark et al., 2008; Ernst & Fudge, 2009). Reductions in emotional reactivity with abstinence

may contribute to improvements in academic and social functioning among nonclinical, heavy drinking youth.

The capacity to withstand aversive internal states, including negative emotions, is integral to daily functioning. Importantly, the emotional reactivity of heavy episodic drinking adolescents appears to reduce with continued abstinence. Additional research is needed to understand factors underlying and facilitating this improvement and whether interventions can further improve emotional reactivity and distress tolerance among youth during early periods of abstinence. It may also be helpful for youth to know that it is typical to experience heightened emotional reactivity and poorer distress tolerance during early periods of abstinence. This knowledge may encourage maintenance of abstinence or a lower compulsion to consume alcohol if they feel confident that their emotional lability will reduce relatively quickly.

Chapter 1 Acknowledgements

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Table 1.1. Demographic and substance use characteristics of participants (16-18 years): non-drinking control youth (CON) and heavy episodic drinking adolescents (HED).

	CON	HED	<i>p</i> -value
	<i>n</i> = 23	<i>n</i> = 23	
	<i>M</i> (<i>SE</i>)	<i>M</i> (<i>SE</i>)	
Age	17.7 (0.1)	17.7 (0.2)	0.184
Gender	11F, 12M	12F, 11M	0.616
Race (% Caucasian)	70%	78%	0.548
Grades Completed	11.0 (0.1)	11.1 (0.2)	0.236
Recent Grade Point Average	3.7 (0.1)	3.4 (0.1)	0.242
Hollingshead Code (SES)	20.9 (1.6)	23.2 (2.1)	0.172
Family History Alcohol Dependence	34%	48%	0.074
Family History Depression	52%	52%	1.000
Lifetime Alcohol Use ^a	0.7 (0.3)	166.6 (7.1)	< .001
Heavy Episodic Drinking Episodes in 3 Months Prior to Starting Study	0.0 (0.0)	16.1 (1.0)	< .001
Lifetime Marijuana Use ^a	0.0 (0.0)	31.4 (4.4)	< .001
Lifetime Other Substance Use ^a	0.0 (0.0)	5.1 (1.7)	< .001

^a The term "lifetime use" refers to the number of days each substance was used in the participant's lifetime

Table 1.2. PASAT-C raw affective change scores for non-drinking controls (CON) and heavy episodic drinking adolescents (HED): Post-Stage 2 minus Pre-Stage 1.

Note: All data reported as M (SE). Mean length of abstinence for HED = 4.26, 18.77, and 32.12 days at Time 1, 2, and 3, respectively.

	Frustration Difference		Irritability Difference		Happiness Difference		Anxiety Difference	
	CON	HED	CON	HED	CON	HED	CON	HED
Time 1	31.7 (5.7)	54.9 (6.3)	17.6 (4.5)	32.2 (5.9)	-10.7 (3.9)	-30.4 (5.5)	13.7 (4.7)	24.2 (4.4)
Time 2	18.8 (4.3)	30.0 (6.2)	14.1 (3.6)	16.8 (5.7)	-8.4 (3.1)	-18.7 (5.5)	5.3 (2.5)	9.7 (3.4)
Time 3	15.3 (4.2)	23.5 (5.7)	12.7 (3.7)	11.0 (3.1)	-6.0 (2.5)	-11.1 (4.5)	3.1 (2.8)	10.7 (4.5)

Table 1.3. Marginal means for PASAT-C performance and for distress tolerance stage discontinuation times (in seconds) of non-drinking controls (CON) and heavy episodic drinking youth (HED).

Note: All data reported as Marginal Means (SE). Task performance and task discontinuation time analyses controlled for performance and pre-task negative mood. Mean length of abstinence for HED = 4.26, 18.77, and 32.12 days at Time 1, 2, and 3, respectively.

	Performance (Stage 1)			Distress Tolerance Discontinuation Times (Stage 3)		
	CON	HED	<i>p</i> -value	CON	HED	<i>p</i> -value
Time 1	24.8 (2.5)	19.5 (2.3)	0.066	263.5 (44.4)	172.5 (44.4)	0.035
Time 2	37.9 (2.6)	33.3 (2.7)	0.327	182.9 (43.5)	188.1 (47.9)	0.469
Time 3	42.8 (2.5)	39.8 (2.6)	0.788	189.4 (41.6)	108.9 (45.8)	0.101

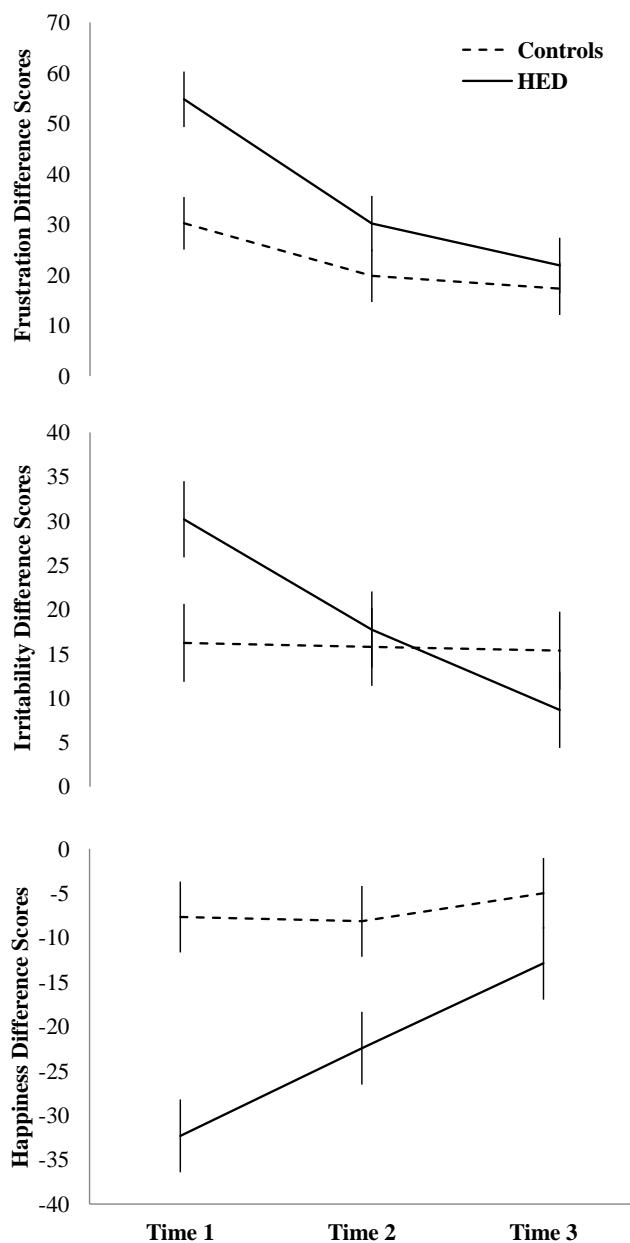


Figure 1.1. PASAT-C frustration, irritability, and happiness marginal mean difference scores (i.e., affect following second stage minus pre-test affect) from linear mixed effects models with standard error bars, controlling for performance and baseline mood, by heavy episodic drinkers (HED; N=23 at Time 1 and N=19 at Times 2 and 3) and controls (N=23 at all time points) at three assessments over four weeks of monitored abstinence. Mean length of abstinence for HED = 4.26, 18.77, and 32.12 days at Time 1, 2, and 3, respectively.

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CHAPTER 2. ADOLESCENT HEAVY EPISODIC DRINKING: NEUROCOGNITIVE
FUNCTIONING DURING EARLY ABSTINENCE

Abstract

Introduction: The present study investigated the rate and pattern of neuropsychological recovery in heavy episodic drinking teens during the initial days to weeks of abstinence from alcohol.

Method: Adolescents (ages 16-18) with histories of heavy episodic drinking (HED; $N=39$) and socio-demographically similar control teens (CON; $N=26$) were recruited from San Diego area schools. HED and CON were comparable on 5th grade standardized math and language arts test performance to ensure similar functioning prior to onset of substance use. Participants were administered three neuropsychological test batteries with 2-week intervals during a 4-week monitored abstinence period.

Results: HED teens performed worse overall than CON on tests of prospective memory ($p=.005$), cognitive switching ($p=.039$), inhibition task accuracy ($p=.001$), verbal memory ($p's<.045$), visuospatial construction ($p's<.043$), and language and achievement ($p's<.008$). The statistically significant group x time interaction for block design demonstrated normalization within the four weeks of abstinence for the HED ($p=.009$).

Discussion: This study identified cognitive performance deficits associated with heavy episodic drinking in adolescence during early abstinence and with sustained 4-week abstention. These findings suggest alcohol-related influences on several underlying brain systems that may predate the onset of alcohol abuse or dependence or take longer than four weeks to recover.

Introduction

Alcohol is the most commonly used intoxicant during adolescence. By their senior year of high school, 71% of students have consumed alcohol and 54% have been drunk (Johnston, O'Malley, Bachman, & Schulenberg, 2012). According to national data, 41% of high school seniors drank alcohol in the past month, and 23% of seniors reported heavy episodic drinking (≥ 5 drinks in males, ≥ 4 drinks in females within a 2-hour period) in the prior two weeks (Johnston et al., 2012). Compared to adults, adolescents drink alcohol less frequently but in higher doses, and such heavy episodic drinking among adolescents may be more harmful than consuming alcohol in moderation (1 or 2 drinks) every day (Tapert & Schweinsburg, 2005). Consuming greater quantities of alcohol in one sitting is concerning because heavy alcohol consumption associates with high risk, life-threatening outcomes including motor vehicle accidents, alcohol poisoning, illegal activities, school failure, and risky sexual behavior (Hingson, Heeren, Winter, & Wechsler, 2005). A growing number of animal and human studies also suggests that heavy episodic drinking appears to alter developmental trajectories and to interfere with normal neuroanatomical and neurocognitive development (Brown et al., 2008; Brown & Tapert, 2004; Crews, Braun, Hoplight, Switzer, & Knapp, 2000; Hommer et al., 1996; Nixon, Tivis, Ceballos, Varner, & Rohrbaugh, 2002; Spear & Varlinskaya, 2005).

Animal research suggests that adolescents are more vulnerable than adults to ethanol-induced decrements in functioning, especially following chronic, intermittent exposure to high levels of ethanol, which is considered the analog of 'heavy episodic drinking' in humans (White et al., 2000). Adolescent rats show more susceptibility to hippocampal injury (Nixon et al., 2002; Slawecki, Betancourt, Cole, & Ehlers, 2001;

Ward et al., 2009) and to frontal-anterior cortical damage (Crews et al., 2000), and adolescent rats exposed to ethanol continue to show structural and functional abnormalities into adulthood (Slawecki, 2002; Slawecki & Roth, 2004; White et al., 2000). In particular, adolescent rats seem to experience (1) lower initial brain sensitivity to ethanol (Roehrs, Beare, Zorick, & Roth, 1994; Silveri & Spear, 1998), (2) abnormal development of sensitivity to alcohol-induced motor impairments (White et al., 2002), and (3) slower onset and magnitude of sedation following alcohol exposure (Little, Kuhn, Wilson, & Swartzwelder, 1996; Silveri & Spear, 1998; Swartzwelder, Richardson, Markwiese-Foerch, Wilson, & Little, 1998). That adolescents have reduced sensitivity to ethanol-induced motor impairing and sedative effects may theoretically allow youth to drink greater quantities of alcohol and attain higher blood alcohol concentrations with less sedation than would be expected in adulthood. The concurrence of reduced susceptibility to the sedating and motor impairing effects of alcohol with an enhanced vulnerability to alcohol-induced neuroanatomical and neurocognitive deficits presents a concerning effect during adolescence.

The extant human literature is consistent with animal research and suggests that heavy and recent alcohol exposure in adolescence is associated with poorer neuropsychological outcomes relative to those of non-drinkers. Studies of adolescents with alcohol use disorders (AUD) and of nonclinical populations of heavy episodic drinkers (HED) have consistently found deficits on executive function measures of planning, decision-making, verbal working memory, and inhibition (Giancola & Mezzich, 2000; Giancola & Moss, 1998; Giancola, Shoal, & Mezzich, 2001; Goudriaan, Grekin, & Sher, 2007; Moss, Kirisci, Gordon, & Tarter, 1994). Adolescents with AUDs

also demonstrate deficits in verbal learning and recognition discriminability (Brown, Tapert, Granholm, & Delis, 2000; Hanson, Medina, Padula, Tapert, & Brown, 2011; Tapert et al., 2001), and they have shown mild decrements in visuospatial memory (Brown et al., 2000) such as delayed recall of a complex figure (Squeglia, Spadoni, Infante, Myers, & Tapert, 2009).

Adolescent and young adult heavy drinkers commonly show decrements in aspects of visuospatial function including block constructions, spatial working memory, and pattern recognition (e.g., Brown et al., 2000; Sher, Martin, Wood, & Rutledge, 1997; Tapert & Brown, 1999; Tapert et al., 2002; Tapert et al., 2004; Weissenborn & Duka, 2003). Studies also suggest higher error rates among AUD youth (Tarter, Mezzich, Hsieh, & Parks, 1995; Tapert et al., 2004) and deficits in processing speed, motor speed, and attention (Medina et al., 2007; Sher et al., 1997). Finally, alcohol abusing adolescents have been shown to have significantly lower verbal and full scale IQ scores (Brown et al., 2000; Giancola et al., 2001) and lower academic achievement in math, reading, and spelling (Moss et al., 1994; Tarter et al., 1995) than their nondrinking peers.

While many of these studies report deficits across several neurocognitive domains, to date no study has investigated the rate and pattern of neuropsychological recovery in heavy episodic drinking teens throughout the initial days to weeks of abstinence from alcohol (Brown et al., 2008). Further, to the best of our knowledge, no existing study has ensured groups' comparable academic functioning that predates initiation of substance use (e.g., standardized academic test scores), which limits the ability to make generalizations about the impact of alcohol as compared to preexisting differences. By ensuring comparable, premorbid academic functioning and by following

adolescents over several weeks of abstinence, this study aimed to elucidate the pattern of neurocognitive recovery during early abstinence from heavy alcohol use. Such knowledge may have important implications for clinical intervention and for strategies to improve academic functioning and reduce relapse risk.

