PHARMACOLOGICAL APPROACHES TO REMEDIATE NEUROCOGNITIVE IMPAIRMENT IN COCAINE-DEPENDENT INDIVIDUALS

A Dissertation Presented to the
Faculty of the College of Education
University of Houston

In Partial Fulfillment
of the Requirements for the Degree

Doctor of Philosophy

by

James J. Mahoney, III

May 2014

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Mahoney, III, James J. Pharmacological Approaches to Remediate Neurocognitive Impairment in Cocaine-Dependent Individuals

Abstract

The goal of this study was to determine whether demographic (e.g. ethnicity, gender, etc.), drug use (e.g. years of cocaine use, days cocaine used in the past 30, comorbid substance use, etc.), or mood (BDI-II, LSC-R, and ASI-Lite scores) variables affected neurocognitive functioning in cocaine-dependent participants. In addition, two candidate medications were evaluated to assess whether they have the potential to improve neurocognitive functioning in cocaine-dependent individuals. There were two separate studys as part of this dissertation. Study 1 involved the investigation of demographic and drug use variables contributing to neurocognitive deficits in 125 cocaine dependent individuals. Study 2 compared the efficacy of two acetylcholinesterase inhibitors: rivastigmine and huperzine (as well as a control group randomized to receive placebo) as potential treatments for cocaine-induced neurocognitive impairment. Twenty-eight individuals were randomized to receive rivastigmine, 29 were randomized to receive huperzine, and 15 were randomized to receive placebo. Before study medication randomization, participants completed a battery of neurocognitive assessments and completed the same battery of assessments following 8 days of medication/placebo treatment. One of the factors that detrimentally affects cocaine-dependent individuals as they seek treatment is the presence of neurocognitive deficits produced or exacerbated by cocaine use. Since long-term, high-dose cocaine use is a risk factor for the onset of neurocognitive impairment in humans, it is critical that these deficits be addressed in order to improve treatment outcomes. Study 1 utilized only baseline data (independent of any medication treatment) and Study 2 used both pre-treatment (baseline, before

medication administration) and post-treatment (following medication administration) data. Pearson product moment correlations and analysis of variance (ANOVA) were used to evaluate the association between demographic and drug use variables and performance on the neurocognitive measures. ANOVA was used to evaluate medication versus placebo effects on test performance pre- and post-treatment. Study 1 revealed that there were no gender or race differences in neurocognition between groups. Further, comorbid substance use (e.g. nicotine, alcohol, or marijuana) did not affect neurocognition. Study 2 showed that treatment with rivastigmine significantly improved episodic memory, though treatment with huperzine did not affect neurocognition. On the basis of outcomes from Study 1 and Study 2, we contend that cocaine associated neurocognitive impairment remains an important target of treatment. Given that cocaine addiction is associated with widespread functional difficulties, such as unemployment and relapse to dependence, it is plausible that reversing neurocognitive impairments will ameliorate these functional difficulties.

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CHAPTER I

INTRODUCTION

A. THE PROBLEM AND DEFINITION OF COCAINE-DEPENDENCE

Cocaine is one of the most commonly abused psychoactive substances in North America. Before understanding the consequences and repercussions of cocaine use and the behavioral manifestations which coincide with cocaine dependence, one must first understand what cocaine dependence entails. As defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR; American Psychiatric Association, 2000), cocaine dependence includes a maladaptive pattern of substance use leading to clinically significant distress, as manifested by *three* (or more) of the following, occurring within a 12-month period: 1) tolerance to the cocaine (a need for more amounts of the cocaine to achieve intoxication or a diminished effect with continued use of the same amount of the drug); 2) withdrawal from the cocaine (including taking more cocaine to avoid symptoms of withdrawal); 3) taking more cocaine in larger amounts or over a longer period than originally intended; 4) a persistent desire or unsuccessful efforts to cut down on cocaine usage; 5) a great deal of time spent in activities necessary to obtain the cocaine (contacting and meeting suppliers), using the cocaine (repeatedly using cocaine) and recovering from the effects produced by cocaine (during withdrawal); 6) important social, occupational, or recreational activities given up or reduced because of cocaine use; 7) cocaine use continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

CHAPTER II

REVIEW OF RECENT LITERATURE

A. NEUROCOGNITIVE DEFICITS AND COCAINE-DEPENDENCE

One of the factors that impedes on treatment success for cocaine-dependent individuals is the presence of neurocognitive deficits produced or exacerbated by cocaine use. Long-term, high-dose cocaine use is a risk factor for the onset of neurocognitive impairment in humans (e.g. Bolla & Cadet, 2007; Jovanovski, Erb, & Zakzanis, 2005). Jovanovski (2005) conducted a meta-analytic review (15 studies that included 586 matched controls and 481 abstinent cocaine users), which revealed effect sizes of moderate or greater magnitude for attention, episodic memory, and working memory, demonstrating that cocaine-dependent individuals experience dysfunction in these domains. Specifically, these neurocognitive impairments affect day-to-day functioning; for example, the presence of cocaine-associated neurocognitive impairment is associated with poor treatment retention (Aharonovich, Amrhein, Bisaga, Nunes, & Hasin, 2008).

These neurocognitive deficiencies are critical as they affect treatment and cocaine abstinence. For example, if there are deficits in attention, cocaine-dependent individuals may be unable to maintain focus, attend, and follow through on treatment plans and goals provided during the therapy process. In addition, if there are deficits in episodic memory, these individuals may have a difficult time remembering both the positive and negative events (including triggers) in their life or specific techniques taught during treatment that may also impede their progress. Also, if their cocaine use has caused deficits in working memory, reasoning, and comprehension, then it is possible that information processing will be affected adversely. Thus, it is important to take all of these factors and

neurocognitive deficiencies into consideration when attempting to treat someone with cocaine-dependence.

It also is important to consider possible drug use and demographic variables that may play a role in neurocognitive functioning. Previous investigations suggested that, in nondrug using individuals, gender moderates neurocognition. In one report of healthy individuals, males performed significantly better than females in spatial and object versions of the n-back working memory task (Lejbak, Crossley, & Vrbancic, 2011). Also, males tended to perform slightly better than females on the Iowa Gambling Task, a measure of decision making and executive functioning (Bechara & Martin, 2004; Bolla, Eldreth, Matochik, & Cadet, 2004). In addition, males performed significantly better than females on several visuospatial tests, including mental rotation (Peters, Manning, & Reimers, 2007), fine motor tasks (Nicholson & Kimura, 1996), and spatial navigation memory (Rahman, Wilson, & Abrahams, 2003; Voyer, Voyer, & Bryden, 1995). Conversely, when comparing the performance on tasks focused on verbal memory, females have performed significantly better than males in verbal recall tasks across different age groups (Bleecker, Bolla-Wilson, Agnew, & Meyers, 1988). Similarly, females were significantly better than men on tests of verbal memory, perceptual speed, and spatial memory for object locations (Herlitz, Nilsson, & Backman, 1997; Rahman et al., 2003). However, the often cited female advantage in verbal fluency is less clear, with the advantage apparent on specific semantic items and higher order category fluency (e.g. Rahman, van Turennout, & Levelt, 2003), but less apparent on letter fluency (Herlitz et al., 1997).

While the literature on gender differences and neurocognitive performance in stimulant dependent individuals is sparse, the topic is of considerable interest considering the differential effects stimulant use has on male versus female users, especially considering that the results from published reports are mixed. For example, long-term cocaine use is associated with more debilitating effects on women (Anker & Carroll, 2011), and this finding may extend to differences in neurocognition. Conversely, Rahman and Clarke (2005) found that among recreational cocaine users who had been abstinent for three days, males exhibited poorer attention and more verbal recognition errors than female users. In addition, in a meta-analytic review by Scott and colleagues (2007), the primary conclusion was that methamphetamine may differentially affect cognitive function in males compared to females. In a separate report, it was found that there were no overall gender differences with regard to neurocognition, specifically in the domains of verbal learning and memory (Chang et al., 2005). Conversely, Price and colleagues found that female cocaine users had fine motor impairment, and this may be attributed to frequency of use in the months prior to testing (Price et al., 2011).

While the role of race variability on the neurocognitive performance of cocaine-dependent individuals is not well described in the literature, it has been reported that, in non-drug using, neurologically normal individuals, African Americans tend to perform more poorly than Caucasians on tests of cognitive functioning (Ford, Haley, Thrower, West, & Harrell, 1996; Kuller et al., 1998; Manly et al., 1998). The data suggest that African Americans may be at greater risk to be misdiagnosed with learning disabilities or general cognitive impairment. There are several possible reasons for this disparity, including parental influence and early educational experiences. Specifically, African

Americans with lower neurocognitive functioning were more likely than their Caucasian counterparts to have parents who did not graduate from high school and reported having non-reading related disabilities (Byrd, Walden Miller, Reilly, Weber, Wall, & Heaton, 2006). While race differences regarding neurocognition have been noted in healthy controls, there have not yet been any published studies investigating this factor in cocaine-dependent individuals.

Previous research suggests that the length of abstinence from cocaine affects neurocognitive functioning in cocaine-dependent participants. For example, on one particular test of executive function, impairment was noted 2-4 weeks following the last cocaine use (Ardila, Rosselli, & Strumwasser, 1991) whereas this impairment was not present during shorter periods of abstinence (within 3 days of last drug use) (Berry et al., 1993). Another factor that needs to be considered as well is co-morbid substance abuse, including cigarettes, alcohol, and marijuana. When compared to healthy control subjects, cocaine-dependent individuals are more likely to smoke cigarettes, and the frequency of cigarette smoking is positively correlated with their concurrent use of cocaine (Budney, Higgins, Hughes, & Bickel, 1993; Roll, Higgins, Budney, Bickel, & Badger, 1996). Neurocognitive deficits, including attention, memory, executive and motor functions, are commonly impaired in alcohol-dependent individuals (Beatty, Tivis, Stott, Nixon, & Parsons, 2000; Ikeda et al., 2003; Parsons & Nixon, 1993); however, there has not been a wealth of literature exploring the neurocognitive effects of concurrent cocaine and alcohol use. In addition, marijuana use interferes with memory as well as a variety of cognitive processes, including attention and processing speeding (Pope & Yurgelun-Todd, 1996). While the impact of other substances, such as nicotine, alcohol, and

marijuana, on neurocognition has been reported in the literature, the impact of concurrent cocaine use and those substances on neurocognition has not yet been discussed.

