Neurocognitive, Affective, and Psychosocial Correlates of Adolescent Substance Use

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DISSERTATION THESIS

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This thesis is dedicated to my parents and to MJS, without their support it may not have been accomplished.

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ASBC	Antisocial Behavior Checklist
BIS	Barratt Impulsiveness Scale-11
CES-D	Center for Epidemiological Scale-Depression
CUDIT-R	Cannabis Use Disorder Identification Test- Revised
FEPT	Facial Emotion Perception Task
GPA	Grade-Point Average
IGT	Iowa Gambling Task
IQ	General Intellectual Abilities
MASQ	Mood and Affect Symptom Questionnaire
mFTQ	Modified Fagerstrom Questionnaire
mMID	Modified Monetary Incentive Delay Task
MPS	Marijuana Problem Scale
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NMR	Negative Mood Regulation Expectancies Scale
SCID	Structured Clinical Interview for DSM-IV
SECASP	Social and Emotional Contexts of Adolescent Smoking Patterns
SJWS	Shiffman/Jarvik Withdrawal Questionnaire- Short Version
SUD	Substance Use Disorder
TOMM	Test of Memory Malingering
THC	Delta-9-tetrahydrocannabinol
UDS	Urine Drug Screen
WTAR	Wechsler Test of Adult Reading
WURS	Wender-Utah Rating Scale

SUMMARY

Alcohol, nicotine, and marijuana are the most widely used substances among adolescents and young adults and their use is a significant public health concern, as it is associated with several negative health, psychosocial, and neurocognitive outcomes. Despite the high prevalence of the co-use of these substances, little is known about the neurocognitive, affective, and psychosocial correlates of poly-substance use in adolescence and the subsequent functional and neurocognitive outcomes associated with use in young adulthood. Although there is some evidence that pre-existing traits and brain abnormalities predict initiation of substance use, several studies suggest that adolescents may also be particularly vulnerable to the neurotoxic effects of alcohol and marijuana, resulting in additive structural brain abnormalities, delayed neurodevelopment, and poorer neurocognitive performance among users. Further, many studies have demonstrated that psychological and psychiatric symptoms are associated with substance use, but no studies to our knowledge have prospectively measured how these factors may be related to adolescent substance use and subsequent neurocognitive functioning. Therefore, the current study examined how clinical risk factors contribute to subsequent cigarette, marijuana, and alcohol use during adolescence, in turn impacting neurocognitive functioning and psychosocial outcomes in young adulthood. Participants were young adults who are enrolled in a longitudinal study on the social and emotional contexts of adolescent smoking and have been followed for 8 years (N=1263). A subset of these individuals (n=80) was also recruited for a laboratory study visit to assess their neurocognitive functioning. It was hypothesized that individuals with more baseline clinical risk factors will have heavier cigarette, marijuana, alcohol use, which will in turn be associated with poorer neurocognitive and functional outcomes. The results expanded upon previous studies, finding that more depression and anxiety, poorer negative mood regulation, and lower GPA is related to more poly-substance over adolescence

and young adulthood and that more poly-substance use in adolescence and young adulthood is associated with poorer educational attainment in young adulthood, but we were not able to replicate findings of how substance use is associated with neurocognitive outcomes. Results indicate that there is tremendous individual variability in use of cigarettes, marijuana, and alcohol, factors related to use of these substances, and the effects of these substances on neurocognitive functioning.

1. INTRODUCTION

A. Background

Alcohol, nicotine, and marijuana are the three most widely used substances among adolescents and young adults. Approximately 35% of 12th graders in the United States report using alcohol; 21% report using marijuana; and 11% report using cigarettes in the past 30 days in 2015 (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2015). Engaging in substance use in adolescence is particularly problematic, as individuals who use alcohol before the age of 18 have a two times greater risk of developing an Alcohol Use Disorder, and individuals who use marijuana before the age of 18 increase their risk of developing a Cannabis Use Disorder four to seven times (Winters & Lee, 2008). Indeed, approximately 75% of young adults who seek treatment for a Substance Use Disorder initiated their substance use before the age of 17 (SAMSHA, 2014). Poly-substance use of alcohol, nicotine, and marijuana is more prevalent than use of one of these substances alone (Hermens et al., 2013; Kandel, Chen, Warner, Kessler, & Grant, 1997; Kendler, Schmitt, Aggen, & Prescott, 2008; Maes et al., 1999; Rhee et al., 2003; SAMSHA, 2013). Therefore, it is critical that we better understand the risk factors and the neurocognitive and functional outcomes of poly-substance use (defined here as nicotine, marijuana, and alcohol) during adolescence and early young adulthood.

B. High Rates of Poly-Substance Use in Adolescence

High rates of poly-substance use are common and are associated with increased substance use and substance-related problems. Several animal and human studies suggest that poly-substance use of substances may potentiate use and dependence for each substance. For example, young adults who use cigarettes are much more likely to also use marijuana than are non-smokers (Ramo & Prochaska, 2012). Epidemiological evidence demonstrates a reciprocal relationship in the prevalence and severity of cigarette and marijuana use (Degenhardt, Hall, & Lynskey, 2001; Kandel & Yamaguchi, 1993; Korhonen et al., 2008; Lynskey, Fergusson, &

Horwood, 1998; Mathers, Toumbourou, Catalano, Williams, & Patton, 2006; G. C. Patton, Coffey, Carlin, Sawyer, & Wakefield, 2006). Specifically, cigarette users are more likely to engage in subsequent marijuana use (Kandel & Yamaguchi, 1993; G. C. Patton et al., 2006; Prince van Leeuwen et al., 2013; Rigotti, Lee, & Wechsler, 2000; Silins et al., 2013), and cigarette users who also use marijuana are more likely to escalate their cigarette use and develop nicotine dependence (Agrawal, Madden, Bucholz, Heath, & Lynskey, 2008; G. C. Patton, Coffey, Carlin, Sawyer, & Lynskey, 2005; G. C. Patton et al., 2006; Timberlake et al., 2007; Tullis, Dupont, Frost-Pineda, & Gold, 2003). Similarly, cigarette use is associated with higher alcohol consumption. More than half of heavy alcohol users aged 12 or older reported smoking cigarettes in the past month compared to only 16% of individuals who did not drink alcohol in the past month (SAMSHA, 2013). Among cigarette users, those individuals with a history of alcohol use disorders have more severe nicotine dependence and symptoms of nicotine withdrawal (Dierker, Selya, Piasecki, Rose, & Mermelstein, 2013; Drobes, 2002; Marks, Hill, Pomerleau, Mudd, & Blow, 1997). Furthermore, there is high comorbidity between alcohol and cannabis use disorders (Mason, Chmelka, Howard, & Thompson, 2013); approximately 58% of adolescent alcohol users also use marijuana (Martin, Kaczynski, Maisto, & Tarter, 1996). Due to the fact that marijuana and alcohol both work through the endocannabinoid system (Hungund, Szakall, Adam, Basavarajappa, & Vadasz, 2003; Pava & Woodward, 2012), there is some evidence that marijuana use may potentiate alcohol's effects (Hurst & Bagley, 1972; Lemos, Takahashi, & Morato, 2007; Lukas et al., 1992; Swartzwelder et al., 2012) and vice versa (Lukas & Orozco, 2001), leading to escalating use. At least one study has found that tobacco use or dependence increases the risk of alcohol and marijuana problems over time (Palmer et al., 2009). Put together, there is substantial evidence that poly-substance use is highly prevalent among substance users, and it may place individuals at greater risk for escalation in use, severity of dependence on each substance, and greater problems associated with use.

C. Poly-Substance Use is Associated with Poorer Health and Psychosocial Outcomes

Poly-substance use may also be associated with poorer health consequences and psychosocial outcomes. Cigarette, alcohol, and marijuana use are each independently associated with negative consequences, including poor health and mental health outcomes (Brook, Lee, Brown, & Finch, 2012; CDC, 2012, 2013; Degenhardt, Hall, & Lynskey, 2003; Fergusson, Boden, & Horwood, 2013; Mathers et al., 2006), lower educational outcomes (Cook & Moore, 1993; Fergusson & Boden, 2008; Grant et al., 2012; Horwood et al., 2010; Lynskey, Coffey, Degenhardt, Carlin, & Patton, 2003), and social problems (Casswell & Thamarangsi, 2009; Fergusson & Boden, 2008; Fergusson et al., 2013; Kraus, Baumeister, Pabst, & Orth, 2009; Mathers et al., 2006), but studies suggest that poly-substance use may have an additive negative effect on these outcomes. For example, cigarette and alcohol use among adolescents is more strongly associated with illicit drug use, including marijuana, as well as several health, mental health and social problems than use of either drug alone (Baggio, Studer, Mohler-Kuo, Daeppen, & Gmel, 2013; Hoffman, Welte, & Barnes, 2001; E. N. Peters, Budney, & Carroll, 2012). Users of each substance often report multiple quit attempts without achieving prolonged abstinence (Budney, Vandrey, Hughes, Thostenson, & Bursac, 2008; Heinz, Beck, Grusser, Grace, & Wrase, 2009). Indeed, treatment outcomes for individuals with poly-substance use are generally poorer than for individuals who only use one substance (Agrawal, Budney, & Lynskey, 2012; Drobes, 2002; Humfleet, Munoz, Sees, Reus, & Hall, 1999). Thus, poly-substance use seems to be associated not only with increased substance use, a higher severity of substance dependence, and more substance-related problems, but also greater negative health consequences and psychosocial outcomes.

D. Shared Clinical Risk Factors in Alcohol, Nicotine, and Cannabis Use Disorders

Evidence indicates that there are shared clinical risk factors for alcohol, nicotine, and cannabis use disorders. Several studies have demonstrated that psychological and psychiatric

symptoms are associated with substance use (Cornelius, Clark, Bukstein, & Salloum, 2005; D. B. Kandel et al., 1997; Najt, Fusar-Poli, & Brambilla, 2011; L. H. Patton, 1995; Shrier, Harris, Kurland, & Knight, 2003; Simkin, 2002; Tarter, 2002; van der Pol et al., 2013). Symptoms of depression (Libby, Orton, Stover, & Riggs, 2005; Volkow, 2004; Weinstein & Mermelstein, 2013b), high negative affect and dysregulated mood regulation (Magid, Colder, Stroud, Nichter, & Nichter, 2009; Weinstein & Mermelstein, 2013a, 2013b), symptoms of antisocial personality disorder (Hawkins, Catalano, & Miller, 1992; Westermeyer & Thuras, 2005; Whitmore et al., 1997), and poor school achievement (Birckmayer, Holder, Yacoubian, & Friend, 2004; Wills, Vaccaro, McNamara, & Hirky, 1996) are all associated with alcohol, nicotine, and cannabis use disorders. However, it is not clear what are the key risk factors for poly-substance use and how these vary over time. To our knowledge, no studies have prospectively measured how clinical risk factors may be related to frequency of adolescent substance use and subsequent neurocognitive functioning. The goals of this study are first, to understand better clinical risk factors for poly-substance use and how these factors vary over time, and then to understand how these key risk factors are related to frequency of cigarette, marijuana, and alcohol use as well as the subsequent neurocognitive and affective functioning of poly-substance users.

E. Shared Neurocognitive Correlates in Cigarette, Marijuana, and Alcohol Users

Emotional processing and reward processing difficulties may be shared neurocognitive correlates present in users of cigarette, marijuana, and alcohol. Reward processing abnormalities are conceptualized as a common mechanism underlying all substance use disorders (Fernandez-Serrano, Perez-Garcia, & Verdejo-Garcia, 2011; Goodman, 2008; Koob & Le Moal, 2008; Verdejo-Garcia, Perez-Garcia, & Bechara, 2006). Evidence indicates that deficits in emotional regulation and reward processing are risk factors for the development of substance use disorders (Andrews et al., 2011; Dawe, Gullo, & Loxton, 2004; Ernst et al., 2010; Gowin, Mackey, & Paulus, 2013; Hulvershorn et al., 2013; Muller et al., 2013; Nees et al., 2012; J. Peters et al.,

2011; Schneider et al., 2012), and deficits in these domains are found in individuals with alcohol use disorders (Clark, Oscar-Berman, Shagrin, & Pencina, 2007; Frigerio, Burt, Montagne, Murray, & Perrett, 2002; Maurage, Campanella, Philippot, Martin, & de Timary, 2008; Maurage, Campanella, Philippot, Pham, & Joassin, 2007; Oscar-Berman, Hancock, Mildworf, Hutner, & Weber, 1990) and cannabis use disorders (Platt, Kamboj, Morgan, & Curran, 2010). Several studies suggest that adolescents may be particularly vulnerable to the neurotoxic effects of alcohol and marijuana, resulting in additive structural brain abnormalities and poorer neurocognitive performance among users (Hanson, Medina, Padula, Tapert, & Brown, 2011; Jacobus, Squeglia, Infante, Bava, & Tapert, 2013; Meier et al., 2012; Squeglia, Spadoni, Infante, Myers, & Tapert, 2009; Tapert, Granholm, Leedy, & Brown, 2002), which may have long-lasting effects (Crane et al., 2013; Jacobus & Tapert, 2013, 2014). Marijuana and alcohol both act on the endocannabinoid system in the brain, a neurotransmitter system that plays a crucial role in neuromaturation and synaptic pruning (Viveros et al., 2012). Therefore, marijuana and alcohol use during adolescence, when the brain is undergoing rapid neurodevelopment, may disrupt normal neuromaturation. Animal studies have shown that adolescent rats exposed to THC show impairments in working memory in adulthood, which is associated with less active synapses in the prefrontal cortex (Rubino et al., 2009a) and shorter dendrites with reduced spine densities in the hippocampus, indicating that adolescent marijuana use may have lasting functional and structural brain changes (Rubino et al., 2009b). Similarly, animal studies have shown that adolescent rats exposed to chronic intermittent alcohol show persistent reductions in hippocampal volume in adulthood, even after 10 weeks of abstinence (Ehlers et al., 2013). The impact of adolescent chronic nicotine use on brain structure or function is not currently well understood (Barron et al., 2005; Lessov-Schlaggar et al., 2013). These disruptions in limbic and prefrontal cortex development may impair individuals' ability to engage in top-down processing to regulate emotional and reward processing.

It is also possible that in addition to exogenous neurotoxic insults of substance use on gray and white matter integrity, experiential and genetic factors associated with an increased risk of substance use may delay or disrupt neurodevelopment. Specifically, these genetic factors may contribute to protracted neurodevelopment, especially in the frontal cortex as seen in other neurodevelopmental disorders (Giedd & Rapport, 2010). Indeed, some evidence suggests that smaller premorbid orbitofrontal cortex gray matter volumes predict initiation of marijuana use (Cheetham et al., 2012), reflecting higher impulsivity (Berlin, Rolls, & Kischka 2004), a trait that is associated with protracted prefrontal cortex development (see Casey et al., 2008). This protracted neurodevelopmental trajectory may be associated with poorer neurocognitive functioning, especially executive functioning, via direct relationships with protracted neurodevelopment and via indirect epigenetic pathways. For example, substance naïve adolescents with a family history of substance use show aberrant white matter connectivity between the nucleus accumbens, which is involved in reward, and the orbitofrontal cortex, which is involved in regulation of reward areas and decision-making (Squeglia, Sorg, Jacobus, Brumback, Taylor, & Tapert, in press). These structural changes in neurodevelopment may result in poorer executive functioning, hypersensitivity to rewards, and disrupted reward learning that may lead adolescents to engage in other risky behaviors in addition to substance use, like delinquency (Giancola & Parker, 2001; Moffitt et al., 2011; Tarter et al., 2003). These risky behaviors may disrupt their learning and social development and in turn, create environmental contexts that may further negatively impact neurocognitive functioning and/or turn on gene expression that contributes to poorer neurocognitive functioning in vulnerable phenotypes.

Relatively few studies have examined the neurocognitive domains of emotional processing or reward processing among adolescent or young adult alcohol- or marijuana-users. Thus, little is known about how substance use in adolescence and young adulthood may impact these domains. Importantly, these are critical periods of neurodevelopment and psychosocial

development, when many individuals transition to dependence. Given that emotional and reward processing may be shared mechanisms related to substance use disorders, it is important to better understand how these domains may relate to frequency of substance use during adolescence and young adulthood. Thus, the second aim of the study is to understand how frequency of cigarette, marijuana, and alcohol use relates to neurocognitive functioning, especially in the domains of emotional and reward processing. Although this study cannot address which components signify clinical vulnerabilities and which reflect chronicity dependent features, it does help identify key markers of concern. As the participants will be a relatively young group, there is great potential for highlighting early signs of vulnerability that may increase risk for subsequent dependence, crucial information that can help to inform prevention and intervention efforts.

The neurocognitive sequalae of cigarette, marijuana, and alcohol use are often studied separately. The majority of studies examining neurocognitive performance investigate the impact of one substance in isolation (or controlling for other substance use). Some more recent studies have found interactive effects of marijuana and alcohol use (Mahmood, Jacobus, Bava, Scarlett, & Tapert, 2010; Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007; Nixon, Paul, & Phillips, 1998; Schweinsburg, Schweinsburg, Nagel, Eyler, & Tapert, 2011), of marijuana and nicotine use (Jacobsen, Pugh, Constable, Westerveld, & Mencl, 2007; Schuster, Crane, Mermelstein, & Gonzalez, 2015), and of nicotine and alcohol use (Durazzo, Gazdzinski, & Meyerhoff, 2007; Durazzo et al., 2013) on neurocognitive functioning. Although studying the unique effects of selective substance use is important in helping us to better understand the effects of specific substances, this approach is problematic in that it does not reflect the reality of substance use: poly-substance use is the most common presentation and is the most debilitating long-term. Therefore, we know relatively little about the impact of poly-substance use during adolescence and young adulthood on neurocognition, especially on key domains like emotional processing and reward processing.

F. Integrating Clinical Risk Factors, Neurocognitive Correlates, and Psychosocial Outcomes of Adolescent Cigarette, Marijuana, and Alcohol Use

Taken together, there is a disconnect between the nature of substance use in the population, which is frequently poly-substance use, and our studies of the correlates of substance use. Furthermore, for many individuals, substance use begins after a period of nascent risk of co-occurring conditions and adverse contexts. Indeed, psychological and psychiatric symptoms like depression (Libby et al., 2005; Volkow, 2004; Weinstein & Mermelstein, 2013b), high negative affect and dysregulated mood regulation (Magid et al., 2009; Weinstein & Mermelstein, 2013a, 2013b), symptoms of antisocial personality disorder (Hawkins et al., 1992; Westermeyer & Thuras, 2005; Whitmore et al., 1997), and poor school achievement (Birckmayer et al., 2004; Wills et al., 1996) are risk factors for cigarette, marijuana, and alcohol use, which in turn are associated with poorer neurocognitive functioning (Hanson et al., 2011; Jacobus et al., 2013; Meier et al., 2012; Squeglia et al., 2009; Tapert et al., 2002) and psychosocial outcomes, including several health, mental health and social problems (Baggio et al., 2013; Hoffman et al., 2001; E. N. Peters et al., 2012). However, to our knowledge, no studies have prospectively measured how clinical risk factors may be related to frequency of adolescent poly-substance use and subsequent neurocognitive functioning and psychosocial outcomes. Thus, the current study provides a unique opportunity to integrate the clinical risk factors, the neurocognitive correlates, and the psychosocial outcomes of alcohol, nicotine, and marijuana use during adolescence and young adulthood to better understand these relationships.

G. Goals of the Proposed Study

Key questions remain about the key clinical risk factors for poly-substance adolescent substance use, the neurocognitive functioning of poly-substance young adult users, and the psychosocial outcomes of poly-substance use during adolescence and young adulthood. The aims of this study are to examine these questions in an ecologically valid manner that reflects

naturalistic substance use patterns among longitudinally studied individuals. We will examine how clinical risk factors contribute to subsequent use of cigarette, marijuana, and alcohol during adolescence, in turn impacting neurocognitive functioning and psychosocial outcomes. These findings have significant public health implications, as the identification of key clinical risk factors of poly-substance adolescent substance use will help inform prevention and early intervention efforts. In addition, these findings will help us to better understand the role of emotional processing and reward processing in poly-substance use and how these domains may be neurocognitive and affective targets for preventing continued use and development of substance use disorders in this critical developmental window between adolescence and young adulthood.

Aim 1. The first aim of the study is to evaluate the key clinical risk factors that are related to poly-substance use (a) at baseline and understand how these key factors (b) vary over time. Given that cigarette, marijuana, and alcohol use are each associated with more symptoms of depression, and negative mood regulation and lower GPAs, we hypothesize that participants with more poly-substance use will have incrementally more psychological dysregulation (e.g. depression, anxiety, and negative mood regulation) and lower GPAs at baseline, and these factors will exacerbate over time as participants' substance use progresses.

Aim 2. The second aim of the study is to examine the neurobiological implications of poly-substance use during adolescence on later affective, reward, and related neurocognitive performance in young adulthood among a subsample of the full cohort of participants who were sampled to represent different longitudinal patterns of poly-substance use. We hypothesize that the extent of impairment in reward and emotion processing and related neurocognitive functioning will be negatively associated with more poly-substance use, as emotional and reward processing may be shared mechanisms related to increased substance use.

Aim 3. The final aim of the study is to examine whether poly-substance use mediates the

relationship between key baseline differences and subsequent neurocognitive and functional outcomes (e.g., highest educational attainment). We hypothesize that individuals with more baseline risk factors will have cumulatively heavier poly-substance use of cigarettes, marijuana, and alcohol, which will in turn be associated with poorer affective processing, reward processing, cognitive, and functional outcomes (see Figure 1).

II. Methods

A. Participants

The Social and Emotional Contexts of Adolescent Smoking Patterns (SECASP) program project recruited a cohort of adolescents (N =1263; mean age at baseline = 15 years) who were oversampled for ever-smoking a cigarette (83% ever-smoked), and thus at high risk for smoking escalation. Many participants progressed to heavier cigarette use, as a well as alcohol and marijuana use over the years. Participants completed questionnaires assessing substance use and psychosocial factors at baseline, 6-, 15-, 24-, 33-months, and 5-, 6-, and 7-years.

To help identify a subsample of participants who could be recruited for participation in the laboratory portion of this study, we used a sampling strategy to more systematically draw from the full range of levels of substance use. This sampling frame involved using growth mixture models, run in Mplus, to identify longitudinal patterns of poly-substance use. All three substances (tobacco cigarettes, alcohol, and marijuana) were modeled together to form combined trajectories with this sample of 1263 high-risk adolescents, from baseline through the 5-year follow-up. Substance use was measured by the frequency of use of each substance over the past month. Selection of the final 4 trajectories was based on meaningful interpretability, best statistical fit index, and also entropy measures. Four trajectories classes were identified: 1) sporadic/minimal poly-substance use (non-user; n= 262), 2) low poly-substance use (low; n= 170), 3) medium poly-substance use (medium; n= 525), and 4) high poly-substance use (high; n= 306).