The present study examined cognitive performance of youth engaged in heavy episodic drinking during adolescence, a critical time of brain development. Drinking and nondrinking participants completed a neuropsychological battery three times at 2-week intervals over four weeks of monitored abstinence. We aimed to (1) identify neuropsychological deficits associated with recent heavy episodic drinking during adolescence, and (2) determine whether alcohol-induced neurocognitive deficits improve with abstinence. Based on prior research, we hypothesized that (1) recent heavy episodic drinking youth would display neuropsychological deficits during early abstinence relative to similar nondrinking peers in the domains of executive functioning, learning and memory, visuospatial construction, working memory, attention, processing speed, and learning and achievement, and (2) abstaining heavy episodic drinkers would demonstrate improvements in these cognitive domains over a four week abstinence period when compared to nondrinking teens studied at comparable timepoints. In other words, we expected that prolonged abstinence would be linked to normalization of functions previously shown to be affected by alcohol.

Method

Participants

In accordance with the University of California, San Diego (UCSD) Human Research Protections Program and high school district policies, written informed assent

(adolescent participant) and consent (parent/legal guardian) were obtained prior to participation. The current study examined 65 adolescents (ages 16-18) who were classified into two groups: heavy episodic drinkers ($N=39$) and nondrinking controls ($N=26$). Classification criteria for the heavy episodic drinkers (HED) included ≥ 50 lifetime drinking episodes, ≥ 1 past month heavy episodic drinking episodes, ≥ 1 alcohol withdrawal symptom in the prior two weeks, and limited experience with marijuana and other drugs. Nondrinking controls (CON) had fewer than 10 lifetime experiences with alcohol; had no history of heavy episodic drinking, alcohol withdrawal symptoms, or drug use; and did not meet criteria for heavy drinking status. HED and CON were drawn from the same schools and similar on socio-demographics including age, gender (46% female), ethnic composition (75% Caucasian), grades completed, socioeconomic status (Hollingshead, 1965), and recent grade point average. 5th grade standardized tests (i.e., California Standards Test) of math and language arts were also comparable between HED and CON (Table 2.1).

Participants were recruited from high schools and colleges throughout the San Diego area via mailings and flier distribution (Tapert et al., 2004). The fliers advertised an “Adolescent Development Project,” and no information regarding substance use criteria was described in the flier or discussed prior to screening. Participants responding by phone were informed of the study protocol and assessment schedule (see below), potential risks and benefits, and the confidentiality of their participation. All interested teens and their guardians underwent an extensive screening process to determine eligibility, and those potentially eligible (i.e., recent heavy episodic drinkers or non-drinkers) were mailed consent packets. After completing the assents/consents, teens and

their guardians participated separately in more detailed, structured clinical interviews performed by a different interviewer for each family member.

To minimize confounds, exclusionary criteria included history of a DSM-IV Axis I disorder other than alcohol abuse, extensive other drug use, head trauma, a learning disorder, neurological dysfunction, or serious medical illness; family history of bipolar I or psychotic disorder; significant prenatal alcohol or drug exposure; sensory problems; use of psychoactive medications; and substance use during the abstinence protocol. Overall, 3% of the 2,300 teens who responded to the recruitment fliers (approximately 15,000 were distributed) initiated the study. Others did not enroll because they were non-users who were not similar to heavy episodic drinkers (46%), had a history of a psychiatric disorder or psychotropic medication use (25%), used marijuana or other drugs extensively (22%), or were eligible but not interested in the abstinence protocol (7%).

Measures

Structured clinical interview. After providing their assent/consent, adolescent participants and their parents were separately administered confidential structured clinical interviews assessing demographics, social and academic functioning (Brown, Vik, & Creamer, 1989), family history of psychiatric disorders using the structured clinical interview of Family History Assessment Module Screener (Rice et al., 1995), and personal history of Axis I psychiatric disorders using the Computerized Diagnostic Interview Schedule for Children (DISC; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). Parents completed the Child Behavior Checklist (CBCL; Achenbach & Ruffle, 2000) and teens completed the Youth Self Report (YSR; Achenbach & Ruffle, 2000) to assess levels of internalizing and externalizing psychopathology. Teen substance

use history was documented using the Customary Drinking and Drug Use Record (CDDR; Brown et al., 1998), which assessed lifetime and recent tobacco, alcohol, and drug use (12 classes), withdrawal symptoms, DSM-IV abuse and dependence criteria, and other negative consequences associated with heavy drinking. Good inter-rater reliability, internal consistency, and test-retest ability have been demonstrated with the CDDR among adolescent participants (Brown et al., 1998; Stewart & Brown, 1995). The Timeline Followback (TLFB; Sobell & Sobell, 1992) modified to include other drugs was used to collect frequency and quantity of alcohol, marijuana, and other drug use for the six weeks prior to initiating the protocol and for the four week duration in the study.

Neuropsychological test battery. The thrice-repeated neuropsychological (NP) battery assessed five key domains: (1) *executive functioning*, (2) *learning and memory*, (3) *visuospatial construction*, (4) *working memory, attention, processing efficiency, and psychomotor speed*, and (5) *language and achievement*. Standardized neuropsychological tests included the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) Vocabulary and Block Design; Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997): Arithmetic, Digit Span, and Digit Symbol; California Verbal Learning Test - Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000); Rey-Osterrieth and Taylor Complex Figures copy and 30-minute delayed recall (Osterrieth, 1944; Strauss & Spreen, 1990; Taylor, 1989); Delis-Kaplan Executive Functioning System (D-KEFS; Delis, Kaplan, & Kramer, 2001) Trail Making and Color-Word Interference; a modified version of the Memory for Intentions Test (MIST; Raskin & Buckheit, 1999) to examine prospective memory; and the Wide Range Achievement Test-4 (WRAT-4; Wilkinson & Robertson, 2006) Reading subtest. Alternate forms were used when

possible to reduce practice effects (i.e., Rey-O figure at times 1 and 3, and Taylor figure at time 2; alternation of CVLT-II lists also).

State measures. At each testing session, teens completed the Hamilton Depression and Anxiety Rating Scales (Hamilton, 1996) and the state scale of the Spielberger State Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970). These measures have well-established psychometric properties (Hamilton, 1996; Spielberger et al., 1970). The Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988) assessed baseline mood prior to testing.

Procedures

All eligible CON and HED participants who initiated study protocol were monitored for abstinence (see below) and assessed using neuropsychological tests at three timepoints over their four-week participation. At each timepoint, a 150-minute NP battery was administered by a trained neuropsychometrist. Prior to each session, all participants provided a urine sample, submitted a breathalyzer reading (Intoximeter, St. Louis, MO), and completed affective state and personality questionnaires. Upon completion of the NP battery, the participants rated their level of focus, how hard they tried, how seriously they took the session, and level of effort on a scale of 1 (low) to 10 (high). Participants were compensated for their participation and abstention throughout the protocol with the largest payment at the third assessment wave to encourage study completion.

At all appointments, adolescents participated in a toxicology screening protocol to minimize the possibility of their substance use. HED were first studied within 14 days of heavy episodic drinking and subsequently at two 2-week intervals over four subsequent

weeks of monitored abstinence (1st testing session: $M = 5.56$ days since last HED episode, $SE = 0.60$; 2nd testing session: $M = 19.52$ days since last HED episode, $SE = 0.70$; 3rd testing session: $M = 32.81$ days since last HED episode, $SE = 0.70$). CON teens followed the same abstinence monitoring and neuropsychological testing protocol at the same time intervals. Abstinence was monitored and facilitated through behavioral and biochemical procedures including 10-panel drug urine testing and breathalyzer. Supervised urine and breath samples were collected three times per week to assess for recent use of alcohol with ethyl glucuronide (EtG) and ethyl sulfate (EtS) metabolites and use of methamphetamines, cocaine, THC (cannabis), benzodiazepines, methadone, barbiturates, ecstasy, opiates, PCP, and oxycodone. We utilized an observed sample collection procedure to minimize the likelihood of participant tampering. Samples were analyzed by Redwood Toxicology (Santa Rosa, CA) using cloned enzyme donor immunoassay (CEDIA) kits. If abstinence maintenance was confirmed via subject self-report, breathalyzer, and quantitative toxicology results, participants continued to be scheduled for neuropsychological assessments. Abstinence was also facilitated using a standardized Motivational Interviewing protocol (Miller & Rollnick, 1991) demonstrated to encourage the maintenance of abstinence for adolescents in prior research (Brown, Anderson, Schulte, Sintov, & Frissel, 2005; Schweinsburg et al., 2005). Eleven HED teens drank alcohol during the abstinence period (detected via positive ETG toxicology screen and then confirmed with self-report) and data collected after their alcohol use were excluded from the analyses.

Data analyses

Chi-square tests (for categorical variables) and t-tests (for continuous variables) compared socio-demographic characteristics between groups. To test for HED-CON *differences and changes over time*, we utilized linear mixed effects models to look for group effects at time 1 and time 3, time effects, and group by time interactions. In the mixed model analyses, the fixed variables were timepoint and group, the random variable was the individual subject, and the dependent variable was the standard, age-scaled, or raw score of the NP domain in question. These analyses modeled error structures among repeated dependent variables by using fixed effects, specifying a covariance structure for both between and within subjects, and fitting the means model accounting for specific covariates (Singer & Willett, 2003; Rabe-Hesketh & Skrondal, 2005; Gelman & Hill, 2007). Because groups differed in their CBCL externalizing behavior ($p=.002$), family history of alcohol dependence ($p=.004$), and lifetime marijuana use ($p<.001$), the mixed model analyses controlled for these variables.

Results

Demographics, substance use, and mood

As mentioned previously, the groups were similar on socio-demographic characteristics (Table 1). To ensure CON and HED were comparable on pre-drinking academic performance, 5th grade California Standards Test (CST) scores in language arts and mathematics were examined, and the groups did not differ statistically ($p's>.05$). While standardized test scores of CON were slightly higher than those of HED (Language Arts: 370.27 ± 11.06 and 354.80 ± 11.48 , respectively, $p=.141$; Math: 394.73 ± 21.59 and 352.30 ± 14.60 , respectively, $p=.064$), both groups ranged from the "basic" to "proficient" level. Participants were typically from lower-middle to upper-middle class

families and of average to above-average intelligence. Heavy episodic drinkers self-reported slightly higher CBCL externalizing behavior ($p=.002$), although still within normal range on average.

Lifetime and recent (i.e., days/month in the 3 months prior to initiating study) heavy episodic drinking episodes were, as designed, greater in the HED sample ($p's<.001$). The lifetime marijuana episodes in HED youth were modest for a population with such high levels of drinking experience (average alcohol exposure of 230.50 ± 27.50 vs. average marijuana exposure of 57.62 ± 11.46). HED youth had limited lifetime episodes with other drugs (Table 2.1).

[INSERT TABLE 2.1 HERE]

STAI anxiety and Hamilton depression ratings were similar and within the normal range at all assessments, and both groups had similar PANAS pre-testing mood states ($p's>.05$). Additionally, groups did not differ in their effort ratings following each NP session with both groups indicating moderately high levels of focus, effort, and seriousness.

Neuropsychological performance

Neuropsychological test scores at each of the three test sessions are presented in Table 2.2. The following analyses investigated neurocognitive differences and changes in adolescent heavy episodic drinkers compared to nondrinking teens. A False Discovery Rate (FDR) correction for multiple comparisons was used to recalculate p -values from the mixed models (Benjamini & Hochberg, 1995). All reported p -values were generated from the FDR correction.

[INSERT TABLE 2.2 HERE]

Executive functioning. The MIST examined prospective memory: abilities to monitor time, maintain a planned activity in mind, and initiate appropriate action. HED youth performed significantly worse on the MIST at the first timepoint (b (SE) = -1.09 (0.30), $z = -3.58$, $p = .005$) and did not improve to levels of CON over repeated testing (p 's > .106; Figure 2.1). CON performed consistently across time (p 's > .483) with an overall 2% increase in performance, on average, from Time 1 to Time 3. HED showed most improvements from the first to second timepoint (i.e., between weeks 1 and 3 of abstinence, on average). HED showed a 6% increase in performance from Time 1 to Time 3, but this improvement still left their performance 11% lower than that of CON. HED youth performed worse on the D-KEFS Trail Making Number-Letter Switching at the first timepoint (b (SE) = -1.15 (0.46), $z = -2.49$, $p = .039$) and did not improve to levels of CON (p 's > .238; Figure 2.1). Both CON and HED showed a 17% score increase from Times 1 to 3, with HED consistently performing 8-10% lower. On D-KEFS Color-Word Interference, HED made 50-100% more errors than CON at Time 1 (b (SE) = 2.56 (0.79), $z = 3.24$, $p = .001$) and across time (p 's > .382; Figure 2.1). While HED accuracy improved with time, they still made nearly double the errors as CON by the third timepoint. No initial differences or group x time interactions were identified on D-KEFS Color-Word Interference Inhibition Switching trial (p 's > .090).

[INSERT FIGURE 2.1 HERE]

Learning and memory. On tests of verbal memory, HED youth showed poorer performance at Time 1 on short delay cued recall (b (SE) = -0.60 (0.27), $z = -2.26$, $p = .044$), long delay cued recall (b (SE) = -0.76 (0.24), $z = -3.19$, $p = .005$), and long delay free recall (b (SE) = -0.70 (0.23), $z = -2.98$, $p = .010$). HED verbal memory did not

improve to levels of CON, performing 0.36-0.48 standard deviations below CON across time (p 's>.292; Figure 2.2). Although HED scores were consistently lower, they did not differ statistically at the first timepoint or across time on verbal learning (CVLT-II total words recalled trials 1-5; p 's>.288) or visuospatial memory (Rey-Osterrieth and Taylor Complex Figures 30-minute delayed recall; p 's>.280).