One critical question is whether stimulant-induced neurocognitive impairment can be reversed or ameliorated using cognition enhancing interventions. For example, following administration of 20 mg of oral methylphenidate (a medication used to enhance cognitive functioning in individuals with attention deficit/hyperactivity disorder), cocaine-dependent individuals made fewer errors on a computerized cognitive salience task (in which participants viewed a drug-related or neutral word on a screen written in blue, green, red, or yellow font, then pressed the matching colored button on a key pad) (Goldstein et al., 2010). Similarly, in a sample of methamphetamine-dependent individuals who demonstrated relatively poor neurocognitive performance at baseline, administration of 400 mg of modafinil for three days significantly improved response accuracy on measures of working memory in study participants (Kalechstein, De La Garza, & Newton, 2010). Another study in methamphetamine-dependent volunteers showed that a single dose of 200 mg modafinil improved performance on a reversal learning task (Ghahremani, Tabibnia, Monterosso, Hellemann, Poldrack, & London, 2011). Similarly, the results of a recent study indicate that modafinil improved working memory in cocaine-dependent individuals, measured by the n-back task (Kalechstein, Yoon, Mahoney, & De La Garza, 2012).

Several reasons support the decision to focus on treating cocaine-induced neurocognitive impairment not only with medications such as methylphenidate or modafinil, but also acetylcholinesterase inhibitors such as rivastigmine and huperzine. For example, rivastigmine is a cognition-enhancing agent used for the treatment of

Alzheimer's disease (Hasselmo & Sarter, 2011) and, in double-blind, placebo-controlled studies, administration of rivastigmine was associated with improved performance on tests of attention and memory in individuals diagnosed with Alzheimer's disease (Feldman & Lane, 2007; Frankfort et al., 2007) and traumatic brain injury (Silver et al., 2009; Tenovuo, Alin, & Helenius, 2009). In these studies, the efficacy of rivastigmine was greatest at higher doses (Silver et al., 2009); however, because the efficacy of rivastigmine has not been evaluated in cocaine-dependent individuals, we sought to determine whether relatively low-dose, short-term administration of rivastigmine would be associated with improved performance on measures of attention, information processing speed, episodic memory, and working memory in this population.

A separate acetylcholinesterase inhibitor, huperzine, has been evaluated in several trials involving several hundred human patients (Li, Wu, Zhou, Liu, & Dong, 2008; Little, Walsh, & Aisen, 2008; Wang, Yan, & Tang, 2006; Zangara, 2003). Of particular interest, huperzine has been shown to ameliorate deficits in learning and memory. A trial investigating potential treatments for Alzheimer's disease revealed that huperzine significantly improved memory deficits in elderly people with benign senescent forgetfulness and in patients with Alzheimer's disease and vascular dementia. These beneficial effects were observed with minimal peripheral cholinergic side effects and no unexpected toxicity, demonstrating that it is not only efficacious, but also safe and well-tolerated.

In conclusion, acetylcholinesterase inhibitors have been shown to improve cognition, reinforcing that these agents may be similarly useful in treating substance abuse disorders, specifically cocaine-dependence. Ameliorating these cognitive deficits

is of great relevance and importance since exposure to cocaine and other drugs of abuse is associated with cognitive deficits in humans, and, as mentioned earlier, intact cognitive functioning has been shown to be positively associated with favorable outcomes in outpatient clinical trials in cocaine-dependent subjects (Aharonovich, Nunes, & Hasin, 2003).

Research Questions

1. Do gender differences exist with regard to neurocognitive functioning in cocaine-dependent individuals?
2. Do race differences exist with regard to neurocognitive functioning in cocaine-dependent individuals?
3. Does comorbid substance use (e.g. nicotine, alcohol, marijuana) exacerbate neurocognitive deficits in cocaine-dependent individuals?
4. What is the relationship between drug use variables (e.g. years of cocaine use, days cocaine used in the past 30, etc.) and neurocognitive functioning in cocaine-dependent individuals?
5. What is the relationship between mood variables (e.g. BDI-II, LSC-R, and ASI-Lite scores) and neurocognitive functioning in cocaine-dependent individuals?
6. Do two different acetylcholinesterase inhibitors (rivastigmine and huperzine) have the capability of improving neurocognitive functioning and ameliorating deficits in cocaine-dependent individuals?

Hypotheses

1. It is hypothesized that males and females will differ in neurocognitive tasks, with females significantly outperforming males on tests of attention and verbal memory.
2. Based on the literature in non-drug using controls, when matching for education and IQ, it is hypothesized that Caucasians will perform comparably on various neurocognitive tests when compared to their African American counterparts.
3. It is hypothesized that comorbid substance use will result in further neurocognitive deficits then when compared to those whom only use cocaine.
4. It is hypothesized that that there will be a significantly negative correlation between the drug use variables (e.g. years of cocaine use, amount of cocaine used per day, etc.) and neurocognitive functioning across a variety of domains.
5. It is hypothesized that that there will be a significantly negative correlation between mood variables (e.g. BDI-II, LSC-R, and ASI-Lite scores) and neurocognitive functioning across a variety of domains.
6. It is hypothesized that both rivastigmine and huperzine will significantly improve various domains of neurocognitive functioning, including attention, verbal memory, and working memory, when compared to placebo.

C. Implications

A major factor that detrimentally affects progress in treatment for cocaine-dependent individuals seeking treatment is the presence of neurocognitive deficits generated or exacerbated by cocaine use. Since long-term, high-dose cocaine use is a risk

factor for the onset of neurocognitive impairment in humans, it is critical that these deficits be addressed in order to improve treatment outcomes. Specifically, deficits in attention or memory may lead to unfavorable outcomes for several reasons. For example, deficits in attention may cause the cocaine-dependent individual to be unable to maintain focus, attend, and follow through on treatment plans and goals provided during the therapy process. In addition, deficits in memory may cause these individuals to have a difficult time remembering both the positive and negative times in their life or specific techniques taught during treatment which would also impede their progress. Also, deficits in memory may cause their reasoning, comprehension, and information processing to be adversely affected causing less favorable treatment outcomes. Thus, it is important to take these factors and neurocognitive deficiencies into consideration when attempting to treat someone with cocaine-dependence. The implications of this study are critical as they will not only determine whether the aforementioned candidate medications are effective for treating neurocognitive impairments, but will also determine which demographic or drug use variables contribute to these neurocognitive deficits so that appropriate treatment plans can be initiated.

CHAPTER III

METHODOLOGY

Procedure – Recruitment/Screening

Participants were recruited from the Houston metropolitan area through newspaper and radio advertisements. The study was approved by the Baylor College of Medicine and Michael E. DeBakey Veterans Association Medical Center (MEDVAMC) Internal Review Boards. All participants completed an initial telephone screen in order to assess basic eligibility. Candidates were then invited to complete an in-person assessment at the Research Commons of the MEDVAMC. During the in-person interview, candidates received an explanation of the study purpose and requirements and were allowed to review, inquire about, and sign the informed consent form. Eligible individuals were required to be between 18-55 years of age, provide at least one urine specimen that was positive for cocaine within the two weeks prior to study enrollment, met DSM-IV criteria for cocaine-dependence, and were experienced with respect to smoking and/or injecting cocaine. Participants were excluded if they had psychiatric or medical illness, serious neurological or seizure disorder, use of any psychoactive medication, and drug or alcohol dependence excluding cocaine, marijuana, and nicotine. Women were classified as ineligible for the study if they were pregnant, breast feeding, or not using a reliable form of birth control. In addition, participants completed a demographic/drug and alcohol use inventory, ASI-Lite, LSC-R, and BDI-II. Participants were compensated with a $40 gift card for completing the in-person screen. These recruitment and screening procedures described above were the same used for Study 2.

A. Procedure – Assessments

Drug and Alcohol Use Questionnaire

Drug use was assessed with a 14-item, self-report questionnaire with frequency assessed in terms of date of last use, days used in the past 30, years of use, grams used per day, and route of administration. In addition to cocaine, substance use frequency was also assessed for alcohol, methamphetamine, opiates, marijuana, and nicotine. In addition, recent drug use was assessed and confirmed via qualitative urine toxicology (testing for cocaine metabolites, amphetamine, methamphetamine, marijuana, and opiates).

Life Stressor Checklist- Revised (LSC-R)

The LSC-R (Wolfe & Kimerling, 1997) measures life stress in 30 areas that could elicit PTSD responses (e.g., being mugged, the death of a loved one, a sexual assault). The LSC-R assesses for whether or not each stressful event occurred, at what ages the events occurred, how many times each event occurred, how dangerous the event was, and whether the individual had an intense emotional reaction to the event(s). The total LSC-R score is obtained by adding up the total number of experiences endorsed (thus the range is 0 – 30 with 30 indicating endorsement of all experiences). There are 30 events included on the checklist involving experiences such as natural disasters, assault, death of family/friends, etc. It should be noted that some of the items are not necessarily traumatic in nature, but would likely be stress-inducing. Test-retest reliability measures indicate that kappa values range from 0.52-0.97 across life stress domains on the LSC-R (McHugo et al., 2005). Additionally, the LSC-R has good concurrent validity with the Impact of Event Scale – Revised (IES-R) and the Symptom Checklist – 90 – Revised

(SCL-90-R), as well as high agreement with clinician ratings (Ungerer et al., 2009). The LSC-R has demonstrated good criterion validity for PTSD in populations with comorbid mental health and substance abuse disorders (McHugo et al., 2005).