All participants from the full cohort who completed at least three waves were used for analyses in Aim 1. Eighty-three participants were recruited in a balanced fashion from each of the four trajectory groups, to complete the laboratory study visit, in order to address Aims 2 and 3. A semi-structured telephone-screening interview determined initial eligibility. Of the individuals who completed the laboratory visit, two individuals met criteria for Bipolar Disorder

and one individual endorsed psychotic symptoms, so these three individuals were excluded from analyses. The remaining 80 participants from the laboratory visit met strict inclusion and exclusion criteria to minimize the presence of any comorbidities that may influence neuropsychological functioning: (1) greater than 8 years of education; (2) estimated full scale IQ of greater than 75; (3) no self-reported formal diagnosis of a learning disability, developmental delay, mental illness (including ADHD, but excluding depression or anxiety), or neurological condition; (4) no significant birth complications; (5) no history of loss of consciousness greater than 10 minutes; (6) no current use of any psychotropic medications (excluding SSRI and SNRI antidepressants); (7) English fluency.

B. Demographics and Substance Use

Demographic information, including race/ethnicity, and gender information, as well as grade-point average (GPA), and education were obtained through self-report questionnaires given in the program project. Current educational attainment information was obtained at the laboratory study visit. For each wave, frequency of marijuana use and cigarette use was measured by asking participants to report the number of days they used marijuana, the number of days they used cigarettes, and the number of days they used alcohol in the past month, and 80 individuals completed this information again at the laboratory study visit (see Table 1 for timeline of assessments).

C. Laboratory Measures of Neuropsychological Functioning

Iowa Gambling Task (IGT). The IGT assesses decision-making and is sensitive to deficits in decision-making caused by ventromedial prefrontal cortical lesions (Bechara, Damasio, Damasio, & Anderson, 1994). The IGT has been used in several studies to demonstrate deficits in decision-making in substance users (Bechara, 2001; Bechara & Martin, 2004; Bolla et al., 2003; Ernst et al., 2003). In the task, participants are shown four decks of cards (labeled A, B, C, and D) and asked to select a card from one of the decks that will result in either a monetary

gain or a loss. They are instructed that the goal of the task is to win as much money as possible. The task ends after participants have selected 100 cards. However, unbeknownst to participants, two of the decks are disadvantageous (C and D; high short-term awards and high long-term penalties) and two of the decks are advantageous (A and B; low short-term awards and low long-term penalties). Healthy participants will make more selections from the advantageous decks and fewer selections from the disadvantageous decks over time in order to win as much money as possible, while participants with deficits in decision-making will continue to make selections from the disadvantageous decks. IGT performance is calculated by subtracting the number of selections from the disadvantageous decks from the number of selections from the advantageous decks, with higher values indicating better decision-making. Participants completed this task at the laboratory study visit.

Modified Monetary Incentive Delay task (mMID). Participants also completed the mMID, which assesses reward processing (Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008) and is sensitive to disruptions in reward processing among substance users (Schneider et al., 2012; Yau et al., 2012). The mMID is designed to elicit responses for both reward anticipation and consumption, and offers actual small and large monetary gains and losses based upon performance. The task consists of a pre-test, a 1st level adjustment, a 2nd level adjustment, and two test phases. For all tests, there is a cue telling the participant whether they will experience a win, a loss, or a no money trial. Then an orienting cue is presented briefly, followed by a response screen (black box). Participants are required to press the button as quickly as possible and before the white box goes away to avoid a potential loss and obtain a potential gain. The pretest is used to assess an individual specific reaction time. This value is then used to calculate a response time for the 1st level adjustment. Performance on this adjustment run is then used to modify the response time to optimize performance for a given individual. The 2nd adjustment is a repeat of the 1st level adjustment, making modifications based upon individual performance

targeting 66% correct rates. The last two are the actual test phases that are used to obtain a measure of incentivization earning potential, or loss of actual money. mMID performance was calculated by adding the amount of money won over all four trials, with higher values indicating better reward learning and processing.

Facial Emotion Perception task (FEPT). The FEPT (Langenecker et al., 2005; Rapport, Friedman, Tzelepis, & Van Voorhis, 2002) is a 7-minute task that will be used to assess accuracy and speed of recognition of facial expressions (e.g., impaired emotion perception). Participants completed this task at the laboratory study visit. During the task, participants were presented with and asked to rapidly categorize faces (Ekman and Friesen, 1976) and animals (control condition). For the face trials, participants categorized the facial expression into one of four possibilities: happy, sad, angry, or fearful. For the animal trials, participants categorized the animal into one of four possibilities: dog, cat, primate, or bird. Stimuli were presented for 300 ms, followed a by a mask for 100 ms, and then 2600 ms as a response window. Trials were separated by the presentation of a cross for 500 ms. The percentage of accurately identified facial expressions is be the primary measure of interest.

Test of Memory Malingering (TOMM). Participants completed the TOMM (Tombaugh, 1997) at the laboratory study visit, which was used as a manipulation check, measuring the participants' effort/engagement. This is an easy forced-choice visual memory recognition task. A score below 45/50 suggests that a participant was unwilling/unable to engage in sufficient effort.

D. Functional Outcome

Highest Educational Attainment. At the laboratory visit, participants were asked how many years of education they had completed. Responses were coded to reflect the highest education achieved (e.g., completed 11^{th} grade= 11 years, graduated high school or received GED= 12 years, 1 year college completed= 13 years, 2 years college completed or Associate's degree= 14 years, completed junior year of 4-year college= 15 years, completed Bachelor's

degree= 16 years, completed 1 year of Master's degree= 17 years, completed Master's degree= 18 years).

E. Psychological Dysregulation

Center for Epidemiological Scale-Depression (CES-D). At each wave, participants completed the CES-D (Radloff, 1977), a 20-item self-report questionnaire of depressive symptoms, and individuals completed this questionnaire again at the laboratory study visit. Participants' total score was used to determine the severity of depressive symptoms. The clinical cutoff for adolescents is 22 for boys and 24 for girls, whiles the adult cut-off is 16 (Lewinsohn, Rohde, & Seeley, 1998).

Adolescent Anxiety and Depressive Symptoms. At each wave, participants completed 12-items from the Mood and Affect Symptom Questionnaire (MASQ; (Wang & Watson, 1995; Watson & Clark, 1991), to assess symptoms in each of the core domains of the tripartite model of depression and anxiety: general distress symptoms, anxious arousal, and anhedonic depression symptoms (Watson & Clark, 1991). Participants also completed this questionnaire at the laboratory study visit. Total score, the sum of all scores, was used.

Negative Mood Regulation Expectancies Scale (NMR). At each wave, participants completed the NMR (Catanzaro & Mearns, 1990), a 30-item self-report questionnaire that measures general expectancies for alleviating negative moods. Items were be averaged to yield a total scale score, with higher scores indicating a strong belief that one can alter negative moods.

F. Assessment of Potential Premorbid and Psychiatric Confounds

Wechsler Test of Adult Reading (WTAR). The WTAR (Wechsler, 2001) is an estimate of premorbid general intellectual abilities (IQ) that was administered to individuals at the laboratory study visit (also estimates English fluency).

Structured Clinical Interview for DSM-IV (SCID). Participants were administered the SCID psychosis and mania modules (First, Spitzer, Gibbon, & Williams, 2002) at the laboratory study visit to diagnose the presence of current or past psychosis and mania.

Wender-Utah Rating Scale (WURS). The WURS (Ward, Wender, & Reimherr, 1993) is a 25-item self-report scale to retrospectively assess symptoms of Attention Deficit Hyperactivity Disorder (ADHD) that was administered to individuals at the study visit. We will look at the proportion of participants with a score >46, who are considered to have a high likelihood for meeting criteria for ADHD.

Barratt Impulsiveness Scale-11 (BIS). At the 5-year wave, all participants completed the BIS (J. Patton, Stanford, & Barratt, 1995), a 30-item self report measure of impulsive personality traits. The total score was used to assess trait levels of impulsivity.

Adolescent Antisocial Behavior Scale. At waves 0, 6-months, 15-months, and 24-months, all participants completed a 22-item scale based on the Antisocial Behavior Checklist (ASBC; (Zucker & Fitzgerald, 1992), to assess the core domains of DSM-IV defined Conduct Disorder: aggression, deceit, police contact, rule violation, theft, vandalism. Total scores and scores for each domain were calculated to reflect the frequency of antisocial behaviors committed by the adolescent during his/her lifetime.

G. Substance Use Measures to Characterize the Sample

Shiffman/Jarvik Withdrawal Questionnaire- Short Version (SJWS). Participants completed the SJWS(Shiffman & Jarvik, 1976), a 15-item self-report questionnaire to measure nicotine withdrawal symptoms, at the laboratory study visit. Higher scores represent more nicotine withdrawal symptoms.

Modified Fagerstrom Questionnaire (mFTQ). For each wave, all participants completed the mFTQ (Prokhorov, Koehly, Pallonen, & Hudmon, 1998; Prokhorov, Pallonen, Fava, Ding, & Niaura, 1996), a 7-item self-report questionnaire that measures nicotine dependence, and

individuals completed this questionnaire again at the laboratory study visit. The total score was used, which is the sum of all items. An mFTQ score of 6 or more is considered to represent a high level of nicotine dependence (Prokhorov et al., 1996).

Cannabis Use Disorder Identification Test – Revised (CUDIT-R). At 5-, 6-, and 7-year waves, participants completed the CUDIT-R (Adamson et al., 2010), an 8-item self-report to assess marijuana related problems and dependence, and individuals completed this questionnaire again at the laboratory study visit. The CUDIT-R total score was used, with higher values representing increased marijuana problems and dependence.

Marijuana Problem Scale (MPS). At 5-, 6-, and 7-year waves, participants completed the MPS, which asks about the negative psychological, social, occupational, and legal consequences of marijuana use in the last 90 days (Stephens, Roffman, & Curtin, 2000). Higher scores represent more marijuana-related problems. Participants also completed this questionnaire at the laboratory study visit.

Alcohol-Related Problems. At waves 0, 6-month, 15-month, and 24-month waves, participants completed the Alcohol Problem Scale, a 5-item scale asking participants about their drinking and how often they have gotten into trouble during the past year due to their drinking. At waves 5-, 6-, and 7-year waves, participants completed the Alcohol Problem Items, a 5-item questionnaire based on the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Task Force 6-item list of recommended alcohol questions for researchers, which asked about participants about their drinking during the past year. Participants also completed this questionnaire at the laboratory study visit.

***Toxicology Testing*.** We obtained breath alcohol content, as well as urine drug screen (UDS) samples to test for recent use of cocaine, methamphetamine, amphetamine, opiates, phencyclidine, methadone, ecstasy, barbiturates, benzodiazepines, oxycodone, tri-cyclic antidepressants, and THC for the individuals who completed the laboratory study visit.

H. General Statistical Procedures

All analyses were carried out using SPSS 20.0 (IBM). All variables were checked for inter- and intra-measure consistency, and distributions examined for unusual data points or distributions. We examined validity of assumptions underlying the statistical procedures (e.g., skewness, sphericity), and employed data transformations as necessary. Accepted practices for handling missing data were used when necessary. Results were deemed statistically significant when p-values $< .05$. The analytic strategy for each aim is described below.

III. Results

A. Participant Characteristics

Participant characteristics and substance use for the whole cohort sample are shown in Table 2. Participant characteristics and substance use for the 80 individuals who completed the laboratory study are shown in Table 3. Correlations between the key risk factors at baseline found that baseline depression symptoms (CES-D) and baseline anxiety symptoms (modified MASQ) were significantly positively correlated, while both of these variables were significantly negatively correlated with a belief that one can do something to feel better when in a bad mood (NMR) at baseline in both the whole sample and the 80 individuals who completed the laboratory study (Table 4). In addition, baseline GPA was negatively correlated with baseline depression symptoms (CES-D) and baseline anxiety symptoms (modified MASQ), but was positively correlated with a belief that one can do something to feel better when in a bad mood (NMR) at baseline in both the whole sample and the 80 individuals who completed the laboratory study (Table 4).

Substance use patterns over time for the whole sample and for the laboratory visit sample are shown in Figure 2. In general individuals increased the frequency of their use of cigarettes, marijuana, and alcohol over time (see Figure 2). Specifically, in the whole sample at baseline 55% reported no use of cigarettes in the past month, 62% reported no use of marijuana in the past month, and 27% reported no use of alcohol in the past month; while 29% reported using cigarettes at least once a week in the past month, 11% reported using marijuana at least once a week in the past month, and 12% reported using alcohol at least once a week in the past month. However, in the whole sample at 7 years 50% reported no use of cigarettes in the past month, 52% reported no use of marijuana in the past month, and 6% reported no use of alcohol in the past month; while 42% reported using cigarettes at least once a week in the past month, 26% reported using marijuana at least once a week in the past month, and 53% reported using alcohol

at least once a week in the past month. Similarly, in the laboratory visit sample at baseline 51% reported no use of cigarettes in the past month, 65% reported no use of marijuana in the past month, and 20% reported no use of alcohol in the past month; while 23% reported using cigarettes at least once a week in the past month, 14% reported using marijuana at least once a week in the past month, and 13% reported using alcohol at least once a week in the past month. On the other hand, in the laboratory visit sample at 7 years 55% reported no use of cigarettes in the past month, 49% reported no use of marijuana in the past month, and 1% reported no use of alcohol in the past month; while 33% reported using cigarettes at least once a week in the past month, 20% reported using marijuana at least once a week in the past month, and 54% reported using alcohol at least once a week in the past month.

Rates of poly-substance use over time for the whole sample and for the laboratory visit sample are shown in Figure 3. In the whole sample at baseline, 20% reported using no substances, 29% reported using 1 substance, 26% reported using 2 substances, and 25% reported using 3 substances; so using one substance was generally as common as poly-substance use. In contrast, in the whole sample at 7 years, about 4% reported using no substances in the past month, while around 33% reported using 1 substance, 34% reported using 2 substances, and 29% reported using 3 substances. Therefore, substance use increased at 7 years, using one substance was generally as common as poly-substance use at 7 years. Among individuals who reported using 2 substances, cigarette and alcohol co-use and marijuana and alcohol co-use were more common (about 35-38% at baseline and 46-47% at 7 years) compared to cigarette and marijuana co-use (26% at baseline and 30% at 7 years; see Figure 4). The patterns of poly-substance use in the laboratory visit sample were a little different. While about 18% of the laboratory visit sample reported using no substances at baseline (similar to the whole sample), about 32% reported using 1 substance, 19% reported using 2 substances, and 31% reported using 3 substances at baseline (Figure 4). At in the laboratory visit sample at 7 years, 1% reported using no substances in the

past month, 38% reported using 1 substance, 39% reported using 2 substances, and 22% reported using 3 substances (Figure 4); so there was less poly-substance use of 3 substances in the laboratory visit sample. Among the laboratory visit sample who reported using 2 substances, cigarette and alcohol co-use were the most common (46% at baseline and 45% at 7 years) compared to marijuana and alcohol co-use (about 35% at baseline and 39% at 7 years) and cigarette and marijuana co-use (31% at baseline and 22% at 7 years; see Figure 4). Interestingly, at 9 years, these patterns change such that marijuana and alcohol co-use becomes the most common (46%), followed by cigarette and alcohol co-use (39%), and then cigarette and marijuana co-use (28%; see Figure 4).

B. Aim 1: Key Risk Factors of Poly-Substance Use

1. Analytic Strategy

To identify the key clinical risk factors at baseline that are associated with poly-substance cigarette, alcohol, and marijuana use - and how these factors vary longitudinally throughout adolescence, multi-level random effects regression models were used. These multi-level models treated observations nested within subjects, allowing for random intercepts and random slopes, and incorporating covariates such as gender, race, and ethnicity (Hispanic or non-Hispanic). For all models, gender was effect coded (-1=male, 1=female), race was dummy coded (1=Caucasian, 0=non-Caucasian), ethnicity was dummy coded (1=Hispanic, 0=non-Hispanic), and time was measured continuously by the year of each assessment wave and centered at baseline. Gender, ethnicity, and race were static and based on reported values at baseline. The main dependent variable of interest was the z-score of poly-substance use (computed by averaging the z-score for each substance over time, which was based on the baseline mean and standard deviation for each substance to allow it to vary over time); however, we also ran separate models with the frequency of each substance use over time to

understand how risk factors were related to each substance individually. For models that assessed risk factors at baseline related to poly-substance use, symptoms of depression, anxiety, negative mood regulation, and GPA were static and based on reported values at baseline. Symptoms of depression, anxiety, negative mood regulation, and GPA were all mean centered. We included the interaction of gender with each risk factor in the respective models. For models that assessed how risk factors vary longitudinally throughout adolescence and young adulthood, symptoms of depression, anxiety, and negative mood regulation were time-varying independent variables and were grand mean centered. Due to the fact that GPA was not assessed at all time-points, models assessing how this risk factor varies over time were not run. Interactions between each risk factor and time, as well as interactions with gender were included in each model. For all models, non-significant covariates and interactions were removed and the reduced model was re-run. Tables 3 and 4 show results from the full model and reduced models. Follow-up analyses of the simple slopes for significant 2-way interactions used linear regression. Analyses with gender were run separately for males and females. Analyses with time used a median split based upon the participants' age to capture developmental and psychosocial differences before age 18 (years 0-2) and after age 18 (years 5-7). Results were deemed statistically significant when p-values < .05.

2. Key Baseline Risk Factors of Poly-Substance Use

At baseline, more symptoms of depression (CES-D), more symptoms of anxiety (MASQ), a weaker belief that one can do something to feel better when in a bad mood (NMR), and lower GPA were each associated with more poly-substance use of cigarette, marijuana, and alcohol use over time (see Table 5). When examining the relationships between these risk factors and each substance individually, more symptoms of depression at baseline and a weaker belief that one can do something to feel better when in a bad

mood at baseline were each related to more cigarette use and to more marijuana use over time, but the relationships of these risk factors with alcohol use were not significant. On the other hand, more symptoms of anxiety at baseline and a lower GPA at baseline were associated with increased use of each substance over time (see Table 5).

In general, as mentioned above, poly-substance use, as well as use of each individual substance, increased over time (see Table 5, Figure 2). Overall, Caucasian individuals had a higher frequency of poly-substance use of cigarette, marijuana, and alcohol use over time, but ethnicity (Hispanic/not Hispanic) was not related to poly-substance use (see Table 5). When examining the relationships between race and ethnicity and each substance individually, Caucasian individuals and non-Hispanic individuals had a higher frequency of cigarette use over time. On the other hand, Caucasian individuals had a higher frequency of alcohol use over time, and ethnicity (Hispanic/not Hispanic) was not related to alcohol use (see Table 5). Frequency of marijuana use over time was not related to race or ethnicity (Hispanic/not Hispanic; see Table 5). Overall, males had a higher frequency of poly-substance use of over time than females and this was also the case when looking at gender differences in use of each substance individually (see Table 5). Specifically, at baseline, males on average used cigarettes 4.02 ± 7.72 days, used marijuana 2.69 ± 6.09 days, and used alcohol 2.23 ± 2.88 days in the last month, while females on average used cigarettes 3.73 ± 7.69 days, used marijuana 1.49 ± 4.03 days, and used alcohol 2.33 ± 2.82 days in the last month. At 7 years, males on average used cigarettes 12.39 ± 13.30 days, used marijuana 6.74 ± 9.99 days, and used alcohol 6.67 ± 4.76 days in the last month, while females on average used cigarettes 7.96 ± 12.05 days, used marijuana 4.34 ± 8.62 days, and used alcohol 5.72 ± 4.31 days in the last month.

The 2-way interaction between gender and baseline GPA was significant for poly-substance use, but not for each substance individually (see Table 5). Follow-up of the simple slopes for the 2-way interaction for poly-substance use revealed that a lower baseline GPA was more strongly associated with more cigarette, marijuana, and alcohol use for males (β= -.14, t(3173)= -8.12, p<.001), than for females, β= -.06, t(4404)= -4.00, p<.001.The 2-way interactions between gender and baseline symptoms of depression, gender and baseline symptoms of anxiety, as well as gender and baseline negative mood regulation, were not significant for poly-substance use or when looking at each substance individually.

3. How Risk Factors Vary Over Adolescence with Poly-Substance Use

In general, similar to what is reported above, more symptoms of depression (CES-D), more symptoms of anxiety (MASQ), and a weaker belief that one can do something to feel better when in a bad mood (NMR) were each associated with more poly-substance use over time (see Table 5). When examining the relationships between these risk factors and each substance individually, more symptoms of depression and more symptoms of anxiety over time were each related to more cigarette use, more marijuana use, and more alcohol use over time (see Table 6). On the other hand, a stronger belief that one can do something to feel better when in a bad mood at baseline was associated with less marijuana use and less alcohol over time, but was not related to cigarette use (see Table 6).

The 2-way interaction between time and symptoms of depression was significant for alcohol use, but was not significant for poly-substance use, cigarette use, or marijuana use (see Table 6). Follow-up of the simple slopes for the 2-way interaction for alcohol use revealed that in adolescence (years 0-2) depression was not related to alcohol use (β= .03, t(4588)= 1.80, p= .07); however, in young adulthood (years 5-7) more symptoms of

depression was associated with less alcohol use, β= -.04, t(3101)= -2.18, *p*= .03. The 2-way interaction between time and symptoms of anxiety was significant for marijuana use and alcohol use, but was not significant for poly-substance use or cigarette use (see Table 6). Follow-up of the simple slopes for the 2-way interaction for marijuana use revealed that in adolescence (years 0-2) more anxiety was related to increased marijuana use (β= .05, t(4579)= 3.31, *p*= .001) and this effect was slightly larger in young adulthood (years 5-7), β= .07, t(3106)= 4.01, *p*<.001. Follow-up of the simple slopes for the 2-way interaction for alcohol use revealed that in adolescence (years 0-2) more symptoms of anxiety was related to increased alcohol use (β= .07, t(4586)= 4.77, *p*<.001), but in young adulthood (years 5-7) symptoms of anxiety was not associated with alcohol use, β= -.01, t(3106)= -0.31, *p*= .76. The 2-way interaction between time and symptoms of negative mood regulation was significant for alcohol use, but was not significant for poly-substance use, cigarette use, or marijuana use (see Table 6). Follow-up of the simple slopes for the 2-way interaction for alcohol use revealed that in adolescence (years 0-2) negative mood regulation was not related to alcohol use (β= -.01, t(4579)= -0.79, *p*= .43); however, in young adulthood (years 5-7) a stronger belief that one can do something to feel better when in a bad mood was associated with more alcohol use, β= .04, t(3109)= 2.01, *p*= .045.

The 2-way interaction between gender and symptoms of depression was significant for poly-substance use and for marijuana use, but not for cigarette use or alcohol use (see Table 6). Follow-up of the simple slopes for the 2-way interaction for poly-substance use revealed that more symptoms of depression was associated with increased poly-substance use for males (β= .11, t(3196)= 6.35, *p*<.001), but not for females, β= -0.03, t(4458)= -1.70, *p*= .09. Similarly, follow-up of the simple slopes for the 2-way interaction for marijuana use revealed that more symptoms of depression was

associated with increased marijuana use for males (β= .13, t(3218)= 7.61, *p*<.001), but not for females, β= 0.00, t(4464)= -0.04, *p*= .97. The 2-way interaction between gender and symptoms of anxiety was significant for poly-substance use and for marijuana use, but not for cigarette use or alcohol use (see Table 6). Follow-up of the simple slopes for the 2-way interaction for poly-substance use revealed that more symptoms of anxiety was associated with increased poly-substance use for males (β= .08, t(3196)= 4.36, *p*<.001), but not for females, β= -0.02, t(4461)= -0.13, *p*= .90. Similarly, follow-up of the simple slopes for the 2-way interaction for marijuana use revealed that more symptoms of anxiety was associated with increased marijuana use for males (β= .09, t(3218)= 5.08, *p*<.001), but not for females, β= 0.02, t(4467)= 1.35, *p*= .18. The 2-way interaction between gender and symptoms of negative mood regulation was significant for marijuana use, but was not significant for poly-substance use, cigarette use, or alcohol use (see Table 6). Follow-up of the simple slopes for the 2-way interaction for marijuana use revealed that a weaker belief that one can do something to feel better when in a bad mood was associated with more marijuana use for males (β= -.05, t(3214)= -3.06, *p*= .002); on the other hand, for females a stronger belief that one can do something to feel better when in a bad mood was related to more marijuana use, β= 0.03, t(4467)= 2.15, *p*= .03.