[INSERT FIGURE 2.2 HERE]

Visuospatial construction. On WASI Block Design, HED performed approximately 9% worse than CON at the initial testing (b (SE) = -5.22 (2.15), z = -2.43, p =.039). A group x time interaction was a trend at the second testing (b (SE) = 2.33 (1.24), z = 1.88, p =.059) and statistically significant at the third testing (b (SE) = 3.63 (1.38), z = 2.63, p =.009) with HED improving their performance to that of CON (Figure 2.3). From Time 1 to Time 3, CON showed a 7% improvement in Block Design performance, while HED scores improved 9% by Time 2 and another 6% from Time 2 to Time 3, showing the bigger percent change from weeks 1-3 of abstinence, on average, and continued improvement from weeks 3-5 of abstinence, on average. On direct copy of the Rey-Osterrieth and Taylor Complex Figures, HED performed more poorly than CON at the initial testing (b (SE) = -2.18 (.99), z = -2.21, p =.043) and did not improve with time (p 's>.585), with HED 6-8% worse than CON across assessments (Figure 2.3).

[INSERT FIGURE 2.3 HERE]

Working memory, attention, processing efficiency, and psychomotor speed.

Groups performed similarly and did not differ statistically in their performance at the first testing or across time on all measures of verbal working memory [WAIS-III Digit Span backwards (p 's>.288) or Arithmetic (p 's>.290)], attention and processing efficiency [D-

KEFS Trail Making Visual Scanning task ($p's > .288$); WAIS-III Digit Span forward ($p's > .634$); D-KEFS Color-Word Interference Color Naming ($p's > .291$) and Word Reading ($p's > .796$), and psychomotor speed [WAIS-III Digit Symbol ($p's > .232$); D-KEFS Trail Making Number Sequencing ($p's > .474$) and Letter Sequencing ($p's > .568$)].

Language and achievement. HED performed, on average, 12% worse than CON on WASI Vocabulary (average versus high average range; $p = .005$) and, on average, 7% worse than CON on WRAT-4 Reading (both groups in average range; $p = .008$). Given the statistically (though not clinically) significant difference in WASI Vocabulary scores between groups, we also conducted the NP analyses covarying for Vocabulary T-score. All results remained consistent, except the finding for the initial difference on the MIST was reduced to a trend ($p = .058$). Of note, covarying for 5th grade math and language arts standardized test scores did not alter findings.

Discussion

This study examined neurocognitive differences and patterns of recovery in abstinent, adolescent heavy episodic drinkers compared to nondrinking peers. Importantly, groups had comparable California Standards Test (CST) math and language performance on standardized tests that pre-date initiation of drinking in the heavy episodic drinking group, suggesting similar functioning prior to alcohol use. We found that adolescents with histories of an average of over 200 lifetime drinking episodes who initiated heavy episodic drinking at an average age of 15.33 differed from socio-demographically similar nondrinkers across several neuropsychological domains both during the early stages of abstinence and with continued abstention. The findings are consistent with prior results in youth with much greater alcohol use histories (e.g., Brown

et al., 2000; Giancola & Moss, 1998). Heavy episodic drinking adolescents performed worse on prospective memory, cognitive switching, inhibition task accuracy, verbal memory, visuospatial abilities, and language and achievement.

Studies on adolescents with alcohol use disorders have consistently found deficits in executive functioning, and the current study, which focused on a nonclinical population of heavy episodic drinkers, also identified deficiencies in prospective memory, cognitive switching, and inhibition task accuracy. Prospective memory requires multiple skills: monitoring time, remembering the task to be performed, and self-initiating the task at the appropriate time. Poorer performance in prospective memory, cognitive switching, and response inhibition may apply to academic and professional settings, as goal-oriented behavior and cognitive flexibility are essential to stay on task, quickly shift mental modes, and respond accurately.

Longer lasting and heavier drinking patterns among adolescents have been linked to disruptions in the hippocampus, a brain structure critical for learning and memory, with adolescent drinkers showing smaller hippocampal volumes and disturbed hippocampal white matter integrity (De Bellis et al., 2000; Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007; Nagel, Schweinsburg, Phan, & Tapert, 2005). Our study involved youth earlier in their drinking careers and identified poorer performance in both short delay and long delay verbal memory that did not resolve within five weeks of abstinence, on average. Poorer verbal memory is likely to have a significant influence on daily functioning as recall of verbal information occurs when following instructions, remembering lists, taking exams, and other daily activities.

Our finding of poorer visuospatial abilities among heavy episodic drinking adolescents is consistent with many adolescent studies reporting an association between visuospatial impairments and frequency of alcohol use (Brown et al., 2000; Hanson et al., 2011; Squeglia et al., 2009) and withdrawal symptoms (Brown et al., 2000; Tapert et al., 2001; Tapert et al., 2002; Tapert and Brown, 1999). We found initial differences on two- and three-dimensional constructions (i.e., complex figure drawing, block design); however, only performance on the block constructions showed improvements to levels of nondrinking peers, while complex figure reproduction remained poorer across time. This finding could suggest more recovery of mental rotation and spatial navigation functions, whereas spatial organization and fine motor skills may take longer to recover.

Alcohol dependent adolescents have frequently demonstrated significantly lower verbal IQ and reading achievement scores (Brown et al., 2000; Giancola et al., 2001; Moss et al., 1994; Tarter et al., 1995). The present study's finding of poorer vocabulary and reading scores in nonclinical, heavy episodic drinking youth is consistent with such prior research. Given that the drinkers and nondrinkers had comparable math and language scores in 5th grade, it is possible that the poorer vocabulary and reading skills observed in adolescence may be at least partially due to related environment, brain, or behavior changes occurring after the onset of heavy drinking.

Unlike prior research, our study did not identify statistically significant deficits in verbal learning, visuospatial memory, working memory, attention, or psychomotor speed when comparing heavy episodic drinking youth, who have not yet experienced substantial alcohol related problems, to nondrinking youth. Intensity of alcohol use may not yet be severe enough to manifest in differences. Alternatively, methodological

differences (e.g., variations in abstinence protocol or drug use eligibility criteria; sample size) may also have contributed to incongruent findings.

The present design allowed us to identify significant improvements across time, suggesting that both groups improved with repeated testing and that the two-week interval between neuropsychological assessments is short enough to evidence practice effects. The improvement seen across time supports the importance of including controls to compare to heavy episodic drinkers. As expected, tasks on which both groups improved with repeated testing showed greater performance increases in the heavy drinkers. Despite greater improvement (i.e., steeper slope) from their Time 1 to Time 3 assessment, heavy drinkers did not perform to levels of nondrinkers on prospective memory, cognitive switching, inhibition task accuracy, verbal memory, or two-dimensional visuospatial construction, performing approximately 5-10% lower and committing 50-100% more errors across time. Assuming adolescents respond to initial abstinence in a similar pattern as adults, they would show an initial improvement in attention, memory, and visuospatial skills within the first two weeks of abstinence, with gradual recovery thereafter (Bates, Voelbel, & Buckman, 2005; Fein, Bachman, Fisher, & Davenport, 1990; Reed, Grant, & Rourke, 1992; Sullivan, Rosenbloom, & Pfefferbaum, 2000). Our study detected significant improvements in prospective memory, cognitive switching, inhibition task accuracy, and visuospatial abilities from weeks 1 to 3 of abstinence, on average. However, we only identified an improvement significant enough to bring drinkers' performance to that of nondrinkers on the three-dimensional visuospatial construction task. It may be that a longer period of recovery is

needed before the expected improvements seen in adult populations become evident among adolescent drinkers.

We demonstrated that we can repeatedly and intensively assess functioning of 16- to 18-year-olds with and without histories of heavy episodic drinking. Our efforts to measure sustained abstinence were sufficient for this length of time. We went to great lengths to measure continuous abstinence, including the collection of urine samples from all participants on Sunday mornings. These procedures were necessary to detect alcohol exposure in 11 heavy episodic drinking participants (who were discontinued from the study) and to report confidently abstinence in the other drinkers. The study also provides preliminary evidence to support the success of the motivational interviewing protocol to sustain abstinence in a population of heavy episodic drinking adolescents (Brown et al., 2005; Miller & Rollnick, 1991; Schweinsburg, et al., 2005).

This study featured many design strengths but has several limitations. First, the sample was carefully selected yet modest in size, which limited our statistical power and prevented further exploration of associations between neuropsychological performance and gender, family history, or alcohol use characteristics. Second, as expected, heavy episodic drinkers had some exposure to marijuana or other drugs. While we did covary for marijuana exposure in the mixed models, it is possible that other substance use, although limited, may have contributed to group differences. Of note, the heavy episodic drinkers consumed alcohol four times more than marijuana in their lifetimes, and had an average of approximately ten lifetime experiences with other drugs. Third, while the study established a relationship between heavy episodic drinking and neurocognitive

impairments among adolescents, the directionality and causality can only be determined by longitudinal studies that examine adolescents prior to any substance involvement.

In summary, consistent with our hypotheses and with previous studies, 16- to 18-year-old heavy episodic drinking adolescents with recent, frequent drinking and limited other drug exposure exhibit modest but significant neurocognitive functioning differences during early abstinence and, in many cases, with sustained abstinence. Though requiring replication, we found decrements in prospective memory, cognitive switching, inhibition task accuracy, verbal memory, visuospatial abilities, and language at the first testing that improve but not to levels of nondrinking peers even after four weeks of sustained abstinence (with the exception of 3-dimensional block construction). In the present sample, scores on tasks of verbal learning, working memory, attention, and psychomotor speed did not differ as a function of youth drinking experience. Our findings, coupled with extant literature in this field, suggest that deficient neuropsychological functioning is present among adolescents with recent histories of heavy episodic drinking relative to their nondrinking peers. These cognitive differences persist across four to six weeks of abstinence, suggesting a possible alcohol-induced impact to underlying brain systems, particularly given that groups were comparable on pre-drinking academic test performance. This possibility coincides with the animal literature's finding that adolescence is a time of enhanced sensitivity to the neurotoxic effects of alcohol.

This study has the potential to contribute to improved methods for (1) measuring changes on important neurocognitive, affective, and behavioral domains associated with heavy episodic drinking in adolescents, and (2) monitoring and facilitating real life behavioral improvements associated with abstinence from alcohol. Poorer performance in

prospective memory, cognitive switching, inhibition accuracy, verbal memory, visuospatial ability, and language may affect adolescents' daily experiences in academic or occupational settings. With this knowledge, educators may be able to improve outcomes for these teens by considering their cognitive abilities during instruction and employing strategies of repetition and active learning to more effectively engage and instruct a population of heavy episodic drinking youth (Myers, Brown, & Mott, 1993; Roehrich & Goldman, 1993).

Chapter 2 Acknowledgements

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Table 2.1. Demographic and substance use characteristics for control (CON) and heavy episodic drinking (HED) adolescents (ages 16-18).

	CON (N=26) M (SE)	HED (N=39) M (SE)	<i>p</i> - value
Age	17.61 (0.12)	17.71 (0.13)	.596
Gender	12F, 14M	18F, 21M	.601
% Caucasian	73%	77%	.687
% Family history positive ^a	31%	69%	.004
Grades completed	11.00 (0.12)	11.05 (0.15)	.805
Hollingshead SES score ^b	23.73 (2.41)	27.42 (2.30)	.285
Grade point average	3.64 (0.11)	3.32 (0.11)	.058
CBCL Externalizing T-score ^c	41.46 (1.60)	49.03 (1.49)	.002
CBCL Internalizing T-score ^c	43.54 (1.80)	45.58 (1.71)	.424
5 th grade standardized language arts score ^d	370.27 (11.06)	354.80 (11.48)	.141
5 th grade standardized mathematics score ^d	394.73 (21.59)	352.30 (14.60)	.064
Lifetime episodes using alcohol	0.73 (0.41)	230.50 (27.50)	.000
HED episodes in the 3 months prior to study	0.00	16.62 (1.81)	.000
Age at first HED episode	n/a	15.33 (0.18)	
Lifetime episodes using marijuana	0.00	57.62 (11.46)	.000
Marijuana days/month, 3 months prior to study	n/a	2.44 (0.70)	
Lifetime episodes using other drugs	0.00	9.90 (2.90)	.008
Time 1: days since heavy episodic drinking	n/a	5.56 (0.60)	
Time 2: days since heavy episodic drinking	n/a	19.52 (0.70)	
Time 3: days since heavy episodic drinking	n/a	32.81 (0.70)	

^a A first-degree biological relative with alcohol or drug related dependence

^b Hollingshead (1965) SES (socioeconomic status): Higher scores = lower SES

^c CBCL: Child Behavior Checklist

^d Scaled score on California Standards Test (CST)

Table 2.2. Marginal means (SE) of control (CON) and heavy episodic drinking (HED) adolescents (age 16-18) demonstrate differences and changes in neuropsychological performance with extended abstinence.

