Examining Neuropsychological Sex Differences in Young Adult Cannabis Users

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THESIS

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ANOVA	Analysis of Variance
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory-II
BIS	Barratt Impulsiveness Scale-11
CB1 & CB2	Cannabinoid Receptors 1 & 2
CU	Cannabis Users
DUHQ	Drug Use History Questionnaire
HVLT	Hopkins Verbal Learning Task
IGT	Iowa Gambling Task
IQ	General Intellectual Abilities
NU	Non-Using Controls
PHQ	Participant History Questionnaire
SCID	Structured Clinical Interview for DSM-IV
THC	Delta-9-tetrahydrocannabinol
WTAR	Wechsler Test of Adult Reading
WURS	Wender-Utah Rating Scale

SUMMARY

Cannabis is the most widely used illicit substance worldwide, and its use is especially prevalent among adolescents and young adults. This is concerning, given that cannabis use is associated with deficits in neuropsychological functioning. A burgeoning area of research indicates there may be important sex differences in cannabis use and the effects of cannabis on neurocognition, perhaps due to sex-specific vulnerabilities to the neuropharmacological effects of cannabis and differences in age of initiated use. The goal of the present study was to examine potential neurocognitive sex differences among a sample of young adult cannabis users and non-users, and to examine how important factors, such as amount of use and age of initiation of use, may differentially affect neurocognition in male and female cannabis users. We found that young adult cannabis users showed deficits in immediate and delayed recall, but not decision-making, compared to non-users and there were no sex differences in these relationships. However, among cannabis users, more lifetime cannabis use was associated with poorer episodic memory, especially for females. In contrast, more lifetime and past month cannabis use predicted worse decision-making only for males. Further, we found that, surprisingly, an earlier age of first use and an earlier age of regular initiated use was associated with better decision-making for both males and females, but poorer episodic memory for only females, not males. These findings indicate there may be important, sex-specific differences in how amount of cannabis use and age of initiated use related to neurocognition in male and female cannabis users.

STUDY INTRODUCTION & AIMS

Cannabis is the most widely used illicit substance worldwide (UNODC, 2011) and its use is especially prevalent among adolescents and young adults (SAMSHA, 2011). Exogenous cannabinoids like, delta-9-tetrahydrocannbinol (THC; the main psychoactive compound in cannabis), bind to cannabinoid receptors in the brain that are densely concentrated in the hippocampus, amygdala, basal ganglia, and prefrontal cortex (Mackie, 2005; Piomelli, 2003). Through the stimulation of these receptors, cannabis use may disrupt the endocannabinoid system, a neurotransmitter system implicated in important aspects of learning, memory, drug- and reward-seeking behaviors, and neurodevelopment (i.e., synaptic pruning and sex-specific neuromaturation; Viveros et al., 2012) and consequently lead to various neurocognitive impairments. Indeed, several studies have found cannabis users to demonstrate deficits on neuropsychological measures of episodic memory (Bolla, Brown, Eldreth, Tate, & Cadet, 2002; Cunha, Nicastri, de Andrade, & Bolla, 2010; Pope & Yurgelun-Todd, 1996; Solowij et al., 2002; Wagner, Becker, Gouzoulis-Mayfrank, & Daumann, 2010) and decision-making (even after 25-days abstinence; Bolla, Eldreth, Matochik, & Cadet, 2005; Verdejo-Garcia et al., 2007). However, there are important sex differences in endocannabinoid receptor densities across several brain structures (Reich, Taylor, & McCarthy, 2009) and neurodevelopmental, pharmacological, metabolic, behavioral, and hormonal sex-differences may all contribute to sex differences in neurocognitive impairments among cannabis users (Crane, Schuster, Fusar-Poli, & Gonzalez, In press). However, few studies have examined this issue. As such, the current study examined sex differences in: 1) measures of neurocognition in young adult cannabis users and non-users; 2) the relationship between amount of cannabis use and neurocognition in male and female cannabis users; and 3) how age of first cannabis use and age of onset of regular cannabis use relate to neuropsychological functioning in male and female cannabis users.

1. BACKGROUND

Importance of Studying Sex Differences in Cannabis Use

In 2010 alone, approximately 17.4 million people, or 18.4% of the U.S. population, used cannabis in the past month. Use is especially high among adolescents and has increased in recent years. Indeed, between 2009 and 2011 more adolescents reported using cannabis (22.6%) than cigarettes (18.7%) in the past month (Johnston, 2012). These statistics are concerning, as cannabis users who begin their use at an earlier age are at an increased risk of developing a cannabis use disorder (SAMSHA, 2011). Importantly, males and females have different patterns of use and progress to cannabis use disorders at different rates. Males are more likely to use cannabis (SAMSHA, 2011), and initiate their use at a younger age compared to females (Gfroerer & Epstein, 1999; Pope et al., 2003). However, a telescoping effect (i.e., accelerated progression of a substance-use disorder) seems to occur in female cannabis users, such that females enter treatment for marijuana use disorders after fewer years of use and less cumulative cannabis use compared to males (Hernandez-Avila, Rounsaville, & Kranzler, 2004). This speaks to a growing public health concern, as cannabis addiction has been linked with several negative health consequences (Kalant, 2004), decreased academic achievement (Fergusson, Horwood, & Beautrais, 2003; Horwood et al., 2010), as well as significant psychosocial and cognitive impairments (Fergusson & Boden, 2008; Kalant, 2004; Solowij & Pesa, 2010). These differences in use, initiation of use, and progression to cannabis use disorders, suggest that cannabis use may affect males and females differently, especially in regard to the impact of cannabis on neurocognitive functioning.

Sex-specific Effects of Cannabis on Brain Function

There are apparent sex differences in the impact of cannabis on the endogenous cannabinoid system may have sex-specific effects. Cannabis has at least 489 known compounds and at least 70 cannabinoids (Elsohly & Slade, 2005). The main active psychoactive cannabinoid in cannabis is delta-9-tetrahydrocannabinol (THC), which acts through the endogenous cannabinoid system, binding to cannabinoid (CB1 and CB2) receptors in the brain. These receptors are densely concentrated in the hippocampus and prefrontal cortex, regions involved in learning, memory and executive functions, including decision-making (Piomelli, 2003). However, endocannabinoid receptor density is different for males and females. Males have higher CB1 receptor density in early adulthood, especially in the hippocampus (Reich et al., 2009). Neuroimaging studies show that while males maintain or lose CB1 binding sites later in adulthood (i.e., 45-70 years old), females continue to have increases in CB1 receptor density throughout their lives, eventually surpassing that of males (Van Laere et al., 2008). THC may dysregulate the endocannabinoid system through the stimulation of CB1 and CB2 receptors, in turn leading to neurobiological and behavioral alterations. Indeed, recent evidence suggests exogenous cannabinoids, like THC, inhibit synaptic transmission in the neocortex (Kovacs, Illes, & Szabo, 2011), which may help to explain the well-documented short-term cognitive deficits induced by THC administration (Bhattacharyya et al., 2009; Ranganathan & D'Souza, 2006). As such, it may be that males are more vulnerable to the negative impact of cannabis use on neurocognition if their use occurs during early adulthood, as higher CB1 density may lead to greater susceptibility to neurobiological and behavioral alterations. On the other hand, animal studies indicate adolescent females have more efficient CB1 receptors, evidenced by higher G protein activation after stimulation (Burston, Wiley, Craig, Selley, & Sim-Selley, 2010; Rubino

et al., 2008). Thus, it remains unclear how the differences in density and efficiency of cannabinoid receptors among males and females may differentially impact sex differences in neurocognitive function.

Neurocognitive Functioning Among Male and Female Cannabis Users

Numerous studies have documented domain-specific deficits in cognitive functioning in cannabis users, especially in episodic memory (i.e., the autobiographical memory of specific events, situations, and experiences; Tulving, 2001) (Bolla et al., 2002; I. Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003; Wadsworth, Moss, Simpson, & Smith, 2006) and decision-making (i.e., often defined as processes of evaluating a variety of response options and choosing the option considered to be optimal in the present moment without sensitivity to long-term outcomes; Clark, Cools, & Robbins, 2004) (J. Grant, Chamberlain, Schreiber, & Odlaug, 2012; Verdejo-Garcia et al., 2007; Wesley, Hanlon, & Porrino, 2011; Whitlow et al., 2004). Sex differences are evident among healthy, non-using adults in these domains, such that females perform better on measures of episodic memory (Kramer, Delis, & Daniel, 1988), while males perform better on measures of decision-making (Bolla, Eldreth, Matochik, & Cadet, 2004; Overman et al., 2004; Reavis & Overman, 2001). However, studies have examined potential sex differences in these domains among cannabis users. In the two studies that investigated sex differences among cannabis users and non-using controls, no interactions of group or sex were found on episodic memory (Solowij et al., 2011; Tait, Mackinnon, & Christensen, 2011). To date, no studies have examined sex differences in the relationship between cannabis use and performance on decision-making tasks. As such, the dearth of studies examining sex differences in neurocognition in the extant literature makes it difficult to conclude how cannabis use may

differentially affect males and females, especially given that the aforementioned studies did not consider important factors like amount of use or age of initiated use.

Sex Differences in Cannabis Use and the Pharmacological Effects of Cannabis

In general, amount of cannabis use and duration of use seem to be negatively associated with cognitive functioning (Bolla et al., 2002; Cunha et al., 2010; Pope & Yurgelun-Todd, 1996; Solowij et al., 2002; Wagner et al., 2010) and structural brain changes in cannabis users (Yucel et al., 2008). These dose-dependent cognitive deficits and reductions in hippocampal volume suggest chronic, daily use may be particularly harmful to episodic memory (Yucel et al., 2008). However, accumulating evidence indicates different behavioral patterns in cannabis use and sex-specific pharmacological effects of cannabis that could lead to sex differences in neurocognitive functioning in cannabis users. Preclinical evidence indicates that female rats preferentially metabolize THC to only its highly active metabolite, while male rats metabolize THC to multiple compounds (Narimatsu, Watanabe, Yamamoto, & Yoshimura, 1991). Additionally, physiological data indicates females may develop tolerance to cannabis more quickly than males (Cocchetto, Owens, Perez-Reyes, DiGuiseppi, & Miller, 1981), which may lead to more rapidly escalating use among females. Moreover, some evidence suggests females may feel greater hedonic reinforcement from cannabis than males and ovarian hormones (i.e., estrogen and progesterone) may play a role in facilitating stronger learned associations between drug effects and drug-related stimuli (Fattore et al., 2007). Together, these data suggest that females may be more sensitive to the negative pharmacological effects of cannabis. Therefore, more cannabis use may be more detrimental to females than males when examining cognitive functioning.