Addiction Severity Index-Lite (ASI-Lite)

The ASI-Lite (McLellan, Cacciola, Alterman, Rikoon, & Carise, 2006) is a shortened version of the ASI which is a semi-structured assessment used to evaluate lifetime and recent (past 30 days) problem behaviors. As mentioned earlier, the ASI-Lite is divided into 7 separate composite scores: medical, employment, alcohol use, drug use, family, legal, and psychiatric. The total ASI-Lite score, as well as the composite scores, are intended to provide the clinician/researcher a more detailed perspective of issues surrounding ongoing drug use. In general, the ASI-Lite has been found to have good test-retest reliability with kappa values of approximately 0.60 (Drake & Noordsy, 1995). Inter-rater reliability measures of the ASI-Lite range from 0.83-1.00 (Stoffelmayr Mavis &, Kasim, 1994). In cocaine-dependent samples specifically, the ASI-Lite has shown good test-retest reliability, especially in the domains of lifetime medical, psychiatric, and substance abuse history (Cacciola, Koppenhaver, McKay, & Alterman 1999).

Beck Depression Inventory – II (BDI-II)

The BDI-II (Beck, 2006) is a 21-question, self-report inventory that evaluates the presence of depressive symptoms, such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex.

B. Procedure – Neurocognitive Battery

Participants were provided with standardized instructions, both oral and written, before the administration of each task. Additionally, participants were reminded to respond as quickly and as accurately as possible. The tests were selected based on studies demonstrating that these and or similar measures were shown to be valid and reliable with respect to differentiating between cocaine-dependent individuals and matched controls (Gooding, Burroughs, & Boutros, 2008; Verdejo-Garcia, Vilar-Lopez, Perez-Garcia, Podell, & Goldberg, 2006).

Wechsler Adult Intelligence Scale-III (WAIS-III). The Vocabulary and Matrix Reasoning subtests of the WAIS-III were administered. The raw scores from these subtests were included in an algorithm, the Oklahoma Premorbid Intelligence Estimation algorithm (Schoenberg, Scott, Duff, & Adams, 2002), which estimates level of intellectual function prior to the onset of drug use (Wechsler, 2007).

Continuous Performance Test-II (CPT- II). The CPT-II measures sustained attention. Participants were instructed to press the space bar whenever any letter, except for X, appeared on the computer screen. The letters were presented for 250 milliseconds, and new letters appeared at intervals of 1, 2, or 4 seconds. The inter-stimuli time intervals varied pseudo-randomly.

The variables of interest included three measures of inattention: sensitivity – level of discrimination between signal (X) and non-signal responses; omissions – failure to press the space bar when letters other than X appear; and hit rate – reaction time in milliseconds for correct responses. The indices will be transformed into standard scores, i.e. T-scores, for the data analysis (Conners, 2002).

Hopkins Verbal Learning Test-Revised (HVLT-R). The HVLT-R is a measure of verbal learning and memory that includes six different forms. Participants were initially read a list of 12 words, approximately one word per second, and asked to repeat back as many words as possible. This procedure was repeated twice, for a total of three learning trials. Following a 20 to 25 minute delay period (the Dual N-Back assessment was administered during the delay period), participants were asked to recall the words without the aid of reminders. The 2 dependent variables of interest for the HVLT-R were the standard scores (T-scores) for the total words recalled during all of the three learning trials and the number of words remembered following the 20 to 25 minute delay period (Brandt, 2005).

Dual N-back Task. For this computerized working memory task developed by Susanne Jaeggi, participants were presented with a series of visual stimuli (blue squares) and auditory stimuli (letters) simultaneously presented across 20 blocks of 21 trials each. The visual stimulus was presented in one of eight locations on the screen, and the auditory stimulus was one of eight different letters. For each trial, stimuli were presented simultaneously for 500 milliseconds, with a 2500 millisecond latency period between the presentation of stimuli.

Participants started with the 1-back condition, where they were required to provide a "yes" response (pressing a blue button with the left forefinger) if the location of the presented visual stimulus matched the location of the stimulus presented immediately beforehand. Similarly, if the auditory stimulus matched the stimulus presented immediately beforehand, the participants were required to provide a "yes" response (pressing a red button with the right forefinger). If both the visual and auditory stimuli

matched those presented in the previous trial, then participants were expected to concurrently press the red and blue buttons, and finally, no response was required if none of the stimuli matched.

While completing the 20 blocks, the task difficulty varied as a function of participants' performance. Specifically, if participants achieved at least 90% accuracy rate for both visual and auditory modalities in a particular block, the n-back level increased by one (e.g., from 1-back to 2-back). Conversely, participants regressed to simpler conditions, e.g., from 2-back to 1-back, if they achieved less than 70% accuracy for either the visual and auditory modalities in a particular block. Finally, the n-back level stayed the same if participants performed at an accuracy level between 70 and 90%. For all levels, a "yes" response was required if the presented visual stimulus or auditory stimulus matched the stimulus that was presented n trials previously. Dependent variables were mean n-back level reached in those 20 + n blocks, maximum n-back level reached, visual accuracy, and auditory accuracy (defined as the ratio of accurate responses to total responses) (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008).

Order of Test Administration: The battery of neurocognitive tests were administered in the following order: the HVLT-R learning recall trials, the dual N-back tests, delayed recall of the HVLT-R, and lastly the CPT-II. The average duration of these neurocognitive procedures was an hour and a half. The reaction time tests were programmed on a laptop computer. The WAIS-III was administered on a separate day, after verifying that the volunteer was not experiencing withdrawal symptoms from cocaine, and before randomization into the study arms.

C. Study 1 - Overview

This study investigated the demographic (e.g. gender, ethnicity, age), drug use (e.g. years, recent, and daily cocaine use and smoking status) variables that may affect neurocognition. In addition, we also investigated other variable such as LSC-R, ASI-Lite, and BDI-II scores and their potential impact on neurocognition.

Study 1 - Participants

The final sample size for Study 1 included 125 cocaine-dependent participants who were not seeking treatment for their cocaine-dependence at time of the assessment.

Study 1 - Procedures

All eligible participants who completed a baseline neurocognitive battery (before randomization to one of the many study medication evaluated in the laboratory) were included in this study.

Study 1 - Statistical Analysis

To alleviate the potential confound of demographic and drug use variability when assessing gender differences, female cocaine users (n= 21) were matched with male counterparts (n= 21) on the following variables: age, education, IQ, years of stimulant use, recent stimulant use, and amount of stimulant used per day. In similar fashion, Caucasians (n= 16) were matched with their African Americans counterparts to determine race differences, non-cigarette smokers (n= 17) were matched with cigarette smokers to determine the impact of cigarette smoking on neurocognitive performance, alcohol users (n= 15) were matched with non-alcohol users to determine the impact of alcohol use on neurocognitive performance, and marijuana smokers (n= 20) were matched with non-marijuana smokers to determine the impact of marijuana smoking on

neurocognitive performance. One-way analysis of variance (ANOVA) was utilized to detect gender, race, or other drug use differences on neurocognition. Since females, Caucasians, non-smokers, non-dependent alcohol and marijuana users rarely enroll in our ongoing studies for cocaine-dependent individuals, the distribution was skewed, which served as the rationale for matching these participants to an equal number of their counterparts on the aforementioned characteristics. Pearson product moment correlations were used to evaluate the association between continuous demographic variables (e.g. age, education, and IQ) and performance on neurocognitive measures. Similarly, Pearson product moment correlations were used to evaluate the association between continuous drug use variables (e.g. years of cocaine use, recent cocaine use in the past 30 days, and daily use of cocaine in grams) and performance on the neurocognitive measures. In addition, Pearson product moment correlations were used to evaluate the association between mood symptoms, stress, and addiction severity (e.g. BDI-II, LSC-R, ASI-Lite scores) and performance on the neurocognitive measures. For demographic, drug use, and mood comparisons, significance was set at $p < 0.05$, and when assessing neurocognitive performance, significance was set at $p < 0.006$ after incorporating a Bonferroni correction for multiple comparisons. All analyses were conducted with SPSS version 17.

Study 2 - Overview

This study investigated the independent efficacy of rivastigmine and huperzine as potential treatments to ameliorate cocaine-induced neurocognitive impairment.

D. Study 2 - Participants

The sample size for Study 2 included 72 cocaine-dependent participants who were

not seeking treatment for their cocaine-dependence at time of the assessment.

Study 2 - Procedures

The study involved a between-subjects, double-blind, placebo-controlled design. Baseline neurocognitive testing was performed on Day 0 prior to randomization to study medication. Medication of placebo was administered twice daily beginning on Day 2. 28 participants were randomized to rivastigmine, 29 participants were randomized to huperzine, and 15 were randomized to placebo. Neurocognitive testing was repeated on Day 9 following seven days of medication administration which was sufficient for each drug to reach steady state levels.

Study 2 - Statistical Analysis

Initially, if there were differences between groups at baseline, a within-subjects, repeated measures ANOVA would have been utilized to evaluate the effects of rivastigmine, huperzine, and placebo on test performance at baseline (Day 0) and at the point in time at which sustained rivastigmine or huperzine exposure results in peak blood levels of the medication (Day 9). However, after preliminary analysis, there were no differences between any of the groups at baseline (Day 0) so only post-medication (Day 9) groups were compared using one-way ANOVA. For demographic and drug use comparisons, significance was set at $p < 0.05$, and when assessing neurocognitive performance, significance was set at $p < 0.006$ after incorporating a Bonferroni correction for multiple comparisons. All analyses were conducted with SPSS version 17.

CHAPTER IV

RESULTS

A. Study 1 – Demographic and drug use variables which may affect neurocognition

Demographic and drug use characteristics for the entire sample (n = 125) can be found in **Table 1**. Cocaine-dependent participants were primarily African American and ~45 years of age. Participants reported using cocaine for ~18 years, 17 days out of the last 30, and used ~2.0 grams of cocaine/day. A majority of participants also reported concurrent use of nicotine, alcohol, and/or marijuana.