	Time 1		Time 2		Time 3	
	CON (N=26) M (SE)	HED (N=39) M (SE)	CON (N=26) M (SE)	HED (N=31) M (SE)	CON (N=26) M (SE)	HED (N=28) M (SE)
Executive Functioning						
MIST Intention Total raw ^a	7.67 (0.23)	6.58 (0.19)	7.71 (0.22)	7.14 (0.20)	7.83 (0.22)	7.01 (0.20)
D-KEFS Trail Making Number-Letter Switching SS ^a	10.71 (0.34)	9.56 (0.28)	11.86 (0.34)	11.15 (0.30)	12.56 (0.34)	11.61 (0.30)
D-KEFS Color-Word Inhibition Switching SS	11.75 (0.43)	10.55 (0.36)	12.71 (0.43)	12.05 (0.38)	13.48 (0.42)	12.45 (0.38)
D-KEFS Color-Word Total Errors ^a	4.40 (0.58)	6.95 (0.49)	2.94 (0.58)	4.71 (0.53)	2.47 (0.58)	4.68 (0.54)
Learning and Memory						
Complex Figure Accuracy raw (30-min delay)	16.40 (0.92)	15.82 (0.77)	20.98 (0.92)	19.97 (0.84)	21.63 (0.93)	19.41 (0.85)
CVLT-II Trial 1-5 Total Recall T-score	52.02 (1.95)	52.86 (1.89)	50.04 (2.48)	50.97 (2.46)	59.97 (2.96)	55.41 (2.55)
CVLT-II Short Delay Cued Recall z-score ^a	0.36 (0.19)	-0.24 (0.16)	0.44 (0.19)	-0.40 (0.17)	0.84 (0.19)	0.38 (0.17)
CVLT-II Short Delay Free Recall z-score	0.16 (0.19)	-0.18 (0.16)	-0.05 (0.19)	-0.38 (0.17)	0.68 (0.19)	0.54 (0.17)
CVLT-II Long Delay Cued Recall z-score ^a	0.37 (0.18)	-0.40 (0.15)	0.37 (0.18)	-0.47 (0.16)	0.71 (0.18)	0.35 (0.16)
CVLT-II Long Delay Free Recall z-score ^a	0.42 (0.17)	-0.28 (0.14)	0.00 (0.17)	-0.66 (0.15)	0.88 (0.17)	0.40 (0.16)
Visuospatial Construction						
WASI Block Design T-score ^b	59.40 (1.43)	54.19 (1.39)	61.77 (1.53)	58.89 (1.49)	63.75 (1.62)	62.16 (1.51)
Complex Figure Accuracy raw (Direct Copy) ^a	27.89 (0.73)	25.70 (0.61)	29.31 (0.73)	26.93 (0.65)	28.74 (0.73)	27.05 (0.66)
Working Memory						
WAIS-III Digit Span Backward SS	7.17 (0.55)	7.94 (0.54)	8.854 (0.61)	8.37 (0.55)	7.86 (0.68)	8.97 (0.61)
WAIS-III Arithmetic SS	11.96 (0.61)	11.95 (0.60)	12.65 (0.67)	12.30 (0.65)	13.88 (0.71)	13.19 (0.66)
Attention						
D-KEFS Trail Making Visual Scanning SS	11.09 (0.28)	11.57 (0.23)	12.10 (0.28)	12.37 (0.24)	12.68 (0.28)	12.69 (0.25)
WAIS-III Digit Span Forward SS	11.01 (0.39)	11.01 (0.33)	11.28 (0.39)	11.47 (0.35)	11.66 (0.39)	11.52 (0.35)
Processing Efficiency						
D-KEFS Color-Word Int.: Color Naming SS	10.17 (0.52)	9.59 (0.44)	10.40 (0.51)	10.54 (0.46)	10.71 (0.52)	10.00 (0.46)
D-KEFS Color-Word Int.: Word Reading SS	11.35 (0.45)	10.99 (0.38)	11.62 (0.45)	11.00 (0.39)	11.66 (0.45)	11.15 (0.40)
Psychomotor Speed						
WAIS-III Digit Symbol SS	10.17 (0.50)	9.14 (0.42)	12.48 (0.50)	10.56 (0.43)	12.94 (0.50)	11.13 (0.43)
D-KEFS Trail Making Number Sequencing SS	10.96 (0.34)	11.03 (0.28)	12.80 (0.34)	12.77 (0.31)	13.30 (0.34)	13.03 (0.31)
D-KEFS Trail Making Letter Sequencing SS	11.39 (0.40)	11.09 (0.34)	12.46 (0.40)	12.46 (0.36)	13.42 (0.40)	13.29 (0.36)
Language and Achievement						
WASI Vocabulary T-Score ^c	62.69 (1.25)	54.90 (1.33)				
WRAT-4 Reading Standard Score ^c			105.85 (1.57)	98.81 (1.42)		

^a Initial group difference (at Time 1) but no group x time interaction

^b Initial group difference (at Time 1) and group x time interaction at 3

^c Group difference

Note: SS = scaled score; Complex Figure = Rey-Osterrieth and Taylor Complex Figures copy and 30-minute delayed recall (Osterrieth, 1944; Strauss & Spreen, 1990; Taylor, 1989); D-KEFS = Delis-Kaplan Executive Functioning System (Delis, Kaplan, & Kramer, 2001); CVLT-II = California Verbal Learning Test - Second Edition (Delis et al., 2000); MIST = Memory for Intentions Test (Raskin & Buckheit, 1999); WASI = Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999); WAIS-III = Wechsler Adult Intelligence Scale-III (Wechsler, 1997; WRAT-4 = Wide Range Achievement Test-4 (Wilkinson & Robertson, 2006)

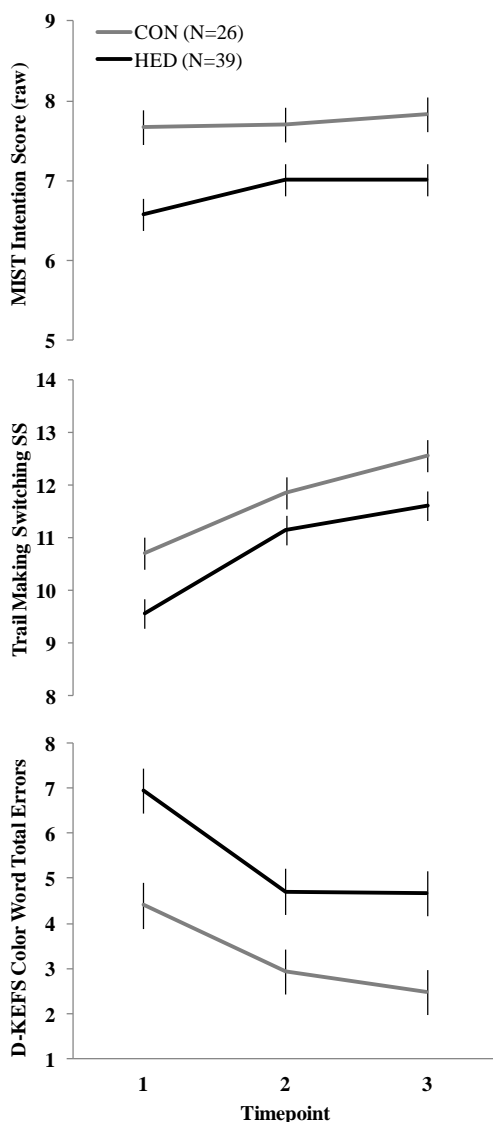


Figure 2.1. Executive functioning tasks of Memory for Intentions Test (MIST), D-KEFS Trail Making Number-Letter Switching, and D-KEFS Color Word Interference by heavy episodic drinking youth (HED) and controls (CON).^{a, b}

^a From linear mixed effects models with standard error bars, controlling for externalizing behavior, family history of alcohol or drug related dependence, and lifetime marijuana use at three assessments over four weeks of abstinence. Average number of days since last heavy episodic drinking episode in HED youth was 5.56 days at Timepoint 1, 19.52 days at Timepoint 2, and 32.81 days at Timepoint 3.

^b At the first timepoint, HED youth performed worse on MIST ($p=.005$) and Trail Making Switching standard score (SS; $p=.039$) and committed more errors than CON on Color Word Interference Inhibition ($p=.001$). Performance did not improve with time on all three tasks (p 's $>.238$).

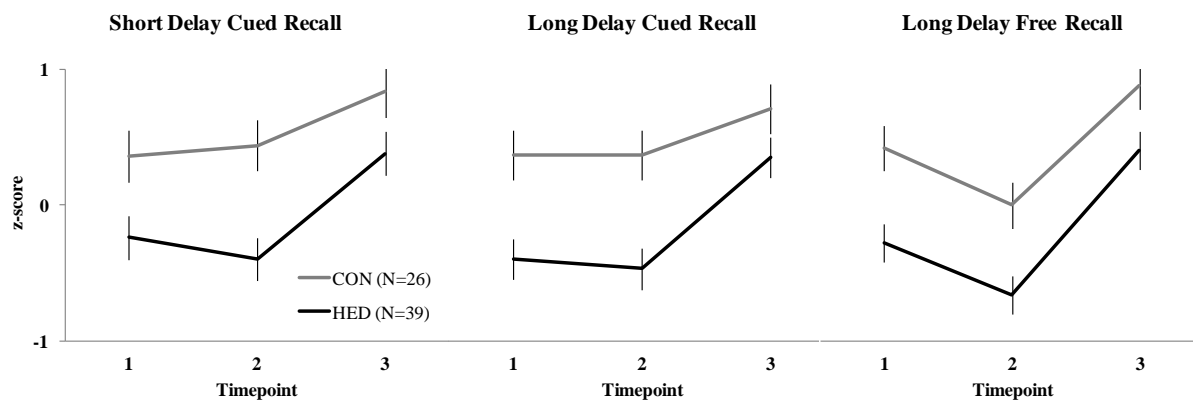


Figure 2.2. CVLT-II short and long delay verbal memory z-scores by heavy episodic drinking youth (HED) and controls (CON).^{a, c}

^a From linear mixed effects models with standard error bars, controlling for externalizing behavior, family history of alcohol or drug related dependence, and lifetime marijuana use at three assessments over four weeks of abstinence. Average number of days since last heavy episodic drinking episode in HED youth was 5.56 days at Timepoint 1, 19.52 days at Timepoint 2, and 32.81 days at Timepoint 3.

^c HED evidenced poorer short delay cued recall ($p=.044$), long delay cued recall ($p=.005$), and long delay free recall ($p=.010$) than CON at the initial testing. Poorer verbal memory continued across time (p 's $>.292$).

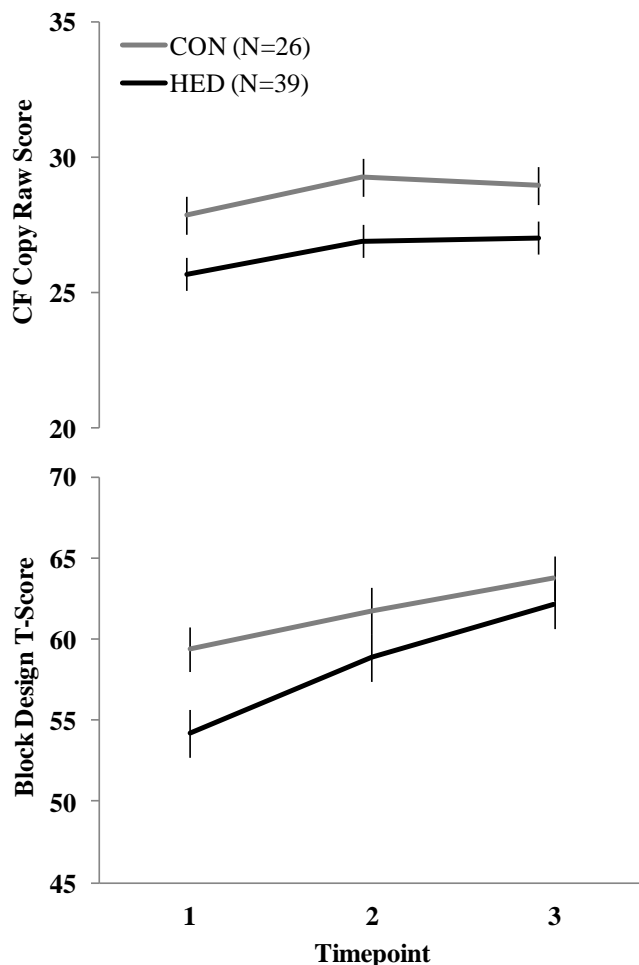


Figure 2.3. Visuospatial construction tasks of Rey-Osterrieth and Taylor Complex Figures (CF) and Wechsler Abbreviated Scale of Intelligence (WASI) Block Design by heavy episodic drinking youth (HED) and controls (CON).^{a, d}

^a From linear mixed effects models with standard error bars, controlling for externalizing behavior, family history of alcohol or drug related dependence, and lifetime marijuana use at three assessments over four weeks of abstinence. Average number of days since last heavy episodic drinking episode in HED youth was 5.56 days at Timepoint 1, 19.52 days at Timepoint 2, and 32.81 days at Timepoint 3.

^d HED performed more poorly than CON at the initial testing ($p=.043$) and across time ($p's>.585$) on 2-dimensional CF copying. On 3-dimensional block construction, HED performed worse than CON at the initial testing ($p=.039$) but improved their performance to that of CON by the third testing ($p=.009$), showing the biggest improvement between, on average, weeks 1-3 of abstinence.

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CHAPTER 3. HEAVY ALCOHOL USE, MARIJUANA USE, AND CONCOMITANT
USE BY ADOLESCENTS ARE ASSOCIATED WITH UNIQUE AND SHARED
COGNITIVE DECREMENTS

Abstract

Introduction: To assess recovery of cognitive effects, we investigated neuropsychological performance after one month of monitored abstinence in teens with histories of heavy episodic drinking, protracted marijuana use, or concomitant use of alcohol and marijuana.

Method: Adolescents (ages 16-18) with histories of heavy episodic drinking (HED; $n=24$), marijuana use (MJ; $n=23$), both heavy alcohol and marijuana use (HED+MJ; $n=29$), and socio-demographically similar control teens (CON; $n=55$) completed a neuropsychological battery following four weeks of monitored abstinence. Groups were similar on 5th grade standardized test scores, suggesting comparable academic functioning prior to onset of substance use.

Results: Relative to CON, HED showed poorer cognitive flexibility ($p=.007$), verbal recall ($p=.026$), semantic clustering ($p=.010$), and reading skills ($p=.018$). MJ performed worse than CON on inhibition task accuracy ($p=.023$), cued verbal memory ($p=.027$), and psychomotor speed ($p=.010$). Similar to HED youth, HED+MJ showed differences relative to CON on cognitive flexibility ($p=.023$) and verbal recall ($p=.048$). As with MJ teens, HED+MJ showed poorer task accuracy ($p=.021$). Unique to the HED+MJ group was poorer working memory ($p=.028$) relative to CON. For all substance using participants, worse performance across domains correlated with more lifetime use of alcohol and of marijuana, more withdrawal symptoms from alcohol, and earlier age of onset of marijuana use ($p's < .05$).