Sex Differences in Neurodevelopment and Age of Initiated Cannabis Use

Initiation of cannabis use often occurs in adolescence, a critical period of neurodevelopment when growth of the prefrontal cortex, structures in the limbic system, and white matter associational, commissural, and projectional myelination takes place (Giedd et al., 1999). Therefore, the adolescent brain may be especially vulnerable to impacts and disturbances from exogenous compounds. This effect may be particularly salient due to the high density of CB1 receptors in the prefrontal cortex and limbic areas. Importantly, the endocannabinoid system plays a crucial role in neuromaturation and synaptic pruning (Viveros et al., 2012). As such, initiation of cannabis use during this time may disrupt normal neuromaturation (Bava & Tapert, 2010), and in turn, lead to impairments in neurocognition. Indeed, several studies have found an earlier age of initiated regular cannabis use is associated with poorer cognitive functioning (Battisti et al., 2010; Ehrenreich et al., 1999; Fontes et al., 2011; Gruber, Sagar, Dahlgren, Racine, & Lukas, 2012; Pope et al., 2003; Solowij et al., 2011; Solowij et al., 2012), including poorer episodic memory (Pope et al., 2003; Solowij et al., 2012).

Recent evidence suggests endocannabinoid signaling also plays a crucial role in establishing normal sex differences in the brain (Viveros et al., 2012) and disruption of this process may also cause sex-specific cognitive deficits. Given these differences, cannabis may differentially affect males and females, especially when taking into account the age of initiation of use. Importantly, males and females have different neurodevelopmental trajectories. Female's total brain size peaks when they are about 10-11 years old, while male's total brain size peaks when they are about 14-15 years old (Lenroot et al., 2007). Similarly, prefrontal cortex gray matter volume seems to peak 1-2 years earlier in females than in males (Giedd et al., 1999). This evidence indicates the female brain may mature at an earlier age than the male brain. Therefore,

if cannabis use is initiated in adolescence, it may affect males more than females, as males' brains are undergoing more sensitive neurodevelopment during that time. This, coupled with the fact that males often initiate their use earlier than females, may make cannabis' negative impact on neurocognitive functioning even more pronounced among males.

Given sex differences in neurodevelopment, the pharmacological effects of cannabis, and cognitive functioning, it seems that cannabis use may differentially affect males and females; however, few studies have examined the impact of this interaction on neuropsychological functioning. It is important to identify potential sex differences in cognitive functioning among cannabis users to better understand 1) how long-term cannabis use affects cognitive functioning in males and females and 2) how important aspects of use (i.e., amount of use and age of onset) affect cognitive functioning in male and female cannabis users. It may be that more cannabis use leads to poorer cognitive functioning in females, while an earlier age of initiated use predicts worse cognitive functioning in males, after controlling for amount of use.

Goal of the Present Study

The goal of the present study is to examine potential sex differences in neurocognition among a sample of young adult cannabis users and how important factors such as amount of use and age of initiation of use may differentially affect neurocognitive function in male and female cannabis users. To our knowledge, this is one of the first studies to examine how amount of use and age of initiation may differentially affect males and females.

Aim 1. We compared measures of neurocognitive functioning and potential neurocognitive sex differences among cannabis users and non-using controls. Based on documented pharmacological and metabolic sex differences, we hypothesized that 1) cannabis users will perform more poorly than non-users on measures of episodic memory (Hopkins

Verbal Learning Task; HVLT) and decision-making (Iowa Gambling Task; IGT); 2) in general, males will perform more poorly than females on the HVLT, while females will perform more poorly than males on the IGT; and 3) sex will moderate the relationship between cannabis use and neuropsychological functioning, such that female cannabis users will perform even more poorly on the HVLT and the IGT than male cannabis users.

Aim 2. The second aim was to assess how amount of lifetime, past year, and past month cannabis use relates to episodic memory and decision-making performance in male and female cannabis users. Based on pharmacological and metabolic sex-differences, we hypothesized that 1) more cannabis use will be associated with poorer episodic memory and decision-making performance in male and female cannabis users; 2) overall, males will perform more poorly than females on the HVLT, while females will perform more poorly than males on the IGT; and 3) the relationship between amount of use and neurocognition will be moderated by sex, such that more cannabis use will be associated with even poorer episodic memory and decision-making performance in females, than in males. Exploratory analyses will be conducted for each period of use (i.e., lifetime, past year, past month) to determine how recent versus cumulative cannabis use may related differentially to neurocognition in male and female users. Some previous evidence suggests that more proximal use (i.e., past month use) will be more relevant to episodic memory performance, while more distal use (i.e., lifetime use) will be more relevant to decision-making performance.

Aim 3. The third aim was to investigate the relationship between age of first cannabis use and age of onset of regular cannabis use on neuropsychological functioning in male and female cannabis users. Based on behavioral and neurodevelopmental sex-differences, we hypothesized that 1) an earlier age of use will be associated with worse episodic memory and decision-making

in male and female cannabis users, even after controlling for lifetime cumulative amount of cannabis use; 2) in general, males will have poorer episodic memory than females and females will have worse decision-making than males after controlling for lifetime cumulative amount of cannabis use; 3) age of initiated use will be moderated by sex, such that males will have even poorer episodic memory and decision-making than females as age of initiated use is younger after controlling for cumulative amount of cannabis use. We controlled for amount of cannabis use to specifically identify the unique association between age of initiated use and neuropsychological performance. Further, in order to determine if age of first use or age of regular use differentially predict neurocognitive outcomes in male and female cannabis users, both variables will be examined in analyses. As found in previous studies, it is thought that age of regular use will be more predictive of cognitive functioning than age of first use.

2. METHODS

Participants

Participants were 69 cannabis users (CU; *n*= 25 female) and 66 non-users (NU; *n*= 33 female) aged 17-24 years from the Chicago metropolitan area. Participants were a subset of individuals from a larger study examining cannabis use and neurocognition (K23 DA023560; PI: R. Gonzalez, PhD) recruited primarily through word-of-mouth and informational fliers posted throughout the community. A few participants were also screened and recruited from a large natural history study of the social-emotional contexts of adolescent smoking (P01 CA098262; PI: R. Mermelstein, PhD). The Institutional Review Board at the University of Illinois at Chicago approved the study and written informed consent (or parental consent and participant assent for minors) was obtained.

A semi-structured telephone-screening interview determined initial eligibility. All participants 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 formal diagnosis of a learning disability, developmental delay, mental illness (including ADHD), 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; (7) English fluency. In addition, cannabis users met the following criteria: 1) used cannabis: >200 in life, >4x per week during peak use, and in the last 45 days; (2) no cannabis use on testing day; and (3) identified cannabis as drug of choice.

All participants were required to demonstrate no significant alcohol breath content level (AlcoMate Prestige Model AL6000; Palisades Park, NJ) and no recent illicit drug use other than

cannabis via rapid urine toxicology screening at testing (10-panel Drug Check Cup; Express Diagnostics, Blue Earth, Minnesota).

Assessment of Substance Use History

Drug Use History Questionnaire (DUHQ). We used the DUHQ (Gonzalez et al., 2012) to collect history of cannabis, alcohol, and nicotine use. Participants were asked about the amount and frequency of their use of each substance during their lifetime, the past year and the past month.

Laboratory Measures of Neuropsychological Functioning

Hopkins Verbal Learning Test–Revised (HVLT-R). The HVLT-R (Benedict, Schretlen, Groninger, & Brandt, 1998) is a test of episodic verbal memory in which the participants are asked to recall a list of 12 words, comprised from three groups of four (non-consecutive) semantically associated words. Participants were asked to immediately recall this list of words after each of three trials and then again after a 25-minute delay. Total number of words recalled immediately and after the delay were our primary variables of interest.

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.

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).

Participant History Questionnaire (PHQ). The PHQ (Gonzalez et al., 2012) is a brief, examiner-led questionnaire to obtain demographic information. Participants were asked about their ethnicity, family of origin (e.g., parental education status, income, mental health and substance use history), mental health history, medical conditions, and developmental history.

Structured Clinical Interview for DSM-IV (SCID). Participants were administered the SCID substance use and mood modules (First, Spitzer, Gibbon, & Williams, 2002) to diagnose the presence of alcohol and substance use disorders during their lifetime and in the past 30 days and any current or past mood (i.e., Major Depressive Disorder, Bipolar I, Bipolar II) disorder. In addition, participants completed a self-administered, brief SCID screener for conduct disorder.

Beck Depression Inventory-II (BDI-II). The BDI-II (Beck, Brown, & Steer, 1996) is a 21-item self-report questionnaire of depressive symptoms. Participants' total score was used to determine the severity of depressive symptoms. Total scores >13 indicate mild to severe depression.

Beck Anxiety Inventory (BAI). Participants completed the BAI (Beck & Steer, 1990), a 21-item self-report questionnaire of anxiety symptoms. The total score was used to access anxiety disturbance. Total scores >9 indicate mild to severe anxiety.

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). We looked 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). The BIS (Patton, Stanford, & Barratt, 1995) is a 30-item self report measure of impulsive personality traits. The total score was used to assess trait levels of impulsivity.

Toxicology Testing. We obtained breath alcohol and exhaled carbon-monoxide content, as well as urine samples to test for recent use of cocaine, opiates, propoxyphene, phencyclidine, methadone, ecstasy, barbiturates, benzodiazepines, oxycodone, and THC.

General Statistical Procedures

All analyses were carried out using SPSS 20.0 (IBM). Data were inspected for non-normal distribution and outliers. Square-root transformations or nonparametric procedures were used with data that violated assumptions of parametric procedures, including amount of cannabis, alcohol, and nicotine use. In addition, we controlled for alcohol and nicotine use within the relevant period for each analysis (i.e., lifetime, past year, past month). To preserve power, non-significant covariates were removed from final models and only reduced models are reported. Due to the small sample size, potential issues with power, and a priori hypotheses, all results will be deemed statistically significant when p-values <.10.

Aim 1. Two-way between subject analysis of variance (ANOVA) models were used with sex and group (CU, NU) and their interaction as independent variables and the score on each measure of cognition as separate dependent variables, to test effects of group and sex, and their interaction on neurocognition.

Aim 2. To access the impact of amount of use on neurocognition among cannabis users, we conducted three moderated hierarchical multiple regression analyses with centered lifetime, past year, and past month cannabis use entered as separate independent variables in the first block, dummy vectors for sex (i.e., male, female) in the second block, and their interaction in the third block as predictors, and performance on neuropsychological measures as separate dependent variables. Significant interactions were followed-up by testing simple slopes of the neurocognitive measure for female CU versus male CU to see if the slopes are significantly different from zero. For these analyses, periods of use were computed to be orthogonal, such that lifetime cannabis use equals cumulative lifetime use minus cumulative past year use, past year use equals cumulative past year use minus cumulative past month use, and past month use was unchanged.

Aim 3. To examine how age of onset of first use and age of onset of regular use may impact male and female CU's neurocognitive functioning, we conducted two separate moderated hierarchical regression analyses using standard multiple regression for each cognitive measure with male and female CU's centered age of first use and age of regular use entered as separate independent variables in the first block of each regression, respectively; dummy vectors for sex (i.e., male, female), as well as with centered lifetime use (in order to control for the effects of amount of use) in the second block; and the interaction of age of use and sex in the third block. Performance on neuropsychological measures served as the separate dependent variables.