C. Aim 2: Neurocognitive and Functional Outcomes of Poly-Substance Use

1. Analytic Strategy

To examine how poly-substance use during adolescence and young adulthood is related to neurocognitive and functional outcomes during young adulthood, we used hierarchical multiple regression analyses with a z-score of computed mean poly-substance use over time as the independent variable in the first block, covariates of interest in the second block, including gender (female=0, male=1), race/ethnicity (0= non-Caucasian or Hispanic, 1= Caucasian & non=Hispanic), family history of a

substance use disorder (SUD; 0= no family history of SUD, 1= family history of SUD), SJWS total score from the laboratory visit, and positive UDS for THC at the laboratory visit (0= THC negative, 1= THC positive), and performance on neurocognitive measures or functional outcome (i.e., highest educational attainment) as separate dependent variables. The z-score of mean poly-substance use was computed by creating a z-score for averaging each individual's frequency of use for each substance over time, creating a z-score for each substance based on the sample's mean and standard deviation for each substance, and then the z-scores for each substance were averaged. We were also interesting in understanding the relationship between neurocognitive and functional outcomes and each substance individually, so we ran separate hierarchical multiple regression analyses with the centered (a statistical approach of subtracting the mean from continuous predictor variables in order to help reduce multi-collinearity) frequency of each substance averaged over time for each individual as the independent variable in the first block, covariates of interest in the second block, including gender (female=0, male=1), race/ethnicity (0= non-Caucasian or Hispanic, 1= Caucasian & non=Hispanic), and family history of a substance use disorder (SUD; 0= no family history of SUD, 1= family history of SUD) and performance on neurocognitive measures or functional outcome (i.e., highest educational attainment) as separate dependent variables. For models with neurocognitive measures as the dependent variable, we also included SJWS total score and positive UDS for THC from the laboratory visit (0= THC negative, 1= THC positive) as covariates in the second block, in order to control for any potential acute effects of nicotine withdrawal or marijuana use on performance. To preserve power, for all models non-significant covariates were removed from final models and only reduced models are reported. Results were deemed statistically significant when *p*-values $< .05$.

2. Relationships Between Poly-Substance Use and Neurocognitive Outcomes

Reward processing (mMID) and emotional processing (FEPT) were not related to poly-substance use of cigarettes, alcohol, and marijuana (see Table 7). On the other hand, surprisingly, more poly-substance use was associated with better decision-making (IGT), but after controlling for relevant covariates, this effect only trended toward significance (*p= .06*; see Table 7). When examining the relationships between these neurocognitive outcomes and each substance individually, reward processing was not related to cigarette, marijuana, or alcohol use (see Table 7). Similarly, cigarette and marijuana use were not associated with decision-making. More alcohol use was related to better decision-making, but after controlling for relevant covariates this relationship was no longer significant (see Table 7). More marijuana use was related to poorer overall emotional processing after controlling for relevant covariates, but cigarette and alcohol use were not associated with emotional processing (see Table 7).

In general, reward processing performance was not related to gender (although trending for cigarette and alcohol use), race/ethnicity, family history of SUD, SJWS total score, or UDS positive for THC (see Table 7). In addition, gender, family history of SUD, SJWS total score, and UDS positive for THC were not associated with decision-making performance, but race/ethnicity was related to decision-making (see Table 7). Specifically, Caucasian/non-Hispanic individuals had better decision-making performance (*M*= 49.89, *SD*= 10.54) than non-Caucasians or Hispanic individuals (*M*= 43.17, *SD*= 9.62). Furthermore, family history of SUD, SJWS total score, and UDS positive for THC were not associated with emotional processing performance, but gender and race/ethnicity were related to emotional processing (see Table 7). Specifically, females had better emotional processing performance (*M*= 0.29, *SD*= 0.95) than males (*M*= -0.24, *SD*= 1.05) and Caucasian/non-Hispanic individuals had better emotional

processing performance (*M*= 0.34, *SD*= 0.83) than non-Caucasians or Hispanic individuals (*M*= -0.42, *SD*= 1.13).

Examining Relationships Between Substance Use and Processing of Specific Emotions. To better understand if poly-substance use was related to the ability to identify specific emotions on the FEPT task, we also ran separate hierarchical multiple regression analyses with the z-score of poly-substance use and the centered frequency of each substance averaged over time for each individual as the independent variable in the first block, covariates that were significant for the overall accuracy FEPT in the second block (gender (female=0, male=1) and race/ethnicity (0= non-Caucasian or Hispanic, 1= Caucasian & non=Hispanic)), and the accuracy score for each emotion (fear, anger, happy, sad, and neutral) as the dependent variables. We found that although poly-substance use and cigarette use were not related to accuracy of identifying fearful faces (*p*-values > .05), after controlling for gender and race/ethnicity, more marijuana use was associated with poorer accuracy of identifying fearful faces (*trending*; β= -.20, t(75)= -1.77, *p*=.08). On the other hand, more alcohol use was associated with better accuracy of identifying fearful faces (β= .25, t(77)= 2.24, *p*=.03), but after controlling for gender and race/ethnicity, this relationship was no longer significant, β= .13, t(75)= 1.08, *p*=.28. Substance use measures were not related to accuracy of identifying angry, happy, sad or neutral faces.

3. Relationships Between Poly-Substance Use and Functional Outcome

More poly-substance use of cigarette, marijuana, and alcohol was associated with attaining less education (see Table 7). When examining the relationships between educational attainment and each substance individually, more cigarette use, and more marijuana use were related to attaining less education, but alcohol use was not associated with educational attainment (see Table 7).

Overall, gender or family history of SUD (although trending for marijuana and alcohol use) was not related to educational attainment (see Table 7). On the other hand, race/ethnicity was associated with educational attainment, such that Caucasian/non-Hispanic individuals had higher educational attainment (*M*= 14.82, *SD*= 1.89) than non-Caucasians or Hispanic individuals (*M*= 14.14, *SD*= 1.79).

4. Exploratory Analysis: Gender and Race/Ethnicity Differences in Neurocognitive Performance and Highest Educational Attainment

Due to the fact that gender and/or race/ethnicity seemed to significantly affect performance on neurocognitive measures and educational attainment, we examined gender and race/ethnicity differences in neurocognitive performance and educational attainment. We found that in general, males earned more money than females on the mMID (*trending*, $F(3,80)= 3.76$, $p= .056$), but there was no group difference for race/ethnicity ($p > .05$; see Figure 5). On the IGT, non-Caucasian or Hispanic individuals had poorer decision-making performance than Caucasian, non-Hispanic individuals ($F(3,80)= 9.15$, $p= .003$), but there was no gender difference ($p > .05$; see Figure 5). On the FEPT, females had better emotional processing performance than males ($F(3,79)= 11.80$, $p= .001$), and Caucasian, non-Hispanic individuals had better had better emotional processing performance than non-Caucasian or Hispanic individuals ($F(3,79)= 17.59$, $p< .001$; see Figure 5). For educational attainment, Caucasian, non-Hispanic individuals had slightly more years of education than non-Caucasian or Hispanic individuals (*trending*; $F(3,80)= 3.25$, $p= .08$), but there was no difference between males and females ($p > .05$; see Figure 5). There were also no significant interactions of gender and race/ethnicity for any of these outcomes.

5. Exploratory Analysis: Gender and Race/Ethnicity Differences in the Relationships Among Substance Use Measures, Neurocognition, and Highest Educational Attainment

First, we performed linear regressions separately for males and females with each substance use measure as the independent variables and performance on neurocognitive measures or functional outcome (i.e., highest educational attainment) as separate dependent variables. As shown in Table 7, reward processing was not related to substance use for males or females, but decision-making and emotional processing showed gender-specific relationships with substance use measures. Specifically, for males, more poly-substance use and more alcohol use were related to better decision-making, but decision-making was not associated to substance use measures for females (see Table 7). Additionally, for males, more alcohol use was related to better decision-making, but there was no association between these variables for females (see Table 7). Similarly, there were gender-specific relationships between substance use measures and educational attainment, such that more poly-substance use and more marijuana use was related to less educational attainment for females, but these relationships were not significant for males (see Table 7). More cigarette use was associated with less educational attainment for both males and females, but this effect was slightly greater for females than males (see Table 7).

We then performed bivariate correlations among neurocognitive and functional outcomes, substance use measures, and relevant covariates separately for gender and race/ethnicity to see how the relationships among these variables may differ for Caucasian, non-Hispanic females, non-Caucasian or Hispanic females, Caucasian, non-Hispanic males, and non-Caucasian or Hispanic males.

Females. We found that for Caucasian, non-Hispanic females: poorer emotional processing was associate with more alcohol use; more poly-substance use was associated with more marijuana use, with more alcohol use, with a higher total score on the SJWS, with a higher likelihood that an individual would test positive for THC on UDS screening, and with less educational attainment; more marijuana use was associated with a higher total score on the SJWS, with a higher likelihood that an individual would test positive for THC on UDS screening, and with less educational attainment; a family history of SUD was negatively associated with total score on the SJWS and with the likelihood that an individual would test positive for THC on UDS screening, but positively related to educational attainment; and less education was associated with a higher total score on the SJWS and with a higher likelihood that an individual would test positive for THC on UDS screening (see Table 8, panel A). In contrast, for non-Caucasian or Hispanic females: more alcohol use was associated with poorer reward processing; more poly-substance use was associated with more cigarette use, with more marijuana use, with more alcohol use, with a higher total score on the SJWS, and with a higher likelihood that an individual would test positive for THC on UDS screening; more cigarette use was associated with more marijuana use, with a higher total score on the SJWS, and with a higher likelihood that an individual would test positive for THC on UDS screening; and more marijuana use was associated with a higher total score on the SJWS, and with a higher likelihood that an individual would test positive for THC on UDS screening (see Table 8, panel A).

Males. We found that for Caucasian, non-Hispanic males: more poly-substance use and more alcohol use were each associated with better decision-making; more poly-substance use was associated with more cigarette use, with more marijuana use, with more alcohol use, with a higher total score on the SJWS, and a higher likelihood that an

individual would test positive for THC on UDS screening; more cigarette use was associated with more marijuana use, with more alcohol use, with a higher total score on the SJWS, and with less educational attainment; more marijuana use was associated with a higher likelihood that an individual would test positive for THC on UDS screening; more alcohol use was associated with a higher total score on the SJWS; and a higher total score on the SJWS was associated with less educational attainment (see Table 8, panel B). On the other hand, for non-Caucasian or Hispanic males: poorer reward processing was associated with a higher total score on the SJWS; poorer decision-making was associated with more poly-substance use; poorer emotional processing was associated with a higher total score on the SJWS; more poly-substance use was associated with more cigarette use, with more alcohol use, and with a higher total score on the SJWS; and more marijuana use was associated with a higher likelihood that an individual would test positive for THC on UDS screening (see Table 8, panel B).

D. Aim 3: Substance Use as a Mediator

1. Analytic Strategy

To examine if poly-substance use mediates the relationship between the key clinical baseline risk factors identified in Aim 1 and participants' subsequent neurocognitive and functional outcomes, we will use Mackinnon's mediation analyses (Mackinnon & Fairchild, 2009; MacKinnon, Fairchild, & Fritz, 2007) to run separate mediation analyses with each neurocognitive outcome (3) and functional outcome (1) as the dependent variables. Analyses to test mediation were conducted using a nonparametric bootstrapping method, in line with recommendations by MacKinnon, Lockwood, and Williams (2004). Models were tested using the SPSS macro PROCESS (Hayes, 2012), which calculates a bootstrap estimate of the indirect effect between the independent variable and dependent variable, an estimated standard error, and 95%

confidence intervals (CI) for the population value of the indirect effect. Analyses were conducted using 1000 bootstrap samples. Z-scores were computed for GPA, years of education, IGT net total T-score ((T-score-50)/10), and mMID total score, so that all variables in each mediation model were z-scores or factor scores (mean=0, SD=1) in order for the results to have standardized beta-weights.

The 3 risk factors (MASQ, CES-D, and NMR) were highly correlated at baseline (see Table 4), so Principal Components Analysis (PCA) was run for data reduction. Initial eigenvalues indicated that the first component explained 82% of the variance and was the only component that had an eigenvalue greater than one, resulting in a 1-component solution. Factor scores were computed for each participant with higher scores indicating more negative affect at baseline (mean=0, SD=1).

Due to the fact that gender and race/ethnicity were found to be important factors in how substance use is related to neurocognitive functioning and educational attainment, mediation models were tested for four groups (Caucasian, Non-Hispanic Females; Non-Caucasian or Hispanic Females; Caucasian, Non-Hispanic Males; Non-Caucasian or Hispanic Males) separately. The sample size for each group was small (n=15-26), reducing our ability to find significant effects. Therefore, all results from the mediation models were reported, even if the "a" and "b" paths were not significant.

2. Gender and Race/Ethnicity Differences in Participant Characteristics

The four groups (Caucasian, Non-Hispanic Females; Non-Caucasian or Hispanic Females; Caucasian, Non-Hispanic Males; Non-Caucasian or Hispanic Males) of individuals who completed the laboratory visit differed on several important variables at baseline and at the laboratory visit (see Table 3). Overall, males were slightly older, were more likely to have a family history of SUD, and were more likely to test positive for THC on their UDS than females at the laboratory visit. In addition, Caucasian or non-

Hispanic individuals (regardless of gender) had a higher estimated FSIQ, were less likely to attend high school with a high percentage of low-income students, had lower anxiety symptoms, had lower depression symptoms, and had higher poly-substance use than Non-Caucasians or Hispanics at the laboratory visit. Among non-Caucasian or Hispanics only 35% of females and 46% of males had mothers who had more than a high school education. In contrast, among Caucasian, non-Hispanics, 84% of females and 65% of males had mothers who had more than a high school education. Caucasian, Non-Hispanic males had higher marijuana use than Caucasian, Non-Hispanic females and non-Caucasian or Hispanic males, who had higher marijuana use than non-Caucasian or Hispanic females. Caucasian, non-Hispanic males reported more alcohol use and alcohol related problems than Caucasian, non-Hispanic females, who reported more alcohol use (but had similar alcohol related problems) compared to non-Caucasian or Hispanic females, and all of these groups had more alcohol use and alcohol related problems than non-Caucasian or Hispanic males at the laboratory visit.

Caucasian, Non-Hispanic Females. Results indicated that baseline negative affect did not significantly predict poly-substance use (a paths), but more baseline negative affect was associated with more poly-substance use (B= .19, t(18)= 1.41, *p*= .18) for non-Hispanic, Caucasian females. In addition, poly-substance use did not significantly predict decision-making (B= .26, t(18)= 0.61, *p*= .55), reward processing (B= .28, t(18)= 0.49, *p*= .63), or emotional processing (B= -.55, t(18)= -1.56, *p*= .14) (b paths). On the other hand, more poly-substance use predicted poorer educational attainment (B= -1.02, t(18)= -2.41, *p*= .03) (b path). The direct effect of baseline negative affect was not significantly associated with outcomes (decision-making, B= .29, t(18)= 1.17, *p*= .26; emotional processing, B= -.17, t(18)= -0.85, *p*= .41; reward processing B= -.22, t(18)= -0.65, *p*= .53; educational attainment, B = -.07, t(18)= -0.30, *p*= .77). However, poly-substance use

mediated the relationship between baseline negative affect and educational attainment, B= -.19, 95% CI [-0.57, -0.02]. Poly-substance use did not mediate the relationship between baseline negative affect and decision-making (B= .05, 95% CI [-0.74, 0.40]), emotional processing (B= -.10, 95% CI [-0.40, 0.13]), or reward processing (B= .05, 95% CI [-0.14, 0.28]).

As found in the larger sample in Aim 1, lower baseline GPA was related to more poly-substance use (B= -.26, t(18)= -2.26, *p*= .04) for non-Hispanic, Caucasian females (a paths). Poly-substance use did not significantly predict decision-making (B= .26, t(18)= 0.55, *p*= .59), reward processing (B= .00, t(18)= 0.00, *p*> .99), emotional processing (B= -.78, t(18)= -2.03, *p*= .06; *trending*), or educational attainment (B= -.55, t(18)= -1.47, *p*= .16) (b paths). The direct effect of baseline GPA was not significantly associated with decision-making (B= -.18, t(18)= -0.71, *p*= .49), emotional processing (B= -.15, t(18)= -0.71, *p*= .49), or reward processing (B= -.18, t(18)= -0.53, *p*= .60), but a higher GPA was related to higher educational attainment, B= .59, t(18)= 2.88, *p*= .01. Poly-substance use mediated the relationship between baseline GPA and emotional processing, (B= .20, 95% CI [0.20, 0.73]; however, since the b path was not significant (only trending) this mediation is not considered to be significant. Poly-substance use did not mediate the relationship between baseline GPA and decision-making (B= -.07, 95% CI [-0.64, 0.16]), reward processing (B= .00, 95% CI [-0.31, 0.38]), or educational attainment, B= .14, 95% CI [-0.02, 0.77].

Non-Caucasian or Hispanic Females. Baseline negative affect did not significantly predict poly-substance use (B= -.04, t(19)= -0.35, *p*= .73; a paths) for non-Caucasian or Hispanic females. In addition, poly-substance use did not significantly predict decision-making (B= -.22, t(19)= -0.47, *p*= .65), reward processing (B= -.52, t(19)= -1.17, *p*= .26), or emotional processing (B= -.05, t(19)= -0.12, *p*= .91), or

educational attainment (B= -.55, t(19)= -1.47, *p*= .16) (b paths). Furthermore, the direct effect of baseline negative affect was not significantly associated with outcomes (emotional processing, B= -.02, t(19)= -0.08, *p*= .94; educational attainment, B= -.07, t(19)= -0.40, *p*= .69), but more baseline negative affect was related to better decision-making (B= .32, t(19)= 1.41, *p*= .18), and worse reward processing (B= -.30, t(19)= -1.41, *p*= .18). Poly-substance use did not mediate the relationship between baseline negative affect and decision-making (B= .01, 95% CI [-0.07, 0.21]), emotional processing (B= -.00, 95% CI [-0.07, 0.11]), reward processing (B= .02, 95% CI [-0.06, 0.33]), or educational attainment, B= .02, 95% CI [-0.08, 0.28].

Unlike the finding in the larger sample in Aim 1, lower baseline GPA was not related to more poly-substance use (B= -.10, t(19)= -0.57, *p*= .57) for Hispanic or non-Caucasian females (a paths). Poly-substance use did not significantly predict decision-making (B= -.27, t(19)= -0.54, *p*= .60), reward processing (B= -.40, t(19)= -0.88, *p*= .39), emotional processing (B= .01, t(19)= 0.02, *p*= .99), or educational attainment (B= -.44, t(19)= -1.32, *p*= .20) (b paths). The direct effect of baseline GPA was not significantly associated with decision-making (B= .02, t(19)= 0.05, *p*= .96), emotional processing (B= .27, t(19)= 0.93, *p*= .37), or reward processing (B= .39, t(19)= 1.20, *p*= .24), but a higher GPA was related to higher educational attainment, B= .53, t(19)= 2.21, *p*= .04. Poly-substance use did not mediate the relationship between baseline GPA and decision-making (B= .03, 95% CI [-0.16, 0.42]), emotional processing (B= .00, 95% CI [-0.20, 0.13]), reward processing (B= .04, 95% CI [-0.04, 0.50]), or educational attainment, B= .04, 95% CI [-0.10, 0.44].

Caucasian, Non-Hispanic Males. Baseline negative affect did not significantly predict poly-substance use (a paths), but more baseline negative affect was associated with more poly-substance use (B= .20, t(25)= 1.06, *p*= .30) for non-Hispanic, Caucasian

males. In addition, poly-substance use did not significantly predict reward processing (B= .18, t(25)= 1.00, *p*= .33), emotional processing (B= -.11, t(25)= -0.63, *p*= .53), or educational attainment (B= -.20, t(25)= -1.01, *p*= .32) (b paths). On the other hand, more poly-substance use predicted better decision-making (B= .56, t(25)= 2.48, *p*= .02) (b path). The direct effect of baseline negative affect was not significantly associated with decision-making (B= .09, t(25)= 0.43, *p*= .67), reward processing (B= .01, t(25)= 0.05, *p*= .96), or emotional processing (B= .04, t(25)= 0.23, *p*= .82), but more baseline negative affect was related to less educational attainment, B= -.45, t(25)= -2.40, *p*= .03. Furthermore, poly-substance use mediated the relationship between baseline negative affect and educational attainment, B= -.45, 95% CI [-0.84, -0.06]. Poly-substance use did not mediate the relationship between baseline negative affect and decision-making (B= .11, 95% CI [-0.12, 0.47]), emotional processing (B= -.02, 95% CI [-0.23, 0.06]), or reward processing (B= .04, 95% CI [-0.04, 0.26]).

Unlike the finding in the larger sample in Aim 1, lower baseline GPA was not significantly related to more poly-substance use (B= -.26, t(25)= -1.62, *p*= .12) for non-Hispanic, Caucasian males (a paths). More poly-substance was associated with better decision-making (B= .59, t(25)= 2.51, *p*= .02), but was not significantly related to reward processing (B= .14, t(25)= 0.74, *p*= .47), emotional processing (B= -.07, t(25)= -0.36, *p*= .72), or educational attainment (B= -.09, t(25)= -0.52, *p*= .61) (b paths). The direct effect of baseline GPA was not significantly associated with decision-making (B= .01, t(25)= 0.05, *p*= .96), emotional processing (B= .09, t(25)= 0.68, *p*= .51), or reward processing (B= -.12, t(25)= -0.81, *p*= .43), but a higher GPA was related to higher educational attainment, B= .54, t(25)= 3.62, *p*= .001. Poly-substance use did not mediate the relationship between baseline GPA and decision-making (B= -.15, 95% CI [-0.49,

0.02]), reward processing (B= -.04, 95% CI [-0.35, 0.03]), emotional processing (B= .02, 95% CI [-0.08, 0.22]), or educational attainment, B= .02, 95% CI [-0.03, 0.16].