Discussion: Heavy alcohol use, marijuana use, and concomitant use of both substances during adolescence appear to be associated with decrements in cognitive functioning, and

each substance (or combination of substances) may be linked to poorer performance in specific cognitive domains.

Introduction

Brain maturation during adolescence appears to mirror developments in cognition, suggesting the overwhelming importance of healthy brain maturation processes during this critical time (Fryer et al., 2008; Nagel, Barlett, Schweinsburg, & Tapert, 2005; Sowell, Delis, Stiles, & Jernigan, 2001). Given the confluence of neuromaturational activity (Giedd et al., 1999; Gogtay et al., 2004; Paus et al., 1999) and initiation of alcohol and marijuana use during adolescence, the potential impact of these substances on neurocognitive development is important to understand. Alcohol and marijuana are drugs of particular concern since they are the most commonly used among adolescents. Over 68% of U.S. high school seniors report having tried alcohol and 46% have tried marijuana (Johnston et al., 2014), and in the past month, alcohol was used by 39% and marijuana by 22% (Johnston et al., 2014). Heavy episodic drinking (i.e., attaining a blood alcohol concentration of .08 or higher, which is typically achieved with ≥ 5 drinks for males or ≥ 4 drinks for females within a 2-hour period; NIAAA, 2002) occurred among nearly a quarter of seniors in the prior two weeks, and 7% endorsed daily marijuana use (Johnston et al., 2014).

The extant animal literature suggests that adolescents experience heightened vulnerability to the deleterious effects of both ethanol and cannabis (Cha, White, Kuhn, Wilson, & Swartzwelder, 2006; Roehrs, Beare, Zorick, & Roth, 1994; Schneider, Schomig, & Leweke, 2008; Silveri & Spear, 1998; Slawecki & Roth, 2004; Stiglick & Kalant, 1982). In general, the animal literature suggests a more widespread impact by ethanol on the hippocampus (Nixon, Tivis, Ceballos, Varner, & Rohrbaugh, 2002; Slawecki, Betancourt, Cole, & Ehlers, 2001; Ward et al., 2009) and frontal-anterior

cortical areas (Crews, Braun, Hoplight, Switzer, & Knapp, 2000), which leads to persistent structural and functional abnormalities into adulthood (Slawecki, 2002; Slawecki & Roth, 2004; White, Ghia, Levin, & Swartzwelder, 2000). Adolescent rats also show reduced sensitivity to ethanol-induced motor impairing and sedative effects (Slawecki & Roth, 2004; Roehrs, Beare, Zorick, & Roth, 1994; Silveri & Spear, 1998), which may theoretically enable youth to drink greater quantities of alcohol and attain higher blood alcohol concentrations with less sedation than would be expected in adulthood. Similar to effects seen in adolescent rats exposed to ethanol, long-lasting effects on learning, memory, and object recognition have been shown in adolescent rats with chronic cannabis exposure (Cha, White, Kuhn, Wilson, & Swartzwelder, 2006; Schneider & Koch, 2003; Schneider, Schomig, & Leweke, 2008; Stiglick & Kalant, 1982), which have been attributed to a reduction in quality or efficiency of synaptic connections in the hippocampus (Rubino et al., 2009).

While most existing studies examine the impact of alcohol or marijuana use separately, understanding the impact of concomitant use is also highly relevant. One study found that use of cannabinoids in a neonatal rat brain enhanced sensitivity to damage from ethanol (Hansen et al., 2008). The combination of THC and mildly intoxicating doses of ethanol produced widespread and severe neuronal degradation similar to levels observed from much higher doses of ethanol administration. In sum, animal literature has linked both independent and concurrent alcohol and marijuana use to microstructural and macrostructural changes that likely contribute to observed behavioral and cognitive differences, including poorer neuropsychological functioning.

The extant human literature also suggests that heavy and recent alcohol exposure in adolescence is associated with poorer neuropsychological outcomes relative to those of non-drinkers (Brown et al., 2008; Brown & Tapert, 2004). A recent study examining community youth of heavy episodic drinkers relative to their nondrinking peers found that even after one month of monitored abstinence, adolescent drinkers still showed differences in prospective memory, cognitive switching, inhibition task accuracy, verbal memory, and visuospatial construction (Winward, Hanson, Bekman, Tapert, & Brown, 2014). Such deficits are consistent with a vast number of other studies on adolescent drinkers (Brown, Tapert, Granholm, & Delis, 2000; Giancola & Mezzich, 2000; Giancola & Moss, 1998; Giancola, Shoal, & Mezzich, 2001; Goudriaan, Grekin, & Sher, 2007; Moss, Kirisci, Gordon, & Tarter, 1994; Sher, Martin, Wood, & Rutledge, 1997; Tapert & Brown, 1999; Tapert, Granholm, Leedy, & Brown, 2002; Tapert et al., 2004; Weissenborn & Duka, 2003). More specifically, numerous studies examining neuropsychological impact of drinking among adolescents with alcohol use disorders (AUD) suggest deficits in verbal memory and recognition discriminability (Brown et al., 2000; Tapert et al., 2001) and in recall of nonverbal information (Brown et al., 2000) such as delayed recall of a complex figure (Squeglia, Spadoni, Infante, Myers, & Tapert, 2009).

Similar to alcohol use, marijuana use during adolescence may also disrupt the normal neuromaturational processes that take place during this time period (Benes, Turtle, Khan, & Farol, 1994; Gogtay et al., 2004; Jernigan & Gamst, 2005; Pfefferbaum et al., 1994). After at least three weeks of abstinence, adolescent marijuana users still show decrements in memory, attention, psychomotor speed, and planning and sequencing

(Medina et al., 2007; Millsaps, Azrin, & Mittenberg, 1994; Schwartz, Gruenewald, Klitzner, & Fedio, 1989); increased errors on a speeded visuomotor sequencing task; and more intrusions on word list learning (Tapert et al., 2007). One study that tested adolescent marijuana users once per week over three weeks of sustained abstinence found initial differences in verbal memory and verbal working memory that improved with three weeks of sustained abstinence, but not to levels of controls (Hanson et al., 2010). Deficits in accuracy on a visual attention task were seen at the first assessment and across time (Hanson et al., 2010). Another study found that MJ-using teens continued to show poorer functioning in complex attention, sequencing ability, verbal story memory, and psychomotor speed following one month of monitored abstinence (Medina et al., 2007).

While multiple studies report neuropsychological deficits in alcohol and marijuana using teens, even after one month of abstinence, one major limitation across these studies is the high rate of comorbid substance use among participants. Many alcohol-using populations have moderate to high levels of marijuana use; similarly, many marijuana-using teens have significant exposure to heavy drinking. Therefore, much of the existing literature cannot report confidently if cognitive decrements are primarily related to alcohol, to marijuana, or to use of both substances. Additionally, few studies have directly compared alcohol-using youth and marijuana-using youth to each other. One study comparing non-using teens, alcohol users, and marijuana users used 12-hour abstinence protocols and 9th grade scores as indications of pre-morbid academic functioning (Solowij et al., 2011); another study used marijuana users who had consumed alcohol up to 810 times and other drugs up to 70 times (Mahmood, Jacobus, Bava, Scarlett, & Tapert, 2010). Therefore, there is a great need to distinguish the impact of

alcohol, marijuana, and concomitant use on neuropsychological outcomes using extended abstinence protocols, indicators of premorbid functioning that predate initiation of substance use, and group eligibility criteria to limit exposure to other substances much more stringently. These limitations are addressed in the current study.

Current Study

We examined the effects of alcohol and marijuana use during adolescence in a sample of substance using teens and demographically similar non-using teens using a neuropsychological battery after four weeks of monitored abstinence. Using strict criteria to differentiate groups, we compared neuropsychological performance among (1) alcohol users, (2) marijuana users, (3) those who use both marijuana and alcohol, and (4) non-using controls. Based on prior adolescent research, we hypothesized that even following one month of sustained abstinence, users of marijuana and alcohol would show poorer performance relative to non-users. Poorer executive functioning and visuospatial ability were expected in the alcohol group, but not in the marijuana group. Poorer task accuracy and psychomotor speed were expected to be most notable among the marijuana users. Given previous animal and human research (Hansen et al., 2008; Hanson, Medina, Padula, Tapert, & Brown, 2011), we expected youth who use both marijuana and alcohol to show poorest performance in the same domains as heavy users of alcohol or marijuana, while also possibly showing unique changes attributable to concomitant use.

Method

Participants

In accordance with the University of California, San Diego (UCSD) Institutional Review Board and high school district policies, written informed assent (adolescent

participant) and consent (parent/legal guardian) were obtained prior to participation. The current study examined 131 adolescents (ages 16-18) who were classified into four groups using "episode" to describe the number of days on which a substance was used in a participant's lifetime: (1) heavy episodic drinking adolescents (HED; $n=24$; >100 drinking episodes, <25 marijuana episodes), (2) protracted marijuana users (MJ; $n=23$; >150 marijuana episodes, <75 drinking episodes), (3) heavy alcohol and marijuana using teens (HED+MJ; $n=29$; >100 marijuana and alcohol episodes), and (4) control teens (CON; $n=55$; <10 drinking episodes, <5 marijuana episodes). The higher group cutoff for alcohol use among MJ youth was used because three MJ participants had 50-75 alcohol episodes; however, they had over 800 marijuana episodes, so 10-20 times more marijuana than alcohol in their lifetimes. Also, in the three months prior to starting the study, MJ youth reported 0 heavy episodic drinking episodes and 0 alcohol withdrawal symptoms. The HED and HED+MJ groups, however, reported 5-20 heavy episodic drinking episodes per month and 3-9 alcohol withdrawal symptoms in the three months prior to study initiation.

All participants were drawn from the same schools, and groups were similar on socio-demographic factors including age, gender (34% female), ethnicity (73% Caucasian), grades completed, grade point average (GPA), socioeconomic status (Hollingshead, 1965), family history of substance dependence, and 5th grade California Achievement Test, 6th Edition (CAT-6) language arts and mathematics scores (Table 1). Groups who used similar substances (e.g., HED and HED+MJ both used alcohol heavily and MJ and HED+MJ both used marijuana heavily) were matched on their common substance in the following areas: lifetime episodes, frequency of recent use (i.e., three

months prior to study initiation), days since use at study initiation, and age of onset of regular use (i.e., more than one day per week). HED and HED+MJ had a heavy episodic drinking experience 4.18 and 6.75 days per month, respectively; MJ and HED+MJ smoked marijuana 17.78 and 18.38 days per month, respectively (Table 3.1).

[INSERT TABLE 3.1 HERE]

Participants were recruited from San Diego high schools and colleges via mailings and fliers that advertised an “Adolescent Development Project.” No information regarding alcohol or drug use criteria was described in the flier or discussed prior to screening. Participants responding by phone were informed of the study protocol and assessment schedule, potential risks and benefits, and the confidentiality of their participation. All interested teens and their guardians underwent an extensive screening process to determine eligibility, and those potentially eligible were mailed consent packets. After completing the assents/consents, teens and their guardians participated in more detailed, structured clinical interviews.

To minimize confounds, exclusionary criteria included history of a DSM-IV Axis I disorder other than substance abuse; extensive other drug use (i.e., greater than 25 combined lifetime use of other drugs); head trauma (i.e., loss of consciousness over 30 seconds); a learning disorder; neurological dysfunction; serious medical illness; family history of bipolar I or psychotic disorder; significant prenatal alcohol or drug exposure; sensory problems; use of psychoactive medications; and substance use during the abstinence protocol.

Measures

Structured Clinical Interview and Substance Use History. After providing their assent/consent, adolescent participants and their parents were separately administered confidential structured clinical interviews assessing demographics, social and academic functioning (Brown, Vik, & Creamer, 1989), family history of psychiatric disorders using the structured clinical interview of Family History Assessment Module Screener (Rice et al., 1995), and personal history of Axis I psychiatric disorders using the Computerized Diagnostic Interview Schedule for Children [DISC; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000]. Parents completed the Child Behavior Checklist [CBCL; Achenbach & Ruffle, 2000] and teens completed the Youth Self Report [YSR; Achenbach & Ruffle, 2000] to assess levels of internalizing and externalizing psychopathology.

Teen substance use history was documented using the Customary Drinking and Drug Use Record [CDDR; Brown et al., 1998], which assessed both lifetime and recent tobacco, alcohol, and drug use (12 classes), withdrawal symptoms, DSM-IV abuse and dependence criteria, and other negative consequences associated with heavy drinking. Good inter-rater reliability, internal consistency, and test-retest ability have been demonstrated with the CDDR among adolescent participants (Brown et al., 1998; Stewart & Brown, 1995). The Timeline Followback [TLFB; Sobell & Sobell, 1992] modified to include other drugs was used to collect frequency and quantity of alcohol, marijuana, and other drug use for the four weeks prior to initiating protocol and for the four week duration in the study.

Neuropsychological Battery. Following at least one month of monitored abstinence in all participants, a 150-minute neuropsychological (NP) battery was

administered by extensively-trained neuropsychometrists to assess five domains: (1) *executive functioning*, (2) *learning and memory*, (3) *visuospatial construction*, (4) *working memory, attention, and psychomotor speed*, and (5) *language and achievement*.

Standardized neuropsychological tests included the Wechsler Abbreviated Scale of Intelligence [WASI; Wechsler, 1999] Vocabulary and Block Design subtests; Wechsler Adult Intelligence Scale-III [WAIS-III; Wechsler, 1997]: Arithmetic, Digit Span, and Digit Symbol Coding subtests; California Verbal Learning Test - Second Edition [CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000]; Rey-Osterrieth Complex Figure copy and 30-minute delayed recall (Osterrieth, 1944); Delis-Kaplan Executive Functioning System [D-KEFS; Delis, Kaplan, & Kramer, 2001] Trail Making subtest; and the Wide Range Achievement Test-4 [WRAT-4; Wilkinson & Robertson, 2006] Reading subtest.