Significant interactions were followed-up by testing simple slopes of neurocognitive performance for female CU versus male CU to see if the slopes are significantly different from zero.

3. RESULTS

Demographics, Mental Health, Substance Use and Other Potential Confounds

Male and female CU and NU reported minimal mental health complaints and did not significantly differ on demographic information, with the exception that female controls had significantly less annual household income than male controls (Table 1). As evidenced by Table 2, significantly less male NU and female CU met criteria for current alcohol abuse than male CU and significantly less male and female NU met criteria for lifetime alcohol abuse than male CU. As predicted, a significant proportion of male and female CU met criteria for current and lifetime cannabis abuse and dependence and tested positive for THC, while no NU met criteria for a cannabis use disorder or tested positive for THC. In addition, male and female CU did not differ in their lifetime, past year, and past month cannabis use, but used significantly more cannabis than male and female NU (see Table 2). Female NU smoked significantly less cigarettes in their lifetime and during the past month than male and female CU, and male and female NU smoked significantly less cigarettes than male CU during the past year. Female NU drank significantly less alcohol than male CU during their lifetime and during the past year. Male NU drank significantly less alcohol during the past year than male and female CU and also drank significantly less alcohol during the past month than male CU.

Aim 1

In general, CU had poorer immediate ($F(4,130) = 2.82$, $p = .096$) and delayed recall ($F(4,130) = 3.53$, $p = .06$) compared to controls. On the other hand, CU performed similarly to controls on decision-making, $F(4,130) = 1.42$, $p = .24$. Further, there were no sex differences in performance on immediate ($F(4,130) = 1.87$, $p = .17$) and delayed recall ($F(4,130) = 0.37$, $p = .55$) or decision-making, $F(4,130) = 0.82$, $p = .37$. Moreover, there were no significant

interactions between group (CU, NU) or sex (male, female) on immediate recall ($F(4,130) = 2.17$ $p = .14$), delayed recall ($F(4,130) = 0.80$, $p = .37$), or decision-making, $F(4,130) = 0.85$, $p = .36$.

Aim 2

Relationships between Amount of Cannabis Use and Neurocognitive Performance in CU. We found a significant negative, dose-dependent relationship between amount of cumulative lifetime, past year, and past month cannabis use on immediate recall (β = -.36, $p = .003$; β = -.26, $p = .03$; β = -.25, $p = .04$, respectively), and delayed recall (β = -.47, $p < .001$; β = -.32, $p = .007$; β = -.35, $p = .003$, respectively) on the HVLT, and decision-making performance on the IGT, β = -.27, $p = .03$; β = -.34, $p = .004$; β = -.35, $p = .003$, respectively.

Interactions between Amount of Cannabis Use and Sex on Neurocognition in CU. The interaction between lifetime cannabis use and sex was significant for decision-making (β = .27, $p = .057$) and delayed recall (β = -.23, $p = .07$). In addition, the interaction between past month cannabis use and sex was significant on decision-making (β = .26, $p = .099$) as well. No other interactions were significant (see Table 3).

Learning and Memory. Follow-up analyses of the simple slopes revealed more lifetime cannabis use had greater detrimental effects on delayed recall for females (β = -.42, $p < .001$) than males (β = -.29, $p = .008$) (Figure 1).

Decision-Making. Follow-up analyses of the simple slopes of the interaction between sex and amount of cannabis use indicated that more cannabis use predicted poorer decision-making in males for lifetime (β = -.35, $p = .004$) and past month (β = -.39, $p = .001$) use, but not for females during those periods of use (β = .05, $p = .68$ and β = -.10, $p = .40$, respectively) (Figure 2).

Aim 3

Relationships between Age of First Use and Neurocognitive Performance in CU. There were no significant associations between age of first use and immediate or delayed recall, even after controlling for cumulative lifetime cannabis use, nor was there a significant relationship between age of first use and decision-making performance (see Table 4). However, after controlling for cumulative lifetime cannabis use, an earlier age of first use predicted better decision-making, β = -.26, p = .04.

Interactions between Age of First Use and Sex on Neurocognition in CU. The interaction between age of first use and sex was significant for immediate (β = .38, p = .01) and delayed recall (β = .32, p = .03), but was not significant for decision-making, β = -.05, p = .76.

Learning and Memory. Follow-up analyses of the simple slopes revealed that an earlier age of first use was associated with better immediate recall for males (β = -.20, p = .09), but worse immediate recall for females, β = .21, p = .06 (Figure 3). However, age of first initiated use did not predict delayed recall for males or females (β = -.17, p = .14 and β = .18, p = .11, respectively) (Figure 4).

Relationships between Age of Regular Initiated Use and Neurocognitive Performance in CU. An earlier age of regular initiated use predicted poorer immediate and delayed recall (β = .22, p = .07 and β = .23, p = .06, respectively), but after controlling for cumulative lifetime use, these relationships were no longer significant (see Table 4). On the other hand, decision-making performance was not significantly associated with age of regular initiated use (see Table 4), however, after controlling for cumulative lifetime use, an earlier age of regular initiated use predicted better decision-making, β = -.23, p = .07.

Interactions between Age of Regular Initiated Use and Sex on Neurocognition. The interaction between age of regular initiated use and sex was significant for immediate (β = .38, *p* = .01) and delayed recall (β = .25, *p* = .09), but was not significant for decision-making (see Table 4).

Learning and Memory. Follow-up analyses of the simple slopes revealed an earlier age of regular cannabis use was associated with poorer immediate (Figure 3) and delayed recall (Figure 4) for females (β = .28, *p* = .01 and β = .20, *p* = .08, respectively), but not for males, β = -.11, *p* = .35 and β = -.06, *p* = .61, respectively.

Exploratory Analyses

To better understand our results indicating that an earlier age of first use and age of regular initiated use predicts better decision-making, we performed several exploratory analyses. Bivariate correlations between several theoretically relevant measures and decision-making performance for males and females are shown in Tables 5 & 6. Due to the fact that BAI and WURS scores were the strongest predictors of decision-making performance for females, we controlled for these variables to see if ADHD or anxiety symptoms influenced how age of first use related to neurocognition. After controlling for BAI total scores, the results remained similar, with an earlier age of regular use associated with better decision-making, β = -.22, *p* = .08. Similarly, after controlling for WURS total scores, an earlier age of regular use was associated with better decision-making, β = -.21, *p* = .09.

Interactions between Age of First Use and Cumulative Lifetime Cannabis Use. The interaction between age of first use and cumulative lifetime use was not significant for decision-making (or immediate recall and delayed recall; see Table 7).

Interactions between Age of Regular Initiated Use and Cumulative Lifetime Cannabis Use. The interaction between age of regular initiated use and cumulative lifetime use was not significant for decision-making (or immediate recall and delayed recall; see Table 7).

Interactions between Age of First Use and Sex on Decision-Making. Follow-up analyses of the simple slopes and earlier age of first cannabis use did not significantly predict decision-making in females (β = -.19, p = .11) or in males (β = -.18, p = .15) (Figure 5).

Interactions between Age of Regular Initiated Use and Sex on Decision-Making. Follow-up analyses of the simple slopes found that an earlier age of initiated regular cannabis use predicted better decision-making in females (β = -.28, p = .02), but not in males (β = -.05, p = .67) (Figure 5).

Analyzing Age of Regular Initiated Use using a Median-Split. Based on previous studies that have used a median-split of age of regular initiated use, we chose to use to compare individuals who began their regular use of cannabis before the age of 16 (early-onset) to those who began their regular use of cannabis at age 16 and older (late-onset) without controlling for cumulative amount of cannabis use. There were no differences between individuals with an early-onset and those with a late-onset on decision-making performance (F(3,65) = 0.29, p = .59), nor was there an interaction between onset and sex, F(3,65) = 2.09, p = .15.

Further, using ANOVA and chi-square analyses, early-onset users were compared to late-onset on several theoretical variables. Early-onset users did not differ from late-onset on IQ, education, mother's education, BDI total, BAI total, WURS total, or past or current cannabis abuse or dependence (all p-value's > .10). However, early-onset users had higher total scores on the BIS (F(1,67) = 3.24, p = .08) and the Marijuana Problem Scale, F(1,54) = 3.69, p = .06. Not surprisingly, early-onset users also had used more cannabis in their lifetime (F(1,67) = 11.66, p =

.001), but early- and late-onset users did not differ on amount of cannabis used per year, $F(1,67) = 1.11$, $p = .30$. Of note, when examining these relationships only among female cannabis users, early-onset female users' mothers had less years of education than late-onset female users' mothers ($F(1,21) = 4.38$, $p = .049$), but no other significant relationships emerged, all p-value's > .10.

4. DISCUSSION

In this study we examined group and sex differences among young adult CU and NU on measures of neuropsychological functioning, and how important aspects of cannabis use (i.e., amount of cannabis use and age of initiated use) may differentially impact neuropsychological performance on indices of episodic memory and decision-making among male and female CU (see Table 8). We found CU showed deficits in immediate and delayed recall, but not decision-making, compared to NU and there were no sex differences in these relationships. However, several important sex-specific and domain specific relationships were found when examining how amount of cannabis use and age of initiated cannabis use may impact neurocognition in male and female CU.

Aim 1

Consistent with the hypotheses and previous studies (Bolla et al., 2002; Cunha et al., 2010; Pope & Yurgelun-Todd, 1996; Solowij et al., 2002; Wagner et al., 2010), young adult CU showed deficits in immediate and delayed recall compared to NU. However, contrary to our hypothesis, CU and NU did not differ on their decision-making performance, which may reflect that decision-making problems are not severe among CU, or they may only be present among a subset of individuals, making group differences more difficult to detect. In addition, unlike what previous studies have demonstrated in NU (Bolla et al., 2004; Kramer et al., 1988; Overman et al., 2004; Reavis & Overman, 2001), there were no sex differences on measures of episodic memory and decision-making. Nor were there any interactions of group membership and sex on neurocognitive performance, similar to what others have found (Solowij et al., 2011; Tait et al., 2011). As mentioned previously, it may be that group and sex differences are more subtle among young adult CU, and therefore impairments were not captured with the present

neuropsychological measures, or that deficits in neurocognitive domains are only present among a subset of individuals and would emerge only with a larger sample. These factors may have precluded our ability to detect significant group and sex differences. On the other hand, the fact that we did not find sex-differences in episodic memory and decision-making, domains that have been shown to have sex-differences in performance among healthy NU, may be an important finding in itself. It may be that cannabis use compromises female's advantage on episodic memory (Kramer et al., 1988) and male's advantage on decision-making (Bolla et al., 2004; Overman et al., 2004; Reavis & Overman, 2001), so that male and female CU do not differ on their performance on this task.

