Chapter 3: Methods

**Introduction**

Neuropsychological studies indicate that cognitive and executive function deficits are more persistent, detrimental and often more life-threatening in cocaine and methamphetamine (MA) addicted females compared to addicted males (Fridberg et al., Luo et al., 2013; van der Plas 2009). Completion of addiction treatment is one of the strongest indicators of favorable rehabilitation outcomes; however, non-completion often places females at higher risk for continuing abuse and a deeper commitment to addiction. In addition to lower treatment entry rates, failure to complete prescribed or mandated programs can result in reduced efficiency of rehabilitation and increased cyclical patterns of relapse. Although it is not the goal of this research to investigate specific treatment components for women; studies demonstrate that gender disparities in all aspects of clinical intervention are more likely affect women more negatively than men (Greenfield et al., 2007; Hagen et al., 2016).

One of the most significant risk factors associated with treatment non-completion among addicted females are neuropsychological deficits in brain behavior (Brorson, H et al., 2013). Both pre-clinical and clinical research suggests that repeated use of drugs of abuse result in significant brain alternation (Balconi et al., 2015, Du, J. et al., 2013; Goldstein, R., 2011). Multiple studies have found impaired neurocognitive functioning in cocaine and MA abusers relative to normal control participants. It has been suggested that the brain changes and neurocognitive impairments associated with stimulant abuse are likely to have inadequate performance on neurocognitive measures is predictive of treatment attrition in cocaine and methamphetamine dependent individuals (Gould, 2010, Jasinka et al., 2014; Koob et al., 2010; Moeller, et al., 2014).

Poor performance on tests of cognitive and executive function has been linked to higher treatment attrition rates among adult males and females; however recent studies have shown that reduced neurocognitive performance by females is more predictive of treatment attrition and greater propensities to relapse (Ballard et al., 2015; Thakkar et al., 2014). This research examined the relationship between tests of cognitive and executive function in cocaine and MA addicted males and females. More specifically, this study focused on cognitive and executive function impairments in terms of gender differences in treatment completion rates.

**Research Design** **and Rationale**

In this study, we will focus on six performance measures tests: the Stroop Word Color Task, the Rey Auditory-Verbal Learning Test (RALVT), Wisconsin Card Sorting Task (WCST), the Iowa Gambling Task, the Barratt Impulsiveness Scale Version-11 (BIS 11), the Frontal Systems Behavior Scale (FrSBE), (ordinal variables), and one outcome variable (treatment completion). Our goal was to found out whether gender plays any role and ultimately drive the treatment outcome. We are also interested whether other covariates (i.e. education, age and race) are associated with addition level and have impact on the result by testing the following hypotheses.

**Research Questions**

**Research Question 1**: Does performance on a test of neurocognitive interference predict differences in treatment completion rates for cocaine and methamphetamine addicted individuals when controlling for gender?

H0: Performance on tests of neurocognitive interference are not statistically significant in predicting differential treatment completion for cocaine and methamphetamine addicted individuals when controlling for gender.

Ha: Performance on tests of neurocognitive interference are statistically significant predictors of differential treatment completion for cocaine and methamphetamine addicted individuals when controlling for gender.

**Research Question 2**: Does performance on a test of cognitive and executive function predict differences in treatment completion rates for cocaine and methamphetamine addicted individuals when controlling for gender?

H0: Performance on tests of cognitive and executive functionare not statistically significant in predicting differences in treatment attrition rates for cocaine and methamphetamine addicted individuals when controlling for gender.

Ha: Performance on tests of cognitive and executive function are statistically significant in predicting differences in treatment attrition rates for cocaine and methamphetamine addicted individuals when controlling for gender.

**Research Question 3**: Does performance on a test of cognitive and executive function predict differences in treatment completion rates for cocaine and methamphetamine addicted individuals when controlling for education?

H0: Performance on tests of cognitive and executive function are not statistically significant in predicting differences in treatment attrition rates for cocaine and methamphetamine addicted individuals when controlling for education?

Ha: Performance on tests of cognitive and executive function are statistically significant in predicting differences in treatment attrition rates for cocaine and methamphetamine addicted individuals when controlling for education.

**Research Question 4**: Does performance on a test of cognitive and executive function predict differences in treatment completion rates for cocaine and methamphetamine addicted individuals when controlling for age?

H0: Performance on tests of cognitive and executive functionare not statistically significant in predicting differences in treatment attrition rates for cocaine and methamphetamine addicted individuals when controlling for age.

H0: Performance on tests of cognitive and executive functionare not statistically significant in predicting differences in treatment attrition rates for cocaine and methamphetamine addicted individuals when controlling for age.

**Research question 5**: Does performance on tests of cognitive and executive function predict differences in treatment attrition rates for cocaine and methamphetamine addicted individuals when controlling for race?

H0: Performance on tests of cognitive and executive functionare not statistically significant in predicting differences in treatment attrition rates for cocaine and methamphetamine addicted individuals when controlling for education.