Table 1

Demo/Drug Use Statistics and overall Neurocognitive Performance for the entire sample

Participant Characteristics	Cocaine-Dependent Pts (N = 125)
Demographics	
Males	104 (83%)
Females	21 (17%)
Caucasian	29 (23%)
African American	96 (77%)
Age (years)	44.9±0.60
Education (years)	12.4±0.1
IQ (WAIS-III)	97.7±1.1
Drug Use	
Cocaine	100%
Years of use	17.5±0.7
Days used in past 30	16.7±0.8
Grams per day	2.0±0.2
Cigarette	86%
Years of Use	22.6±0.8
Cigarettes/day	13.6±0.8
Alcohol	89%
Years of Use	21.3±0.9
Days used in past 30	10.4±0.9
Marijuana	64%
Years of Use	18.8±1.2
Days used in past 30	5.0±0.9
Neurocognitive Performance	
CPT-II Performance	
D' (Sensitivity)	49.74±0.81
Hit Rate – RT^	49.85±1.27
Omissions^^	66.58±3.02
HVLT-R Performance	
Trials 1-3	36.78±0.96
Delayed Recall	39.14±1.07
N-Back Performance	
Auditory Accuracy	0.58±0.02
Visual Accuracy	0.46±0.01
N-value (mean)	1.42±0.03
N-value (max)	2.02±0.06

Values represent Mean±SEM

^RT=reaction time

^^Higher scores are indicative of poorer performance

Neurocognitive Functioning in Males versus Females

When investigating neurocognitive differences between genders, cocaine-dependent males (n=21) and females (n= 21) were statistically similar with regard to all demographic/drug use variables (**Table 2**). Cocaine-dependent participants were primarily African American and ~42 years of age. Participants reported using cocaine for ~15 years, ~15 days out of the last 30, and used ~2.0 grams of cocaine/day.

Males and females did not differ on measures of sustained attention as measured by the CPT, including sensitivity ($F_{1,40} = 0.368$, $p = 0.548$), hit rate ($F_{1,40} = 1.670$, $p = 0.204$), and omissions ($F_{1,40} = 1.178$, $p = 0.284$). In addition, males and females scored similarly on measures of immediate episodic memory ($F_{1,40} = 1.858$, $p = 0.181$) nor delayed episodic memory ($F_{1,40} = 4.536$, $p = 0.039$) as measured by the HVLT. Finally, males and females did not differ on indices of working memory as measured by the dual n-back, including mean length of the n-back trials for each block working memory ($F_{1,40} = 0.114$, $p = 0.738$), maximum block length during each assessment ($F_{1,40} = 0.780$, $p = 0.382$), accuracy of responding to auditory stimuli ($F_{1,40} = 0.383$, $p = 0.540$), and accuracy of responding to visual stimuli ($F_{1,40} = 0.429$, $p = 0.516$).

Table 2

Neurocognitive Functioning in Males versus Females

Participant Characteristics	Males (N = 21)	Females (N = 21)	*p*
Demographics			
Males	21 (100%)	0	
Females	0	21 (100%)	
Caucasian	6 (29%)	6 (29%)	
African American	15 (71%)	15 (71%)	
Age (years)	41.5±1.4	43.9±1.5	.26
Education (years)	11.8±0.3	12.3±0.5	.39
IQ (WAIS-III)	96.3±3.2	93.5±3.4	.56
Drug Use			
Cocaine			
Years of use	16.3±1.4	15.0±2.1	.59
Days used in past 30	16.5±1.9	15.4±2.1	.71
Grams per day	2.1±0.7	2.0±0.4	.97
Cigarette	95%	86%	
Years of Use	20.7±1.6	22.4±2.5	.56
Cigarettes/day	13.2±1.9	15.7±1.9	.83
Alcohol	86%	86%	
Years of Use	16.8±1.9	18.8±2.5	.55
Days used in past 30	11.6±2.4	9.8±2.6	.63
Marijuana	62%	52%	
Years of Use	20.3±2.4	13.7±3.3	.11
Days used in past 30	6.6±2.6	6.3±2.9	.93
Neurocognitive Performance			
CPT-II Performance			
D' (Sensitivity)	51.85±1.79	49.97±2.53	.55
Hit Rate – RT^	44.49±3.83	50.47±2.61	.20
Omissions^^	59.17±5.43	68.03±6.09	.28
HVLT-R Performance			
Trials 1-3	35.62±2.11	39.90±2.33	.18
Delayed Recall	35.57±2.59	43.10±2.41	.04
N-Back Performance			
Auditory Accuracy	0.61±0.22	0.56±0.24	.54
Visual Accuracy	0.43±0.03	0.46±0.03	.52
N-value (mean)	1.40±0.10	1.36±0.07	.74
N-value (max)	2.05±0.18	1.86±0.13	.38

Values represent Mean±SEM

^RT=reaction time

^^Higher scores are indicative of poorer performance

*$p<0.05$

**$p<0.006$

Neurocognitive Functioning in African Americans versus Caucasians

When investigating neurocognitive differences between races, cocaine-dependent African Americans (n = 16) and Caucasians (n = 16) were statistically similar with regard to all demographic/drug use variables with the exception of years of nicotine use ($F_{1,28}$ = 5.461, p = 0.027), cigarettes per day ($F_{1,28}$ = 11.567, p=0.002), and years of marijuana use ($F_{1,22}$ = 5.467, p = 0.029) where Caucasians reported using significantly more cigarettes and marijuana than African Americans (**Table 3**). Cocaine-dependent participants were primarily male and ~43 years of age. Participants reported using cocaine for ~16 years, ~17 days out of the last 30, and used ~2.5 grams of cocaine/day.

African Americans and Caucasians did not differ on measures of sustained attention as measured by the CPT, including sensitivity ($F_{1,30}$ = 2.884, p = 0.100), hit rate ($F_{1,30}$ = 0.151, p = 0.700), omissions ($F_{1,30}$ = 0.135, p = 0.716). In addition, African Americans and Caucasians did not differ on measures of immediate or delayed episodic memory. Specifically, African Americans and Caucasians did not differ with respect to performance over three learning trials ($F_{1,30}$ = 0.004, p = 0.951), nor did they differ following a 15 minute delay period ($F_{1,30}$ = 0.122, p = 0.730). Finally, African Americans and Caucasians did not differ on indices of working memory as measured by the dual n-back, including mean length of the n-back trials for each block working memory ($F_{1,30}$ = 2.543, p = 0.0121), maximum block length during each assessment ($F_{1,30}$ = 0.429, p = 0.518), accuracy of responding to auditory stimuli ($F_{1,30}$ = 0.293, p = 0.592), and accuracy of responding to visual stimuli ($F_{1,30}$ = 0.459, p = 0.503).

Table 3

Neurocognitive Functioning in African Americans versus Caucasians

Participant Characteristics	African- American (N = 16)	Caucasian (N = 16)	*p*
Demographics			
Males	14 (88%)	13 (81%)	
Females	2 (12%)	3 (19%)	
Caucasian	0	16 (100%)	
African American	16 (100%)	0	
Age (years)	43.1±0.50	43.2±1.9	.98
Education (years)	12.6±0.3	12.9±0.5	.50
IQ (WAIS-III)	99.1± 3.15	102.0±2.39	.48
Drug Use			
Cocaine			
Years of use	16.8±1.2	15.8±2.5	.74
Days used in past 30	17.8±2.0	16.8±2.7	.76
Grams per day	2.5±0.9	2.5±1.0	.98
Cigarette	100%	88%	
Years of Use	19.4±1.8	26.1±2.2	**.03***
Cigarettes/day	10.6±1.5	18.6±1.9	**.002****
Alcohol	88%	94%	
Years of Use	19.9±2.1	25.8±2.2	.06
Days used in past 30	11.6±2.3	8.7±2.5	.42
Marijuana	81%	69%	
Years of Use	14.2±2.7	23.3±2.7	**.03***
Days used in past 30	1.5±0.4	6.0±2.7	.09
Neurocognitive Performance			
CPT-II Performance			
D' (Sensitivity)	49.86±1.83	54.51±2.03	.10
Hit Rate – RT^	47.60±3.36	45.60±3.89	.70
Omissions^^	58.44±5.04	60.85±4.19	.72
HVLT-R Performance			
Trials 1-3	39.25±2.49	39.0±3.19	.95
Delayed Recall	42.60±3.16	41.13±2.82	.73
N-Back Performance			
Auditory Accuracy	0.61±0.03	0.63±0.03	.59
Visual Accuracy	0.48±0.04	0.51±0.02	.50
N-value (mean)	1.41±0.07	1.57±0.08	.12
N-value (max)	2.13±0.13	2.25±0.14	.52

Values represent Mean±SEM

^RT=reaction time

^^Higher scores are indicative of poorer performance

*$p<0.05$

**$p<0.006$

Neurocognitive Functioning in Cigarette Smokers versus Non-Cigarette Smokers

When investigating neurocognitive differences between cigarette smokers and non-smokers, cocaine-dependent cigarette smokers (n = 17) and non-cigarette smokers (n = 17) were statistically similar with regard to all demographic/drug use variables with the exception of years ($F_{1,27} = 6.995$, $p = 0.013$) and recent alcohol use ($F_{1,27} = 4.236$, $p = 0.049$) (**Table 4**). Cocaine-dependent participants were primarily male, African American and ~46 years of age. Participants reported using cocaine for ~17 years, ~16 days out of the last 30, and used ~2.0 grams of cocaine/day. Those cigarette smokers included in the analyses reporting using cigarettes for ~27 years and smoked ~23 cigarettes per day.