Mood/Affect Measures. At the NP testing session, teens completed the Hamilton Depression and Anxiety Rating Scales (Hamilton, 1996) and the state scale of the Spielberger State Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970), both of which have well-established psychometric properties (Hamilton, 1996; Spielberger et al., 1970).

Procedures

All eligible participants who initiated the study protocol were monitored for abstinence from substance use for four weeks and then assessed using neuropsychological tests at the completion of their abstention period. Prior to the NP testing session, participants provided a urine sample, submitted a Breathalyzer reading (Intoximeter, St. Louis, MO), and completed emotional state measures. To minimize the possibility of substance use during the four-week abstention period, supervised urine and

breath samples were collected three times weekly to assess for recent use of alcohol with ethyl glucuronide (EtG) and ethyl sulfate (EtS) metabolites and use of methamphetamines, cocaine, THC (cannabis), benzodiazepines, methadone, barbiturates, MDMA (ecstasy), opiates, PCP, and oxycodone. We utilized an observed sample collection procedure to minimize the likelihood of participant tampering. Samples were analyzed by Redwood Toxicology (Santa Rosa, CA) using cloned enzyme donor immunoassay (CEDIA) kits. If abstinence maintenance was confirmed via subject self-report, Breathalyzer, and quantitative toxicology results, participants continued to be scheduled for appointments. Abstinence was also facilitated using a standardized Motivational Interviewing protocol (Miller & Rollnick, 1991) demonstrated to encourage the maintenance of abstinence for adolescents in prior research (Brown, Anderson, Schulte, Sintov, & Frissell, 2005; Schweinsburg et al., 2005). To minimize the impact of study participation on subjects' daily lives, research staff worked closely with enrolled youth to select a one-month period that did not conflict with birthdays, school events, or breaks. As this was not a treatment-seeking sample (i.e., "nonclinical"), eligibility was not contingent upon a teen's expressed desire to quit substance use. Instead, participants were motivated by financial compensation and the opportunity to contribute to research.

HED, MJ, and HED+MJ youth started the study protocol within three weeks of exposure to the substance of interest (i.e., HED had a heavy episodic drinking episode within 21 days of study initiation but their last exposure to marijuana did not impact eligibility). At the time of assessment following one month of monitored abstinence, average days since exposure to the substance of interest ranged from 31-35 days in HED, MJ, and HED+MJ youth (Table 3.1).

Data analyses

We used chi-square tests (for categorical variables) and Analysis of Variance (ANOVA; for continuous variables) to compare demographic characteristics among groups. We used Multivariate Analysis of Covariance (MANCOVA) to test for group effects on neuropsychological task performance after one month of monitored abstinence. Given that poor externalizing behavior has been linked to academic underachievement, impulsivity, poor decision making, and neurocognitive deficits (Ernst et al., 2003; Giancola & Moss, 1998; McGue, Iacono, Legrand, & Elkins, 2001), CBCL externalizing behavior was used as a covariate in the analyses since the three groups of substance using teens scored higher on this trait. Post-hoc contrasts were examined using Tukey's HSD tests. Secondary analyses examined the associations between alcohol and marijuana use characteristics (i.e., lifetime episodes, age of onset of regular use, quantity of recent withdrawal symptoms, days since last use) and performance on tasks of executive functioning, learning and memory, visuospatial construction, attention and psychomotor speed, and language and achievement. Due to non-normal distribution of substance use characteristics, Spearman's correlations were calculated to describe these relationships. A False Discovery Rate (FDR) correction for multiple comparisons was used to recalculate *p*-values from the outputs (Benjamini & Hochberg, 1995). All reported *p*-values were generated from the FDR correction.

Results

Demographics, substance use, and mood

As mentioned previously, the groups were similar on socio-demographic characteristics and on their pre-substance use academic performance (Table 3.1).

Participants were typically from lower-middle to upper-middle class families (Hollingshead, 1965) and of average to above-average intelligence (based on WASI Vocabulary T-Scores). Both HED and HED+MJ drank alcohol heavily, approximately 1-2 times per week. Both MJ and HED+MJ smoked marijuana approximately 4-5 days per week. Lifetime exposure to drugs other than alcohol and marijuana was modest (<10 on average) and similar among the three substance using groups (Table 3.1).

Substance using participants (i.e., HED, MJ, and HED+MJ) self-reported slightly higher CBCL externalizing behavior than control teens ($F(3,107)=4.53, p=.005$), although still within normal range, on average. CBCL externalizing behavior was used as a covariate in the analyses. STAI anxiety and Hamilton depression ratings were similar and within the normal range for all groups following one month of monitored abstinence ($p's>.05$).

Neuropsychological performance

The following results summarize the differences in neuropsychological performance among CON, HED, MJ, and HED+MJ youth following one month of monitored abstinence (Table 3.2). There was a statistically significant difference in neuropsychological test performance based on a participant's substance use history group classification ($F(72, 246) = 1.87, p<.001$, Wilks' $\Lambda = 0.27$, partial η squared = 0.35). Descriptive information for the statistically significant findings is provided as the means and standard error estimates from the MANCOVA model, p -value from the Tukey's HSD post-hoc contrast, and 95% confidence interval for the model's mean estimates.

[INSERT TABLE 3.2 HERE]

Executive functioning. Statistically significant group differences were identified for D-KEFS Trail Making Number-Letter Switching ($F(3,126)=3.06, p=.031$), with both HED ($M=9.55(SE=0.41), p=.007, 95\% \text{ CI: } [8.70-10.40]$) and HED+MJ ($M=9.84(SE=0.37), p=.023, 95\% \text{ CI: } [9.09,10.59]$) performing 11-14% worse than CON ($M=11.04(SE=0.21), 95\% \text{ CI: } [10.62-11.45]$) teens. On D-KEFS Trail Making all errors ($F(3,126)=2.73, p=.048$), accuracy rates (i.e., fewer set loss and sequencing errors) were 10% higher in CON ($M=11.31(SE=0.15), 95\% \text{ CI: } [11.00-11.61]$) as compared to both MJ ($M=10.18(SE=0.44), p=.023, 95\% \text{ CI: } [9.25,11.10]$) and HED+MJ ($M=10.28(SE=0.29), p=.021, 95\% \text{ CI: } [9.68,10.87]$) youth.

Learning and memory. An overall group difference was identified on semantic clustering z-score ($F(3,124)=3.87, p=.011$) with HED ($M=-0.28(SE=0.30), p=.010, 95\% \text{ CI: } [-0.89,0.34]$) performing 0.96 standard deviations poorer than CON ($M=0.68(SE=0.16), 95\% \text{ CI: } [0.36,1.00]$) when recalling a verbal list. An overall group difference was also found for CVLT-II total recall discriminability z-score ($F(3,124)=2.97, p=.034$), with HED ($M= -0.32(SE=0.27), p=.026, 95\% \text{ CI: } [-0.87,0.23]$) performing 0.71 standard deviations below CON ($M=0.39(SE=0.13), 95\% \text{ CI: } [0.13,0.65]$), and HED+MJ ($M = -0.09(SE=0.16), p=.048, 95\% \text{ CI: } [-0.42,0.23]$) performing 0.48 standard deviations below CON. An overall group difference was identified on the long delay cued recall z-score ($F(3,124)=3.56, p=.017$) with MJ ($M= -0.48(SE=0.32), p=.027, 95\% \text{ CI: } [-1.15,0.20]$) performing 0.76 standard deviations poorer than CON ($M=0.28(SE=0.11), 95\% \text{ CI: } [0.05,0.50]$) when recalling a verbal list with category cues. No group effects were found for verbal word-list learning in Trials 1-5 on the CVLT-II task ($F(3,124)=1.07, p=.363$), long delay (20-minute) free recall of the

CVLT-II word list ($F(3,124)=1.44, p=.234$), CVLT-II total recognition discriminability ($F(3,124)=0.38, p=.766$), CVLT-II intrusion rate ($F(3,124)=.737, p=.532$), or for accuracy on a 30-minute delayed recall of the Rey-Osterrieth complex figure ($F(3,126)=1.77, p=.156$).

Visuospatial construction. No statistically significant group differences were found on the two visuospatial tasks: Rey-Osterrieth complex figure copy ($F(3,126)=1.72, p=.167$) and WASI Block Design T-score ($F(3,125)=1.29, p=.282$).

Working memory, attention, and psychomotor speed. A group difference was found for working memory ability on the WAIS-III Arithmetic task ($F(3,126)=2.75, p=.046$), with HED+MJ ($M=10.08(SE=0.46), p=.028, 95\% CI: [9.14,11.03]$) performing 14% worse than CON ($M=11.78(SE=0.29), 95\% CI: [11.21,12.36]$) teens. In the domain of psychomotor speed, an overall group difference was identified for WAIS-III Digit Symbol Coding ($F(3,126)=3.17, p=.027$), with MJ ($M=9.27(SE=0.58), p=.010, 95\% CI: [8.07,10.48]$) performing 14% more slowly than CON ($M=10.75(SE=0.27), 95\% CI: [10.20,11.29]$) youth. No statistically significant group difference was identified on the WAIS-III Digit Span task ($F(3,126)=0.85, p=.968$), the visual scanning condition of the D-KEFS Trail Making Test ($F(3,126)=1.49, p=.222$), or on the D-KEFS Trail Making Number ($F(3,126)=0.79, p=.502$) or Letter ($F(3,126)=1.88, p=.138$) Sequencing tasks.

Language and achievement. On the WRAT-4 Reading task, a group effect was found ($F(3,107)=3.24, p=.025$) with HED ($M=100.75(SE=2.23), p=.018, 95\% CI: [96.13,105.37]$) performing 6% worse than CON ($M=107.14(SE=1.14), 95\% CI: [104.83,109.45]$) teens. No overall group effect was found for WASI Vocabulary ($F(3,127)=0.405, p=.742$).

Associations between substance use characteristics and neuropsychological performance

We combined the three substance use groups (i.e., excluded controls) and found associations between cognitive performance and *lifetime alcohol use episodes*, number of recent *alcohol withdrawal symptoms* (i.e., sum of reported typical withdrawal symptoms including headaches, heart racing, shaking, anxiety, trouble sleeping, etc.) *lifetime marijuana use episodes*, and *age of onset* of regular marijuana use (i.e., greater than 1 time per week), as described below. No associations were found for *days since use* of alcohol or of marijuana.

Alcohol. We found that more *lifetime alcohol use* was associated with lower WAIS-III Arithmetic scores ($\rho = -.27, p = .024$), and having more *alcohol withdrawal symptoms* was associated with lower performance on D-KEFS Trail Making Number-Letter Switching ($\rho = -.29, p = .014$). In addition, having more *alcohol withdrawal symptoms* was related to a higher error rate on the D-KEFS Trail Making visual scanning task ($\rho = .34, p = .004$). While statistically significant group differences were not found using MANCOVA for visuospatial construction or verbal learning, more *alcohol withdrawal symptoms* were associated with worse 2-dimensional visuospatial construction copying ($\rho = -.30, p = .011$), worse performance on the 30-minute delay of the same complex figure ($\rho = -.26, p = .030$), and worse verbal learning on the CVLT-II task ($\rho = -.28, p = .019$) among the combined groups of substance users.

Marijuana. More *lifetime marijuana use* was associated with having a higher false positive error rate on a verbal memory task ($\rho = .32, p = .007$), and an earlier *age of onset* of regular marijuana use was associated with slower psychomotor speed on the D-KEFS Trail Making Motor Speed subtest ($\rho = .51, p = .017$). While a statistically

significant group difference was not found in reading achievement among MJ-using youth, worse performance on WRAT-4 Reading was associated with an earlier *age of onset* of regular marijuana use ($\rho = .29, p = .040$).

Discussion

We examined neuropsychological differences following one month of monitored abstinence among adolescents with limited substance use history compared to those who predominantly use alcohol, marijuana, or both substances. This study features the design strengths of matching groups on premorbid academic functioning, lifetime and recent substance use characteristics, and recency of use at time of testing. While the performances for each group were predominantly in the average range and no group means suggested clinical impairment, subtle differences were evident between groups, with substance-using groups scoring lower than non-using controls in multiple domains. Importantly, these differences were observed after one month of abstinence, on average, which is sufficient time for acute withdrawal symptoms to abate and for THC to be eliminated from the body. Our results suggest that use of alcohol and/or marijuana produces unique and shared cognitive differences in teens earlier in their use continuum than shown previously. These differences seem to emerge in youth prior to the onset of clinical dependence and in the midst of ongoing brain development.

Alcohol Findings

Teens with histories of heavy drinking showed poorer cognitive flexibility, recall and semantic organization of verbal information, and reading achievement relative to non-using controls. Worse performance among HED youth on the D-KEFS Trail Making Number-Letter Switching task suggests poorer cognitive flexibility (e.g., ability to

rapidly switch between categories). Importantly, greater *alcohol withdrawal frequency* among HED youth was associated with their diminished performance on this cognitive flexibility task. HED youth showed worse recall discriminability scores, suggesting poorer recall of target words relative to intrusion rate, and they also showed poorer organization of verbal information into semantic categories when learning a word list. Importantly, these differences in cognitive flexibility and verbal recall were also seen in teens who used both alcohol and marijuana, but not in those who predominantly used marijuana. This overlap suggests that heavy alcohol use may be linked to these executive and verbal weaknesses; furthermore, this finding is consistent with prior research (Brown, et al., 2000; Hanson et al., 2011). Differences in executive functioning appear consistently among heavy drinking youth and may be related to more volume reduction and white matter abnormalities in prefrontal brain areas (DeBellis, Narasimhan, Thatcher, Keshavan, Soloff, & Clark, 2005; McQueeny, Schweinsburg, Schweinsburg, Jacobus, Bava, & Frank, 2009; Medina, McQueeny, Nagel, Hanson, Schweinsburg, & Tapert, 2008).