Non-Caucasian or Hispanic Males. Baseline negative affect did not significantly predict poly-substance use (a paths), but more baseline negative affect was associated with more poly-substance use (B= .17, t(14)= 0.98, *p*= .35) for non-Caucasian or Hispanic males. In addition, poly-substance use did not significantly predict reward processing (B= -.48, t(14)= -0.93, *p*= .37), emotional processing (B= .47, t(14)= 0.71, *p*= .49), or educational attainment (B= -.54, t(14)= -0.87, *p*= .40) (b paths). On the other hand, more poly-substance use predicted poorer decision-making (B= -0.85, t(14)= -2.40, *p*= .04) (b path). The direct effect of baseline negative affect was not significantly associated with outcomes (decision-making, B= .11, t(14)= 0.46, *p*= .66; reward processing, B= .03, t(14)= 0.10, *p*= .92; educational attainment, B= .14, t(14)= 0.33, *p*= .74); but more baseline negative affect was related to poorer emotional processing (B= -.76, t(14)= -1.77, *p*= .10; *trending*). Poly-substance use did not mediate the relationship between baseline negative affect and decision-making (B= -.14, 95% CI [-0.55, 0.15]), emotional processing (B= .09, 95% CI [-0.21, 0.63]), reward processing (B= -.08, 95% CI [-0.68, 0.07]), or educational attainment, B= -.09, 95% CI [-0.50, 0.21].

Unlike the finding in the larger sample in Aim 1, lower baseline GPA was not significantly related to more poly-substance use (B= -.11, t(14)= -0.88, *p*= .40) for Hispanic or non-Caucasian males (a paths). More poly-substance was associated with poorer decision-making (B= -.72, t(14)= -2.13, *p*= .055; *trending*), but was not significantly related to reward processing (B= -.33, t(14)= -0.68, *p*= .51), emotional processing (B= .35, t(14)= 0.50, *p*= .63), or educational attainment (B= -.21, t(14)= -0.40, *p*= .69) (b paths). The direct effect of baseline GPA was not significantly associated with decision-making (B= .17, t(14)= 1.10, *p*= .29), emotional processing (B= .38, t(14)= 1.19,

p= .26), or reward processing (B= .28, t(14)= 1.27, *p*= .23), but a higher GPA was related to higher educational attainment, B= .53, t(14)= 2.20, *p*= .048. Poly-substance use did not mediate the relationship between baseline GPA and decision-making (B= .08, 95% CI [-0.07, 0.41]), reward processing (B= .04, 95% CI [-0.07, 0.40]), emotional processing (B= -.04, 95% CI [-0.59, 0.08]), or educational attainment, B= .02, 95% CI [-0.08, 0.26].

IV. DISCUSSION

In this study we examined how clinical risk factors contribute to subsequent cigarette, marijuana, and alcohol use during adolescence, in turn impacting neurocognitive functioning and psychosocial outcomes in young adulthood. The study examined these relationships among clinical risk factors and substance use among a large, well-characterized, longitudinal sample of high-risk adolescents transitioning into adulthood. In addition, a subset of this longitudinal sample participated in a laboratory visit to understand how substance use during adolescence impacts neurocognitive functioning and psychosocial outcomes in young adulthood. The laboratory visit sample was recruited to draw from the full range of patterns of cigarette, marijuana, and alcohol use and the sampling strategy was successful in obtaining variability in poly-substance use patterns across adolescence and young adulthood. The laboratory visit sample reflected similar mean past month alcohol use over time as the whole cohort, but had less mean past month cigarette use at baseline and also had less mean past month cigarette use throughout adolescence and young adulthood. Therefore, the laboratory visit sample was a less high-risk sample and more representative of national cigarette use patterns during adolescence and young adulthood than the whole cohort. Further, the laboratory visit sample also had less mean past month marijuana use in young adulthood and had less poly-substance use of 3 substances throughout adolescence and young adulthood than the whole cohort.

Table 9 summarizes the main findings of the study. Results revealed that at baseline and over time, more symptoms of depression, more symptoms of anxiety, a weaker belief that one can do something to feel better when in a bad mood, and lower GPA were each associated with more poly-substance use over time. There were also substance specific relationships among these variables. Results also found that reward processing, emotional processing, and decision-making were not related to poly-substance use after controlling for relevant covariates. In contrast, more poly-substance use was associated with attaining less education. There were substance specific

relationships among these variables as well. However, there were tremendous individual differences and the effects of substances were highly variable. Specifically, race/ethnicity and gender seemed to moderate the relationships between substance use and neurocognitive and functional outcomes. Exploratory analyses demonstrated that socioeconomic status at baseline was confounded with race/ethnicity, which influenced these relationships, but did not seem to fully explain these relationships. Mediation analyses were conducted separately according to race/ethnicity and gender due to these differences, but the sample sizes were very small. While the results are descriptive of the sample, the results require replication with a larger sample before one can confidently generalize from them.

A. Aim 1

Consistent with the hypotheses and previous studies with this sample and other samples (Baggio et al., 2013; Birckmayer et al., 2004; Crane, Langenecker, & Mermelstein, 2015; Hoffman et al., 2001; Libby et al., 2005; Magid et al., 2009; E. Peters et al., 2012; Volkow, 2004; Weinstein & Mermelstein, 2013a, 2013b; Wills et al., 1996), at baseline (and over time) more symptoms of depression, more symptoms of anxiety, a weaker belief that one can do something to feel better when in a bad mood, and lower GPA were each associated with more poly-substance use. Of note, when examining how each substance was associated with baseline clinical risk factors, alcohol use was not related to symptoms of depression and anxiety, but all other associations were significant (as stated above). In addition, examining how each substance was associated with clinical risk factors over time, cigarette use was not related to a stronger belief that one can do something to feel better when in a bad mood, but all other associations were significant (as stated above).

There were important gender and race/ethnicity differences in these relationships. Overall, Caucasian, non-Hispanic individuals had a higher frequency of poly-substance use and use of each substance individually over time. Additionally, males, compared to females, had a

higher frequency of both poly-substance use over time as well as use of each substance individually. Furthermore, a lower baseline GPA was more strongly associated with more poly-substance use for males than for females. In line with our previous findings (Crane et al., 2015; Schuster, Mermelstein, & Wakschlag, 2013), more poly-substance use and more marijuana use was related to more depression symptoms and more anxiety symptoms in males, but not in females. A weaker belief that one can do something to feel better when in a bad mood was associated with more marijuana use for males; however, a stronger belief that one can do something to feel better when in a bad mood was related to more marijuana use for females. These findings support the hypothesis that males with higher negative affect and less perceived ability to regulate their negative affect may use marijuana as a way to regulate their affect (Crane et al., 2015), while females use marijuana for other reasons that are not fully understood.

Time also played an important role in the relationship between clinical risk factors and substance use. A higher frequency of marijuana use was associated with more anxiety symptoms in adolescence (approximately ages 14-16), but this effect was even larger in young adulthood (approximately ages 22-24). Thus, anxiety seems to play an important role in not only the initiation of marijuana use, but also the continued use of marijuana. While alcohol use was not related to depression symptoms or negative mood regulation in adolescence, more alcohol use was associated with less depression symptoms in young adulthood and a stronger belief that that one can do something to feel better when in a bad mood. It is not clear what is driving these relationships in young adulthood, although it may be that young adults who have more symptoms of depression and have a weaker belief that they can do something to feel better when in a bad mood are isolating themselves and not engaging in social situations that may facilitate drinking alcohol more frequently. On the other hand, more alcohol use was related to more anxiety symptoms in adolescence, but not in young adulthood; indicating anxiety may be involved in early initiation of alcohol use, but anxiety may not play a role in continued alcohol

use. It is important to note that alcohol use is legal and normative in the U.S. in young adulthood and that the majority of the sample (about 94%) used alcohol in young adulthood. Therefore, alcohol use may not be related to anxiety in young adulthood because the majority of sample is using alcohol for social and environmental reasons that are not necessarily related to anxiety.

B. Aim 2

Contrary to hypotheses and many previous studies (Andrews et al., 2011; Clark et al., 2007; Dawe et al., 2004; Ernst et al., 2010; Frigerio et al., 2002; Gowin et al., 2013; Hulvershorn et al., 2013; Maurage et al., 2008; Maurage et al., 2007; Muller et al., 2013; Nees et al., 2012; Oscar-Berman et al., 1990; J. Peters et al., 2011; Platt et al., 2010; Schneider et al., 2012), reward processing and emotional processing were not related to poly-substance use and surprisingly, more poly-substance use was associated with better decision-making, but after controlling for relevant covariates this effect only trended toward significance.

When examining the relationships between these neurocognitive outcomes and each substance individually, more alcohol use was related to better decision-making, but after controlling for relevant covariates this relationship was no longer significant. Indeed, race/ethnicity and gender significantly influenced the relationship between alcohol use and decision-making. First, Caucasian, non-Hispanic males drank alcohol more frequently and reported more alcohol related problems than any other group, followed by Caucasian, non-Hispanic females (see Table 2). Second, non-Caucasian or Hispanic individuals had poorer decision-making performance than Caucasian, non-Hispanic individuals (see Figure 5). Third, group correlations found that for Caucasian, non-Hispanic males and females more alcohol use was associated with better decision-making, but for non-Caucasian or Hispanic males and females more alcohol use was associated with worse decision-making. Lastly, Caucasian, non-Hispanic males and females had significantly higher socioeconomic status, based on mother's education and percent of low income students that attended their high school, compared to non-

Caucasian or Hispanic males and females (see Table 2). Taken together, although Caucasian, non-Hispanic males and females drink more heavily, their higher socioeconomic may be a protective factor, positively affecting their decision-making performance. Conversely, for non-Caucasian or Hispanic individuals, without the protection of higher socioeconomic factors, more alcohol use is related to poorer decision-making.

In addition, more marijuana use was related to poorer overall emotional processing after controlling for covariates. However, when examining the relationship between marijuana use and emotional processing in groups stratified on gender and race/ethnicity (Caucasian and non-Hispanic; non-Caucasian or Hispanic) no significant relationships were found, but the relationship was stronger among Caucasian, non-Hispanic males and females than among non-Caucasian or Hispanic males and females (see Table 8). Importantly, there were significant gender and race/ethnicity differences in emotional processing, such that females had better emotional processing performance than males and Caucasian, non-Hispanic individuals had better emotional processing performance than non-Caucasian or Hispanic individuals, so these group differences may have influenced the relationship between performance and substance use. In addition, emotional processing was also significantly associated with IQ (r= .44) and IQ differed between Caucasian, non-Hispanic individuals and non-Caucasian or Hispanic individuals, which may have contributed to the relationship between performance and substance use as well.

On the other hand, consistent with hypotheses and previous studies looking at cigarette use, alcohol use and marijuana use separately (Cook & Moore, 1993; Fergusson & Boden, 2008; Grant et al., 2012; Horwood et al., 2010; Lynskey et al., 2003), more poly-substance use was associated with attaining less education. When examining the relationships between educational attainment and each substance individually, more cigarette use, and more marijuana use were related to attaining less education, but in contrast to previous studies (Cook & Moore, 1993),

alcohol use was not associated with educational attainment. Therefore, cigarette and marijuana use seemed to drive the relationship between more substance use and lower educational attainment. It is important to note that the high prevalence of alcohol use in the sample, which is normative in young adulthood, may have limited our ability to find a relationship between alcohol use and educational attainment.

In general, individuals' GPA, substance use, and negative mood patterns at baseline seemed to greatly influence their substance use patterns over adolescence and young adulthood, as well as their educational attainment. As such, individuals with low GPAs had higher substance use over time and lower educational attainment. Additionally, individuals with more negative mood patterns and substance use at baseline also seemed to have more negative mood patterns and substance use over time. Without a baseline IQ estimate or baseline neurocognitive functioning, we are not able to determine individuals' optimal abilities and thus, we are not able to capture decline these individuals may have experienced related to their substance use.

There were also important gender and race/ethnicity differences in neurocognitive outcomes and their relationship with substance use measures. Overall, non-Hispanic Caucasians had better performance on neurocognitive measures and had slightly higher educational attainment than Hispanic or Non-Caucasian individuals. In general, females performed better on emotional processing, while males had slightly better, but not significantly so, performance on reward processing. Given that many neuropsychological tests are culturally-bound and are known to have race/ethnicity and gender differences (Bolla, Eldreth, Matochik, & Cadet, 2004; Gasquonie, 2009; Gur et al., 2012; Kramer, Delis, & Daniel, 1988; Olson & Jacobson, 2014; Overman et al., 2004; Reavis & Overman, 2001; Rule, Freeman, & Ambady, 2013), these findings were not surprising. Furthermore, exploratory analyses exploring the gender and race/ethnicity specific correlations between substance use measures and outcomes showed differences among groups. For non-Hispanic, Caucasian females, more alcohol use was

associated with poorer emotional processing, while more poly-substance use, more marijuana use, higher scores of nicotine withdrawal (a proxy for current cigarette use), and testing positive for THC on UDS testing were each associated with less educational attainment. For Hispanic or non-Caucasian females, more alcohol use was related to poorer reward processing. For non-Hispanic, Caucasian males, more poly-substance use and more alcohol use were each associated with better decision-making, indicating that this group may be driving the significant relationship in the whole sample, and more cigarette use and higher scores of nicotine withdrawal (a proxy for current cigarette use) were each associated with less educational attainment. For Hispanic or non-Caucasian males, higher scores of nicotine withdrawal (a proxy for current cigarette use) was related to less educational attainment. Therefore, most groups (except for non-Caucasian females) demonstrated a similar negative relationship between at least one substance use measure and educational attainment, but all groups showed very different relationships between substance use measures and neurocognitive outcomes. Overall, these findings were surprising and highlight the large individual variability in substance use and the effects of substance use on neurocognitive functioning. It is also possible that a different sampling strategy that recruited more individuals, especially a greater number of individuals with more substance use, could address some of our sample irregularities. The sampling strategy employed was intended to elicit a range of substance use within the sample, and was successful in doing so. Inadvertently, the ethnicity/race, SES, and estimated IQ effects may have obscured the ability to address key questions of interest.

C. Aim 3

Mediation analyses were conducted separately according to race/ethnicity and gender, given that these factors seemed to largely influence substance use and the neurocognitive outcomes of substance use. For Caucasian, non-Hispanic males and females, more poly-substance use mediated relationship between baseline high negative affect and lower educational

attainment, but these relationships were not found in non-Caucasian or Hispanic males or females. However, it is important to note that the sample sizes were very small for these analyses. The results are relatively descriptive of the sample, but the results are not necessarily generalizable and require replication.

D. Limitations

Although overall the study has a large and diverse sample, the findings should be considered in the context of several limitations. First, Aims 2 & 3 used a subset of the sample, limiting the generalizability of the findings. In addition, several analyses in Aims 2 & 3 grouped the laboratory visit sample into sample sizes that were too small to account for the race/ethnicity and gender differences, making it difficult to make meaningful interpretations of the findings. Second, although the whole sample and the laboratory visit sample captured individuals at different levels of cigarette use, marijuana use, and alcohol use, most of the participants were selected for having ever smoked a cigarette at baseline, limiting the generalizability of our findings. Third, while every attempt was made to recruit the laboratory visit sample from the whole sample in a representative manner to capture individuals with varying levels of substance use, the laboratory visit sample was a convenience sample and is not representative of the whole sample. Indeed, the inclusion/exclusion criteria we used to decrease potential confounds (e.g., no self-reported formal diagnosis of a learning disability, developmental delay, mental illness (including ADHD, but excluding depression or anxiety), or neurological condition; no significant birth complications; no history of loss of consciousness greater than 10 minutes; no current use of any psychotropic medications (excluding SSRI and SNRI antidepressants)), may have excluded many individuals with heavier substance use from participating in the laboratory visit sample. Further, we required that individuals could not test positive for any other substance other than marijuana at the laboratory visit, which may have discouraged individuals with heavier substance use from participating in the laboratory visit. Moreover, individuals were required to

come into the university for the laboratory visit, which limited who was able to participate in the study. In particular, individuals with heavier, problematic substance use and poorer outcomes from their use (e.g., incarceration, house arrest, loss of income and/or transportation) were not able to participate in the laboratory visit. Fourth, data on substance use and psychosocial measures were not captured between years 2 and 5, diminishing our ability to understand the relationships between marijuana use, cigarette use, depression symptoms, and gender during this time.

E. Conclusion

Taken together, we were able to expand upon previous findings to show how more depression and anxiety, poorer negative mood regulation, and lower GPA is related to more poly-substance over adolescence and young adulthood and how more poly-substance use in adolescence and young adulthood is associated with poorer educational attainment in young adulthood, but we were not able to replicate findings of how substance use is associated with neurocognitive outcomes. Surprisingly, we did not find significant relationships between poly-substance use and neurocognitive functioning. However, several factors, including race/ethnicity and gender seemed to differentially influence the relationship between substance use and neurocognitive functioning, but these factors did not fully account for variability in these relationships. Results indicate that there is tremendous individual variability in substance use of cigarettes, marijuana, and alcohol, factors related to use of these substances, and the effects of these substances on neurocognitive functioning. It is also possible that random variation in the sample influenced the findings. Therefore, it is still not clear what the key moderators are in the relationship between cigarette, marijuana, and alcohol poly-substance use and neurocognitive outcomes. It is important that future longitudinal studies recruit large and diverse samples to better understand the key moderators that influence substance use patterns and how substance use influences neurocognitive outcomes.

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Table 1

Timeline of Assessments

	Whole Sample							***n=80***
Variables of Interest	**Baseline**	**6 mo**	**15 mo**	**2 yrs**	**5 yrs**	**6 yrs**	**7 yrs**	**Laboratory visit (9 yrs)**
Substance Use								
Cigarette Use Frequency	X	X	X	X	X	X	X	X
Marijuana Use Frequency	X	X	X	X	X	X	X	X
Alcohol Use Frequency	X	X	X	X	X	X	X	X
Clinical Risk Factors								
GPA	X							
CES-D	X	X	X	X	X	X	X	X
Modified MASQ	X	X	X	X	X	X	X	X
NMR	X	X	X	X	X	X	X	X
Neurocognition								
TOMM								X
IGT								X
mMID								X
FEPT								X
Functional Outcome								
Highest Educational Attainment								X
Potential Premorbid & Psychiatric Confounds								
WTAR FSIQ								X
SCID-IV Interview								X
WURS								X
BIS					X			
Adolescent ABS	X	X	X	X				
Measures to Characterize Sample								
Family History of SUD								X
SJWS								X
mFTQ	X	X	X	X	X	X	X	X
CUDIT-R					X	X	X	X
MPS					X	X	X	X
Alcohol Problem Scale	X	X	X	X				
Alcohol Problem Items					X	X	X	X
Urine Drug Screen								X

Note: GPA, Grade-Point Average; CES-D, Center for Epidemiological Scale-Depression; MASQ, Mood and Affect Symptom Questionnaire; NMR, Negative Mood Regulation Expectancies Scale; TOMM, Test of Memory Malingering; IGT, Iowa Gambling Task; mMID, modified Monetary Incentive Delay task; FEPT, Facial Emotion Perception Task; WTAR FSIQ; Wechsler Test of Adult Reading Full Scale Intellectual Abilities; WURS, Wender-Utah Rating Scale; BIS, Barratt Impulsiveness Scale; ABS, Antisocial Behavior Scale; SUD, Substance Use Disorder; SJWS, Shiffman/Jarvik Withdrawal Questionnaire; mFTQ, modified Fagerstrom Questionnaire; CUDIT-R, Cannabis Use Disorders Identification Test-Revised; MPS, Marijuana Problem Scale.

Table 2

Participant Characteristics of Whole P01 Sample for Aim 1

Demographics	**Baseline** (n=1211)	**6 months** (n=1144)	**15 months** (n=1128)	**2 years** (n=1144)	**5 years** (n=1026)	**6 years** (n=1068)	**7 years** (n=1066)
Age	15.63 (0.61)	16.14 (0.62)	16.89 (0.62)	17.59 (0.60)	21.38 (0.81)	22.41 (0.83)	23.41 (0.83)
Gender (% female)	57%	57%	58%	58%	59%	59%	59%
GPA	2.72 (0.75)	2.88 (0.71)	2.82 (0.74)	2.85 (0.75)	--	--	--
Ethnicity/Race							
Caucasian	57%	57%	57%	57%	58%	57%	57%
Black	17%	17%	17%	17%	17%	17%	17%
Hispanic	17%	16%	17%	17%	16%	16%	16%
Asian	4%	4%	4%	4%	4%	4%	4%
Other	5%	6%	5%	5%	5%	6%	6%
CES-D Total Score	16.85 (9.83)	16.37 (9.93)	14.64 (9.27)	15.06 (9.47)	13.42 (9.85)	12.78 (9.69)	12.44 (9.43)
Modified MASQ Total Score	28.40 (7.85)	27.60 (8.11)	26.48 (7.57)	26.08 (7.26)	25.08 (7.49)	24.59 (7.30)	24.29 (7.47)
NMR Total Score	3.49 (0.69)	3.52 (0.71)	3.60 (0.70)	3.62 (0.69)	3.81 (0.72)	3.88 (0.74)	3.92 (0.71)
BIS Total Score	--	--	--	--	33.22 (7.49)	--	--
Adolescent ASB Total Score	34.87 (8.28)	31.64 (7.19)	30.98 (6.67)	31.21 (6.79)	--	--	--
Substance Use							
Cigarettes							
Frequency of cigarette use in past month (days)	3.74 (7.61)	4.36 (8.41)	5.57 (9.98)	6.48 (10.64)	3.32 (5.12)	10.07 (12.67)	9.78 (12.76)
Nicotine Dependence (mFTQ)	1.38 (1.18)	1.48 (1.32)	1.64 (1.42)	1.71 (1.46)	2.57 (1.53)	2.67 (1.59)	2.73 (1.65)
Cigarette Use Z-score- based on baseline	0.00 (1.00)	0.08 (1.11)	0.24 (1.31)	0.36 (1.39)	-0.05 (0.67)	0.83 (1.66)	0.79 (1.68)
Marijuana							
Frequency of marijuana use in past month (days)	2.01 (5.12)	2.42 (5.79)	2.94 (6.45)	3.84 (7.55)	5.35 (8.93)	5.20 (9.01)	5.32 (9.27)
Marijuana-Related Problems (CUDIT-R)	--	--	--	--	5.91 (7.28)	5.40 (6.77)	5.10 (6.78)
Marijuana Use Z-score- based on baseline	0.00 (1.00)	0.08 (1.13)	0.18 (1.26)	0.36 (1.48)	0.65 (1.74)	0.62 (1.76)	0.65 (1.81)
Alcohol							
Frequency of alcohol use in past month (days)	2.28 (2.84)	2.42 (3.19)	2.82 (3.48)	3.11 (3.46)	5.79 (4.56)	5.97 (4.38)	6.10 (4.52)
Alcohol Problem Scale	3.62 (1.67)	3.82 (1.74)	4.05 (1.74)	4.31 (1.72)	--	--	--
Alcohol Problem Items	--	--	--	--	2.77 (2.10)	3.47 (1.47)	3.41 (1.42)
Alcohol Use Z-score- based on baseline	0.00 (1.00)	0.05 (1.12)	0.19 (1.22)	0.29 (1.22)	1.24 (1.61)	1.30 (1.54)	1.35 (1.59)
Poly-substance Use Z-score- based on baseline	0.00 (0.73)	0.70 (0.84)	0.20 (0.95)	0.33 (1.00)	0.61 (0.94)	0.92 (1.22)	0.92 (1.12)

Note: all values are means or standard deviations unless otherwise noted; GPA, Grade-Point Average; CES-D, Center for Epidemiological Scale-Depression; MASQ, Mood and Affect Symptom Questionnaire; NMR, Negative Mood Regulation Expectancies Scale; BIS, Barratt Impulsiveness Scale; ABS, Antisocial Behavior Scale; mFTQ, modified Fagerstrom Questionnaire; CUDIT-R, Cannabis Use Disorders Identification Test-Revised.