Cigarette smokers and non-cigarette smokers did not differ on measures of sustained attention as measured by the CPT, including sensitivity ($F_{1,32} = 0.609$, $p = 0.441$), hit rate ($F_{1,32} = 0.305$, $p = 0.584$), and omissions ($F_{1,32} = 0.040$, $p = 0.844$). In addition, cigarette smokers and non-cigarette smokers did not differ on measures of immediate or delayed episodic memory. Specifically, cigarette smokers and non-cigarette smokers did not differ with respect to performance over three learning trials ($F_{1,32} = 0.178$, $p = 0.676$), nor did they differ following a 15 minute delay period ($F_{1,32} = 0.034$, $p = 0.855$). Finally, cigarette smokers and non-cigarette smokers did not differ on indices of working memory as measured by the dual n-back, including mean length of the n-back trials for each block working memory ($F_{1,32} = 0.373$, $p = 0.545$), maximum block length during each assessment ($F_{1,32} = 2.299$, $p = 0.139$), accuracy of responding to auditory stimuli ($F_{1,32} = 1.381$, $p = 0.249$), and accuracy of responding to visual stimuli ($F_{1,32} = 0.809$, $p = 0.375$).

Table 4

Neurocognitive Functioning in Cigarette Smokers versus Non-Smokers

Participant Characteristics	Smoker (N = 17)	Non-Smoker (N = 17)	*p*
Demographics			
Males	14 (82%)	14 (82%)	
Females	3 (18%)	3 (18%)	
Caucasian	4 (12%)	6 (35%)	
African American	13 (76%)	11 (65%)	
Age (years)	46.7±1.1	46.6±1.2	.94
Education (years)	12.5±0.3	12.5±0.3	.90
IQ (WAIS-III)	98.3±3.0	99.3±3.4	.84
Drug Use			.97
Cocaine			.13
Years of use	17.6±2.1	17.8±1.8	.97
Days used in past 30	18.8±2.4	14.0±2.0	
Grams per day	1.8±0.3	1.8±0.3	
Cigarette			
Years of Use	27.0±7.9	-	**<.001****
Cigarettes/day	22.8±5.6	-	**<.001****
Alcohol	76%	94%	
Years of Use	24.9±2.9	16.2±1.8	**.01***
Days used in past 30	14.2±3.5	6.6±1.8	**.05***
Marijuana	47%	41%	
Years of Use	20.9±4.3	19.0±2.2	.70
Days used in past 30	2.4±1.0	5.1±4.2	.52
Neurocognitive Performance			
CPT-II Performance			
D' (Sensitivity)	50.91±1.98	53.23±2.22	.44
Hit Rate – RT^	49.60±3.98	46.70±3.42	.58
Omissions^^	68.38±6.89	71.11±11.88	.84
HVLT-R Performance			
Trials 1-3	37.88±3.07	36.24±2.42	.68
Delayed Recall	39.35±2.49	38.63±3.09	.86
N-Back Performance			
Auditory Accuracy	0.62±0.05	0.51±0.07	.25
Visual Accuracy	0.44±0.03	0.47±0.03	.38
N-value (mean)	1.37±0.07	1.43±0.09	.55
N-value (max)	1.82±.0.13	2.12±0.15	.14

Values represent Mean±SEM

^RT=reaction time

^^Higher scores are indicative of poorer performance

*$p<0.05$

**$p<0.006$

Neurocognitive Functioning in Alcohol Drinkers versus Non-Drinkers

When investigating neurocognitive differences between alcohol users and non-users, cocaine-dependent alcohol users (n = 15) and non-alcohol users (n = 15) were statistically similar with regard to all demographic/drug use variables (**Table 5**). Cocaine-dependent participants were primarily male, African American and ~44 years of age. Participants reported using cocaine for ~15 years, ~20 days out of the last 30, and used ~2.0 grams of cocaine/day. Those alcohol users included in the analyses reporting using alcohol for ~25 years and ~25 days out of the past 30.

Alcohol users and non-alcohol users did not differ on measures of sustained attention as measured by the CPT, including sensitivity ($F_{1,28} = 0.668$, $p = 0.421$), hit rate ($F_{1,28} = 2.630$, $p = 0.116$), and omissions ($F_{1,28} = 0.005$, $p = 0.945$). In addition, alcohol users and non-alcohol users did not differ on measures of immediate or delayed episodic memory. Specifically, alcohol users and non-alcohol users did not differ with respect to performance over three learning trials ($F_{1,28} = 0.187$, $p = 0.669$); nor did they differ following a 15 minute delay period ($F_{1,28} = 0.151$, $p = 0.700$). Finally, alcohol users and non-alcohol users did not differ on indices of working memory as measured by the dual n-back, including mean length of the n-back trials for each block working memory ($F_{1,28} = 0.360$, $p = 0.554$), maximum block length during each assessment ($F_{1,28} = 1.923$, $p = 0.176$), accuracy of responding to auditory stimuli ($F_{1,28} = 0.819$, $p = 0.373$), and accuracy of responding to visual stimuli ($F_{1,28} = 0.275$, $p = 0.604$).

Table 5

Neurocognitive Functioning in Alcohol Drinkers versus Non-Drinkers

Participant Characteristics	Drinker (n = 15)	Non-Drinker (n = 15)	*p*
Demographics			
Males	10 (67%)	12 (80%)	
Females	5 (33%)	3 (20%)	
Caucasian	7 (47%)	3 (20%)	
African American	8 (53%)	12 (80%)	
Age (years)	44.2±2.1	44.6±1.9	.89
Education (years)	12.5±0.4	11.9±0.4	.31
IQ (WAIS-III)	98.9±2.0	92.0±3.7	.11
Drug Use			
Cocaine			
Years of use	17.7±2.6	13.1±1.6	.14
Days used in past 30	19.9±2.0	20.3±1.7	.88
Grams per day	1.6±0.3	2.3±0.4	.15
Cigarette	87%	93%	
Years of Use	23.9±2.7	21.3±2.4	.48
Cigarettes/day	14.7±1.8	13.3±2.2	.63
Alcohol			
Years of Use	24.6±2.3	-	**<.001****
Days used in past 30	24.3±1.1	-	**<.001****
Marijuana	67%	53%)	
Years of Use	15.8±3.5	14.6±3.7	.81
Days used in past 30	3.0±2.5	6.3±3.4	.43
Neurocognitive Performance			
CPT-II Performance			
D' (Sensitivity)	50.05±2.55	52.90±2.39	.42
Hit Rate – RT^	48.52±2.92	41.58±3.12	.12
Omissions^^	59.13±6.05	59.66±4.46	.95
HVLT-R Performance			
Trials 1-3	38.47± 2.74	36.93±2.25	.67
Delayed Recall	42.27± 2.93	40.73±2.64	.70
N-Back Performance			
Auditory Accuracy	0.62±0.04	0.56±0.06	.37
Visual Accuracy	0.47±0.05	0.44±0.03	.60
N-value (mean)	1.46±0.08	1.38±0.11	.55
N-value (max)	2.20±0.18	1.87±0.17	.18

Values represent Mean±SEM

^RT=reaction time

^^Higher scores are indicative of poorer performance

*$p<0.05$

**$p<0.006$

Neurocognitive Functioning in Marijuana Smokers versus Non-Smokers

When investigating neurocognitive differences between marijuana smokers and non-smokers, cocaine-dependent marijuana smokers (n = 20) and non-marijuana smokers (n= 20) were statistically similar with regard to all demographic/drug use variables (**Table 6**). Cocaine-dependent participants were primarily male, African American and ~43 years of age. Participants reported using cocaine for ~14 years, ~18 days out of the last 30, and used ~2.0 grams of cocaine/day. Those marijuana users included in the analyses reporting using marijuana for ~24 years and ~16 days out of the past 30.

Marijuana smokers and non-marijuana smokers did not differ on measures of sustained attention as measured by the CPT, including sensitivity ($F_{1,38} = 0.199$, $p = 0.658$), hit rate ($F_{1,38} = 0.070$, $p = 0.792$), and omissions ($F_{1,38} = 0.529$, $p = 0.471$). In addition, marijuana smokers and non-marijuana smokers did not differ on measures of immediate or delayed episodic memory. Specifically, marijuana smokers and non-marijuana smokers did not differ with respect to performance over three learning trials ($F_{1,38} = 1.157$, $p = 0.289$), nor did they differ following a 15 minute delay period ($F_{1,38} = 1.964$, $p = 0.169$). Finally, marijuana smokers and non-marijuana smokers did not differ on indices of working memory as measured by the dual n-back, including mean length of the n-back trials for each block working memory ($F_{1,38} = 0.063$, $p = 0.804$), maximum block length during each assessment ($F_{1,38} = 0.239$, $p = 0.628$), accuracy of responding to auditory stimuli ($F_{1,38} = 0.976$, $p = 0.329$), and accuracy of responding to visual stimuli ($F_{1,38} = 0.086$, $p = 0.771$).

Table 6

Neurocognitive Functioning in Marijuana Smokers versus Non-Smokers

Participant Characteristics	Marijuana (n = 20)	Non-Marijuana (n = 20)	*p*
Demographics			
Males	17 (85%)	16 (80%)	
Females	3 (15%)	4 (20%)	
Caucasian	6 (30%)	5 (20%)	
African American	14 (70%)	15 (75%)	
Age (years)	43.3±2.0	42.1±1.5	.65
Education (years)	12.2±0.3	12.2±0.2	1.00
IQ (WAIS-III)	95.8±11.6	97.5±12.3	.68
Drug Use			
Cocaine			
Years of use	15.8±1.8	13.7±1.1	.33
Days used in past 30	20.4±1.8	16.3±1.5	.09
Grams per day	1.5±0.2	1.6±0.2	.72
Cigarette	85%	85%	
Years of Use	23.5±2.3	20.1±1.9	.27
Cigarettes/day	13.5±1.6	11.7±1.7	.45
Alcohol	90%	80%	
Years of Use	21.1±1.9	16.6±2.5	.15
Days used in past 30	9.2±2.0	7.6±1.6	.54
Marijuana			
Years of Use	24.2±7.52	-	**<.001****
Days used in past 30	16.2±8.58	-	**<.001****
Neurocognitive Performance			
CPT-II Performance			
D' (Sensitivity)	49.58±2.20	48.08± 2.51	.66
Hit Rate – RT^	50.29±3.34	48.90± 4.01	.79
Omissions^^	71.00±9.47	62.59± 6.63	.47
HVLT-R Performance			
Trials 1-3	33.25±2.0	36.0± 1.59	.29
Delayed Recall	34.65±2.40	39.42± 2.41	.17
N-Back Performance			
Auditory Accuracy	0.63±0.05	0.57±0.04	.33
Visual Accuracy	0.44±0.03	0.45±0.04	.77
N-value (mean)	1.44±0.09	1.41±0.08	.80
N-value (max)	1.95±0.15	2.05±0.14	.63

Values represent Mean±SEM

^RT=reaction time

^^Higher scores are indicative of poorer performance

*$p<0.05$

**$p<0.006$

Correlations between Demographic, Drug Use, and Mood Variables and Neurocognitive Performance

Despite considerable heterogeneity in responses among participants, Pearson product-moment correlation revealed that age was negatively and significantly correlated with mean length of the n-back trials for each block working memory ($p < 0.001$) and maximum length of the n-back trials for each block of working memory; however, the r values were very low ($r < 0.400$ for all measures) indicating that these relationships were more likely explained by other factors. Pearson product-moment correlation revealed that IQ was positively and significantly correlated with respect to episodic memory performance over three learning trials ($p < 0.001$), delayed performance over three learning trials ($p < 0.001$), accuracy of responding to auditory stimuli ($p < 0.001$), mean length of the n-back trials for each block working memory ($p < 0.001$), maximum block length during each assessment ($p < 0.001$); however, the r values were all quite low ($r < 0.460$ for all measures) indicating that these relationships were more likely explained by other factors. All other demographic, drug use, and mood variables were not significantly correlated with neurocognitive performance ($p>0.006$).