Aim 2

Consistent with our hypotheses, we found that in general, more lifetime, past year, and past month cannabis use was associated with poorer immediate and delayed recall, on a measure of episodic memory, and poorer decision-making in young adult male and female CU. These findings are similar to what has been reported in other studies that have shown a negative, dose-dependent relationship between amount of cannabis use on episodic memory (Bolla et al., 2002; Cunha et al., 2010; Pope & Yurgelun-Todd, 1996; Solowij et al., 2002; Wagner et al., 2010) and decision-making (Bolla et al., 2005), although this is not always the case (Lisdahl & Price, 2012). Of note, we took steps in this investigation to separate the effects of distal versus proximal use (lifetime cannabis use was calculated by subtracting past year use from lifetime use and past year cannabis use was calculated by subtracting past month use from pasty year use), suggesting that both distal and recent use may be harmful to neurocognition. Further, we found evidence of a dissociation in how amount of cannabis use is related to decision-making and delayed recall among male and female CU. More lifetime cannabis use was associated with

worse delayed recall for both males and females, but this relationship was stronger among females. Conversely, more lifetime and past month cannabis use was associated with worse decision-making only for males, not for females. To our knowledge, this is the first evidence of sex-specific relationships between amount of cannabis use and episodic memory or decision-making.

This evidence may help to explain our finding of no overall sex-differences in neurocognitive performance in Aim 1, as we found that the domain each sex has an advantage in among healthy non-users (i.e., decision-making for males and episodic memory for females) is the same domain that is differentially negatively impacted by more cannabis use in male and female CU. Thus, despite similar overall performance in episodic memory and decision-making among male and female CU, amount of cannabis use seems to impact neuropsychological functioning in a domain and sex-specific manner, perhaps through different mechanisms of action. It is possible that gonadal hormones may contribute to these differences. Indeed, estrogen is known to be important in hippocampal neurodevelopment, especially dendritic spine density (Gillies & McArthur, 2010) and several animal studies point to estrogen-related influences on the effects of THC administration on learning and memory performance (see Viveros et al., 2012). For example, chronic THC administration was found to impair learning and memory in female rats, however, the long-term behavioral and pharmacodynamic effects of THC administration were dependent on ovarian hormones, such that THC administration during adolescence increased CB1 density in the hippocampus, but only in females that were not ovariectomized in adolescence (Winsauer et al., 2011). Therefore, females may be more sensitive than males to cannabis-related hippocampal disruptions due to higher circulating estrogens, which may lead to poorer episodic memory performance in females, and our findings suggest this effect may be

dose-dependent. On the other hand, males' protracted neurodevelopment and earlier initiation of use may make them more vulnerable to cannabis-related disruptions in neuromaturation in the orbitofrontal cortex (Crane et al., In press).

Aim 3

Moreover, as we hypothesized, we found an earlier age of regular initiated use was associated with poorer immediate and delayed recall, in line with previous evidence (Pope et al., 2003; Solowij et al., 2012), but contrary to our hypotheses, these relationships were no longer significant after controlling for lifetime cumulative cannabis use. This suggests that amount of cannabis use, rather than age of initiated use, is more strongly associated with episodic memory performance. Similarly, contrary to our hypotheses, there were no relationships between age of first use and episodic memory performance.

However, significant interactions indicated that there may be important sex-differences in how age of initiated use may impact episodic memory. We found an earlier age of first use was associated with better immediate recall for males, but worse immediate recall for females and there was no significant relationship between age of first use and delayed recall for males or females. On the other hand, an earlier age of regular cannabis use was associated with poorer immediate and delayed recall for females, but not males. This evidence provides further evidence that females may be particularly vulnerable to cannabis-related hippocampal disruptions, but when taken together with our findings from Aim 2, these findings also suggest that there may be either additive or synergistic effects of age of initiated use and amount of cannabis use on episodic memory in females. Of note, we controlled for amount of lifetime cannabis use in these analyses in order to specifically parse out the individual variance of age of initiated use and its associations with neurocognition. Thus, our findings indicate that in addition to dose-related

negative effects of cannabis on episodic memory in females (as discussed above in Aim 2), an earlier age of initiated use is also independently related to poorer episodic memory performance in females. Age of initiated use (age of first use vs. age of regular use) may also have some bearing on these findings, as an earlier age of first use was only associated with immediate recall in females, while an earlier age of regular initiated use was associated with poorer immediate and delayed recall in females. Thus, age of regular initiated use may be more important than age of first use in determining episodic memory performance in female CU. It will be important for future studies to look how the relative contributions of age of regular initiated use and amount of use on episodic memory, especially in female CU.

When looking at age of initiated use and decision-making, conversely, we found no relationship with age of regular initiated use and decision-making, but after controlling for lifetime cannabis use, an earlier age of first use and an earlier age of regular initiated use was associated with better decision-making. These findings were the opposite of what was hypothesized and to our knowledge are the first to show a negative correlation between age of first use and age of regular initiated use and decision-making.

Exploratory analyses to try to understand these relationships found evidence for important sex-specific factors associated with decision-making, age of first use, and age of regular initiated use. First, simple slopes analyses found an earlier age of first use did not significantly predict decision-making in males or females, but an earlier age of regular use was associated with better decision-making in females, not in males. This suggests that females may, in part, drive the relationship between age of regular initiated use and decision-making. In addition, bivariate correlations between decision-making performance, age of initiated use, and several theoretically relevant variables found several sex-specific patterns. For example, males

showed significant positive correlations between decision-making and IQ, as well as education. In addition, males had a significant negative relationship between amount of cannabis use per year of use and decision-making, which is in line with our aforementioned findings (Aim 2) that more cannabis use is associated with poorer decision-making in males, but not in females. Thus, for males it may be that the amount of cannabis used per year during adolescence is more closely associated with decision-making performance than age of initiated cannabis use. Although speculative in nature, these findings lend support to the theory that cannabis use itself is negatively impacting decision-making in males, perhaps due to males' protracted neurodevelopment, so poorer decision-making in males cannot be solely attributed to premorbid impairments. In contrast, there were significant positive correlations between BAI and WURS total scores and decision-making performance for females, but not for males. However, after controlling for BAI and WURS in multiple moderated regression, an earlier age of regular use was still associated with better decision-making among male and female CU. Therefore, anxiety and ADHD symptoms in females may not be driving the relationship between an earlier age of initiated use and better decision-making. Further, there were no significant interactions between age of first use or age of regular use and cumulative lifetime cannabis use on decision-making performance, suggesting that heavier and lighter users did not significantly differ in how age of initiated use was associated with decision-making performance. Moreover, using a median-split of age of regular use, early and late onset CU did not differ on decision-making, nor was there an interaction between age of onset and sex. Thus, the age of initiated use does not seem to be the best predictor of decision-making performance among CU. Instead, our findings suggest that age of initiated use is associated with several different factors in a sex-specific manner, such as education and problems related to cannabis use for males, and education and mother's education

for females, which may influence decision-making in different ways. For example, as mentioned previously, it may be that for males more cannabis use per year during adolescence negatively impacts orbitofrontal cortex neurodevelopment, leading to poorer decision-making performance and more cannabis-related problems. An earlier age of cannabis use may provide more opportunities for cannabis use to negatively impact neurodevelopment, but age of initiated use does not directly impact decision-making per-se. In addition, fewer years of education was associated with poorer decision-making and an earlier age of regular use in males, indicating that males who initiate use earlier may be less educated and more susceptible to cannabis-related impairments in decision-making. Conversely, lower IQ, fewer years of education, and fewer years of mothers' education was associated with earlier use of cannabis use among females, but these factors were not associated with decision-making performance in females. We were not able to identify specific factors that may influence the relationship between an earlier age of initiated use and better decision-making in females, but it is possible that unmeasured social and environmental factors play a role (e.g., peer groups or social organizations that provide protective influences). To our knowledge, these findings are the first evidence to find a sex-specific relationship in the association between age of initiated cannabis use and neurocognition.

Conclusion

Taken together, these findings indicate there may be evidence of a dissociation in how amount of cannabis use and age of initiated use is related to decision-making and episodic memory performance among males and females. Cannabis use may adversely affect structures critical for episodic memory (e.g., hippocampus) in both males and females, but may have a greater negative impact among females. In addition, cannabis use initiated earlier in adolescence may adversely affect hippocampal neurodevelopment among females more than in males,

perhaps by disrupting estrogen-related organizational influences on hippocampal development (Gillies & McArthur, 2010). On the other hand, our preliminary results suggest that, among males, cannabis use may disproportionately affect brain structures important to decision-making (e.g., orbitofrontal cortex, amygdala, and insula). Further, several factors including IQ, education, mother's education, amount of cannabis use per year, anxiety symptoms, and ADHD symptoms seem to be related to decision-making performance and age of initiated use in a sex-specific manner, suggesting there may be sex-differences in the reasons why males and females initiate use and then continue to use cannabis.

These findings have several important implications for clinical practice and future interventions. Sex differences in how amount of cannabis use and age of initiated use are related to neurocognition in a domain-specific manner underscores the importance of examining the impact of cannabis on neurocognition separately for males and females. Further, sex differences in the neurocognitive effects of cannabis may mean different functional consequences from use and have implications for prevention and intervention efforts. For example, our group previously that found decision-making performance was associated with more symptoms of cannabis addiction (Gonzalez et al., 2012), but perhaps this relationship is stronger in males. It is possible that deficits in decision-making and reward-processing are more closely related to continued cannabis use and progression to cannabis dependence in males than in females. There may be other factors (e.g., deficits in learning and memory) that place females at risk for continued cannabis use and escalation to cannabis dependence, although the mechanisms of these relationships are not yet clear. It is possible that cannabis-related disruptions in estrogen, especially during neurodevelopment (Winsauer et al., 2011), as well as subsequent estrogen-related learned associations with cannabis use (Fattore et al., 2007), facilitate females'

progression to cannabis dependence. Therefore, males and females may have different neurocognitive vulnerabilities that place them at risk for cannabis dependence. The present study provides preliminary evidence for sex differences in how age of initiated use and amount of cannabis use may differentially impact male and female cannabis users, but more research is needed to identify the sex-specific neurocogntive profiles of males and females who are at risk for cannabis dependence and also the functional consequences of use related to the sex-specific neurocognitive profiles of male and female cannabis users. Additionally, this study found sex-specific factors related to decision-making performance and age of initiated use that may help inform future research and intervention efforts to target at risk youth in order to help to buffer against sex-specific cannabis-related disruptions in neurodevelopment and escalating cannabis use.

Although the present study has many strengths, including well matched groups of male and female NU and CU, who have minimal comorbidities or confounds and a relatively short duration of cannabis use (for CU), the study also has several limitations. First, our sample size was relatively small, which may have limited our ability to find other statistically significant relationships. Second, given the cross-sectional nature of the study, we are limited in our ability to draw causal conclusions or establish temporal relationships. Finally, we were unable to control for important hormonal influences including menstrual cycle fluctuations and contraceptive use, which have been shown to affect drug sensitivity and neurocognitive performance (Broverman et al., 1981; Gogos, 2013; Lokken & Ferraro, 2006; Lukas et al., 1996; Mordecai, Rubin, & Maki, 2008; Wright & Badia, 1999). Future studies will attempt to replicate these findings and explore some of the underlying mechanisms that may account for the observed patterns of results, including the possible role of sex hormones.