Table 3

Participant Characteristics of 80 Individuals from Laboratory Visit for Aims 2 & 3

	Whole Laboratory Visit Sample	**Females**		**Males**		
		Caucasian, Non-Hispanic[1]	***Non-Caucasian or Hispanic[2]***	***Caucasian, Non-Hispanic[3]***	***Non-Caucasian or Hispanic[4]***	*Group Comparisons*
	n= 80	*n*= 19	*n*= 20	*n*= 26	*n*= 15	
Age	24.74 ± 0.87 [23-27]	24.72 ± 0.75	24.30 ± 0.92	24.89 ± 0.86	25.07 ± 0.80	Males > Females
Estimated FSIQ	102.28 ± 9.44 [80-117]	106.44 ± 7.58	96.35 ± 8.36	105.93 ± 8.17	98.60 ± 10.06	1,3 > 2,4
Gender (% Male)	53%	--	--	--	--	--
Years of Education	14.52 ± 1.86 [11-18]	15.17 ± 2.04	14.30 ± 1.63	14.59 ± 1.78	13.93 ± 2.02	*ns*
Baseline GPA *(9th or 10th grade)*	2.71 ± 0.85 [1.00-4.00]	3.00 ± 0.86	2.68 ± 0.63	2.63 ± 0.92	2.50 ± 0.93	*ns*
% Low Income Students in High School Attended at Baseline	17.18 ± 15.94 [1.90-67.50]	10.94 ± 6.54	22.22 ± 17.22	11.94 ± 10.70	27.46 ± 22.75	1,3 > 2,4
Ethnicity/Race						
Caucasian	54%	19	--	26	--	--
Black	20%	--	10	--	6	
Hispanic	19%	--	9	--	6	
Asian	4%	--	0	--	3	
Other	3%	--	1	--	0	
Mother's Education at Baseline						
Grade School or Less	5%	0%	15%	0%	7%	Significant gender and race/ethnicity differences
Some High School	6%	5%	20%	0%	0%	
Completed High School	23%	5%	20%	27%	40%	
Some College	15%	11%	5%	19%	26%	
Completed College	31%	58%	20%	27%	20%	
Attended Graduate School	13%	16%	10%	19%	0%	
Unknown	7%	5%	10%	8%	7%	
% WURS >46	4%	6%	5%	0%	7%	*ns*
MASQ Total Score	22.99 ± 6.92 [14-49]	21.72 ± 4.61	26.60 ± 8.93	20.56 ± 3.98	24.07 ± 8.56	1,3 < 2,4
CES-D Total Score	9.99 ± 9.89 [0-46]	8.11 ± 7.05	15.80 ± 13.52	6.85 ± 6.16	10.13 ± 10.06	1,3 < 2,4
TOMM Trail 2 Score	49.94 ± 0.37 [47-50]	50.00 (0.00)	49.95 (0.22)	49.96 (0.20)	49.80 (0.78)	*ns*
% Family History of SUD	73%	68%	60%	77%	87%	Males > Females
% THC+	23%	11%	15%	31%	33%	Males > Females
SJWS Total Score	2.00 ± 0.62 [1.13-5.20]	1.92 ± 0.37	2.06 ± 0.88	1.99 ± 0.57	2.00 ± 0.60	*ns*
Frequency of Cigarette Use Per Month (mean over time)*	5.59 ± 7.45 [0-30]	5.46 ± 7.88	3.63 ± 5.27	7.51 ± 8.86	4.87 ± 6.42	*ns*
mFTQ*	1.34 ± 1.73 [0-6]	1.42 ± 1.57	0.93 ± 1.79	1.81 ± 1.76	1.00 ± 1.72	*ns*
Frequency of Marijuana Use Per Month (mean over time)*	3.19 ± 5.28 [0-27]	2.10 ± 6.24	1.45 ± 2.26	5.84 ± 6.36	2.02 ± 2.65	3 > 1,4 > 2
Marijuana Related Problems (CUDIT-R)*	3.68 ± 5.33 [0-23]	1.72 ± 2.40	3.55 ± 6.07	5.46 ± 6.29	3.13 ± 4.41	*ns*
Frequency of Alcohol Use Per Month (mean over time)*	4.16 ± 2.44 [0-12]	4.15 ± 1.84	3.15 ± 2.46	5.78 ± 2.07	2.63 ± 2.05	3 > 1 > 2 > 4
Alcohol Related Problems*	3.12 ± 1.30 [0-7.02]	2.95 ± 0.77	2.87 ± 1.31	3.90 ± 1.02	2.34 ± 1.60	3 > 1,2 > 4
Poly-Substance Use (z-score of combined mean over time)*	0.00 ± 0.75 [-1.02-2.89]	-0.10 ± 0.74	-0.45 ± 0.72	0.64 ± 1.17	-0.42 ± 0.68	1,3 > 2,4

Note: all values are means, standard deviations, and ranges unless otherwise noted; GPA, Grade-Point Average; WURS, Wender-Utah Rating Scale; CES-D, Center for Epidemiological Scale-Depression; MASQ, Mood and Affect Symptom Questionnaire; TOMM, Test of Memory Malingering; SUD, Substance Use Disorder; THC, tetrahydrocannabinol from urine drug screen; SJWS, Shiffman/Jarvik Withdrawal Questionnaire; mFTQ, modified Fagerstrom Questionnaire; CUDIT-R, Cannabis Use Disorders Identification Test-Revised; *, $p < .05$.

Table 4

Correlations Among Baseline Clinical Predictors in Laboratory Visit Sample and in Whole Sample

	1	**2**	**3**	**4**
1. Baseline CES-D		.73*	-.69*	-.18*
2. Baseline Modified MASQ	.72*		-.61*	-.08*
3. Baseline NMR	-.75*	-.73*		.11*
4. Baseline GPA	-0.20	-0.19	.23*	

Note. Laboratory visit sample (n=80) on bottom, whole sample (n= 1211) on top in grey. CES-D, Center for Epidemiological Scale-Depression; MASQ, Mood and Affect Symptom Questionnaire; NMR, Negative Mood Regulation Expectancies Scale; GPA, Grade-Point Average; *, $p < .05$

Table 5

Longitudinal Multilevel Regression Models with Substance Use Measures as the Dependent Variables and Baseline Risk Factor Measures as the Independent Variables

	Z-Score of Poly-substance Use				Cigarette Use Frequency				Marijuana Use Frequency				Alcohol Use Frequency			
Predictor	Estimate (SE)	df	t	Sig.	Estimate (SE)	df	t	Sig.	Estimate (SE)	df	t	Sig.	Estimate (SE)	df	t	Sig.
CESD																
Intercept	-0.15 (0.04)	1336.79	-3.71	≤.001	3.04 (0.42)	1335.87	7.31	≤.001	2.50 (0.15)	1206.47	16.82	≤.001	1.30 (0.14)	1340.78	9.59	≤.001
Time (linear)	0.13 (0.00)	1150.41	27.66	≤.001	0.70 (0.05)	1152.69	13.77	≤.001	0.49 (0.04)	1143.33	11.56	≤.001	0.62 (0.02)	1129.88	31.70	≤.001
Baseline CES-D	0.01 (0.00)	1202.27	4.25	≤.001	0.11 (0.02)	1196.97	4.97	≤.001	0.04 (0.01)	1198.93	2.99	≤.001	0.01 (0.01)	1189.55	1.78	.075
Gender	-0.14 (0.02)	1209.71	-7.02	≤.001	-1.06 (0.21)	1204.53	-5.01	≤.001	-0.97 (0.14)	1207.09	-6.95	≤.001	-0.25 (0.07)	1199.98	-3.55	≤.001
Race	0.26 (0.04)	1222.02	5.86	≤.001	1.97 (0.46)	1214.53	4.27	≤.001	0.51 (0.30)+	1211.38	1.67	.095	1.21 (0.15)	1206.99	7.99	≤.001
Ethnicity	-0.06 (0.05)+	1221.06	-1.11	.266	-1.28 (0.54)	1216.15	-2.35	.019	0.08 (0.36)+	1216.72	0.23	.822	0.02 (0.18)+	1216.51	0.09	.93
Table 6																
Interactions																
Gender*CES-D	0.00 (0.00)+	1204.48	-1.18	.238	-0.02 (0.02)+	1199.18	-0.68	.495	-0.02 (0.01)+	1199.23	-1.49	.136	-0.01 (0.01)+	1192.98	-0.94	.349
MASQ																
Intercept	-0.13 (0.04)	1337.10	-3.30	≤.001	3.19 (0.42)	1334.48	7.61	≤.001	2.50 (0.15)	1207.58	16.85	≤.001	1.32 (0.14)	1341.40	9.79	≤.001
Time (linear)	0.13 (0.00)	1152.40	27.70	≤.001	0.71 (0.05)	1153.81	13.83	≤.001	0.49 (0.04)	1145.28	11.56	≤.001	0.62 (0.02)	1131.98	31.74	≤.001
Baseline MASQ	0.01 (0.00)	1211.03	4.03	≤.001	0.11 (0.03)	1206.08	3.94	≤.001	0.06 (0.02)	1210.00	3.26	≤.001	0.02 (0.01)	1201.83	2.24	.025
Gender	-0.14 (0.02)	1211.26	-6.92	≤.001	-0.99 (0.21)	1206.24	-4.66	≤.001	-0.97 (0.14)	1208.34	-6.99	≤.001	-0.25 (0.07)	1201.40	-3.67	≤.001
Race	0.24 (0.04)	1222.78	5.36	≤.001	1.74 (0.46)	1215.98	3.75	≤.001	0.39 (0.30)+	1212.77	1.27	.204	1.17 (0.15)	1207.62	7.74	≤.001
Ethnicity	-0.05 (0.05)+	1222.55	-0.88	.377	-1.18 (0.55)	1217.80	-2.16	.031	0.16 (0.36)+	1218.67	0.43	.664	0.04 (0.18)+	1218.26	0.22	0.827
Interactions																
Gender*MASQ	0.00 (0.00)+	1210.92	-0.40	.691	-0.01 (0.03)+	1205.73	-0.39	.693	-0.02 (0.02)+	1207.46	-0.85	.397	0.00 (0.01)+	1202.21	0.04	.969
NMR																
Intercept	-0.14 (0.04)	1339.65	-3.59	≤.001	3.09 (0.42)	1335.84	7.37	≤.001	2.51 (0.15)	1208.32	16.84	≤.001	1.30 (0.14)	1343.23	9.64	≤.001
Time (linear)	0.13 (0.00)	1152.55	27.71	≤.001	0.71 (0.05)	1153.71	13.83	≤.001	0.49 (0.04)	1145.60	11.57	≤.001	0.62 (0.02)	1132.04	31.74	≤.001
Baseline NMR	-0.09 (0.03)	1208.75	-3.07	≤.001	-0.84 (0.31)	1204.50	-2.72	.007	-0.66 (0.20)	1208.04	-3.30	≤.001	-0.10 (0.10)	1199.51	-0.99	.322
Gender	-0.14 (0.02)	1210.96	-6.75	≤.001	-0.95 (0.21)	1206.37	-4.43	≤.001	-0.99 (0.14)	1208.42	-7.06	≤.001	-0.24 (0.07)	1200.77	-3.39	≤.001
Race	0.25 (0.04)	1223.73	5.70	≤.001	1.89 (0.46)	1217.05	4.08	≤.001	0.46 (0.30)+	1213.55	1.54	.125	1.20 (0.15)	1208.57	7.91	≤.001
Ethnicity	-0.06 (0.05)+	1222.76	-1.13	.257	-1.30 (0.55)	1218.18	-2.36	.018	0.07 (0.36)+	1219.05	0.19	.851	0.02 (0.18)+	1218.08	0.12	.903
Interactions																
Gender*NMR	0.01 (0.03)+	1208.59	0.28	.782	0.07 (0.32)+	1205.19	0.23	.818	0.00 (0.21)+	1205.96	-0.02	.987	0.05 (0.10)+	1199.71	0.51	.611
GPA																
Intercept	-0.16 (0.04)	1318.10	-3.84	≤.001	2.90 (0.42)	1332.87	6.98	≤.001	2.44 (0.15)	1192.45	16.42	≤.001	1.29 (0.14)	1323.28	9.38	≤.001
Time (linear)	0.13 (0.00)	1137.06	27.47	≤.001	0.70 (0.05)	1140.43	13.59	≤.001	0.49 (0.04)	1130.25	11.54	≤.001	0.62 (0.02)	1116.25	31.61	≤.001
Baseline GPA	-0.17 (0.03)	1191.66	-6.20	≤.001	-2.30 (0.27)	1186.12	-8.38	≤.001	-0.84 (0.18)	1192.40	-4.70	≤.001	-0.21 (0.07)	1187.14	-3.12	≤.001
Gender	-0.11 (0.02)	1193.64	-5.35	≤.001	-0.67 (0.20)	1189.62	-3.26	≤.001	-0.76 (0.14)	1192.79	-5.61	≤.001	1.20 (0.15)	1193.65	7.84	≤.001
Race	0.28 (0.05)	1205.86	6.17	≤.001	2.20 (0.46)	1198.63	4.80	≤.001	0.57 (0.30)+	1197.57	1.89	.059	-0.06 (0.09)	1184.40	-0.61	.543
Ethnicity	-0.11 (0.05)	1206.29	-1.99	.047	-2.06 (0.55)	1199.78	-3.77	≤.001	-0.13 (0.36)+	1201.32	-0.35	.728	0.00 (0.18)+	1201.53	-0.02	.982
Interactions																
Gender*GPA	0.05 (0.03)	1192.80	2.01	.044	0.40 (0.27)+	1187.14	1.47	.141	0.33 (0.18)+	1189.78	1.87	.062	0.11 (0.09)+	1183.53	1.21	.225

Note. CES-D, Center for Epidemiological Scale-Depression; MASQ, Mood and Affect Symptom Questionnaire; NMR, Negative Mood Regulation Expectancies Scale; GPA, Grade-Point Average; +, variable removed from final model

Table 6

Longitudinal Multilevel Regression Models with Substance Use Measures as the Dependent Variables and Time-Varying Risk Factor Measures as the Independent Variables

	Z-Score of Poly-substance Use				**Cigarette Use Frequency**				**Marijuana Use Frequency**				**Alcohol Use Frequency**			
Predictor	Estimate (SE)	df	t	Sig.	Estimate (SE)	df	t	Sig.	Estimate (SE)	df	t	Sig.	Estimate (SE)	df	t	Sig.
CESD																
Intercept	0.15 (0.04)	1347.76	-3.78	0.00	2.99 (0.42)	1336.26	7.10	0.00	2.47 (0.15)	1238.17	16.58	0.00	1.27 (0.14)	1355.41	9.40	0.00
Time (linear)	0.14 (0.00)	1187.55	28.05	0.00	0.71 (0.05)	1183.48	13.85	0.00	0.51 (0.04)	1178.44	11.95	0.00	0.62 (0.02)	1172.68	31.69	0.00
CES-D	0.01 (0.00)	7405.82	6.03	0.00	0.04 (0.01)	7437.74	3.29	0.00	0.05 (0.01)	7367.64	6.21	0.00	0.02 (0.01)	5213.22	3.78	0.00
Gender	-0.13 (0.02)	1222.21	-6.58	0.00	-0.86 (0.21)	1214.71	-4.12	0.00	-0.92 (0.13)	1229.36	-6.81	0.00	-0.25 (0.07)	1229.33	-3.62	0.00
Race	0.26 (0.04)	1223.18	5.83	0.00	1.95 (0.46)	1214.66	4.21	0.00	0.51 (0.30)	1216.17	1.70	0.09	1.21 (0.15)	1213.03	7.98	0.00
Ethnicity	-0.06 (0.05)$^{+}$	1223.21	-1.11	0.27	-1.29 (0.55)	1216.11	-2.34	0.02	0.06 (0.35)$^{+}$	1221.90	0.16	0.87	0.01 (0.18)$^{+}$	1222.11	0.08	0.94
Interactions																
Year*CES-D	0.00 (0.00)$^{+}$	6103.01	-0.55	0.58	0.00 (0.00)$^{+}$	5994.23	0.94	0.35	0.00 (0.00)$^{+}$	6275.33	0.45	0.66	-0.01 (0.00)	5224.13	-3.02	0.00
Gender*CES-D	0.00 (0.00)	7456.99	-3.59	0.00	-0.02 (0.01)$^{+}$	7514.69	-1.49	0.14	-0.04 (0.01)	7418.53	-4.23	0.00	-0.01 (0.00)$^{+}$	7441.67	-1.18	0.24
MASQ																
Intercept	-0.14 (0.04)	1338.42	-3.61	0.00	3.04 (0.42)	1330.01	7.24	0.00	2.47 (0.15)	1233.91	16.46	0.00	1.29 (0.13)	1340.73	9.56	0.00
Time (linear)	0.14 (0.00)	1191.80	28.18	0.00	0.70 (0.05)	1187.21	13.81	0.00	0.52 (0.04)	1185.33	12.19	0.00	0.63 (0.02)	1182.71	31.83	0.00
MASQ	0.01 (0.00)	7375.65	5.93	0.00	0.03 (0.01)	7438.77	2.42	0.02	0.03 (0.01)	5625.11	2.24	0.03	0.04 (0.01)	4905.61	4.52	0.00
Gender	-0.13 (0.02)	1225.15	-6.61	0.00	-0.84 (0.21)	1220.60	-4.04	0.00	-0.90 (0.14)	1233.64	-6.66	0.00	-0.26 (0.07)	1227.88	-3.77	0.00
Race	0.25 (0.04)	1223.73	5.52	0.00	1.87 (0.47)	1217.60	4.03	0.00	0.42 (0.30)$^{+}$	1215.82	1.40	0.16	1.17 (0.15)	1210.86	7.74	0.00
Ethnicity	0.06 (0.05)$^{+}$	1223.08	-1.05	0.29	-1.25 (0.55)	1219.23	-2.28	0.02	0.08 (0.36)$^{+}$	1219.99	0.22	0.82	0.03 (0.18)$^{+}$	1220.70	0.15	0.88
Interactions																
Year*MASQ	0.00 (0.00)$^{+}$	6045.54	0.74	0.46	0.00 (0.01)$^{+}$	5919.69	0.03	0.98	0.01 (0.00)	6232.80	3.11	0.00	-0.01 (0.00)	5190.70	-2.56	0.01
Gender*MASQ	0.00 (0.00)	7448.82	-2.75	0.01	-0.03 (0.01)	7510.90	-1.80	0.07	-0.03 (0.01)	7274.86	-2.52	0.01	0.00 (0.01)$^{+}$	7220.75	-0.73	0.46
NMR																
Intercept	0.15 (0.04)	1350.50	-3.72	0.00	3.03 (0.42)	1343.90	7.19	0.00	2.47 (0.15)	1260.41	16.35	0.00	1.28 (0.14)	1361.82	9.42	0.00
Time (linear)	0.14 (0.00)	1230.41	27.66	0.00	0.70 (0.05)	1231.03	13.54	0.00	0.51 (0.04)	1214.26	11.82	0.00	0.62 (0.02)	1228.89	31.03	0.00
Risk Factor	-0.04 (0.01)	7526.36	-2.38	0.02	-0.22 (0.16)	7571.41	-1.38	0.17	-0.43 (0.12)	7165.46	-3.48	0.00	-0.20 (0.09)	4534.48	-2.18	0.03
Gender	-0.13 (0.02)	1234.67	-6.38	0.00	-0.84 (0.21)	1230.36	-4.00	0.00	-0.90 (0.14)	1242.98	-6.62	0.00	-0.24 (0.07)	1238.85	-3.48	0.00
Race	0.25 (0.04)	1224.76	5.63	0.00	1.91 (0.47)	1218.76	4.11	0.00	0.47 (0.30)	1215.22	1.55	0.12	1.20 (0.15)	1210.22	7.95	0.00
Ethnicity	-0.06 (0.05)$^{+}$	1225.55	-1.07	0.29	-1.27 (0.55)	1222.56	-2.30	0.02	0.07 (0.36)$^{+}$	1222.62	0.21	0.84	0.02 (0.18)$^{+}$	1220.95	0.09	0.93
Interactions																
Year*NMR	0.00 (0.01)$^{+}$	5411.12	0.74	0.46	-0.03 (0.06)$^{+}$	5272.34	-0.49	0.62	0.01 (0.04)$^{+}$	5587.19	0.22	0.83	0.05 (0.02)	4401.58	2.07	0.04
Gender*NMR	0.02 (0.02)$^{+}$	7614.70	1.28	0.20	0.15 (0.16)$^{+}$	7648.67	0.93	0.35	0.32 (0.12)	7302.18	2.60	0.01	-0.06 (0.07)$^{+}$	7051.34	-0.95	0.34

Note. CES-D, Center for Epidemiological Scale-Depression; MASQ, Mood and Affect Symptom Questionnaire; NMR, Negative Mood Regulation Expectancies Scale; $^{+}$, variable removed from final model.