Alcohol dependent adolescents have frequently demonstrated significantly lower verbal IQ and reading achievement scores (Brown et al., 2000; Giancola et al., 2001; Moss et al., 1994). Our finding of poorer reading scores in nonclinical, heavy drinking youth is consistent with such prior research. Given that the drinkers and nondrinkers had comparable math and language scores in 5th grade, it is possible that the poorer reading skills observed in adolescence may be at least partially due to associated environmental, brain, or behavior changes occurring after the onset of heavy drinking. And while a statistically significant group difference did not emerge for visual scanning among

drinking youth in this sample, greater *alcohol withdrawal symptoms* were associated with increased error rate on a visual scanning task.

Discordant with prior research on teens with alcohol use disorders (Hanson et al., 2011; Squeglia et al., 2009), our findings on a nonclinical sample of heavy episodic drinkers did not suggest weaknesses in visuospatial construction, visuospatial recall, or verbal learning. While statistically significant group findings did not emerge in these areas, importantly, associations were observed between worse performance and increased *alcohol withdrawal symptoms*. It is therefore possible that the level of withdrawal experience from alcohol use is not yet severe enough to associate with group differences. Longer lasting and heavier drinking patterns among adolescents have been linked to disruptions in the hippocampus, a brain structure critical for learning and memory, with adolescent heavy drinkers showing smaller hippocampal volumes and disturbed hippocampal white matter integrity (De Bellis et al., 2000; Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007; Nagel, Schweinsburg, Phan, & Tapert, 2005). Our study involved youth earlier in their drinking careers, suggesting that cognitive decrements in visuospatial recall and verbal learning could emerge after continued involvement in heavy drinking.

Marijuana Findings

Youth with heavy marijuana use showed a different pattern of neuropsychological outcomes than those evident among heavy drinking teens. Consistent with prior research (Hanson et al., 2010; Medina et al., 2007; Millsaps, Azrin, & Mittenberg, 1994; Schwartz, Gruenewalk, Klitzner, & Fedio, 1989), marijuana users evidenced poorer task accuracy, verbal memory, and psychomotor speed than non-using teens. Specifically, MJ-

using youth demonstrated more errors on the D-KEFS Trail Making Task, and this group difference in inhibition task accuracy was also seen in those using both alcohol and marijuana. Although their verbal learning and delayed free recall were similar to those of other groups, MJ-using teens showed worse performance when recalling a verbal word list with cues following a 20-minute delay. Their lower verbal memory was associated with more *lifetime and recent marijuana use*. MJ-using teens also demonstrated slower psychomotor speed on a digit symbol copying task, and slower performance was correlated with an earlier *age of onset* of regular marijuana use. These findings among both marijuana users and concomitant users might suggest that marijuana use disrupts brain mechanisms that maintain focus and enable one both to process efficiently and to follow instructions on tasks that challenge executive systems. Prior observations in marijuana using teens of abnormal cerebellar volumes and disrupted white matter integrity in both frontal and hippocampal regions may partly explain these differences in sustained attention, psychomotor speed, and verbal memory among marijuana using youth (Ashtari et al., 2011; Churchwell, Lopez-Larson, & Yurgelun-Todd, 2010; Cousijn et al., 2012; Medina, Nagel, & Tapert, 2010; Yucel et al., 2010).

Concomitant Use of Alcohol and Marijuana Findings

As mentioned previously, the youth who heavily used both alcohol and marijuana showed overlap with alcohol users in terms of poorer cognitive flexibility and verbal recall, and they showed overlap with marijuana users on poorer task accuracy relative to non-using teens. In addition to showing overlap with the alcohol-using and marijuana-using groups, the concomitant users showed impairment on an arithmetic task that challenges working memory and mathematical abilities. It is possible that concomitant

use of alcohol and marijuana has a unique influence on working memory abilities, which are thought to be modulated by the dorsolateral prefrontal cortex (Barbey, Koenigs, & Grafman, 2013; Crews et al., 2000). Importantly, greater *lifetime exposure to alcohol* was associated with worse performance on the mental arithmetic task in concomitant alcohol and marijuana users, so in line with prior research, use of cannabinoids may enhance sensitivity to the cumulative effects of alcohol exposure (Hansen et al., 2008).

Conclusions

This study featured many design strengths but has several limitations. While the study used carefully designed and selected groups to establish a relationship between heavy episodic drinking, marijuana use, concomitant alcohol and marijuana use, and neurocognitive differences among adolescents, the samples were modest in size; therefore, findings should be interpreted with care and replicated with larger samples. Additionally, the study design did not include a baseline cognitive assessment (prior to abstinence onset), which prevented exploration of any possible recovery of cognitive functioning during the first month of abstinence. Specifically, we were unable to examine differential rates of recovery or baseline functioning between heavy drinkers and heavy marijuana users. While we made substantial effort to ensure similarity of groups on their premorbid academic functioning, there is a strong need for studies to utilize prospective designs to collect data on participants in their late childhood or early adolescence, prior to their initiation of substance use. Such longitudinal investigations can better determine directionality and causality between adolescent substance use and neurocognitive functioning. Also of note, statistically significant group differences did not emerge for gender, yet the group of teens who predominantly used marijuana was mostly male (3

females, 20 males). Follow-up studies could prioritize acquiring a more gender-balanced sample for marijuana users, though most existing studies on marijuana using teens are predominantly male (Hanson et al., 2010; Harvey, Sellman, Porter, & Frampton, 2007; Medina et al., 2007).

In summary, consistent with previous studies and our hypotheses, 16- to 18-year-old alcohol- and marijuana-using adolescents who drink alcohol heavily 1-2 times per week or smoke marijuana 4-5 times per week exhibited modest but poorer neurocognitive functioning even following one month of sustained abstinence. Though requiring replication, the current and previous findings suggest a possible 10-14% or 0.5-0.75 standard deviation reduction in neuropsychological functioning among adolescents with recent histories of heavy episodic drinking and marijuana use relative to their non-using peers. While average performance for the substance using groups was not in the "impaired" range for the tasks, a relative weakness in cognitive flexibility, verbal recall and semantic organization, and reading skills may be related to *heavy alcohol use* during adolescence, whereas poorer task accuracy, verbal memory, and psychomotor speed may be associated with *protracted marijuana use*. Further, working memory may be uniquely impacted by *concomitant use* of marijuana and alcohol. Poorer performance was correlated most strongly with greater alcohol episodes, greater marijuana episodes, greater alcohol withdrawal symptoms, and younger age of onset of marijuana use. The presence of differences even after the substances are no longer present suggests a possible, more chronic alcohol- and marijuana-induced impact to underlying brain systems including the prefrontal cortex, hippocampus, and cerebellum, particularly given that groups were comparable on pre-substance use academic test performance. This

possibility coincides with evidence in the animal literature that adolescence is a time of enhanced sensitivity to the neurotoxic effects of alcohol and marijuana.

This study has the potential to contribute to improved methods for measuring changes on important neurocognitive domains associated with heavy use of alcohol and marijuana during adolescence. Our findings underscore the importance of methodological components of adolescent substance use research by using strict group eligibility criteria, ensuring similar premorbid functioning prior to the onset of substance use, controlling key risk factors, and employing strict abstinence protocols. Possible decrements in executive functioning and language among heavy drinkers; in task accuracy, verbal memory, and psychomotor speed in heavy marijuana users; and in executive functioning, task accuracy, verbal memory, and working memory in concomitant users may have a significant impact on adolescents' daily experiences in academic, occupational, or personal settings (Anderson, Ramo, Cummins, & Brown, 2010). Given the currently high rates of alcohol, marijuana, and concurrent use, it is important that potential users and their parents and educators better understand the unique influence of each drug and the additive impact of concomitant use to a developing brain.

Chapter 3 Acknowledgements

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Table 3.1. Demographic and substance use characteristics for control (CON), heavy episodic drinking (HED), protracted marijuana using (MJ), and heavy episodic drinking and marijuana using (HED+MJ) adolescents (ages 16-18). Groups were matched on socio-demographic characteristics and differed in their substance use history consistent with how the groups were recruited.

	Model <i>p</i> - Value	CON (<i>n</i> =55) M (SD)	HED (<i>n</i> =24) M (SD)	MJ (<i>n</i> =23) M (SD)	HED+MJ (<i>n</i> =29) M (SD)
Socio-Demographics					
Age	.261	17.71 (0.83)	17.90 (0.63)	17.72 (0.85)	18.05 (0.83)
Gender	.182	23 F, 32 M	10 F, 14 M	3 F, 20 M	24 F, 17 M
% Caucasian	.157	71%	71%	81%	62%
% Family history positive ^a	.221	24%	33%	18%	38%
Grades completed	.165	11.16 (0.90)	11.33 (0.96)	10.91 (0.85)	11.45 (0.87)
Hollingshead SES score ^b	.443	27.89 (15.56)	25.21 (11.12)	24.30 (12.28)	29.97 (14.61)
Grade point average	.250	3.38 (0.61)	3.36 (0.69)	3.23 (0.78)	3.10 (0.50)
CBCL Externalizing T-score ^c	.005 ^g	43.56 (8.51)	50.00 (8.78)	49.00 (9.74)	50.67 (10.24)
CBCL Internalizing T-score ^c	.281	43.85 (7.77)	48.50 (11.13)	44.74 (9.32)	46.38 (10.60)
5 th grade standardized language arts score ^d	.857	682.22 (75.07)	653.00 (43.71)	661.25 (12.44)	675.33 (53.81)
5 th grade standardized mathematics score ^d	.893	695.56 (48.34)	676.00 (45.04)	685.75 (23.10)	694.00 (37.56)
Alcohol Use Characteristics					
Lifetime heavy drinking episodes	.001 ^e	1.07 (2.32)	177.38 (89.29)	43.78 (21.68)	268.35 (127.75)
Heavy drinking days/month, 3 months prior to study	.001 ^e	n/a	4.18 (2.40)	n/a	6.75 (2.28)
Age of onset, regular alcohol use	.187	n/a	16.05 (0.79)	n/a	15.21 (1.96)
Days since heavy drinking at testing	.999	n/a	34.46 (8.92)	n/a	31.48 (5.67)
Marijuana Use Characteristics					
Lifetime marijuana use	.001 ^f	0.20 (0.95)	9.04 (8.01)	587.39 (398.96)	433.45 (309.62)
Marijuana days/month, 3 months prior to study	.001 ^f	0.02 (0.13)	0.63 (0.71)	17.78 (10.65)	18.38 (9.73)
Age of onset, regular marijuana use	.771	n/a	n/a	15.05 (1.56)	15.36 (1.59)
Days since marijuana use at testing	.001 ^f	333.00 (323.16)	168.40 (193.58)	34.27 (11.64)	31.93 (10.83)
Other Drug Use Characteristics					
Lifetime use of other drugs	.001 ^g	0.00 (0.00)	6.71 (8.98)	8.65 (10.52)	9.56 (8.93)

^a Family history positive = Having a first-degree biological relative with alcohol or drug related dependence

^b Hollingshead (1965) SES (socioeconomic status): Higher scores = lower SES

^c CBCL: Child Behavior Checklist

^d Scaled score on California Achievement Test, 6th Edition (CAT-6)

^e (CON, MJ) ≠ (HED, HED+MJ) using $p < .05$ in Tukey's HSD post hoc tests

^f (CON, HED) ≠ (MJ, HED+MJ) using $p < .05$ in Tukey's HSD post hoc tests

^g CON ≠ (HED, MJ, HED+MJ) using $p < .05$ in Tukey's HSD post hoc tests

Table 3.2. Marginal means (SE) demonstrate differences in neuropsychological performance after one month of monitored abstinence in control (CON), heavy episodic drinking (HED), protracted marijuana using (MJ), both heavy episodic drinking and heavy marijuana using (HED+MJ) adolescents (ages 16-18)

	Model <i>p</i> - Value	CON (<i>n</i> =55) M (SE)	HED (<i>n</i> =24) M (SE)	MJ (<i>n</i> =23) M (SE)	HED+MJ (<i>n</i> =29) M (SE)
Executive Functioning					
D-KEFS Trail Making Number-Letter Switching SS	.002 ^{a, c}	11.04 (0.21)	9.55 (0.41)	10.09 (0.40)	9.84 (0.37)
D-KEFS Trail Making All Errors SS	.005 ^{b, c}	11.31 (0.15)	10.92 (0.35)	10.18 (0.44)	10.28 (0.29)
Learning and Memory					
Complex Figure Accuracy raw (30-min delay)	.135	17.62 (0.65)	15.07 (0.98)	18.20 (0.74)	17.53 (1.19)
CVLT-II Trials 1-5 Total Recall T-score	.369	55.76 (1.16)	51.96 (2.57)	53.95 (2.11)	53.48 (1.23)
CVLT-II Long Delay Free Recall z-score	.234	0.22 (0.12)	-0.20 (0.22)	0.00 (0.24)	-0.07 (0.13)
CVLT-II Long Delay Cued Recall z-score	.017 ^b	0.28 (0.11)	-0.30 (0.26)	-0.48 (0.32)	-0.04 (0.12)
CVLT-II Semantic Clustering z-score	.017 ^a	0.68 (0.16)	-0.28 (0.30)	0.10 (0.22)	0.06 (0.24)
CVLT-II Total Recall Disc. z-score	.028 ^{a, c}	0.39 (0.13)	-0.32 (0.27)	0.08 (0.23)	-0.09 (0.16)
CVLT-II Total Recall Intrusion z-score ^d	.528	0.10 (0.12)	0.39 (0.27)	0.40 (0.11)	0.25 (0.19)
CVLT-II Total Recognition Disc. z-score	.748	0.34 (0.10)	0.24 (0.24)	0.23 (0.24)	0.12 (0.13)
Visuospatial Construction					
Complex Figure Accuracy raw (Direct Copy)	.171	28.39 (0.46)	27.04 (0.70)	29.18 (0.80)	28.95 (0.74)
WASI Block Design T-score	.257	56.67 (0.85)	58.51 (0.98)	56.24 (1.20)	54.92 (1.55)
Working Memory					
WAIS-III Arithmetic SS	.019 ^c	11.78 (0.29)	11.27 (0.55)	11.77 (0.57)	10.08 (0.46)
WAIS-III Digit Span SS	.935	10.64 (0.33)	10.52 (0.55)	10.23 (0.58)	10.48 (0.43)
Attention					
D-KEFS Trail Making Visual Scanning SS	.156	11.13 (0.23)	10.89 (0.51)	11.50 (0.34)	11.91 (0.25)
Psychomotor Speed					
WAIS-III Digit Symbol Coding SS	.037 ^b	10.75 (0.27)	9.58 (0.47)	9.27 (0.58)	10.05 (0.42)
D-KEFS Trail Making Number Sequencing SS	.531	11.25 (0.28)	10.85 (0.27)	10.50 (0.57)	11.10 (0.40)
D-KEFS Trail Making Letter Sequencing SS	.103	11.49 (0.30)	11.39 (0.34)	10.18 (0.60)	11.44 (0.33)
Language and Achievement					
WASI Vocabulary T-Score	.117	59.87 (1.10)	55.75 (1.55)	56.57 (2.28)	56.62 (1.21)
WRAT-4 Reading Standard Score	.032 ^a	107.14 (1.14)	100.75 (2.23)	105.91 (1.64)	105.10 (1.37)

Statistically significant ($p < .05$) Tukey's HSD post hoc contrasts for ^aCON vs. HED, ^bCON vs MJ, and ^cCON vs HED+MJ.