In conclusion, we found young adult CU showed deficits in immediate and delayed recall, but not decision-making, compared to NU and there were no sex differences in these relationships. However, among CU, more lifetime, past year, and past month cannabis use was associated with poorer episodic memory and decision-making. Additionally, we found preliminary evidence of a sex-specific dissociation in these relationships. Specifically, more lifetime cannabis use was associated with poorer episodic memory and this relationship was stronger in females than in males, but more lifetime and past month cannabis use predicted worse decision-making only for males, not for females. Further, we found that, surprisingly, after controlling for cumulative lifetime cannabis use an earlier age of first use and an earlier age of regular initiated use was associated with better decision-making for males and females, but poorer episodic memory for females, not males. Moreover, we found evidence for important sex-specific factors associated with decision-making, age of first use, and age of regular initiated use. These findings indicate there may be important, sex-specific differences in how amount of cannabis use and age of initiated use may affect neuropsychological functioning in male and female CU, which may mean different functional consequences from use and have implications for future prevention and intervention efforts.

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Table 1

Demographics and Mental Health

	Male NU (*n*= 33)	Male CU (*n*=44)	Female NU (*n*=33)	Female CU (*n*=25)	*p*-value
Age	20.48 (2.12)	20.75 (1.89)	20.06 (1.89)	20.72 (1.62)	0.42
Estimated FSIQ	103.46 (11.85)	102.11 (10.24)	106.24 (7.97)	102.80 (10.02)	0.37
Years of Education	13.42 (1.89)	13.34 (1.67)	13.91 (1.57)	13.64 (1.68)	0.50
Ethnicity/Race					0.67
Caucasian	31%	43%	49%	36%	
Black	30%	34%	21%	40%	
Hispanic	15%	7%	6%	16%	
Asian	15%	7%	15%	4%	
Other	9%	9%	9%	4%	
Annual Household Income in Thousands of Dollars (Md, IQR)	35 [10, 103]	26 [9, 61]	18 [5, 41]	33 [7, 94]	0.09
Mother's Education	13.67 (3.19)	14.23 (2.68)	13.97 (2.92)	14.13 (3.00)	0.86
BDI-II	6.45 (6.06)	6.07 (5.66)	5.61 (4.93)	6.16 (6.06)	0.94
BAI	6.12 (7.85)	5.84 (5.49)	6.24 (5.55)	6.52 (4.35)	0.97
WURS	6%	2%	0%	8%	0.24
BIS-11	59.24 (10.86)	59.48 (9.16)	56.67 (6.91)	59.04 (10.58)	0.58

Note: all values are means and standard deviations, unless otherwise noted; NU, non-users; CU, cannabis users; Md, Median; IQR, interquartile range; FSIQ, Full Scale IQ; BDI-II, Beck Depression Inventory-2nd Edition; BAI, Beck Anxiety Inventory; WURS, Wender-Utah Rating Scale; and BIS, Barratt Impulsiveness Scale-11th version.

Table 2

Participants Substance Use Characteristics

	NU		CU		
	Male $(33)_A$	Female $(32)_B$	Male $(44)_C$	Female $(25)_D$	Comparisons
Current (30 day) DSM-IV SUD					
Alcohol Abuse	0%	3%	11%	0%	A,D< C*
Cannabis Abuse	0%	0%	34%	28%	A,B < C, D***
Cannabis Dependence	0%	0%	27%	28%	A,B < C, D***
Lifetime DSM-IV SUD					
Alcohol Abuse	6%	6%	25%	16%	A,B < C*
Alcohol Dependence	3%	3%	2%	4%	*ns*
Cannabis Abuse	0%	0%	41%	44%	A,B < C, D***
Cannabis Dependence	0%	0%	34%	28%	A,B < C, D***
Age of first cannabis use	-	-	15.80 (2.12)	16.29 (2.35)	*ns*
Age of regular initiated cannabis use	-	-	17.36 (1.98)	17.96 (2.32)	*ns*
Years of cannabis use	-	-	5.18 (2.44)	4.68 (2.14)	*ns*
Days since last cannabis use	-	-	4.18 (4.05)	5.52 (8.45)	*ns*
% THC+	0%	0%	77%	76%	A,B < C, D***
Lifetime ***(not including the past year)*** [MD, IQR]					
Alcoholic drinks	29 [1, 168.50]	31 [1.5, 107]	457 [113.50, 758.25]	166 [34, 1248.50]	B< C*
Cigarettes	0 [0, 24.50]	0 [0,0]	1032.50 [0, 4907.63]	514 [0, 2839]	B< C,D*
Cannabis (grams)	0 [0, 0]	0 [0, 0]	418.25 [88.95, 1539.07]	288 [93.8, 1168.80]	A,B < C, D***
Past Year ***(not including the past month)*** [MD, IQR]					
Alcoholic drinks	20 [0, 91.50]	18 [6, 135]	122 [21.75, 260.25]	78 [23, 190.50]	A,B< C*; A< C,D*
Cigarettes	0 [0, 0]	0 [0, 0]	52.50 [0.25, 1323.50]	45 [0, 466]	A,B < C*
Cannabis (grams)	0 [0, 0]	0 [0, 0]	109.25 [46.98, 405]	82.50 [21.95, 366.35]	A,B < C, D***
Past 30 days [MD, IQR]					
Alcohol drinks	2 [0, 9.50]	4 [0, 18]	11.50 [2.25, 20.75]	3 [0.50, 15]	A< C**
Cigarettes	0 [0, 0]	0 [0, 0]	6 [0, 90]	7 [0, 45]	B < C, D*
Cannabis (grams)	0 [0, 0]	0 [0, 0]	10.75 [5.15, 36.68]	12 [2.38, 33.55]	A,B < C, D***

Note. All values are means and standard deviations, unless otherwise noted; NU, non-users; CU, cannabis users; Md, Median; IQR, interquartile range; DSM-IV SUD, Diagnostic and Statistical Manual IV substance use disorders; THC+, positive rapid urine toxicology testing; *, p <.05; **, p <.01; ***, p <.001.

Table 3

Hierarchical Moderated Regression Models for Predicting How Amount of Cannabis Use and Sex Affect Neurocognition

Variable	***Lifetime***			***Past Year***			***Past Month***		
	R^2	β	*p*	R^2	β	*p*	R^2	β	*p*
HVLT (Immediate Recall)									
Block 1- Amount of Cannabis Use	0.13	-0.36	***.003***	0.07	-0.26	***.03***	0.07	-0.25	***.04***
Block 2- Sex	0.13	-0.02	.89	0.07	0.000	.99	0.07	0.02	.88
Block 3- Cannabis Use x Sex	0.15	-0.18	.19	0.07	-0.04	.77	0.07	0.05	.78
HVLT (Delayed Recall)									
Block 1- Amount of Cannabis Use	0.22	-0.47	***.001***	0.10	-0.32	***.007***	0.12	-0.35	***.003***
Block 2- Sex	0.22	-0.07	.54	0.11	-0.05	.70	0.12	-0.02	.84
Block 3- Cannabis Use x Sex	0.26	-0.23	***.07***	0.13	-0.18	.24	0.13	-0.11	.47
IGT (Net Total)									
Block 1- Amount of Cannabis Use	0.07	-0.27	***.03***	0.18	-0.34	***.004***	0.12	-0.35	***.003***
Amount of Alcohol Use	--	--	n/a		0.24	***.04***	--	--	n/a
Block 2- Sex	0.07	-0.02	.85	0.18	0.00	.99	0.12	0.004	.97
Block 3- Cannabis Use x Sex	0.12	0.27	***.057***	0.21	0.23	.12	0.16	0.26	***.099***

Note. The sex variable was dummy coded, with males serving as the referent group; covariates were only included in models in which they were significant; HVLT, Hopkins Verbal Learning Task; IGT, Iowa Gambling Task; n/a, non-applicable; bold and italicized p-values are significant or trending significant.

Table 4

Hierarchical Moderated Regression Models for Predicting How Age of Initiated Cannabis Use and Sex Affect Neurocognition

Variable	***Age of 1st Use***			***Age of Regular Use***		
	R^2	β	*p*	R^2	β	*p*
HVLT (Immediate Recall)						
Block 1- Age	0.01	0.08	.53	0.05	0.22	***.07***
Block 2- Age (controlling for lifetime cannabis use)	0.13	-0.02	.91	0.14	0.11	.36
Sex	--	-0.03	.83	--	-0.03	.81
Amount of Lifetime Cannabis Use	--	-0.37	***.004***	--	-0.32	***.01***
Block 3- Age x Sex	0.22	0.38	***.01***	0.22	0.38	***.01***
HVLT (Delayed Recall)						
Block 1- Age	0.01	0.10	.43	0.05	0.23	***.06***
Block 2- Age (controlling for lifetime cannabis use)	0.19	-0.01	.92	0.22	0.09	.44
Sex	--	-0.05	.65	--	-0.08	.49
Amount of Lifetime Cannabis Use	--	-0.44	***.001***	--	-0.44	***.001***
Block 3- Age x Sex	0.25	0.32	***.03***	0.26	0.25	***.09***
IGT (Net Total)						
Block 1- Age	0.03	-0.16	.19	0.01	-0.10	.41
Block 2- Age (controlling for lifetime cannabis use)	0.16	-0.26	***.04***	0.14	-0.23	***.07***
Sex	--	-0.02	.88	--	0.00	.99
Amount of Lifetime Cannabis Use	--	-0.38	***.002***	--	-0.38	***.003***
Block 3- Age x Sex	0.16	-0.05	.76	0.17	-0.23	.14

Note. The sex variable was dummy coded, with males serving as the referent group; covariates were only included in models in which they were significant; HVLT, Hopkins Verbal Learning Task; IGT, Iowa Gambling Task; n/a, non-applicable; bold and italicized p-values are significant or trending significant.

Table 5

Bivariate correlations with Decision-Making Performance for Male CU

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. IGT Net Total													
2. Age of 1st Use	-0.10												
3. Age of Regular Initiated Use	0.07	0.72											
4. FSIQ	0.34	-0.08	0.07										
5. Education	0.34	0.17	0.29	0.21									
6. Mother's Education	0.09	-0.14	0.09	0.15	-0.03								
7. Current Annual Household Income	0.03	-0.01	-0.04	0.03	0.11	0.05							
8. BDI Total	-0.13	-0.14	-0.03	0.10	0.01	0.01	-0.34						
9. BAI Total	0.08	0.02	0.06	0.15	0.02	-0.15	-0.19	0.62					
10. BIS Total	-0.23	-0.15	-0.25	0.03	-0.31	0.07	-0.18	0.27	0.25				
11. WURS Total	-0.16	-0.11	-0.12	0.17	-0.35	-0.13	-0.26	0.47	0.32	0.44			
12. Amount of Cannabis Use (sq) per Year of Use	-0.31	0.13	-0.03	-0.04	-0.49	-0.12	0.04	-0.08	-0.03	0.34	0.37		
13. Marijuana Problems Scale Total	-0.13	-0.32	-0.22	0.13	-0.17	-0.20	-0.20	0.57	0.54	0.33	0.64	0.35	

Note. IGT, Iowa Gambling Task; FSIQ, Full Scale IQ; BDI-II, Beck Depression Inventory-2nd Edition; BAI, Beck Anxiety Inventory; WURS, Wender-Utah Rating Scale; and BIS, Barratt Impulsiveness Scale-11th version; *ns*, non-significant; $p < .10$; $p < .05$.