Table 7

Hierarchical Regression Models with Neurocognitive Measures as the Dependent Variable and Substance Use Measures as the Independent Variable

Variable	Poly-Substance Use Z-Score			Cigarette Use Frequency			Marijuana Use Frequency			Alcohol Use Frequency		
	R^2	**B**	*p*	R^2	**β**	*p*	R^2	**β**	*p*	R^2	**β**	*p*
mMID												
Block 1- Substance Use	0.00	0.06	0.60	0.01	-0.08	0.50	0.03	0.17	0.13	0.00	0.04	0.75
Block 2- Substance Use	0.08	0.02	0.92	0.09	-0.11	0.43	0.11	0.25	0.14	0.08	-0.03	0.84
Gender		0.22	0.10		0.23	0.07		0.19	0.13		0.22	0.08
Race/Ethnicity		0.05	0.72		0.08	0.53		-0.01	0.94		0.07	0.61
Family History of SUD		0.06	0.62		0.05	0.72		0.08	0.53		0.06	0.61
SJWS Total Score		-0.07	0.60		-0.03	0.84		-0.10	0.42		-0.06	0.65
THC+		0.02	0.91		0.05	0.73		-0.12	0.44		0.02	0.86
Males- Substance Use	0.00	0.05	0.76	0.00	0.00	0.98	0.01	0.07	0.65	0.00	0.04	0.80
Females- Substance Use	0.01	-0.07	0.68	0.05	-0.23	0.16	0.03	0.18	0.29	0.00	-0.06	0.71
IGT												
Block 1- Substance Use	0.05	0.23	0.04	0.03	0.17	0.14	0.01	0.10	0.39	0.06	0.24	0.03
Block 2- Substance Use	0.15	0.26	0.06	0.11	0.12	0.29	0.32	0.02	0.86	0.11	0.13	0.29
Gender		2.59^{+}	0.84		0.05^{+}	0.71		0.05^{+}	0.71		0.04^{+}	0.72
Race/Ethnicity		0.21	0.08		0.30	0.01		0.31	0.01		0.26	0.04
Family History of SUD		2.94^{+}	0.31		-0.12^{+}	0.34		-0.13^{+}	0.30		-0.15^{+}	0.23
SJWS Total Score		2.29^{+}	0.61		0.10^{+}	0.46		0.12^{+}	0.34		0.10^{+}	0.41
THC+		-0.23	0.07		-0.21^{+}	0.09		-0.26^{+}	0.10		-0.19^{+}	0.12
Males- Substance Use	0.11	0.33	0.03	0.05	0.22	0.16	0.05	0.23	0.14	0.12	0.34	0.03
Females- Substance Use	0.02	0.12	0.47	0.01	0.12	0.49	0.00	-0.05	0.77	0.02	0.15	0.36
FEPT Overall Accuracy												
Block 1- Substance Use	0.00	-0.01	0.93	0.00	0.03	0.77	0.02	-0.14	0.23	0.01	0.08	0.48
Block 2- Substance Use	0.25	-0.10	0.39	0.24	0.02	0.88	0.30	-0.35	0.01	0.26	-0.01	0.97
Gender		-0.32	<0.01		-0.34	<0.01		-0.32	<0.01		-0.33	<0.01
Race/Ethnicity		0.46	<0.01		0.43	<0.01		0.52	<0.01		0.42	<0.01
Family History of SUD		-0.18^{+}	0.12		-0.16^{+}	0.16		-0.19^{+}	0.08		-0.17^{+}	0.13
SJWS Total Score		-0.20^{+}	0.11		-0.18^{+}	0.10		-0.18^{+}	0.11		-0.14	0.17
THC+		0.10^{+}	0.42		0.05^{+}	0.66		0.26	0.06		0.07^{+}	0.56
Males- Substance Use	0.03	0.16	0.31	0.00	0.01	0.96	0.00	0.01	0.98	0.15	0.38^{+}	0.01
Females- Substance Use	0.01	-0.10	0.54	0.03	0.18	0.29	0.04	-0.19	0.26	0.03	-0.18^{+}	0.28
Highest Educational Attainment												
Block 1- Substance Use	0.06	-0.24	0.03	0.12	-0.35	<0.01	0.19	-0.19	0.09	0.00	0.03	0.82
Block 2- Substance Use	0.15	-0.37	0.00	0.18	-0.39	<0.01	0.31	-0.25	0.03	0.01	-0.09	0.45
Gender		-0.08^{+}	0.49		-0.10^{+}	0.37		-0.11^{+}	0.36		-0.17^{+}	0.16
Race/Ethnicity		0.33	0.01		0.25	0.02		0.25	0.03		0.25	0.05
Family History of SUD		0.18^{+}	0.12		0.15^{+}	0.19		0.21^{+}	0.08		0.21	0.06
Males- Substance Use	0.02	-0.14	0.37	0.01	-0.31	0.05	0.00	-0.03	0.83	0.00	0.01	0.96
Females- Substance Use	0.15	-0.39	0.02	0.15	-0.39	0.02	0.14	-0.37	0.02	0.00	0.02	0.90

Note. mMID, modified Monetary Incentive Delay task; IGT, Iowa Gambling Task; FEPT, Facial Emotion Perception Task; SUD, Substance Use Disorder; SJWS, Shiffman/Jarvik Withdrawal Questionnaire; THC, delta-9-tetrahydrocannabinol from urine drug screen; $^{+}$, variable removed from final model.

Table 8

Correlations Among Aim 2 Variables by Gender and Race/Ethnicity

	Females											**Males**										
	1	2	3	4	5	6	7	8	9	10	11	1	2	3	4	5	6	7	8	9	10	11
1. mMID		-.03	.25	-.24	.13	.04	-.48*	.24	.07	.13	.09		-.07	.28	-.26	-.14	-.15	-.23	-.23	-.59*	-.35	.38
2. IGT	-.09		.27	-.13	.09	-.29	-.15	-.20	.28	-.26	-.06	.29		.02	-.54*	-.41	-.14	*-.46*	.08	-.22	.04	.09
3. FEPT Overall Accuracy	-.17	-.25		-.03	.16	-.13	-.10	-.07	-.02	-.02	-.05	-.06	.14		.05	.06	-.08	.07	.23	-.61*	.20	.49
4. Z-score Poly-substance Use	.07	.24	*-.43*		.70*	.69*	.80*	.11	.51*	.47*	-.33	.21	.48*	-.12		.83*	*.46*	.66*	*-.46*	.57*	*.50*	-.23
5. Mean Cigarette Use Over Time	*-.44*	.09	.12	*.44*		.50*	.20	-.13	.68*	.48*	*-.44*	.07	.35	-.17	.89*		.37	.25	*-.46*	*.45*	.41	-.25
6. Mean Marijuana Use Over Time	.22	-.03	-.33	.71*	-.14		.32	.07	.46*	.64*	-.21	.19	.30	-.24	.86*	.69*		-.15	-.23	.53	.61*	-.20
7. Mean Alcohol Use Over Time	*.43*	*.46*	-.56*	.49*	-.21	.23		.14	.14	.24	-.12	.29	.58*	.20	.64*	*.39*	.31		-.19	.25	-.11	-.03
8. Family History of SUD	.08	-.07	-.26	-.27	-.26	-.18	.11		-.06	-.23	.13	-.04	-.26	-.16	-.24	-.15	-.26	.09		-.27	-.37	.11
9. SJWS Total	-.16	.13	-.17	.54*	.21	.57*	.03	-.49*		.04	-.33	-.05	-.02	-.02	.49*	.44*	.28	.50*	-.02		*.44*	-.40
10. THC+	.03	-.30	-.08	.53*	.22	.49*	-.05	-.51*	.27		-.11	.21	.10	.04	.60*	*.36*	.71*	.10	-.06	.21		.18
11. Highest Educational Attainment	.16	-.10	.07	-.55*	-.40	-.49*	.10	.50*	-.59*	-.47*		.11	.06	-.11	-.28	-.42*	-.06	-.19	.07	-.50*	.11	

Note. Caucasian, non-Hispanic individuals on bottom, non-Caucasian or Hispanic individuals on top in grey. mMID, modified Monetary Incentive Delay task; IGT, Iowa Gambling Task; FEPT, Facial Emotion Perception Task; SUD, Substance Use Disorder; SJWS, Shiffman/Jarvik Withdrawal Questionnaire; THC, tetrahydrocannabinol from urine drug screen. Italicized indicates trending toward significance at $p<.10$; *, $p< .05$.

Table 9
Main Findings from All Aims

	Overall Effects	**Gender & Race/ Ethnicity Mean Differences**	**Increased Concurrent Substance Use**				**Concurrent Substance Use Mediates Relationship Between Baseline Risk Factor and Outcome**
			Caucasian/Non-Hispanic		Non-Caucasian or Hispanic		
			Males	Females	Males	Females	
Substance Use							
Poly-substance Use	↑ over time	Caucasians > Non-Caucasians, Males > Females	↑ cigarette, marijuana & alcohol use, SJWS, & THC+	↑ marijuana & alcohol use, SJWS, & THC+	↑ cigarette & alcohol use & SJWS	↑ cigarette, marijuana & alcohol use, SJWS, & THC+	
Cigarette Use	↑ over time	Caucasians > Non-Caucasians, Males > Females	↑ marijuana & alcohol use & SJWS			↑ marijuana use, SJWS, & THC+	
Marijuana Use	↑ over time	Males > Females	↑ THC+	↑ SJWS & THC+	↑ THC+	↑ SJWS & THC+	
Alcohol Use	↑ over time	Caucasians > Non-Caucasians, Males > Females	↑ SJWS	--	--	--	
Baseline Risk Factors							
↑ *Depression Symptoms (CES-D)*	↑ poly-substance use (not alcohol)						
↑ *Anxiety Symptoms (MASQ)*	↑ poly-substance use (all)						
↓ *Negative Mood Regulation (NMR)*	↑ poly-substance use (not alcohol)						
↓ *Grade Point Average (GPA)*	↑ poly-substance use (all)						
Decision-Making							
↓ *Decision-Making (IGT)*	↓ poly-substance use *(trending)*	Caucasians > Non-Caucasians	↓ poly-substance & alcohol use	--	↑ poly-substance & alcohol use	--	
Emotional Processing							
↓ *Emotional Processing (FEPT)*	↑ marijuana use (not poly-substance use)	Caucasians > Non-Caucasians, Males < Females	--	↑ alcohol use	↑ SJWS	--	
Reward Processing							
↓ *Reward Processing (mMID)*	no significant relationship w/substance use	Males > Females *(trending)*	--	--	↑ SJWS	↑ alcohol use	
Educational Attainment							
↓ *Number of Years of Education*	↑ poly-substance use (not alcohol)	Caucasians > Non-Caucasians *(trending)*	↑ cigarette use & SJWS	↑ poly-substance & marijuana use, SJWS, & THC+	↑ SJWS	--	Caucasian, non-Hispanic Females and Males: poly-substance use mediates relationship between baseline negative affect and educational attainment

Figure 1

Individuals with more baseline risk factors will have heavier nicotine, marijuana, alcohol use, which will in turn be associated with poorer affective, reward, cognitive, and functional outcomes.

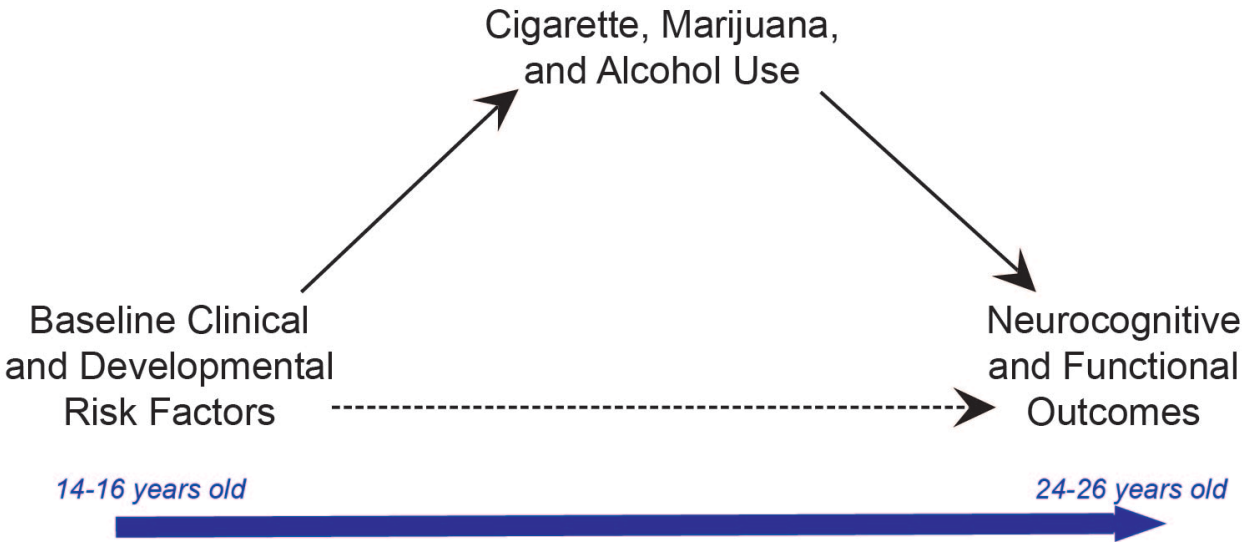
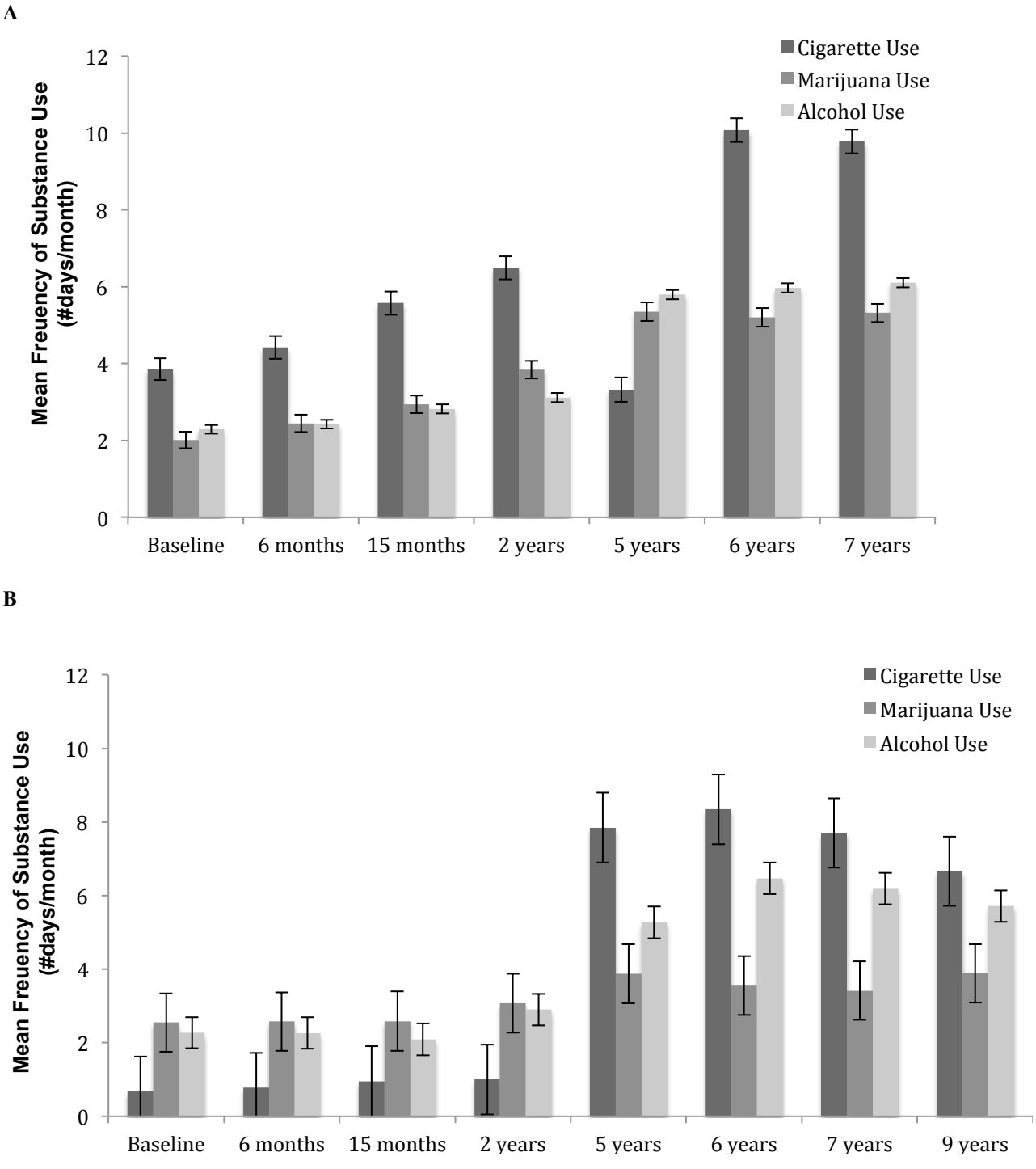


Figure 2

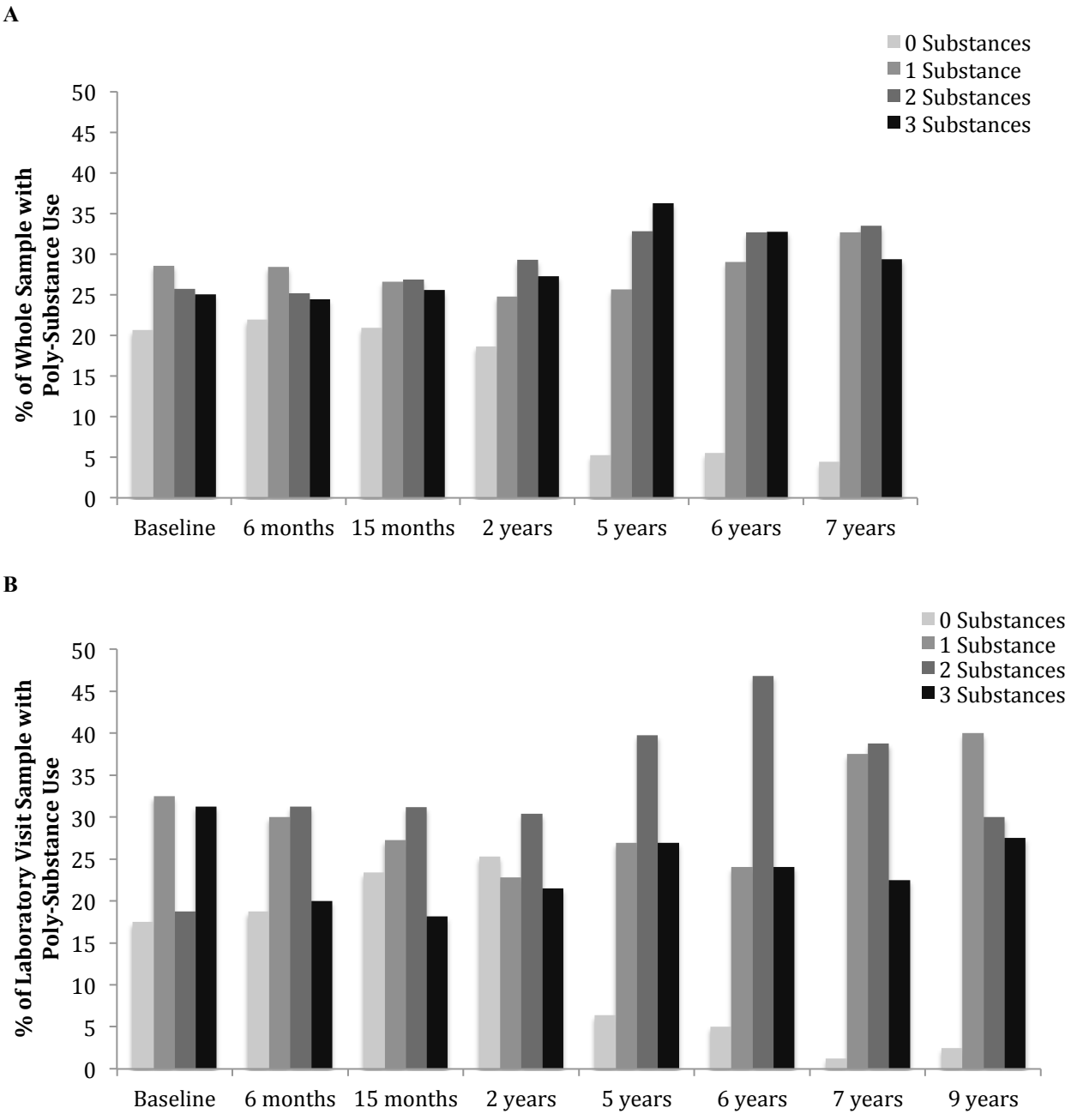
Frequency of Substance Use Over Time in Whole Sample and in Laboratory Visit Sample



Note. Panel A shows means and standard errors for the whole sample (n=1211); Panel B shows means and standard errors for the laboratory visit sample (n=80).

Figure 3

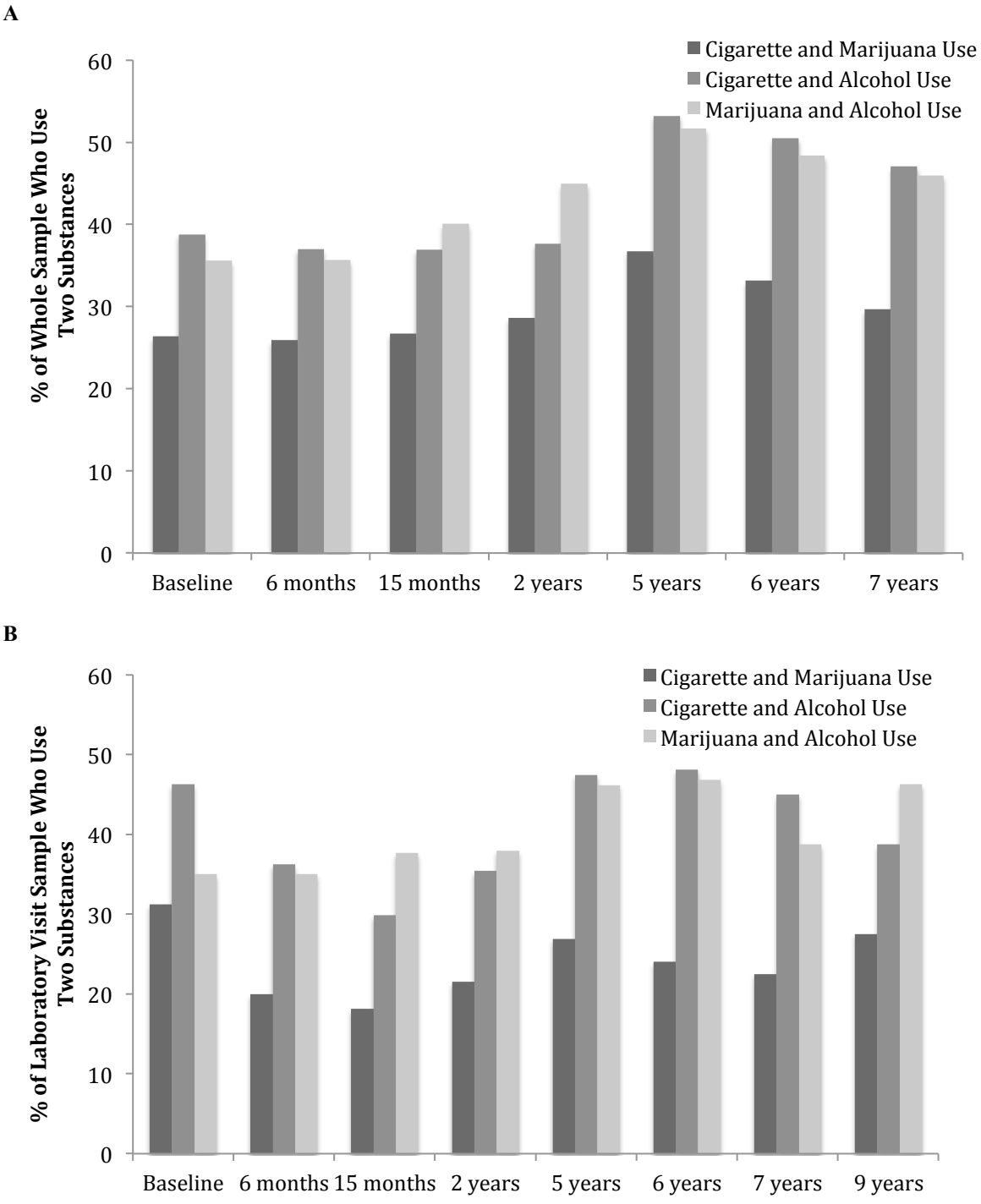
Percent of with Poly-Substance Use in Whole Sample and in Laboratory Visit Sample



Note. Panel A shows percentage for the whole sample (n=1211); Panel B shows percentage for the laboratory visit sample (n=80).