^dItem is reverse-scored, so higher scores indicate poorer performance

Note: SS = scaled score; Complex Figure = Rey-Osterrieth Complex Figure copy and 30-minute delayed recall (Osterrieth, 1944); D-KEFS = Delis-Kaplan Executive Functioning System Trail Making Test (Delis et al., 2001); CVLT-II = California Verbal Learning Test - Second Edition (Delis et al., 2000); WASI = Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999); WAIS-III = Wechsler Adult Intelligence Scale-III (Wechsler, 1997); WRAT-4 = Wide Range Achievement Test-4 (Wilkinson & Robertson, 2006).

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GENERAL DISCUSSION

The three studies of this stapled dissertation are essential to expand the literature's understanding of (1) changes in distress tolerance and emotional reactivity in adolescent heavy drinkers over one month of abstinence, (2) changes in neuropsychological performance in adolescent heavy drinkers over one month of abstinence, and (3) differences in cognition following one month of abstinence among teens who predominantly use alcohol, marijuana, or both alcohol and marijuana. These studies utilized sound methodological approaches that considered multiple risk factors in analyses: gender, age, poor self regulation, family history of substance use, and comorbid Axis I disorders. All investigations utilized highly regulated abstinence monitoring protocols to verify abstention in youth. Unique to this body of work is the collection of data on 5th grade standardized tests of mathematics and language arts to ensure groups' similarity on premorbid academic functioning, strengthening generalizations made about the impact of substance use.

By matching on key risk factors and exploring the relationship between observed lab-based and school-based deficits and substance use characteristics, this body of research elucidates the complex relationship among premorbid functioning, adolescent brain development, and the effects of alcohol and marijuana use during this critical time period. Given the high rates of alcohol and marijuana use among youth, such findings have far-reaching, important implications for educational, professional, and psychological interventions designed to prevent or reduce substance use in adolescence.

Contribution of Study 1

Improvements in emotional reactivity and distress tolerance with abstinence had previously been reported in adult populations, but this possibility had not yet been explored among heavy drinking adolescents. This study was the first to examine changes in emotional reactivity and distress tolerance in relation to length of abstinence among heavy episodic drinking youth. The groups were comparable on demographic and family history of alcoholism dimensions, and the heavy drinking teens were studied prior to onset of alcohol dependence.

This study suggests that with recent (i.e., prior 10 days) exposure to alcohol, youth with histories of heavy drinking show greater negative affective responses and poorer distress tolerance in cognitively challenging situations. Importantly, though, their emotional reactivity diminished with continued abstinence. These findings could reflect a return to functioning that existed prior to onset of heavy drinking, an experience of short-term positive responses to encouraging life events (e.g., end of transient withdrawal symptoms or positive reinforcement for behavior change), or other factors related to recent abstinence.

The study also examined correlations among emotional reactivity, distress tolerance, and task performance with characteristics of teens' alcohol use. Similar to the existing literature, the strongest correlations were seen with greater lifetime and recent alcohol consumption and greater frequency of withdrawal symptoms. Teens with more lifetime and cumulative exposure and with more withdrawal symptoms showed more emotional lability in cognitively challenging situations. This work continues that trend in

the literature in that cumulative exposure and withdrawal may relate most strongly to outcomes associated with heavy alcohol use.

Prior research suggests that intolerance of emotional and somatic sensations is a key mechanism driving continued use. So while this study presented findings based off a modest sample size, it is the first to illustrate heightened emotional reactivity and poorer distress tolerance to a cognitively challenging task in heavy drinking adolescents in early periods of abstinence. It is possible that the combination of elevated negative affect and low distress tolerance during early abstinence may be a mechanism whereby heavy episodic drinking heightens risk for progression to an alcohol use disorder or results in a return to use following periods of abstinence. The capacity to withstand aversive internal states, including negative emotions, is integral to daily functioning. Importantly, the emotional reactivity of heavy episodic drinking adolescents appears to reduce with continued abstinence, and reductions in emotional reactivity with abstinence may contribute to improvements in academic and social functioning among nonclinical, heavy drinking youth. Additional research is needed to understand factors underlying and facilitating this improvement and whether interventions can further improve emotional reactivity and distress tolerance among youth during early periods of abstinence.

Contribution of Study 2

While many existing studies reported deficits across several neurocognitive domains, no previous study had investigated the rate and pattern of neuropsychological recovery in heavy episodic drinking teens throughout the initial days to weeks of abstinence from alcohol. Another distinctive feature of this examination is that it ensured groups' comparable academic functioning that predated initiation of substance use (i.e.,

5th grade standardized academic test scores). In this study, drinking and nondrinking participants completed a neuropsychological battery three times at 2-week intervals over four weeks of monitored abstinence. This study examined neurocognitive differences and patterns of recovery in abstinent, adolescent heavy episodic drinkers compared to their nondrinking peers.

Findings suggest that adolescents with histories of an average of over 200 lifetime drinking episodes who initiated heavy episodic drinking at an average age of 15.33 differed from socio-demographically similar nondrinkers across several neuropsychological domains both during the early stages of abstinence and with continued abstention. This study involved youth earlier in their drinking careers but produced findings similar to prior research on youth with greater alcohol use histories: heavy episodic drinking adolescents performed worse on executive functioning (i.e., prospective memory, cognitive switching, inhibition task accuracy), visuospatial abilities (i.e., complex figure construction), verbal memory, and language and achievement (i.e., reading and vocabulary). Heavy drinking youth performed approximately 5-10% lower and committed 50-100% more errors across time compared to their non-drinking peers. Unlike prior research, this study did not identify statistically significant deficits in verbal learning, visuospatial memory, working memory, attention, or psychomotor speed when comparing heavy episodic drinking youth, who have not yet experienced substantial alcohol related problems, to nondrinking youth. Intensity of alcohol use may not yet be severe enough to manifest in differences, or, alternatively, methodological differences (e.g., variations in abstention protocol, drug use eligibility criteria, or sample size) may also have contributed to incongruent findings.

As expected, heavy episodic drinkers had some exposure to marijuana or other drugs. While the mixed models did covary for marijuana exposure, it is possible that other substance use, although limited, may have contributed to group differences. Of note, the heavy episodic drinkers consumed alcohol four times more than marijuana in their lifetimes, and had an average of approximately ten lifetime experiences with other drugs.

These findings, coupled with extant literature in this field, suggest that deficient neuropsychological functioning is present among adolescents with recent histories of heavy episodic drinking relative to their nondrinking peers. These cognitive differences persist across four to six weeks of abstinence, suggesting a possible alcohol-induced impact to underlying brain systems, particularly given that groups were comparable on pre-drinking academic test performance. This possibility coincides with the animal literature's finding that adolescence is a time of enhanced sensitivity to the neurotoxic effects of alcohol. Poorer performance in prospective memory, cognitive switching, response inhibition, verbal memory, visuospatial ability, vocabulary, and reading may significantly impact daily functioning in both academic and professional settings: goal oriented behavior, cognitive flexibility, and recall of verbal information are essential to stay on task, shift mental modes, respond accurately, follow instructions, and remember lists. Also, given that the drinkers and nondrinkers had comparable math and language scores in 5th grade, it is possible that the poorer functioning observed in adolescents with heavy drinking histories may be at least partially due to related environment, brain, or behavior changes occurring after the onset of heavy drinking.

Contribution of Study 3

This study examined neuropsychological differences following one month of monitored abstinence among adolescents with limited substance use history compared to those who predominantly use alcohol, marijuana, or both substances. Using strict criteria to differentiate groups, the study compared neuropsychological performance among (1) alcohol users, (2) marijuana users, (3) those who use both marijuana and alcohol, and (4) non-using controls. To the best of our knowledge, direct comparisons among these groups following four weeks of monitored abstinence had not been reported previously. Overall, the study featured the design strengths of matching on premorbid academic functioning, lifetime and recent substance use characteristics, and recency of use at time of testing.

Consistent with previous studies, 16- to 18-year-old alcohol- and marijuana-using adolescents exhibited modest but poorer neurocognitive functioning, even following one month of sustained abstinence. In the study, a relative weakness in cognitive flexibility, verbal recall, and reading skills may be related to heavy alcohol use during adolescence, whereas poorer task accuracy, verbal memory, and psychomotor speed may be associated with regular marijuana use. Further, working memory may be particularly impacted by concomitant use of marijuana and alcohol. Prior research on samples of youth with alcohol use disorders and heavier drinking histories suggests deficits in visuospatial performance, processing speed, and attention among adolescent drinkers. While this study, similar to Study 2, failed to replicate those findings, it did identify associations between greater alcohol withdrawal symptoms and lower performance in those areas,

suggesting that those cognitive deficits could emerge after continued involvement in heavy drinking.

The observed deficits in substance-using teens ranged from approximately 10-14%, or from 0.5-0.75 standard deviations, poorer than non-using youth, and poorer performance was correlated most strongly with greater lifetime exposure to alcohol, lifetime exposure to marijuana, and withdrawal experience from alcohol, and with younger age of onset of marijuana use. These findings, coupled with those of the extant literature, suggest that a possible reduction in neuropsychological functioning is present among adolescents with recent histories of heavy episodic drinking and marijuana use relative to their non-using peers. These cognitive differences persisted even after an average of four to five weeks of abstinence, suggesting a possible alcohol- and marijuana-induced impact to underlying brain systems, particularly given that groups were comparable on pre-drinking academic test performance. This possibility coincides with the animal literature's evidence that adolescence is a time of enhanced sensitivity to the neurotoxic effects of alcohol and marijuana.

Main Conclusion

This body of work contributes to the existing literature by identifying improvements in emotional reactivity among abstinent adolescent drinkers; employing strict group eligibility criteria, ensuring similar premorbid academic functioning, and still finding neuropsychological deficits consistent with prior research on adolescents with more pronounced substance use histories; and identifying the unique influence of alcohol and marijuana on functioning by directly comparing groups using each or both of those substances to each other and to non-using peers.

With both ethanol and cannabis appearing to influence the macrostructure and microstructure of specific brain structures - most notably the prefrontal cortex, hippocampus, corpus callosum, and cerebellum - it is not surprising that deficits are consistently seen in areas of executive functioning, learning, memory, and achievement in adolescents who use one or both of these substances. The unique impact of marijuana on the cerebellum possibly explains the psychomotor and attention deficits seen predominantly among marijuana users. In studies 2 and 3, heavy drinking youth did not show deficits in processing speed or attention, which is discordant from prior research on clinical samples and those with heavier substance use histories. It is possible the alcohol users studied in the present sample had not yet used alcohol enough to impact this area of functioning, or it is possible that “alcohol using” teens studied previously had marijuana exposure significant enough to impact their psychomotor speed and attention. Future research is needed to verify this area of discordance and to substantiate the studies’ main findings.

So while alcohol and marijuana appear to influence the brain in ways that both overlap and are unique to each substance, it is important to note that this examination was largely consistent with the existing literature in its findings about correlations between deficits and aspects of substance use. Deficits among heavy drinking youth appear most strongly related to their recent and lifetime exposure and withdrawal, while findings among marijuana using youth appear linked to their age of onset and lifetime use.

This body of research underscores the importance of several methodological components of adolescent substance research: using strict group eligibility criteria and minimizing use of other substances as much as possible, controlling for key risk factors,

and utilizing highly-regulated abstinence monitoring protocols. Additionally, these studies made substantial efforts to ensure group comparability on their premorbid academic functioning; however, there is a strong need for studies to utilize prospective designs to collect data on participants in their late childhood or early adolescence, prior to their initiation of substance use. Such longitudinal investigations can better determine directionality and causality between adolescent substance use and their emotional reactivity and neurocognitive functioning.

Despite the limitations of modest sample size and cross-sectional design, the findings presented here contribute significantly to the extant literature. This body of work suggests that alcohol and marijuana both impact executive functioning, learning, and memory; whereas alcohol has a unique impact on reading and vocabulary, marijuana has a unique impact on attention and processing speed, and use of both substances particularly impacts working memory systems. Heavy, recent alcohol use was also linked to heightened negative emotional reactivity that did reduce within one month of abstinence; however, this possibility was not explored among marijuana using youth. These findings have the potential to improve methods for (1) measuring changes on important neurocognitive, affective, and behavioral domains associated with adolescent substance use, (2) monitoring and facilitating real life behavioral improvements associated with abstinence from alcohol and from marijuana, and (3) improving outcomes for substance using youth by informing teachers, parents, and adolescents about potential impacts to their cognition and affect following heavy use of alcohol and/or marijuana.