Table 6

Bivariate correlations with Decision-Making Performance for Female CU

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. IGT Net Total													
2. Age of 1st Use	-0.26												
3. Age of Regular Initiated Use	-0.35	0.75											
4. FSIQ	0.09	0.36	0.44										
5. Education	-0.15	0.51	0.54	0.65									
6. Mother's Education	0.16	0.54	0.42	0.31	0.40								
7. Current Annual Household Income	0.31	-0.17	-0.16	0.44	-0.04	0.12							
8. BDI Total	0.30	-0.12	-0.09	0.22	0.10	0.34	0.16						
9. BAI Total	0.36	-0.23	-0.20	0.17	0.04	0.08	0.05	0.54					
10. BIS Total	0.23	-0.21	-0.24	-0.24	-0.34	0.00	0.03	0.35	0.25				
11. WURS Total	0.44	0.06	-0.23	-0.01	-0.10	-0.18	0.02	0.04	0.36	0.47			
12. Amount of Cannabis Use (sq) per Year of Use	-0.07	0.27	0.10	-0.20	-0.22	0.16	-0.20	-0.11	-0.22	0.10	-0.11		
13. Marijuana Problems Scale Total	-0.01	-0.19	-0.08	0.17	0.01	-0.31	0.19	0.36	0.21	0.43	0.23	-0.03	

Note. IGT, Iowa Gambling Task; FSIQ, Full Scale IQ; BDI-II, Beck Depression Inventory-2nd Edition; BAI, Beck Anxiety Inventory; WURS, Wender-Utah Rating Scale; and BIS, Barratt Impulsiveness Scale-11th version; *ns*, non-significant; $p < .10$; $p < .05$.

Table 7

Exploratory Analyses Using Hierarchical Moderated Regression Models for Understanding the Relationship Between Age of Initiated Cannabis Use and Amount of Cumulative Cannabis Use

Variable	***Age of 1st Use***			***Age of Regular Use***		
	R^2	β	*p*	R^2	β	*p*
HVLT (Immediate Recall)						
Block 1- Age	0.13	-0.02	.89	0.14	0.11	.37
Cumulative Lifetime Cannabis Use	--	-0.37	***.003***	--	-0.32	***.01***
Block 2- Cannabis Use x Age	0.14	-0.11	.35	0.15	-0.11	.33
HVLT (Delayed Recall)						
Block 1- Age	0.19	-0.02	.89	0.22	0.08	.49
Cumulative Lifetime Cannabis Use	--	-0.44	***.001***	--	-0.43	***.001***
Block 2- Cannabis Use x Age	0.20	-0.12	.31	0.23	-0.13	.23
IGT (Net Total)						
Block 1- Age	0.16	-0.26	***.03***	0.14	-0.23	***.07***
Cumulative Lifetime Cannabis Use	--	-0.38	***.004***	--	-0.38	***.003***
Block 2- Cannabis Use x Age	0.18	0.14	.22	0.16	0.14	.22

Note. The sex variable was dummy coded, with males serving as the referent group; HVLT, Hopkins Verbal Learning Task; IGT, Iowa Gambling Task; bold and italicized p-values are significant or trending significant.

Table 8

Overall findings

	Group Differences	**Increased Amount of Cannabis Use**		**Earlier Age of Initiated Use**		**Factors Associated with Decision-Making & Age of Initiated Use**	
		Male CU	Female CU	Male CU	Female CU	Male CU	Female CU
Episodic Memory							
	CU < NU No sex differences No interaction	↓ immediate recall across all periods of use ↓ delayed recall across all periods of use	↓ immediate recall across all periods of use ↓ delayed recall across all periods of use (relationship is stronger among females)	↑ immediate recall for age of first use ↓ delayed recall for age of first use	↓ immediate for age of first use & age of regular use ↓ delayed recall for age of first use & age of regular use	--	--
Decision-Making							
	No group difference No sex difference No interaction	↓ for past year use ↓ for past month & lifetime use	↓ for past year use	↑ for age of first use & age of regular use	↑ for age of first use & age of regular use (some evidence that females may drive this relationship)	<u>↑ IGT</u>: -↑ IQ -↑ education -↓ cannabis use/per year <u>↓ Age</u>: -↓ education -↑ problems from cannabis use	<u>↑ IGT</u>: -↓ age of regular use -↑ BAI -↑ WURS <u>↓ Age</u>: -↓ education -↓ IQ -↓ mother's education

Note. CU, cannabis users; NU, non-users; BAI, Beck Anxiety Inventory; WURS, Wender-Utah Rating Scale.

Figure 1

Interactions between Amount of Lifetime Cannabis Use and Sex on Delayed Recall Performance

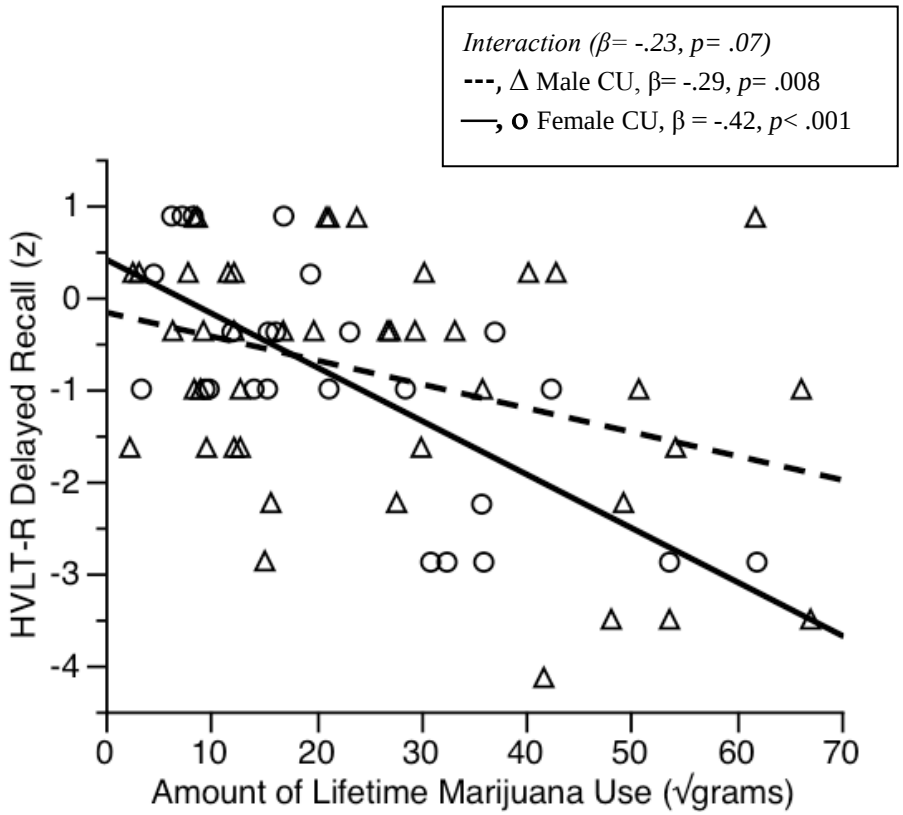


Figure 2

Interactions between Amount of Cannabis Use and Sex on Decision-Making Performance

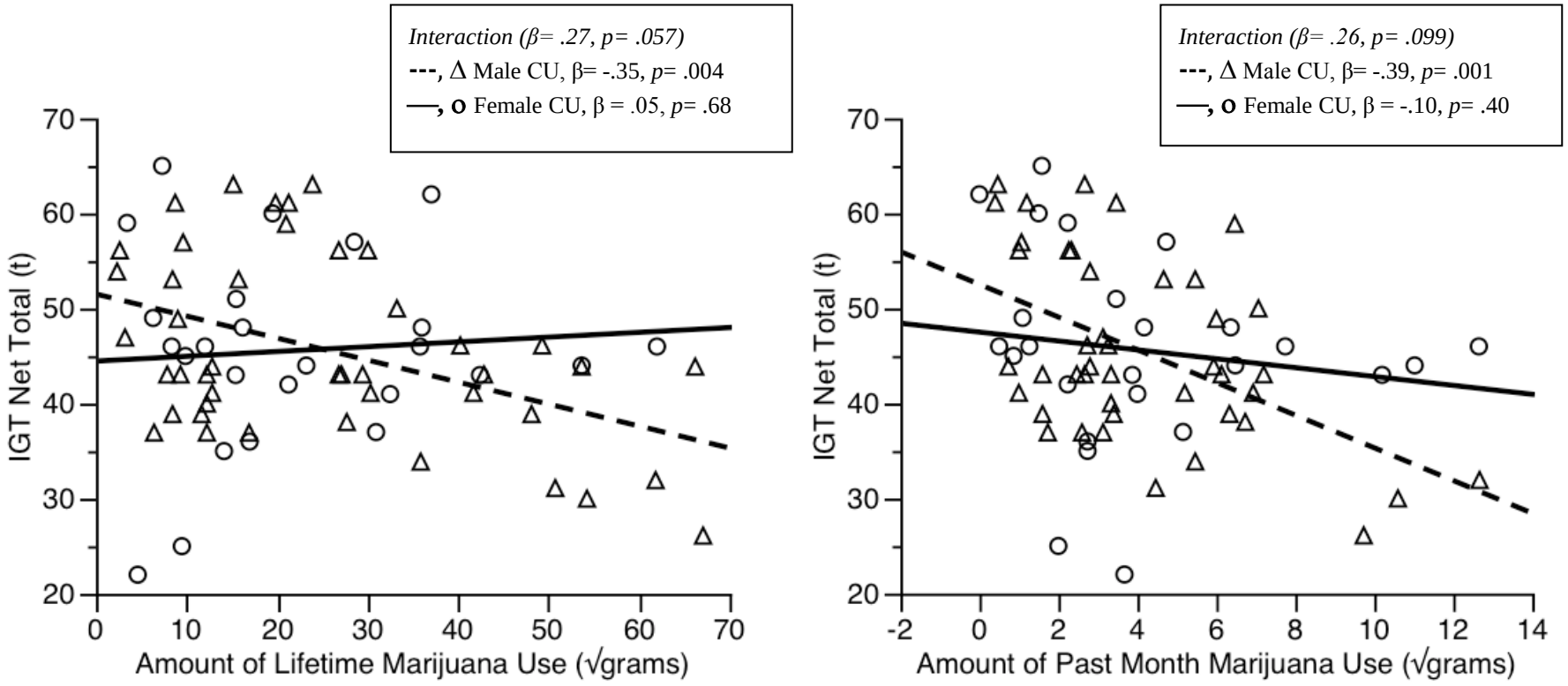


Figure 3

Interactions between Age of Initiated Cannabis Use and Sex on Immediate Recall Performance