Table 7
Correlations between Demographic, Drug Use, and Mood Variables and Neurocognitive Performance

	Demographic			Cocaine Use			Mood		
	Age	Education	IQ	Years	Recent	Daily	BDI	LSC-R	ASI
CPT-II									
D' (Sensitivity)	-.135	.058	.036	-.044	-.114	.022	-.010	.148	.108
Hit Rate – RT^	.190	-.082	-.040	.127	.026	-.172	.024	-.010	.029
Omissions^^	.056	.023	.083	.052	-.066	.076	-.017	.013	.043
HVLT-R									
Trials 1-3	.004	.077	.437*	.089	-.013	.163	-.062	-.067	.015
Delayed Recall	-.041	.056	.348*	-.047	-.102	.122	-.125	-.071	.009
N-Back									
Auditory Accuracy	-.099	.021	.176	-.157	-.039	.120	-.096	.029	-.056
Visual Accuracy	-.152	-.005	.418*	.135	.172	-.007	.018	.093	.161
N-value (mean)	-.379*	.178	.455*	-.065	.147	-.091	-.025	.153	.172
N-value (max)	-.335*	.115	.422*	-.081	.065	-.108	-.041	.132	.180

Values represent Mean±SEM
^RT=reaction time
^^Higher scores are indicative of poorer performance
*$p<0.006$

B. Study 2 – Rivastigmine and Huperzine as treatments for neurocognitive impairment

Demographic and drug use characteristics of the 72 completers in the treatment groups are presented in **Table 8**. A total of 75 participants were enrolled in the study (3 participants withdrew for personal reasons). Cocaine-dependent participants were primarily African American and ~43 years of age. Participants reported using cocaine for ~16 years, 18 days out of the last 30, and used ~2 grams of cocaine/day. The treatment groups did not differ for any basic demographic or drug use variables (all p-values > 0.05).

Preliminary analyses revealed that demographic indices, including age, years of education, estimated level of premorbid IQ, and substance use indices, including lifetime and recent use of alcohol, cocaine, and nicotine, did not correlate with performance on indices of sustained attention, learning and memory, or working memory performance (all p's > 0.05). Thus, no covariates were included in the primary analyses.

The effects of rivastigmine on neurocognitive functioning

Table 9 includes the results of performance on measures of sustained attention, episodic memory, and working memory when comparing those participants receiving 3 or 6 mg rivastigmine and placebo.

Participants randomized to rivastigmine versus placebo did not differ on measures of sustained attention as measured by the CPT, including sensitivity ($F_{1,41} = 0.014$, $p = 0.908$), hit rate ($F_{1,41} = 0.280$, $p = 0.600$), omissions ($F_{1,41} = 0.016$, $p = 0.899$). However, rivastigmine administration was associated with significantly improved performance on measures of immediate memory. Specifically, participants randomized to rivastigmine

had significantly elevated performance over three learning trials ($F_{1,41} = 11.856$, $p < 0.001$). However, there were no differences between groups on performance following a 15 minute delay period ($F_{1,41} = 1.947$, $p = 0.170$). Rivastigmine administration was not associated with significantly improved performance on two indices of working memory, including mean length of the n-back trials for each block working memory ($F_{1,41} = 5.010$, $p = 0.031$) and maximum block length during each assessment ($F_{1,41} = 7.493$, $p = 0.009$). Rivastigmine and placebo groups did not differ on accuracy of responding to auditory stimuli ($F_{1,41} = 3.884$, $p = 0.056$) nor accuracy of responding to visual stimuli ($F_{1,41} = 0.911$, $p = 0.345$).

The effects of huperzine on neurocognitive functioning

Table 10 includes the results of performance on measures of sustained attention, episodic memory, and working memory when comparing those participants receiving 0.4 or 0.8 mg huperzine and placebo.

Participants randomized to 0.4 or 0.8 mg huperzine and placebo did not differ on measures of sustained attention as measured by the CPT, including sensitivity ($F_{1,42} = 0.226$, $p = 0.637$), hit rate ($F_{1,42} = 0.046$, $p = 0.831$), and omissions ($F_{1,42} = 0.077$, $p = 0.783$). Participants randomized to huperzine or placebo did not differ on measures of immediate or delayed episodic memory. Specifically, groups did not differ with regard to performance over three learning trials ($F_{1,42} = 1.262$, $p = 0.268$), nor did they differ on performance following a 15 minute delay period ($F_{1,42} = 0.449$, $p = 0.506$). Participants randomized to huperzine or placebo did not differ on measures of working memory as assessed by the n-back, including mean length of the n-back trials for each block working memory ($F_{1,42} = 0.005$, $p = 0.945$), maximum block length during each assessment ($F_{1,42} =$

0.345, $p = 0.560$), accuracy of responding to auditory stimuli ($F_{1,42} = 2.442$, $p = 0.126$), and accuracy of responding to visual stimuli ($F_{1,42} = 0.159$, $p = 0.692$).

Table 8
Demo/Drug Use Statistics for Study 2

	Placebo (N = 15)	Rivastigmine (N = 28)	Huperzine (N = 29)	*p*
Demographics				
Males	13 (87%)	22 (79%)	22 (76%)	
Females	2 (13%)	6 (21%)	6 (24%)	
Caucasian	4 (27%)	8 (29%)	8 (28%)	
African American	11 (73%)	20 (71%)	21 (72%)	
Age (years)	39.7±2.0	43.9±1.0	43.2±7.6	.16
Education (years)	12.1±0.3	12.9±0.3	12.7±0.4	.36
IQ (WAIS-III)	96.5±3.8	101.1±1.1	97.0±2.4	.39
Drug Use				
Cocaine				
Years of use	15.7±1.9	16.1±1.5	16.0±1.5	.98
Days used in past 30	15.8±1.8	18.6±1.5	17.6±1.8	.72
Grams per day	1.8±0.3	2.3±0.5	2.1±0.3	.60
Cigarette	87%	89%	93%	
Years of Use	17.4±2.3	21.3±1.7	20.66±1.6	.37
Cigarettes/day	20.2±2.8	26.5±1.7	26.37±1.5	.07
Alcohol	93%	82%	79%	
Years of Use	18.7±2.4	20.8±1.5	22.3±1.8	.42
Days used in past 30	9.9±8.2	10.3±1.7	10.2±1.9	.99

Values represent Mean±SEM
*$p<0.05$

Table 9
Neurocognitive Performance on those Randomized to Rivastigmine versus Placebo

	Placebo (N = 15)	Rivastigmine (N = 28)	*p*
Neurocognitive Performance	*Post-tx*	*Post-tx*	
CPT-II Performance			
D' (Sensitivity)	50.23±2.99	49.87±1.58	.91
Hit Rate – RT^	46.93±3.86	49.26±2.48	.60
Omissions^^	60.61±5.06	61.61±5.05	.90
HVLT-R Performance			
Trials 1-3	31.73±2.13	40.43±1.46	**<.001***
Delayed Recall	32.13±2.78	37.29±2.25	.17
N-Back Performance			
Auditory Accuracy	0.52±.05	0.62±0.02	.06
Visual Accuracy	0.50±0.05	0.55±0.03	.35
N-value (mean)	1.55±0.11	1.84±0.08	.03
N-value (max)	2.07±0.18	2.61±0.11	.01

Values represent Mean±SEM
^RT=reaction time
^^Higher scores are indicative of poorer performance
*p<0.006

Table 10
Neurocognitive Performance on those Randomized to Huperzine versus Placebo

	Placebo (N = 15)	Huperzine (N = 29)	*p*
Neurocognitive Performance	*Post-tx*	*Post-tx*	
CPT-II Performance			
D' (Sensitivity)	50.23±2.99	51.70±1.61	.64
Hit Rate – RT^	46.93±3.86	47.90±2.57	.83
Omissions^^	60.61±5.06	63.95±8.22	.78
HVLT-R Performance			
Trials 1-3	31.73±2.13	35.28±1.98	.27
Delayed Recall	32.13±2.78	34.55±2.16	.51
N-Back Performance			
Auditory Accuracy	0.52±0.05	0.61±0.03	.13
Visual Accuracy	0.50±0.05	0.48±0.03	.69
N-value (mean)	1.55±0.11	1.56±0.09	.95
N-value (max)	2.07±0.18	2.21±0.14	.56

Values represent Mean±SEM
^RT=reaction time
^^Higher scores are indicative of poorer performance
**p<0.006

CHAPTER V

CONCLUSION AND SUMMARY

A. Study 1 – Demographic and drug use variables which may affect neurocognition

Overall, as compared to age-matched normative data, the current results indicate that cocaine users perform at a lower level on neurocognitive assessments. Specifically, cocaine-dependent participants tended to perform more poorly in the domains of working memory (since scores on the n-back fell well below the scores of healthy controls reported by Jaeggi, 2008) and episodic memory (since the t-scores on the HVLT were well below the normed 43-55 average range). These data demonstrate that neurocognitive deficits exist in cocaine-dependent individuals irrespective of demographic, drug use, and behavioral characteristics. Importantly, the current results coincide with the meta-analysis performed by Jovanovski (2005) which revealed that cocaine-dependent individuals experienced dysfunction in episodic memory and working memory.