Figure 4

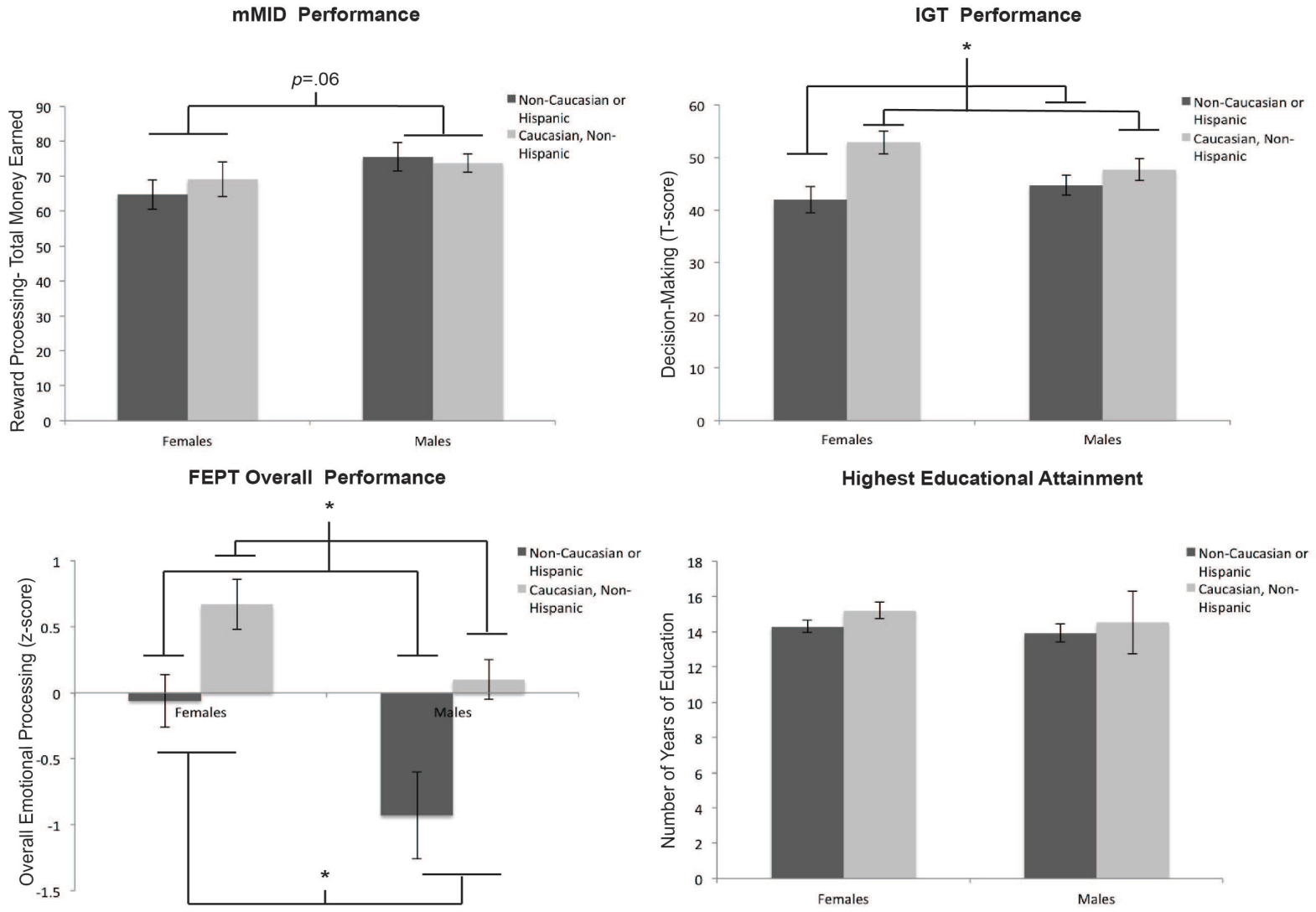
Percent of Individuals Reporting Using Two Substances in Whole Sample and in Laboratory Visit Sample



Note. Panel A shows percentage for the whole sample (n=1211); Panel B shows percentage for the laboratory visit sample (n=80).

Figure 5

Neurocognitive and Functional Outcomes by Gender and Race/Ethnicity



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EDUCATION

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2004-2008	**NORTHEASTERN UNIVERSITY** *Bachelor of Arts* Major: Psychology Cum Laude	**Boston, MA**

AWARDS/HONORS

2016	*UIC Psychology Department, Leonard D. Eron Award for Outstanding Scholarly Accomplishment*
2015	*NIDA Director's Travel Award for the 2015 meeting of the College on Problems of Drug Dependence*
2015	*NIH Travel Fellowship for 2015 Training Course in fMRI at the University of Michigan*
2014	*American Psychological Foundation's 2014 Ungerleider/Zimbardo Travel Scholarship*
2014	*UIC Psychiatry Department's Extravaganza Best Poster Award*
2013	*NIDA Women & Sex/Gender Junior Investigator Travel Award for the 2013 meeting of the College on Problems of Drug Dependence (CPDD)*
2012	*NIDA Women & Sex/Gender Junior Investigator Travel Award for the 2012 meeting of the College on Problems of Drug Dependence (CPDD)*
2012-Present	*UIC Psychology Department Presenter's Award*
2012-Present	*UIC Graduate College and Graduate Student Council Presenter's Awards*
2012-Present	*UIC College of Liberal Arts & Sciences PhD Student Travel Award*
2004-2008	*Academic Scholarship Award*
2004-2008	*Dean's List*

GRANTS AND FELLOWSHIPS

2014 - 2017 **National Institute on Drug Abuse F31DA038388 (PI: Crane)** **$128,028 (direct costs)**
Ruth L. Kirschstein National Research Service Award (NRSA)
"Neurocognitive, Affective and Psychosocial Correlates of Adolescent Substance Use."

2013 - 2014 **National Institute of Mental Health T32MH067631-09 (PI: Rasenick) $42,232 (direct costs)**
Ruth L. Kirschstein National Research Service Award (NRSA) Predoctoral Fellow
"Training in the Neuroscience of Mental Health."

2012 - 2014 **Chancellor's Graduate Research Fellowship** **$8,000 (stipend)**
University of Illinois at Chicago

PUBLICATIONS

1. Stange, J.P., Bessette, K.L., Jenkins, J.M., Peters, A.T., Feldhaus, C., **Crane, N.A.**, Jacobs, R.H., Ajilore, O., Watkins, E.R., & Langenecker, S.A. (in press). Attenuated Intrinsic Connectivity within

Cognitive Control Network Among Individuals with Remitted Depression: Temporal Stability and Association with Negative Cognitive Styles. *Human Brain Mapping*.

2. **Crane, N.A.**, Jenkins, L.M., Bhaumik, R., Dion, C., Gowins, J.R., Mickey, B.J., Zubieta, J.K., & Langenecker, S.A. (in press). Multidimensional Prediction of Treatment Response to Antidepressants with Cognitive Control and fMRI. *Brain.*
3. **Crane, N.A.**, Jenkins, L.M., Dion, C., Meyers, K.K., Weldon, A.L., Gabriel, L.B., Walker, S.J., Hsu, D.T., Noll, D.C., Klumpp, H., Phan, K.L., Zubieta, J.K., & Langenecker, S.A. (2016). Comorbid Anxiety Increases Cognitive Control Activation in Major Depressive Disorder. *Depression and Anxiety,* 33(10): 967-977. PMID: 27454009.
4. **Crane, N.A.**, Gorka, S.M., Giedgowd, G.E., Conrad, M., Langenecker, S.A., Mermelstein, R.J., & Kassel, J.D. (2016). Adolescent's Baseline Respiratory Sinus Arrhythmia is Associated with Smoking Rate Five Years Later. *Biological Psychology,* 118: 107-113. PMID: 27235685.
5. Tadayonnejad, R., Ajilore, O., Mickey, B.J., **Crane, N.A.**, Hsu, D.T., Kumar, A., Zubieta, J.K., & Langenecker, S.A. (2016). Pharmacological modulation of pulvinar resting-state regional oscillations and network dynamics in major depression. *Psychiatry Research: Neuroimaging,* 252: 10-18. PMID: 27148894.
6. Jenkins, L.M., Kassel, M.T., Gabriel, L.B., Gowins, J.R., Hymen, E.A., Verges, A., Calamia, M., **Crane, N.A.**, Jacobs, R.H., Ajilore, O., Welsh, R.C., Drevets, W.C., Phillips, M.L., Zubieta, J-K. & Langenecker, S.A. (2016). Amygdala and dorsomedial hyperactivity to emotional faces in youth with remitted Major Depression. *Social Cognitive and Affective Neuroscience,* 11(5): 736-745. PMID: 26714574.
7. Peters, A.T., Jacobs, R.H., **Crane, N.A.**, Ryan, K.A., Weisenbach, S.L., Ajilore, O., Lamar, M., Kassel, M.T., Gabriel, L.B., West, A.E., Zubieta, J.K., & Langenecker, S.A. (in press). Domain-specific impairment in cognitive control among remitted youth with a history of major depression. *Early Intervention in Psychiatry.* PMID: 26177674.
8. **Crane, N.A.**, Langenecker, S.A., & Mermelstein, R.J. (2015). Gender differences in the associations among marijuana use, cigarette use, and depression during adolescence and young adulthood. *Addictive Behaviors,* 49: 33-39. PMID: 26036667.
9. **Crane, N.A.**, Schuster, R.M., Mermelstein, R.J., & Gonzalez, R. (2015). Neuropsychological sex differences associated with age of initiated use among young adult cannabis users. *Journal of Clinical and Experimental Neuropsychology,* 37(4): 389-401. PMID: 25832823.
10. Gabel, N.M., **Crane, N.A.**, Avery, E.A., Kay, R.E., Laurent, A., Giordani, B., Alexander, N.B., & Weisenbach, S.L. (2015). Dual-tasking gait variability, and cognition in late-life depression. *International Journal of Geriatric Psychiatry,* 30(11): 1120-1128. PMID: 26251013.
11. Deldonno, S.R., Weldon, A.L., **Crane, N.A.**, Passarotti, A.M., Pruitt, P.J., Gabriel, L., Yau, W., Meyers, K.K., Hsu, D.T., Taylor, S.F., Heitzeg, M.M., Herbener, E., Shankman, S.A., Mickey, B.J., Zubieta, J.K., & Langenecker, S.A. (2015). Affective Personality Predictors of Disrupted Reward Learning and Pursuit in Major Depressive Disorder. *Psychiatry Research,* 230(1): 56-64. PMID: 26319737.
12. Passarotti, A.M., **Crane, N.A.**, Hedecker, D., & Mermelstein, R.J. (2015). Longitudinal Trajectories of Marijuana Use from Adolescence to Young Adulthood. *Addictive Behaviors,* 45:301-308. PMID: 25792233.
13. Schuster, R. M., **Crane, N.A.**, Mermelstein, R., & Gonzalez, R. (2015). Tobacco May Mask Poorer Episodic Memory Among Young Adult Cannabis Users. *Neuropsychology,* 29(5): 759-766. PMID: 25558879.

14. Meyers, K.K., **Crane, N.A.,** O'Day, R., Zubieta, J.K., Pomerleau, C.S., Horowitz, J.C., & Langenecker, S.A. (2015). The Impact of Smoking History and Depression on Executive Functioning and Emotional Processing. *Addictive Behaviors,* 41: 210-217. PMID: 25452067.
15. Jacobs, R.H., Jenkins, L.M., Gabriel, L.B., Barba, A., Ryan, K.A., Weisenbach, S.L., Verges, A., Baker, A.M., Peters, A.T., **Crane, N.A.,** Gotlib, I.H., Zubieta, J.K., Phan, K.L., Langenecker, S.A., & Welsh, R.C. (2014). Increased Coupling of Intrinsic Networks in Remitted Depressed Youth Predicts Rumination and Cognitive Control. *PLoS ONE,* 9(8): e104366. PMID: 25162661.
16. **Crane, N.A.,** Schuster, R.M., & Gonzalez, R. (2013). Preliminary evidence for a sex-specific relationship between amount of cannabis use and neurocognitive performance in young adult cannabis users. *Journal of the International Neuropsychological Society,* 19(9): 1009-1015. PMID: 23962414.
17. Heinz, A.J., Giedgowd, G.E., **Crane, N.A.**, Conrad, M., Braun, A.R., Veilleux, J.C., Olejarska, N.A., & Kassel, J.D. (2013). A comprehensive examination of hookah smoking in college students: Use patterns and contexts, social norms and attitudes, harm perception, psychological correlates and co-occurring substance use. *Addictive Behaviors,* 38(11): 2751-2760. PMID: 23934006.
18. **Crane, N.A.**, Schuster, R.M., Fusar-Poli, P., & Gonzalez, R. (2013). Effects of cannabis on neurocognitive functioning: recent advances, neurodevelopmental influences, and sex differences. *Neuropsychology Review,* 23(2): 117-137. PMID: 23129391.
19. Schuster, R.M., **Crane, N.A.**, Mermelstein, R.J., & Gonzalez, R. (2012). The influence of inhibitory control and episodic memory on the risky sexual behavior of young adult cannabis users. *Journal of the International Neuropsychological Society*, 18(5): 827-833. PMID: 22676889.
20. Higley, A.E., **Crane, N.A.**, Goodell, V., Quello, S.B., Spadoni, A.D., & Mason, B.J. (2011). Craving in response to stress induction in a human laboratory paradigm predicts treatment outcome in alcohol-dependent individuals. *Psychopharmacology,* 218(1): 121-129. PMID: 21607563.
21. Crean, R.D., **Crane, N.A.**, & Mason, B.J. (2011). An evidence-based review of acute and long-term effects of cannabis use on executive cognitive functions. *Journal of Addiction Medicine*, 5(1): 1-8. PMID: 21321675.
22. Crean, R.D., Tapert, S.F., Minassian, A., MacDonald, K., **Crane, N.A.**, & Mason, B.J. (2011). Effects of chronic, heavy cannabis use on executive functions. *Journal of Addiction Medicine*, 5(1): 9-15. PMID: 21643485.

MANUSCRIPTS UNDER REVIEW & IN PREPARATION

1. **Crane, N.A.**, Verges, A., Kamali, M., Bhaumik, R., Ryan, K.A., Marshall, D.F., Saunders, E.F., Kassel, M.T., Weldon, A.L., McInnis, M.G., & Langenecker, S.A. (revise and resubmit). Developing Dimensional, Integrated Constructs of Self-Report and Neuropsychological Data for Inhibitory Control.
2. Deldonno, S.R., Jenkins, L.M., **Crane, N.A.**, Nusslock, R., Ryan, K.A., Shankman, S., Phan, K.L., & Langenecker, S.A. (under review). Disrupted Functional Connectivity of the Ventral Striatum in Young Adults with Remitted Depression.
3. **Crane, N.A.**, Gorka, S.M., Weafer, J., Langeneker, S.A., de Wit, H., & Phan, K.L. (under review). Binge Drinkers Exhibit Abnormal Neural Reactivity and Functional Connectivity during Reward.

RESEARCH EXPERIENCE

2012- 2016 **COGNITIVE NEUROSCIENCE CENTER** **Chicago, IL**
***Graduate Research Assistant*,** Department of Psychiatry
Grant Funding: *NIMH- R01MH101487, R01MH091811, & K23RR017607*

- Longitudinal study investigating the neurobiology of intermediate phenotypes in Major Depressive Disorder
- Develop and validate a neurocognitive task of inhibitory control. A primary clinician in charge of clinical interviews. Assist in collection and analysis of project data, pre-processing and analysis of fMRI data, collaboration on publications and conference presentations.
- Use existing functional magnetic resonance imaging (fMRI) datasets to answer empirical questions and prepare manuscripts for publication.
- Participate in weekly supervision meetings and annual fMRI data analysis workshops.

Supervisor: *Scott Langenecker, Ph.D.*

2012 –2016 **INSTITUTE FOR HEALTH RESEARCH AND POLICY** **Chicago, IL**
Graduate Research Assistant
Grant Funding: *NCI- P01CA098262*

- Longitudinal study on the social and emotional contexts of adolescent smoking and health behaviors
- Assist in analysis of project data, collaboration on publications and conference presentations
- Laboratory-based research on the effects of binge drinking on executive function and mood
- Administer neuropsychological assessments. Assist in data collection and management

Supervisors: *Robin Mermelstein, Ph.D. & Jon Kassel, Ph.D.*

2011 –2012 **HIV & ADDICTIONS NEUROSCIENCE** **Chicago, IL**
Graduate Research Assistant, Department of Psychiatry
Grant Funding: *NIDA- K23DA023560*

- Laboratory-based research on the role of neurocognitive disinhibition in the development and maintenance of cannabis addiction
- Assist in management and analysis of project data. Ongoing collaboration on publications and conference presentations

Supervisor: *Raul Gonzalez, Ph.D.*

2008 –2011 **THE SCRIPPS RESEARCH INSTITUTE** **La Jolla, CA**
COMMITTEE ON THE NEUROBIOLOGY OF ADDICTIVE BEHAVIORS
Sub-Investigator & Study Coordinator, Laboratory of Clinical Psychopharmacology
Grant Funding: *NIDA- R01DA026758, R01DA030988-01, & P20DA024194-03; NIAAA-R01AA012602*

- Randomized clinical trials on the efficacy of neuropharmacological interventions for the treatment of cannabis dependence, longitudinal study examining the neurobiology of cannabis dependence, and human laboratory cue-reactivity study for medication development for protracted abstinence in alcoholism
- Led studies start up, recruitment, and data collection. Assisted in creation and maintenance of IRB materials and developed protocol materials in collaboration with the PI. A primary clinician in charge of patient contact including interviewing, neuropsychological assessment, psychotherapeutic intervention, psychophysiological assessment, fMRI behavioral paradigms, and medication distribution. Collaborated on publications and conference presentations
- Assisted in recruitment and patient contact, including interviews and neuropsychological assessment. Ran fMRI scans as a certified operator at UCSD's Keck Center for Functional Imaging in analysis of project data, collaboration on publications and conference presentations

Supervisors: *Barbara Mason, Ph.D., Rebecca Crean, Ph.D.*

2007 –2008 NORTHEASTERN UNIVERSITY Boston, MA
NEUROSCIENCE OF STRESS, ADDICTION, & MOOD LABORATORY
NEUROBIOLOGY OF AGGRESSION LABORATORY
Laboratory Research Assistant, Northeastern University Department of Psychology

- Animal laboratory study examining kappa-opioid mediation of stress-induced potentiation of cocaine-conditioned place preference and self-administration, and animal study examining the neurobiology of offensive aggression and the effects of adolescent exposure to anabolic/androgenic steroids
- Ran behavioral and pharmacological paradigms including Resident/Intruder, Open-field elevated plus maze, Seed finding, Conditioned Place Preference, Tail Flick Assays, Forced Swim Tests, Dose response, Competition binding assay and injected subcutaneous and intraperitoneal study drug or placebo and anesthesia with Syrian hamsters and mice. Performed bioassays including Western Blot, Polymerase Chain Reaction, Restriction Enzyme Digest, Immunohistochemistry, and Immunoflorescence. Proficient at Bright field, Dark field, BioQuant image analysis microscopy. Assisted with general lab maintenance, ordering, and preparation of stock solutions

Supervisors: *Richard Melloni Jr., Ph.D., Maria Carrillo, Ph.D., & Jay McLaughlin, Ph.D.*

CLINICAL EXEPERIENCE

2015 – 2016 ADOLESCENT NEUROPSYCHOLOGY MOOD DISORDER CLINIC Chicago,IL
Clinical Neuropsychology Extern, Institute for Juvenile Research

- Neuropsychological assessment of adolescent outpatients drawn from several of the medical center's departments, including the Pediatric Mood Disorder Clinic, and from outside referral sources
- Referrals span neuropathological conditions including mood disorders, ADHD, developmental disorders, substance use disorders, and traumatic brain injury in order to provide differential diagnosis, development/modification of IEP's, developmental transition plans for leaving the home and maintaining continuity and responsiveness of care networks, in addition to evaluation of medication effects and side effects
- Receive supervised experience in planning test selection, implementing, and writing up neuropsychological evaluations using a broad range of tests and procedures, as well as oral communication of test results to referral sources
- Attend a weekly Neuroanatomy Seminar as well as the Behavioral Neurosciences & Cognitive Neuroscience Seminars, weekly meetings devoted to special topics and case presentations in the clinical neurosciences

Supervisor: *Scott Langenecker, Ph.D.*

2014 – 2015 UNIVERSITY OF ILLINOIS NEUROPSYCHOLOGY SERVICE Chicago, IL
Clinical Neuropsychology Extern, Neuropsychiatric Institute

- Neuropsychological assessment of adult outpatients drawn from several of the medical center's departments and from outside referral sources
- Referrals span the entire list of neuropathological conditions such as dementia, cerebrovascular disorders, tumor, HIV, epilepsy, degenerative disorders, ADHD, learning disabilities, developmental disorders, and traumatic brain injury
- Externship promotes proficiency and mastery of the following specific competencies:
- Assessment and treatment of psychological disorders stemming from cognitive, psychiatric, and medical disability
- Selection, administration, scoring, and interpretation of neuropsychological tests
- Case conceptualization through integration of history, test data, and behavioral observation

- Communication of test results through written reports and oral presentation
- Development of a working knowledge and experiential base in neurological and psychiatric diagnosis
- Receive supervised experience in planning test selection, implementing, and writing up neuropsychological evaluations using a broad range of tests and procedures, as well as oral communication of test results to referral sources
- Attend a weekly Neuroanatomy Seminar as well as the Behavioral Neurosciences & Cognitive Neuroscience Seminars, weekly meetings devoted to special topics and case presentations in the clinical neurosciences

Supervisors: *Neil Pliskin, Ph.D., ABPP-CN, Julie Janecek, Ph.D.*

2011 – 2016 OFFICE OF APPLIED PSYCHOLOGICAL SERVICES Chicago, IL
Clinical Practicum Student, UIC Department of Psychology

- Conduct weekly individual psychotherapy and intake interviews for adult, adolescent, and child populations presenting with a variety of emotional, behavioral, and personality disorders at a community-based outpatient psychology clinic.
- Administer neuropsychological evaluations with low-income adolescent and adult patients. Responsible for selecting, administering, scoring and interpreting assessments. Communicated test results, interpretations, and recommendations to clients. Provided referrals to clients based on the assessment
- Engage in weekly supervision meetings involving reviewing video recordings, receiving live feedback, and reviewing clinical readings.

Supervisors: *Amanda Lorenz, Ph.D., Ellen Herbener, Ph.D., Neil Pliskin, Ph.D., ABPP-CN, Nancy Dassoff, Ph.D., & Gloria Balague, Ph.D.*

2012 – 2016 COGNITIVE NEUROSCIENCE CENTER Chicago, IL
Graduate Research Assistant, Department of Psychiatry

- Administer the Diagnostic Interview for Genetic Studies (DIGS) to individuals with mood disorders

Supervisor: *Scott Langenecker, Ph.D.*

2008 – 2011 THE SCRIPPS RESEARCH INSTITUTE La Jolla, CA
COMMITTEE ON THE NEUROBIOLOGY OF ADDICTIVE BEHAVIORS
Sub-Investigator & Study Coordinator, Laboratory of Clinical Psychopharmacology

- Conduct neuropsychological assessment batteries individuals with substance use disorders
- Provide Cognitive Behavioral Therapy and Motivational Enhancement Therapy to treatment-seeking, cannabis dependent participants
- Administer the Structured Clinical Interview for DSM-IV (SCID) to individuals with substance use disorders

Supervisors: *Barbara Mason, Ph.D., Rebecca Crean, Ph.D.*

2007 – 2008 BOSTON MEDICAL CENTER Boston, MA
Patient Safety Associate, Emergency Department, Psychiatric Ward

- Ensured safety of psychiatric patients who were at risk of harming themselves or others
- Assisted Psychiatric Nurse and Clinician with patient assessment and plan of action
- Maintained ongoing communication with Psychiatric Nurse and Clinician regarding patient behavior
- De-escalated violent and/or angry patients

RESEARCH TRAININGS

2015 **TRAINING COURSE IN fMRI** **Ann Arbor, MI**
University of Michigan
- 10-day fMRI course that included lectures and hands-on training on topics such as fMRI data acquisition, SPM program and features, individual and group statistical analyses with fMRI data, region of interest (ROI) drawing, diffusion tensor imaging (DTI), arterial spin labeling (ASL), and functional connectivity.