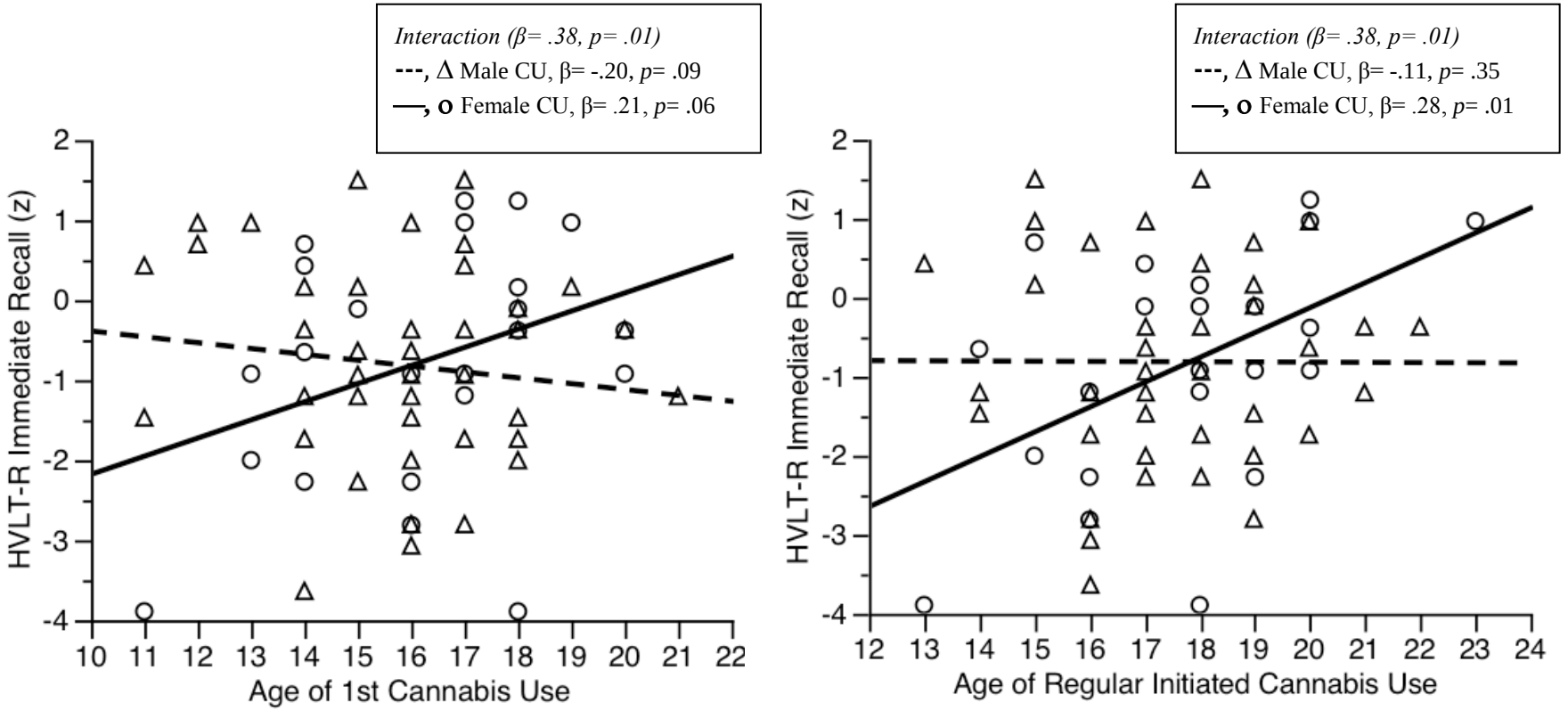


Figure 4

Interactions between Age of Initiated Cannabis Use and Sex on Delayed Recall Performance

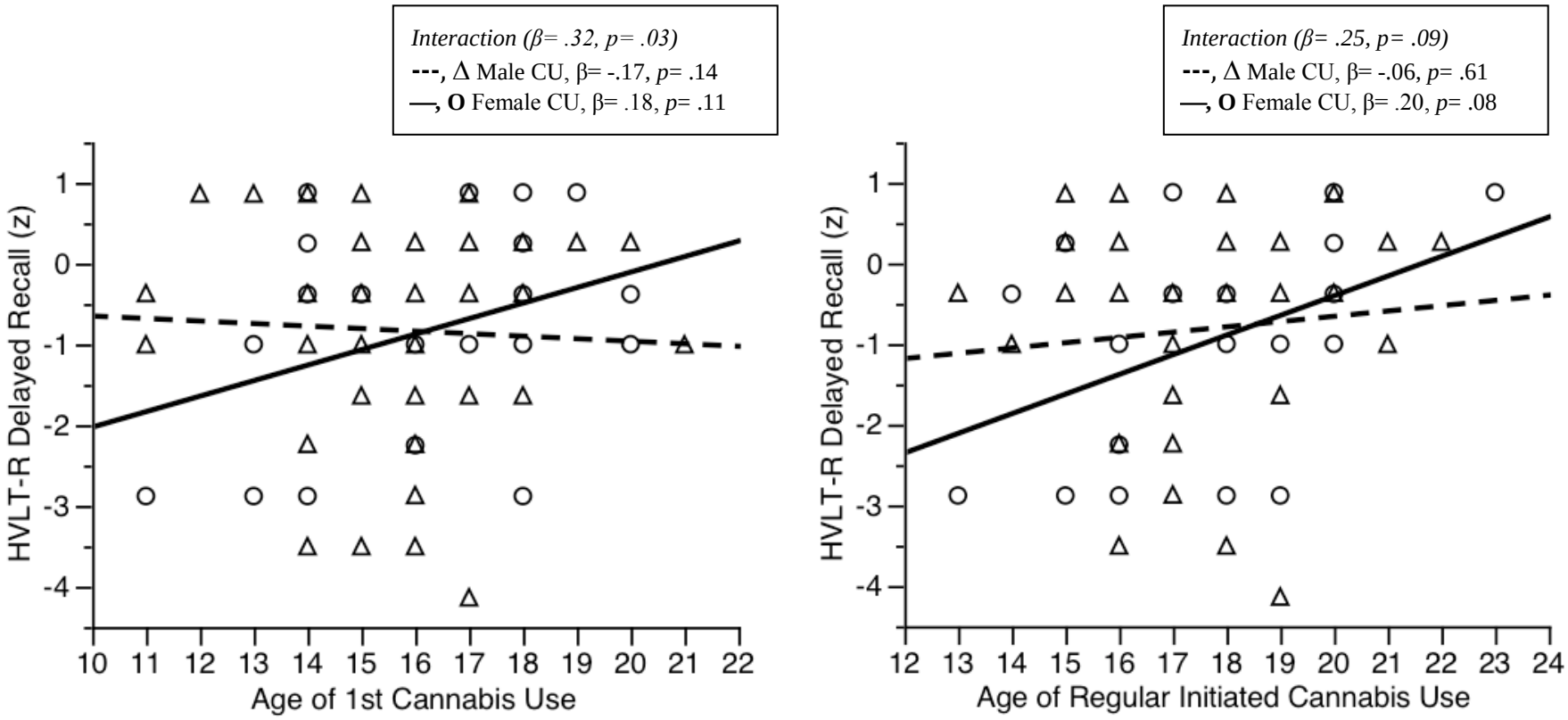
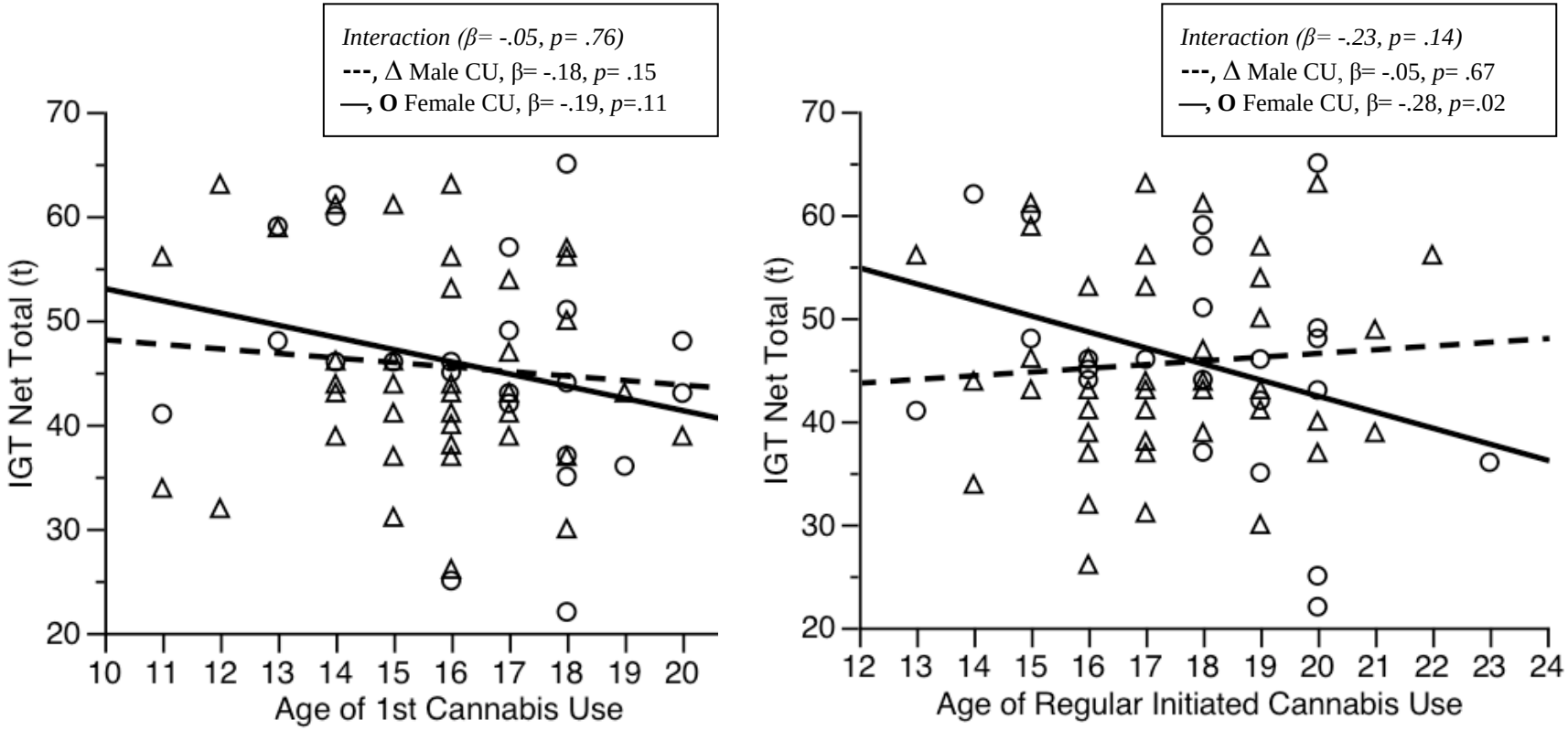


Figure 5

Interactions between Age of Initiated Cannabis Use and Sex on Decision-Making Performance



UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval Notice
Amendment to Research Protocol and/or Consent Document – Expedited Review
UIC Amendment # 4

May 4, 2012

Raul Gonzalez, PhD
Psychiatry
1601 W.Taylor Street, Room 408
M/C 912
Chicago, IL 60612
Phone: (312) 413-5956 / Fax: (312) 413-8147

RE: Protocol # 2008-0969
"Neurocognitive Disinhibition and Cannabis Addiction: Adult Protocol"

Dear Dr. Gonzalez:

Members of Institutional Review Board (IRB) #1 have reviewed this amendment to your research and/or consent form under expedited procedures for minor changes to previously approved research allowed by Federal regulations [45 CFR 46.110(b)(2)]. The amendment to your research was determined to be acceptable and may now be implemented.