The data did not reveal gender differences in the domains of attention, working memory, verbal memory. This finding is of considerable interest since there have been notable gender differences reported for several neurocognitive domains in the literature in both healthy controls and cocaine users. Some explanations as to why males and females performed similarly on neurocognitive tasks warrants discussion. When investigating the subjective effects of cocaine, males, when compared to females, detected cocaine's effects faster and reported more intense positive (e.g. euphoria) and negative (e.g. dysphoria) subjective responses (Lukas, 1996). In addition, after receiving cocaine in the laboratory, males who received the same mg/kg dose of cocaine as females, achieved

significantly higher plasma cocaine levels when compared to women (Lukas, 1996). Moreover, females achieve similar cardiovascular increases in heart rate when compared to males suggesting that females may be more sensitive to the cardiovascular effects of cocaine when taking into consideration these differences in plasma cocaine levels. It has previously been reported that elevated levels of progesterone markedly increased the cardiotoxic effects produced by cocaine (Woods & Plessinger, 1990; Sharma, Plessinger, Sherer, Liang, Miller, & Woods 1992; Plessinger & Woods, 1990). This may further explain the impact of hormones on gender differences and stimulant use. While not directly correlated with neurocognition, gender differences in the behavioral and cardiovascular responses to cocaine may provide insight into potential mediators into cocaine's effect on brain function and neurocognitive performance. However, it must be noted that the gender differences mentioned above were reported following *acute* cocaine administration, which may explain the inconsistency between the findings mentioned in the literature and our current findings. In our studies, the participants had been abstinent from cocaine for >3 days, the acute effects of the drug were not present (i.e. the intention was to determine the effects of long-term, *chronic* cocaine use rather than evaluating performance in an intoxicated state). The finding that males and females performed statistically similar in the cocaine-abstinent condition provides the first evidence that gender differences do not exist with respect to the long lasting effects of cocaine on neurocognition. Future studies could assess neurocognition immediately following acute cocaine administration to determine whether gender differences emerge in that situation. For example, a recent study by our group demonstrated that acute methamphetamine exposure improved neurocognition (specifically attention and working memory);

however, the sample had an insufficient number of females to conduct a gender analysis (Mahoney, 2012).

The finding that there were no neurocognitive deficits in cocaine-dependent individuals who were concurrent cigarette smokers as compared cocaine users alone is interesting due to the neurocognitive stimulating effects (e.g. improved attention) as well as deficits produced by nicotine (Mancuso, Lejeune, & Ansseau, 2001). In a recent review of the literature, cigarette smoking was associated with deficiencies in executive functioning, cognitive flexibility, general intellectual abilities, learning, episodic memory, processing speed, and working memory (Durazzo, Meyerhoff, & Nixon, 2010). Specifically, cigarette smokers exhibit poorer working memory as measured by the n-back task (similar to the task used in the current study) when compared to non-smokers (Ernst, Heishman, Spurgeon, & London, 2001, Jacobsen, Krystal, Mend, Westerveld, Frost, & Pugh, 2005), and perform poorly on tasks focusing on visuospatial working memory (George et al., 2002). In addition, smokers performed worse than non-smokers on measure of auditory-verbal memory as measured by assessment such as the Wechsler Memory Scale (Fried, Watkinson, & Gray, 2006; Cerhan et al., 1998). Conversely, other studies noted no differences on measures of auditory-verbal learning and memory and verbal fluency (Kalmijn, van Boxtel, Verschuren, Jolles, & Launer, 2002; Sakurai & Kanazawa, 2002). Heavy smokers (defined as those who smoked ~40 cigarettes a day) performed worse than light smokers (defined as those who smoked ~5 cigarettes a day) on the Wisconsin Card Sorting Task (an assessment of executive functioning (Razani, Boone, Lesser, & Weiss, 2004). In addition, other reports found that smokers and non-smokers did not differ on some tasks of executive functioning such as the Trail Making

Test B and the Paced Auditory Serial Attention Task (Elwan et al., 1997). Due to the cognitive deficits produced by cigarette smoking alone (with the exception of the few studies mentioned), one may assume that comorbid cigarette smoking and cocaine use may exacerbate cognitive deficiencies; however, the results of this study do not support this assumption. One potential explanation for this is perhaps that the cocaine use had caused deficits severe enough that concurrent cigarette smoking caused minimal additional impairment (the concept of "floor" effects will be discussed later).

The finding that there were no neurocognitive deficits in cocaine-dependent individuals who were concurrent alcohol users when compared to those whom were cocaine-dependent alone is interesting due to the neurocognitive deficits produced by alcohol. Evidence indicated that chronic (long-term, consistent) alcohol exposure may result in brain shrinkage which can affect numerous cognitive abilities. For example, psychomotor speed (the speed at which you are able to physically perform tasks) and visuospatial abilities (those involving conceptualizing and understanding physical properties of objects) are both affected by chronic alcohol abuse (Lezak, Howieson, & Loring, 2004; Parsons & Farr, 1981; Ryan & Butters, 1986). However, other skills, such as language and arithmetic abilities, are less affected which may lead one to believe that the chronic alcohol use is not affecting them. In addition, the onset age of alcohol drinking may account for positive relationships between age/duration and level of cognitive dysfunction (Pishkin, Lovallo, & Bourne, 1985). Also, it has been reported that alcohol abuse causes accelerated aging in the brain (Blusewicz, Dustman, Schenkenberg, & Beck 1977; Graff-Radford, Heaton, Earnest, & Rudikoff, 1982) which in turn causes impairments of problem-solving skills, memory, and learning (Craik, 1977). While

memory may remain intact initially, as the difficulty of tasks increase, performance of memory functioning gradually declines. It has also been reported that alcohol abuse leads to deficits in executive functioning. Executive functioning involves several different aspects of day- to-day life including inhibitory control (being able to stop doing something inappropriate), initiation (starting a process rather than waiting for someone else to start it for you), and working memory (holding information in your short-term memory). In addition, those whom abuse alcohol have problem-solving issues, decreased flexibility in thinking, as well as problems remembering, which are all related to executive functioning.

During the detoxification period (which occurs over the 2 weeks following the stoppage of alcohol use), there are neurocognitive deficits across several cognitive domains, even those that remain unaffected during active alcohol usage (Ryan, 1986). However, the brain is resilient and has the ability to "bounce back." So many cognitive deficits, such as memory and learning abilities, are restored following abstinence. Memory deficits include problems with declarative memory (long-term memory where facts and knowledge are stored) and includes anterograde (creating new memories) and retrograde (remembering old memories) deficits (Butters & Stuss, 1989; O'Connor & Verfaillie, 2002).

Due to the numerous cognitive deficits produced by alcohol alone, one may assume that comorbid alcohol and cocaine use may exacerbate or have more of an additive effect to these cognitive deficiencies; however, the results of this study indicate that cocaine users alone when compared to concurrent cocaine and alcohol users, do not differ with respect to neurocognitive functioning. One potential explanation for the

groups being statistically similar in the current study is because none of the individuals included in this study met criteria for alcohol-dependence (the dependence criteria for alcohol is identical to the criteria for dependence criteria for cocaine mentioned on page 7). Thus, since these individuals were not alcohol-dependent, their regular patterns of daily alcohol use may not have affected nor caused further decrements in neurocognitive capabilities. Future studies should investigate the differences between cocaine-dependent and comorbid cocaine- and alcohol-dependent individuals to further explore the deficits caused by this comorbidity.

The finding that there were no neurocognitive deficits in cocaine-dependent individuals who were concurrent marijuana users when compared to those whom were cocaine-dependent alone is interesting due to the neurocognitive deficits produced by marijuana. Marijuana interferes with memory as well as a variety of cognitive processes, leaving the chronic user less able to adapt, excel, and respond to typical life challenges (Pope, Gruber, & Yurgelun-Todd, 1996). The cognitive effects produced by marijuana should be divided into 3 different categories: acute (during marijuana intoxication), residual (when intoxication wears off, but marijuana is still present in the system), and chronic (long after marijuana is out of the system) (Solowij, 1999). During the acute phase, very high doses of marijuana may result in psychotic-like states (Brust, 1993; Colback & Crowe, 1970). The acute effects of marijuana are noticed in reactive emotional states including perceptual changes and psychomotor slowing. While several studies have also reported equivocal results for behavior and cognitive changes following acute marijuana exposure, there have been reports demonstrating reduced memory capabilities while under the influence of marijuana (Brust, 2000). However, it has also

been reported that, despite subjective report of intoxication, these individuals perform fairly well on tests of attention while deficits are noted on factual memory and short-term recall (Iverson, 2000). With regard to the subacute consequences of marijuana use, there have been reports of decreased performance on tests of attention, memory, and motor abilities (for review see Pope, Gruber, & Yurgelun-Todd, 1996; Sofuoglu, Sugarman, & Carroll, 2010). However, in a separate review, when setting stringent criteria including the inclusion of studies where there was a subacute presence of marijuana and not intoxication, it was reported that only 55% of individuals demonstrated a level of cognitive impairment (Gonzalez, Carey, & Grant, 2002). As a result, the long-term consequences (residual effects) of marijuana usage is not quite clear. The literature has demonstrated that learning and reaction time tests in marijuana users and controls demonstrated no differences (Lezak et al., 2004). While there appear to be no significant long-term cognitive deficits in marijuana users, there are noted personality changes. For example, it has been reported that marijuana users express apathy (a general "not caring"), restlessness, and sluggishness (Brust, 1993; Carlin & O'Malley, 1996). These characteristics lead to lessened motivation, poor relationships, and not being able to perform tasks as usual. It must be noted though that these reports have been subjected to great debate since several other studies have found no long-term deficits (Lezak et al., 2004). The reduced memory capabilities may be a result of poor attention. Also, since marijuana is frequently used with alcohol, there may be additive effects which may lead to impaired functioning and may contribute to poor decision making resulting in unsafe behaviors (e.g. driving under the influence).