2014 **fMRI IMAGE ACQUISITION & ANALYSES COURSE WITH SPM &ICA**
The MIND Research Network & University of New Mexico **Albuquerque, NM**
- 4-day fMRI workshop that included lectures and hands-on training on topics such as fMRI data acquisition, SPM program and features, individual and group statistical analyses with fMRI data using independent components analyses (ICA).

CLINICAL WORKSHOPS

2015 **NEUROANTOMICAL DISSECTION: HUMAN BRAIN AND SPINAL CORD**
Marquette University **Milwaukee, WI**
- 3-day neuroanatomical dissection course that included lectures and hands-on dissection to better understand the neuroanatomy of the human brain and spinal cord. Topics covered included neuroanatomy of major neural structures and white matter tracts in the brain and of the spinal cord, cranial nerves, cerebrovascular system, as well as clinical neuroanatomy of neural systems and functional implications of lesions and pathologies.

2014 **DIALECTICAL BEHAVIOR THERAPY SKILLS TRAINING**
University of Illinois at Chicago **Chicago, IL**
- 8-hour Dialectical Behavior Therapy (DBT) training that covered the history and theory of DBT and review of the clinical skills and applications. Workshop included lectures, demonstrations, and role-playing.

2014 **MOTIVATIONAL INTERVIEWING TRAINING COURSE**
University of Illinois at Chicago **Chicago, IL**
- 8-hour Motivational Interviewing (MI) training that covered the history and theory of MI and review of the clinical skills and applications. Workshop included lectures, demonstrations, and role-playing.

MEMBERSHIP IN PROFESSIONAL ASSOCIATIONS

- *American Psychological Association- Division 28, Division 40, & Division 50*
- *American Psychological Association of Graduate Students*

PRIMARY AND AD HOC REVIEWER EXPERIENCE

- *Drug and Alcohol Dependence*
- *Journal of the International Neuropsychological Society*
- *Archives of Clinical Neuropsychology*
- *Psychiatry Research*
- *Addiction*
- *Substance Abuse: Research and Treatment*
- *Translational Psychiatry*
- *Journal of Affective Disorders*
- *American Journal of Preventive Medicine*

INVITED TALKS & ORAL PRESENTATIONS

1. **Crane, N.A.** (November, 2015). *Neuropsychological, Affective, and Psychosocial Correlates of Adolescent Substance Use: Preliminary Data.* Psychiatric Institute & Center for Alcohol Research in Epigenetics Neuroscience Seminar: University of Illinois at Chicago. Chicago, IL.
2. **Crane, N.A.** (June, 2015). *Affective, psychosocial, and neuropsychological sex differences in adolescent and young adult marijuana users.* Symposia presented at the 77th annual meeting of the College on Problems of Drug Dependence, Phoenix, AZ, June 13-18. *[Recipient of NIDA Director's Travel Award]*
3. Langenecker, S.A., **Crane, N.A.**, DelDonno, S.R., Gabriel, L.B., Gowins, J.R., Nagel, C., Mickey, B.J., Zubieta, J.K., Mermelstein, R.J., & Martin, E. (June, 2015). *Adaptive Reward Learning and Pursuit is Intact in Young Adults with Remitted Depression and Substance Use Disorders*. Oral presentation at the 77th annual meeting of the College on Problems of Drug Dependence, Phoenix, AZ, June 13-18.
4. **Crane, N.A.** (November, 2014). *Introduction to Neuropsychological and Psychological Testing Intakes*. Graduate Interviewing Course, Department of Psychology: University of Illinois at Chicago. Chicago, IL.
5. Langenecker, S.A., **Crane, N.A.**, Dawson, E.L., Mickey, B.J., Ransom, M.T., Walker, S.L., Meyers, K.K., Hazlett, K.E., Welson, A.L., Giordani, B., & Zubieta, J.K. (October, 2014). *Cognitive control and neuronal functioning biomarkers as predictors of treatment response in Major Depression*. Department of Psychiatry UI Center on Depression & Resilience Launch and 5th Annual Research Extravaganza, Chicago, IL, October 21.
6. **Crane, N.A.** (September, 2014). *Examining Neuropsychological Sex Differences in Young Adult Cannabis Users.* Clinical Brown Bag, Department of Psychology: University of Illinois at Chicago. Chicago, IL.
7. **Crane, N.A.**, Schuster, R.M., Mermelstein, R.J., & Gonzalez, R. (August, 2014). *Neuropsychological & Affective Sex Differences in Cannabis Users.* Symposium presented at the American Psychological Association Annual Convention, Washington, DC, August 7-10.
8. Giedgowd, G.E., Conrad, M., **Crane, N.A.**, Palmeri, M., & Kassel, J.D. (May, 2014). *Sex Differences in Avoidance Coping, Cigarette Use, and Dependence.* Paper presentation at the Annual Meeting of the Midwestern Psychological Association, Chicago, IL, May 1-3.
9. **Crane, N.A.** (March, 2014). *Neuropsychological Functioning of Young Adult Marijuana Users.* Undergraduate Laboratory in Clinical Psychology Course, Department of Psychology: University of Illinois at Chicago. Chicago, IL.
10. Gonzalez, R., Schuster, R.M, & **Crane, N.A.** (June, 2013). *The Impact of Decision-Making Performance and ADHD Symptoms on Cannabis-Related Problems Among Emerging Adults.* Symposia presented at the 23rd Annual International Cannabinoid Research Society on the Cannabinoids, Vancouver, British Columbia, Canada, June 15-20.
11. **Crane, N.A.**, Schuster, R.M., & Gonzalez, R. (June, 2013). *Sex Differences in Associations between Age of Initiated Cannabis Use and Neuropsychological Performance.* Oral presentation at the 75th annual meeting of the College on Problems of Drug Dependence, San Diego, CA**,** June 15-20. *[Recipient of NIDA Women & Sex/Gender Junior Investigator Travel Award]*
12. Langenecker, S., Ryan, K., Marshall, D., Gabriel, L., Weldon, A., Kassel, M., **Crane, N.,** Weisenbach, S., & Zubieta, J-K. (February, 2013). *Strong Reliability for Intermediate Phenotypes in the Multifaceted Investigation of the Neurobiology of Depression Subtypes (MINDS) Study.* Symposia presented at the 41st annual meeting of the International Neuropsychological Society, Waikoloa, HI, February 6-9**.**

POSTER PRESENTATIONS

1. Cerney, B., Kling, L., Gabriel, L.B., **Crane, N.A.**, Passarotti, A., & Langenecker, S.A. (February, 2017). *Convergence between scores on the BIS-11 and measures of executive function in individuals with remitted major depression.* To be presented at the 45th annual meeting of the International Neuropsychological Society, New Orleans, LA, February 1-4.
2. Stange, J.P., Bessette, K.L., Jenkins, L., Burkhouse, K.L., Peters, A.T., Feldhaus, C., **Crane, N.A.**, Ajilore, O., Jacobs, R. H, Watkins, E.R., & Langenecker, S.A. (September, 2016). *Attenuated Intrinsic Connectivity within the Cognitive Control Network Among Individuals with Remitted Depression is Associated with Cognitive Control Deficits and Negative Cognitive Styles.* The Federation of European Neuroscience Societies Brain Conference on New Insights into Psychiatric Disorders through Computational, Developmental and Biological Approaches, Copenhagen, Denmark, September 25-28.
3. DelDonno, S., Jenkins, L., **Crane, N.**, Barba, A., Dion, C., Ryan, K., & Langenecker, S. (September, 2016). *Functional connectivity of the ventral striatum in remitted depressed individuals with and without substance abuse history.* The 56th Annual Meeting of the Society for Psychophysiological Research in Minneapolis, MN, September 21-15.
4. Bunford, N., **Crane, N.A.**, Passarotti, A.M., Walker, S.J., & Langenecker, S.A. (September, 2016). *Enhanced Activation in the Cognitive Control Network Following Unsuccessful Response Inhibition is Associated with Conscientiousness in Adults without a History of Mental Illness.* The British Association for Cognitive Neuroscience Annual Meeting, Budapest, Hungary, September 12-14.
5. **Crane, N.A.**, Jenkins, L.M., Dion, C., Meyers, K.K., Weldon, A.L., Gabriel, L.B., Walker, S.J., Hsu, D.T., Noll, D.C., Klumpp, H., Phan, K.L., Zubieta, J.K., & Langenecker, S.A. (May, 2016). *Comorbid Anxiety Increases Cognitive Control Activation in Major Depressive Disorder.* The Society of Biological Psychiatry's 71st Annual Meeting, Atlanta, Georgia, May 12-14.
6. **Crane, N.A.**, Gabriel, L.B., Meyers, K.K., Weldon, A.L., Kassel, M.T., Mermelstein, R.J., Zubieta, J.K., & Langenecker, S.A. (June, 2015). *Shared & Distinct Neural Mechanisms of Inhibitory Control in Individuals with a History of a Substance Use Disorder & Depression*. The 77th annual meeting of the College on Problems of Drug Dependence, Phoenix, AZ, June 13-18.
7. **Crane, N.A.**, Jenkins, L.M., Gowins, J.R., Barba, A.M., Gabriel, L.B., Kassel, M.T., Weldon, A.L., Baker, A.M., DelDonno, S.R., Zubieta, J.K., Mermelstein, R.J., & Langenecker, S.A. (May, 2015). *History of Substance Use Disorder Modulates Neural Emotional Processing in Individuals with Remitted Major Depression.* The Society of Biological Psychiatry's 70th Annual Meeting, Toronto, Ontario, May 14-16.
8. Jenkins, L.M., Skerrett, K., **Crane, N.A.**, Gowins, J.R., Patrón, V.G., Dion, C., Kassel, M.T., Weldon, A.L., Gabriel, L.B., Weisenbach, S.L., Zubieta, J-K., Passarotti, A., & Langenecker, S.A. (May, 2015). *Decreased Neural Activity During Successful and Unsuccessful Cognitive Control in Remitted Major Depressive Disorder.* The Society of Biological Psychiatry's 70th Annual Meeting, Toronto, Ontario, May 14-16.
9. **Crane, N.A.**, Gowins, J.R., Barba, A.M., DelDonno, S.R., Jenkins, L.M., Meyers, K.K., Hazlett, K.E., Hsu, D.T., Mickey, B.J., Zubieta, J.K., & Langenecker, S.A. (February, 2015). *Independent Component Analysis of Cognitive Control as Treatment Predictors for Major Depressive Disorder.* The 43rd annual meeting of the International Neuropsychological Society, Denver, CO, February 4-7.
10. Jenkins, L., Barba, A., Kassel, M., **Crane, N.**, Verges, A., Calamia, M., Gabriel, L., Hymen, E., Weisenbach, S.L., Maki, P., & Langenecker, S.A. (October, 2014). *Differential Brain Activation in Males and Females in the Remitted Phase of Major Depressive Disorder, Despite No Performance Differences.* The National Network of Depression Centers 2014 Annual Conference, Chicago, IL, October 22-14.

11. **Crane, N.A.**, Gowins, J.R., Barba, A.M., DelDonno, S.R., Jenkins, L.M., Meyers, K.K., Hazlett, K.E., Hsu, D.T., Mickey, B.J., Zubieta, J.K., & Langenecker, S.A. (October, 2014). *Cognitive Control Neural Markers of Treatment Response for Depression using Independent Component Analysis.* The National Network of Depression Centers 2014 Annual Conference, Chicago, IL, October 22-14.
12. Deldonno, S.R., Weldon, A.L., Passarotti, A.M., Mickey, B.J., Pruitt, P.J., **Crane, N.A.**, Gabriel, L., Yau, W., Meyers, K.K., Hsu, D.T., Taylor, S.F., Heitzeg, M.M., Shankman, S., Zubieta, J.K., & Langenecker, S.A. (October, 2014). *Reward-Processing Deficits in Active but not Remitted Depression.* The National Network of Depression Centers 2014 Annual Conference, Chicago, IL, October 22-14.
13. Peters, A.T., Jacobs, R.H., **Crane, N.A.**, Ryan, K.A., Weisenbach, S.L., Ajilore, O., Lamar, M., Kassel, M.T., Gabriel, L.B., West, A.E., Zubieta, J.K., Langenecker, S.A. (October, 2014). *Reliable Impairment in Cognitive Control among Youth with Remitted Major Depressive Disorder.* The National Network of Depression Centers 2014 Annual Conference, Chicago, IL, October 22-14.
14. Langenecker, S.A., Deldonno, S.R., Jacobs, R.H., Barba, A., Ryan, K.A., Gowins, J.R., Jenkins, J., **Crane, N.A.**, Zubieta, J.K., Nusslock, R., Phan, K.L., & Shankman, S. (October, 2014). *Diminished Learning and Pursuit of Reward and Disrupted Resting State Connectivity of Reward Networks in Remitted Major Depressive Disorder (MDD)*. Department of Psychiatry UI Center on Depression & Resilience Launch and 5th Annual Research Extravaganza, Chicago, IL, October 21.
15. Jenkins, L, Barba, A., Kassel, M., **Crane, N.**, Verges, A., Calamia, M., Gabriel, L., Hymen, E., Weisenbach, S., Maki, P., & Langenecker, S. (September, 2014). *Differential brain activation in males and females in the remitted phase of major depressive disorder.* The 28th Annual Meeting of the Society for Research in Psychopathology, Evanston, IL, September 18-21.
16. **Crane, N.A.**, Barba, A.M., Gabriel, L.B., Weldon, A.L., Baker, A.M., Nagel, C.E., Kassel, M.T., Hymen, E.A., Ryan, K.A., Mickey, B.J., Zubieta, J.K., & Langenecker, S.A. (May, 2014). *History of Substance Use Disorder Modulates Reward Processing Depending on Depression State.* The Society of Biological Psychiatry's 69th Annual Meeting, New York, NY, May 8-10.
17. DelDonno, S.R., Weldon, A.L., Meyers, K.K., Gabriel, L.B., Pester, B., Kassel, M.T., **Crane, N.A.**, Hsu, D.T., Mickey, B.J., Zubieta, J.K., & Langenecker, S.A. (May, 2014). *Behavioral Activation Predicts Reward-Seeking in Depression.* The Society of Biological Psychiatry's 69th Annual Meeting, New York, NY, May 8-10.
18. **Crane, N.A.**, Langenecker, S.A., & Mermelstein, R.J. (April, 2014). *Gender Differences in Marijuana Use, Cigarette Use, and Depression During Adolescence and Young Adulthood.* The UIC Women's Health Research Day, Chicago, IL, April 28.
19. **Crane, N.A.**, Kamali, M., Bhaumik, R., Ryan, K.A., Marshall, D.F., Saunders, E.F., Kassel, M.T., Weldon, A.L., McInnis, M.G., & Langenecker, S.A. (February, 2014). *Developing Dimensional, Integrated Constructs of Self-Report and Neuropsychological Data for Inhibitory Control.* The 42nd annual meeting of the International Neuropsychological Society, Seattle, WA, February 12-15**.**
20. Jenkins, L.M., Gabriel, L.B., Kassel, M.T., Hymen, E.A., Verges, A., Calamia, M., **Crane, N.A.**, Jacobs, R., Ajilore, O., Welsh, R.C., & Langenecker, S.A. (February, 2014). *Hyperactivation and hyperconnectivity of the emotional salience network are associated with intact facial emotion perception in young adults with remitted major depressive disorder.* The 42nd annual meeting of the International Neuropsychological Society, Seattle, WA, February 12-15**.**
21. **Crane, N.A.**, Conrad, M., Giedgowd, G.E., Gorka, S.M., & Kassel, J.D. (February, 2014). *Adolescent's Respiratory Sinus Arrhythmia Predicts Smoking Behavior Five Years Later.* The 20th annual meeting of the Society for Research on Nicotine and Tobacco, Seattle, WA, February 5-8.

22. Kassel, J.D., Conrad, M.C., **Crane, N.A.**, Giedgowd, G.E., & Mermelstein, R.J. (February, 2014). *Assessment of Psychophysiological and Self-Report Indices of Emotional Response in Adolescent Smokers: Mechanisms, Motives, and Predictive Validity.* The 20th annual meeting of the Society for Research on Nicotine and Tobacco, Seattle, WA, February 5-8.
23. Giedgowd, G.E., Conrad, M., **Crane, N.A.**, & Kassel, J.D. (February, 2014). *Sex Differences in Perceived and Actual Relief of Negative Affect as a Result of Smoking in an Adolescent Sample.* The 20th annual meeting of the Society for Research on Nicotine and Tobacco, Seattle, WA, February 5-8.
24. Langenecker, S.A., Jacobs, R.H., **Crane, N.A.**, Ryan, K.A., Weisenbach, S.L., Ajilore, O., Kassel, M.T., Gabriel, L., & Zubieta, J-K. (December, 2013). *Reduced Impairment, Yet Increased Reliability of Cognitive Control Measurements in Remitted MDD.* The 52nd annual meeting of the American College of Neuropharmacology, Hollywood, FL, December 8-12.
25. Meyers, K.K., **Crane, N.A.,** O'Day, R., Zubieta, J.K., Pomerleau, C.S., Horowitz, J.C., & Langenecker, S.A. (June, 2013). *The Influence of Cigarette Smoking and Major Depressive Disorder on Emotion Processing and Executive Functioning.* The 11th Annual American Academy of Clinical Neuropsychology Conference, Chicago, IL, June 19-22.
26. **Crane, N.A.,** Meyers, K., O'Day, R., Zubieta, J.K., Pomerleau, C.S., Horowitz, J.C., & Langenecker, S.A. (May, 2013). *The Impact of Smoking History and Depression on Executive Functioning and Emotional Processing.* The Society of Biological Psychiatry's 68th Annual Meeting, San Francisco, CA, May 16-18.
27. **Crane, N.A.**, Schuster, R. M., & Gonzalez, R. (February, 2013). *Sex Differences in Associations between Amount of Cannabis Use and Neuropsychological Performance.* The 41st annual meeting of the International Neuropsychological Society, Waikoloa, HI, February 6-9**.**
28. Schuster, R.M., **Crane, N.A.**, Mermelstein, R., & Gonzalez, R. (February, 2013). *Interactions between Cannabis and Tobacco on Episodic Memory among Young Adult Cannabis Users.* The 41st annual meeting of the International Neuropsychological Society, Waikoloa, HI, February 6-9.
29. Braun, A.R., Conrad, M., Giedgowd, G., **Crane, N.**, Greenstein, J., Colflesh, G. Veilleux, J., Heinz, A., & Kassel, J. (November, 2012). *The Effects of Nicotine on Selective Attention.* The 46th annual convention of the Association for Behavioral and Cognitive Therapies, National Harbor, Maryland, November 15-18.
30. **Crane, N.A.**, Schuster, R. M., & Gonzalez, R. (2012, June). *Examining Sex Differences in Decision-Making and Episodic Memory in Young Adult Cannabis Users.* The 74th annual meeting of the College on Problems of Drug Dependence, Palm Springs, CA, June 9-14. *[Recipient of NIDA Women & Sex/Gender Junior Investigator Travel Award]*
31. Schuster, R. M., **Crane, N.A.**, & Gonzalez, R. (2012, June). *Neurocognitive Correlates of Risky Sexual Behavior Among Young Adult Cannabis Users*. The 74th annual meeting of the College on Problems of Drug Dependence, Palm Springs, CA, June 9-14.
32. Schuster, R. M., **Crane, N.A.**, Mermelstein, R., Gonzalez, R. (2012, April). *A Nuanced Assessment of Cannabis Use and Risky Sexual Behaviors.* The 33rd annual meeting of the Society of Behavioral Medicine, New Orleans, LA, April 11-14.
33. Gonzalez, R., Schuster, R., **Crane, N.**, Martin, E. M., & Vassileva, J. (2012, February). *Interactions between Decision-Making and Cannabis Harm Perception on Negative Consequences of Cannabis Use among Young Adult Cannabis Users: Preliminary Analyses.* The 40th annual meeting of the International Neuropsychological Society, Montreal, Canada, February 15-18.
34. Gonzalez, R., Schuster, R., **Crane, N.**, Martin, E. M., & Vassileva, J. (2012, February). *Decision-Making Performance Influences the Relationship between Amount of Cannabis use and its Negative*

Consequences. The 40th annual meeting of the International Neuropsychological Society, Montreal, Canada, February 15-18.

35. Higley, A.E., **Crane, N.A.**, Goodell, V., Spadoni, A.D., Squello, S., Mason, B.J. (2011, June). *Craving in Response to Stress-Induction in a Human Laboratory Paradigm Predicts Treatment Outcome in Alcohol Dependent Individuals.* The 34th Annual Research Society on Alcohol Conference, Atlanta, GA, June 25-29.
36. Mason, B.J., Higley, A.E., **Crane, N.A.**, Goodell, V. (2010, September). *Evaluation of Craving and Sleep in a Human Laboratory Study of Acamprosate, Naltrexone and Placebo in Alcohol Dependent Volunteers.* Symposia presented at the 15th biennial International Society for Biomedical Research on Alcoholism Conference, Paris, France, September 13–16.
37. Spadoni, A.D., **Crane, N.A.,** Higley, A.E., Goodell., V., Tapert, S.F., Mason, B.J. (2010, June). *Cue-Reactivity in Alcohol Dependent Volunteer Treated with Acamprosate, Naltrexone, or Placebo: fMRI Findings in Relation to Human Laboratory Results.* The 33rd Annual Research Society on Alcohol Conference, San Antonio, TX, June 26-30.
38. Carrillo M., Ricci L.A., **Crane, N.A.**, Melloni R.H. Jr. (2007, October*). Increased activation of glutamatergic neurons in the LAH; implications for AAS-induced offensive aggression.* The NorthEast Under/graduate Research Organization for Neuroscience (NEURON) Conference, Boston, MA, October 6.

TEACHING EXPERIENCE

2011 - 2016 UIC DEPARTMENT OF PSYCHOLOGY Chicago, IL

*Teaching Assistant***,** Psychology of Interviewing- Spring 2016
- Professor: *S. Bibiana Adames, Ph.D.*

*Teaching Assistant***,** Psychology of Interviewing- Spring 2015
- Professor: *Steve DuBois, Ph.D.*

*Teaching Assistant***,** Theories of Personality- Fall 2014
- Professor: *Julie Chen, Ph.D.*

*Teaching Assistant***,** Abnormal Psychology- Spring 2014
- Professor: *Katherine Noll, Ph.D.*

*Teaching Assistant***,** Introduction to Research Methods in Psychology- Spring 2012
- Professor: *Evelyn Behar, Ph.D.*

*Teaching Assistant***,** Introduction to Psychology- Fall 2011
- Professor: *Mike Rosanova, Ph.D.*