Please note the following information about your approved amendment:

Amendment Approval Date: May 3, 2012

Amendment:

Summary: UIC Amendment #4, dated April 17, 2012 (received April 26, 2012), is an amendment to add Ms. Natania Crane as Key Research Personnel.

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
04/26/2012	Amendment	Expedited	05/03/2012	Approved

Please be sure to:

→ Use your research protocol number (2008-0969) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,

"UIC Investigator Responsibilities, Protection of Human Research Subjects"

Please note that the UIC IRB #1 has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact the OPRS at (312) 996-1711 or me at (312) 413-7323. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Jennifer Joaquin, MPH, CIP
Assistant Director, IRB # 1
Office for the Protection of Research Subjects

Enclosure(s):

1. **UIC Investigator Responsibilities, Protection of Human Research Subjects**

cc: Anand Kumar, Psychiatry, M/C 912

Natania Anne Crane

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EDUCATION

2011-Present	**UNIVERSITY OF ILLINOIS AT CHICAGO (UIC)**	**Chicago, IL**
	Doctoral Program in Clinical Psychology Masters of Arts (received March 2013) Doctor of Philosophy (expected May 2017)	
2004-2008	**NORTHEASTERN UNIVERSITY**	**Boston, MA**
	Bachelor of Arts Major: Psychology Cum Laude	

AWARDS/HONORS

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*

PUBLICATIONS (*n=5*)

- **Crane, N.A.**, Schuster, R.M., Fusar-Poli, P., Gonzalez, R. (2013). Effects of Cannabis on Neurocognitive Functioning: Scientific Updates, Neurodevelopmental Factors, and Sex Differences. *Neuropsychology Review,* 23(2): 117-137.

- Schuster, R.M., **Crane, N.A.**, Mermelstein, R., & 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.

- 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.

- 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.

- 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.

MANUSCRIPTS UNDER REVIEW & IN PREPARATION (*n=4*)

- **Crane, N.A.,** Schuster, R.M., & Gonzalez, R. (under review). Preliminary Evidence for a Sex-Specific Relationship between Amount of Cannabis Use and Neurocognitive Performance.

- Schuster, R. M., **Crane, N.A.**, Mermelstein, R., & Gonzalez, R. (under review). Compensatory Effects of Tobacco on Episodic Memory among Young Adult Cannabis Users.

- Heinz, A.J., Giedgowd, G.E., **Crane, N.A.**, Conrad, M., Braun, A.R., Veilleux, J.C., Olejarska, N.A., & Kassel, J.D. (under review). An examination of hookah smoking in college students: Use patterns and

contexts, social norms and attitudes, harm perception, psychological correlates and co-occurring substance use.

- Meyers, K., **Crane, N.A.,** O'Day, R., Zubieta, J.K., Pomerleau, C.S., Horowitz, J.C., & Langenecker, S.A. (in preparation). The Impact of Smoking History and Depression on Executive Functioning and Emotional Processing.

***ABSTRACTS, SYMPOSIA, AND POSTER PRESENTATIONS* (*n=16*)**

- Gonzalez, R., Schuster, R.M, & **Crane, N.A.** *The Impact of Decision-Making Performance and ADHD Symptoms on Cannabis-Related Problems Among Emerging Adults.* Symposia to be presented at the 23rd Annual International Cannabinoid Research Society Sympoisum on the Cannabinoids, Vancouver, British Columbia, Canada.

- **Crane, N.A.**, Schuster, R.M., & Gonzalez, R. *Sex Differences in Associations between Age of Initiated Cannabis Use and Neuropsychological Performance*. To be presented as an oral communication at the 75th annual meeting of the College on Problems of Drug Dependences, San Diego, CA**.**

- **Crane, N.A.,** Meyers, K., O'Day, R., Zubieta, J.K., Pomerleau, C.S., Horowitz, J.C., & Langenecker, S.A. *The Impact of Smoking History and Depression on Executive Functioning and Emotional Processing.* To be presented at the Society of Biological Psychiatry's 68th Annual Meeting, San Francisco, CA.

- **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**.**

- 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**.**

- 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**.**

- 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.

- **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.

- 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.

- 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.

- 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.

- 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.

- 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.

- 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.

- 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.

- 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.

SCIENTIFIC ACTIVITIES

Ad Hoc Journal Reviewer
2013 *Drug and Alcohol Dependence*

Professional Memberships
American Psychological Association- Division 40

RESEARCH POSITIONS

UNIVERSITY OF ILLINOIS AT CHICAGO *August 2012-*
DEPARTMENT OF PSYCHIATRY *Present*
Graduate Research Assistant, Cognitive Neuroscience Center
Grant Funding: *NIMH- R01 MH091811 (BRAINS Award) & K23 RR017607*

- 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, collaboration on publications and conference presentations.
- Supervisor: *Scott Langenecker, Ph.D.*

UNIVERSITY OF ILLINOIS AT CHICAGO *May 2012-*
DEPARTMENT OF PSYCHOLOGY *Present*
Graduate Research Assistant, Substance Abuse Research Laboratory
Grant Funding: *NCI- P01 CA098262*

- 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.
- Supervisor: *Jon Kassel, Ph.D.*

UNIVERSITY OF ILLINOIS AT CHICAGO *August 2011-*
DEPARTMENT OF PSYCHIATRY *Present*
Graduate Research Assistant, Cannabis Addiction and Neurocognition
Grant Funding: *NIDA- K23 DA023560*

- 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.*

THE SCRIPPS RESEARCH INSTITUTE *Aug. 2008-*
THE COMMITTEE ON THE NEUROBIOLOGY OF ADDICTIVE DISORDERS *July 2011*
Sub-Investigator & Study Coordinator, Laboratory of Clinical Psychopharmacology
Grant Funding: *NIDA- R01 DA026758, R01 DA030988-01, & P20 DA024194-03; NIAAA- R01 AA012602*

- Randomized clinical trials on the efficacy of neuropharmacological interventions for the treatment of cannabis dependence
    - 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, and medication distribution. Collaborated on publications and conference presentations.
- Longitudinal study examining the neurobiology of cannabis dependence
    - 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.
- Human laboratory cue-reactivity study for medication development for protracted abstinence in alcoholism
    - Led recruitment and patient contact, including interviews, psychophysiological assessment, fMRI behavioral paradigms, and medication distribution. Assisted in creation and maintenance of IRB materials and developed protocol materials in collaboration with the PI. Assisted in data collection and management. Ran fMRI scans as a certified operator at UCSD's Keck Center for Functional Imaging.
- Supervisor: *Barbara Mason, Ph.D., Rebecca Crean, Ph.D.*

NORTHEASTERN UNIVERSITY *April 2007-*
DEPARTMENT OF PSYCHOLOGY *June 2008*
Laboratory Research Assistant, Melloni Aggression Lab

- Animal laboratory 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, 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, 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.*

NORTHEASTERN UNIVERSITY *Jan. 2008-*
DEPARTMENT OF PSYCHOLOGY *June 2008*
Student Laboratory Research Assistant, Jay McLaughlin's Laboratory

- Animal study examining kappa-opioid mediation of stress-induced potentiation of cocaine-conditioned place preference and self-administration
    - Ran behavioral paradigms including Conditioned Place Preference, Tail Flick Assays, Forced Swim Tests, and Competition binding assay. Performed bioassays including Polymerase Chain Reaction and Restriction Enzyme Digest.
- Supervisor: *Jay McLaughlin, Ph.D.*

NEUROPSYCHOLOGICAL CLINICAL EXPERIENCE

UNIVERSITY OF ILLINOIS AT CHICAGO *August 2012-*
Clinical Assessment Practicum Student, Office of Applied Psychological Services (OAPS) *Present*

- Neuropsychological and psychodiagnostic test administration to ethnically and economically diverse children, adolescents, and adults
- Responsible for selecting, administering, scoring and interpreting assessments. Communicated test results, interpretations, and recommendations to clients. Provided referrals to clients based on the assessment
- Supervisor: *Amanda Lorenz, Ph.D., Ellen Herbener, Ph.D.*

PSYCHOTHERAPY CLINICAL EXPERIENCE

UNIVERSITY OF ILLINOIS AT CHICAGO *August 2011-*
Clinical Therapy Practicum Student, Office of Applied Psychological Services (OAPS) *Present*

- Conduct intake interviews, formulate treatment plans, and provide psychotherapy to adult, adolescent and child outpatient populations presenting with a variety of emotional, behavioral, and personality disorders.
- Extensive experience in individual and couple treatment modalities
- Therapeutic approaches include cognitive-behavioral, emotion-focused, interpersonal, motivational interviewing, and mindfulness- and acceptance-based approaches.
- Weekly group and individual supervision involving review of video recordings.
- Supervisors: *Amanda Lorenz, Ph.D., Gloria Balague, Ph.D. & Evelyn Behar, Ph.D.*

UNIVERSITY OF ILLINOIS AT CHICAGO *August 2012-*
DEPARTMENT OF PSYCHIATRY *Present*
Graduate Research Assistant, Cognitive Neuroscience Center

- Administer the Diagnostic Interview for Genetic Studies (DIGS) to individuals with mood disorders.
- Supervisor: *Scott Langenecker, Ph.D.*

THE SCRIPPS RESEARCH INSTITUTE *Aug. 2008-*
Sub-Investigator & Study Coordinator, Laboratory of Clinical Psychopharmacology *July 2011*

- Provide Cognitive Behavioral Therapy and Motivational Enhancement Therapy to treatment-seeking, cannabis dependent participants
- Administer the Structured Clinical Interview for DSM-IV (SCID) to substance dependent adults
- Supervisor: *Barbara Mason, Ph.D., Rebecca Crean, Ph.D.*

BOSTON MEDICAL CENTER *July 2007-*
Patient Safety Associate, Emergency Department, Psychiatric Ward *June 2008*

- 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

TEACHING EXPERIENCE

UNIVERSITY OF ILLINOIS AT CHICAGO *Aug. 2011-*
DEPARTMENT OF PSYCHOLOGY *May 2012*

*Teaching Assistant***,** Introduction to Psychology- Fall 2011

- Professor: *Mike Rosanova, Ph.D.*

*Teaching Assistant***,** Introduction to Research Methods in Psychology- Spring 2012

- Professor: Evelyn Behar, Ph.D.