Due to all of the cognitive deficits produced by marijuana alone, one may assume that comorbid marijuana and cocaine use may exacerbate cognitive deficiencies; however, the results indicate that cocaine users alone when compared to concurrent cocaine and marijuana users, do not differ with respect to neurocognitive functioning. One potential explanation for the groups being statistically similar is that none of the individuals included in this study met criteria for marijuana-dependence (the dependence criteria for marijuana is identical to the criteria for dependence criteria for cocaine mentioned on page 7). . Thus, since these individuals were not marijuana-dependent, their casual use of marijuana appears to not affect neurocognition. Future studies could investigate the differences between cocaine-dependent and comorbid cocaine- and marijuana-dependent individuals.

Despite the detailed and informative outcomes presented in the studies conducted, some methodological limitations should be noted. First of all, the sample sizes are relatively small and much larger sample sizes should be obtained before making conclusive statements as to whether gender, ethnic, or comorbid drug use differences exist in cocaine users. Secondly, since this neurocognitive battery only focused on working memory, attention, and verbal learning and memory, a more comprehensive battery may demonstrate differences in other domains. In addition, the study would have been strengthened by including a comparison of a non-drug using, healthy control group to determine exactly how prevalent the neurocognitive deficits are in cocaine-dependent individuals (rather than relying on the age-matched normative values as a comparison). Notwithstanding, the current results demonstrate that gender, ethnic, or comorbid drug

use differences in neurocognitive performance in cocaine-dependent participants may not be prevalent.

Although there were no strong correlations between demographic and drug use variables and neurocognition, there were some interesting findings by on the significance values. For example, when comparing the oldest and youngest participants, younger participants performed significantly better on 2 separate indices of working memory. This supports the notion that prefrontal cortex functioning worsens over time. In addition, there were no differences between those with the highest education versus those with the lowest education. This is a critical finding because it demonstrates that level of education (or years of formal learning) did not affect neurocognitive processes. Interestingly, however, participants with the highest IQ's performed significantly better when compared to those with the lowest IQ's across several domains including episodic memory (both immediate and delayed) and working memory. These data support the rationale for matching groups (involved in the gender, ethnic, and comorbid substance use comparisons) on IQ in addition to the other demographic variables (e.g. age, education, drug use variables, etc.). Moreover, this finding may demonstrate that IQ may be protective against deficits caused by cocaine use in the domains of verbal and working memory.

It has previously been reported that cocaine induced neurocognitive deficits are correlated with the severity of cocaine use, suggesting a dose related effect (Bolla, Rothman, and Cadet, 1999). Our findings indicate that individuals who used cocaine for more years and for more days in the past 30 did not differ from those individuals that used for the fewest years and the fewest days in the past 30. However, those individuals

who used more grams per day had significantly higher auditory accuracy (a measure of working memory) when compared to those reporting using fewer grams per day. It may be logically hypothesized that more years of use, recent use, and grams per day would lead to further cognitive impairment which makes this finding especially interesting. One potential explanation for this unexpected finding is that once a certain threshold is met, further impairment does not occur. In other words, if an individual uses cocaine for a certain number of years, it appears that the neurocognitive damage is done and further years of use do not exacerbate those deficits. Similarly, if an individual uses for a certain number of days per month or uses a certain amount of cocaine per day, those neurocognitive deficits occur and remain at a consistent "steady state", so that additional use does not cause further impairment. This is speculation, however, and would need to be evaluated in future studies.

With regard to the behavioral questionnaires (BDI-II, LSC-R, and the ASI-LITE), there were no differences in neurocognition between those who scored the highest (e.g. endorsed the most symptoms) versus those who scored the lowest (e.g. endorsed the fewest symptoms) indicating that these behavioral variables may not affect neurocognition. Memory deficits caused by clinical depression is a common occurrence and has been termed "pseudodementia" (Patterson, 1986; Wells, 1979) which may lead to speculation that increased BDI-II scores (endorsing more depressive symptoms) may result in deficits in episodic or working memory; however, this was not found in the current study. One possible explanation for this finding is that none of the individuals had an Axis I psychiatric diagnosis of depression (rather they simply endorsed depressive symptoms without meeting actual diagnostic criteria. Factors related to and potentially

affecting BDI-II symptomatology include lifetime stress and addiction severity. Previous research has found that individuals with higher lifetime stress have significantly higher BDI-II scores as well as addiction severity (Mahoney, Newton, Omar, Ross, & De La Garza, 2012). In addition, chronic stress leads to deficits in declarative memory (McEwen, 2004). In addition, higher ASI-LITE scores indicate elevated levels of psychosocial dysfunction which may result in higher reported stress. However, in the current study, those individuals with higher LSC-R scores and ASI-LITE scores did not endorse more neurocognitive deficits. One potential explanation for these findings is that their cocaine usage resulted in neurocognitive deficits, but they were not further affected by stress nor addiction severity.

B. Study 2 – Rivastigmine or Huperzine as a treatment for neurocognitive impairment

The findings from this study demonstrated that while there was no effect of rivastigmine on sustained attention, rivastigmine administration did significantly improve episodic memory (as measured by increased immediate recall on the HVLT) and working memory (by increased values on both the mean and max block length on the n-back assessment). Since rivastigmine has previously been shown to reduce the positive subjective effects (e.g. desire and likely to use) produced by the stimulant methamphetamine, the cognitive enhancing effects of rivastigmine found in this population of cocaine-dependent individuals is critical. A current trend in the development of pharmacotherapies for cocaine-dependence involves the utilization of combination medications (more than one medication that have different brain or neurochemical targets to combat the various effects produced by cocaine use). Thus, one solution would be to pair a cognitive enhancing agent with another medication that

decreases the reinforcing or positive effects produced by cocaine in an attempt to maximize the potential benefit and outcomes. However, rivastigmine alone may accomplish both of these tasks – by improving neurocognition and reducing the positive subjective effects associated with cocaine usage. This is of great importance because isolating a single efficacious compound may result in fewer side effects, less time titrating to the most effective dose since there is only one medication being utilized, and also eliminate the potential for adverse medication-medication interactions. Furthermore, the results of this study are especially interesting given the fact that the same doses of rivastigmine (3 and 6 mg) for a similar duration (6 days) showed no effect on neurocognition in methamphetamine-dependent individuals (Kalechstein, 2011). This demonstrates that the neurocognitive deficits produced by cocaine use may be more easily treated by rivastigmine when compared to those deficits produced by methamphetamine.

It is important to concede some limitations with this study that may have affected the outcomes. Specifically, rivastigmine administration was most likely to be associated with improved neurocognitive function in studies that utilized higher doses, e.g., up to 12 mg per day for much longer period of times, e.g., 39 weeks (Silver et al., 2009); for this study, the maximum dose was 6 mg for a period of 8 days. It is plausible that this aspect of the study design mitigated the efficacy of rivastigmine, especially on the domain of attention where no effect was demonstrated as well as other domains of neurocognitive functioning which were not evaluated.

There were no changes in neurocognition with respect to the domains of attention, episodic memory, or working memory following huperzine administration. Since there is

no published literature on the effects of huperzine on neurocognition in cocaine-dependent individuals, speculation as to why huperzine did not improve cognition in this population warrants further discussion. Huperzine administration was most likely to be associated with improved neurocognitive function in studies that utilized a longer duration of treatment, e.g., 12 weeks (Xu, Liang, Juan-Wu, Zhang, Zhu, & Jiang2012), whereas in this study, the maximum dose was 0.8 mg for a period of 8 days. It is plausible that this aspect of the study design mitigated the efficacy of huperzine across all domains. Because huperzine is characterized as a cognition enhancing agent that modulates the acetylcholine system, it seemed reasonable to study whether low-dose, short-term huperzine administration might remedy, at least in part, cocaine associated neurocognitive impairment. Another explanation is that participants were exposed to low-dose cocaine (40 mg) during the study; nonetheless, it probably was not a confound given that exposure was identical for each study arm with regard to the amount and timing of the cocaine dose.

C. Overall Conclusion and Summary

Respective of these outcomes from Study 1 and Study 2, we contend that cocaine associated neurocognitive impairment remains an important target of treatment. This perception is consistent with that of other leading researchers in the field, particularly given the prevalence of cocaine associated neurocognitive impairment and the fact that the condition does not resolve with protracted abstinence (Sofuoglu, 2010). Furthermore, the association between neurocognitive impairment and functional outcomes, such as employment status for participants diagnosed with other disorders, e.g., traumatic brain injury, epilepsy, and HIV, is well-documented (Kalechstein, Newton, & van Gorp, 2003).

Given that cocaine addiction is associated with widespread functional difficulties, such as unemployment and relapse to dependence, it is plausible that reversing neurocognitive impairments associated with this disease will concurrently ameliorate these functional difficulties as well.

Future studies might also examine the degree to which improved neurocognition influences day-to-day functioning in long-term, high-dose cocaine users. While laboratory-based studies, such as those conducted above, provide potentially important information regarding the possibility of remediating cocaine-associated neurocognitive impairment, the ultimate determination of medication efficacy will be whether administration of a medication will confer some sort of benefit in terms of important daily activities. For example, such individuals are often required to complete treatment for the initiation and maintenance of abstinence from cocaine. Moreover, previous studies have revealed an associated between poor working memory function and increased likelihood of dropout from treatment (Jovanovski et al., 2005). Thus, a future study might examine whether administration of rivastigmine concurrently improves performance on episodic and working memory tasks *and* treatment outcome.

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