Ha: Performance on tests of cognitive and executive function are statistically significant in predicting differences in treatment attrition rates for cocaine and methamphetamine addicted individuals when controlling for race.

**Study Design**

The data presented in this study are taken from (CTN-0031-A), an ancillary study derived from (CTN-0031); a randomized controlled trial of Stimulant Abuser Groups to Engage in12-Step (STAGE-12) (NIDA, 2013). Nine study sites were involved in the CTN-0031 study; however, it was only necessary to recruit participants from six sites for the CTN-0031-A study. Both the ancillary (CTN-0031-A) and the original datasets from (CTN-0031) were released by the National Institute on Drug Abuse and made available for public research through the Clinical Trials Network (CTN) (NIDA, 2013). Participants were randomized from CTN-0031 groups and screened for eligibility for CTN-0031-A. All participants in the CTN-0031-A study were volunteers who met study eligibility requirements. Each qualified individual completed neurocognitive tests during a clinic study visit. Clinic staff recorded the treatment attendance of each participant over the course of the eight-week intervention phase of CTN-0031. Substance use data information originally collected for CTN-0031 was used in the CTN-0031-A study analysis.

This study design is quasi-experimental utilizing six neuropsychological tests intended to measure cognitive and executive function among males and females engaged in a substance abuse treatment program for cocaine and MA addiction. The neuropsychological tests used in this analysis are consistent with previous research concerning gender and substance abuse treatment attrition (NIDA, 2013). At the most basic level, a binary response in the form of (complete/not complete) is predicted by Response Time (RT) on the Stroop Word Color Task. Censoring is not considered problematic in this portion of the study as an early termination of treatment attendance will be labeled “not complete.” Using logistic regression, the bivariate test is expected to predict completion status based on RT. Since randomization of completion status is not possible, the analysis requires covariate adjustment to control for potential moderation and mediation. Statistical significance of this test of this primary model will be declared under this covariate adjusted model. To accomplish this task, the covariate model will be developed without regard to RT.

Variables will be included into the logistic regression as a block in a forward stepwise fashion. Since adjustment for confounding rather than statistical significance is the purpose, variables will be entered and retained in the regression using a .10 p-value level for entry and retention. For continuous variables, the assumption of linearity will be checked and, if necessary, remedial measures employed. Only after the final model is developed will RT be added, the p-value from this final model will provide the test of significance for the primary model.

Due to the nature of this study, no census or intervention was required. The primary hypothesis of this study posits that Reaction Time (RT) on the Comalli-Kaplan version of the Stroop Word Color Task is associated with gender differences in the completion phases of the CTN-0031 study. For the second hypothesis, female treatment completers compared to non-completers will: 1) have significantly better verbal learning and memory as measured by the RALVT, 2) have significantly better delay and risk assessment as assessed by the WGT, 3) be significantly better at response reversal as assessed by the WCST, 4) be significantly less impulsive as measured by the BIS-11, and 5) have significantly fewer frontal-lobe related behavioral problems as measured by the FrSBE. This study advances knowledge of gender differences in terms of demonstrated deficits in cognition and executive function and the link to treatment attrition.

Participants completed a research visit to a selected site within two weeks of study eligibility. Clinic staff utilized prescribed record-keeping as a measure of documenting a participant’s treatment attendance over the eight-week intervention phase of the study. Current substance use of cocaine and MA will be used in the analysis portion of this research. The CTN-0031 and CTN-0031-A studies were supported in part by the Clinical Trials Network (CTN) (NIDA 2013b). Prior to initiating the CTN-0031-A study, a study investigator at each site obtained written Institutional Review Board (IRB) approval to conduct the research. Data collected on behalf of qualified participants from (CTN-0031-A) were used in this secondary study.

**Methodology**

**Target Population**

A convenience sample of 27 participants from six sites in the CTN-0031 study were randomly assigned to CTN-0031-A. The study sites were substance abuse community treatment programs (CTPs), located in the states of Florida, Oregon, Washington, Texas, Ohio, and the Appalachian Tri-State node. A total sample size of 164 male and female participants from a cocaine/MA group were selected to participate in the CTN-0031-A ancillary study.

**Inclusion Criteria**: Participants deemed eligible for this study were required to meet the following criteria, including : (1) that the participant be at least 18 years of age at time of selection from CTN-0030 study, (2) the participant must meet the DSM-IV criteria of abuse or dependence on MA and/or cocaine, (2) the participant must declare the use of MA and/or cocaine as the primary drug(s) of choice, (4) possessing the ability to understand the relevant content of the study, (5) that the participant is able to provide written informed consent in English, (5) able to sign all appropriate study documentation for study access, and (6) that the participant is able to fully distinguish the colored stimuli on the Stroop Word Color Task.

**Exclusion Criteria**: In this study exclusion criteria followed the protocol of both the CTN-0031 and the CTN-0031-A study. Study participants were excluded from the study if they had previously experienced strokes or certain seizure disorders; however, participant verification of rare or isolated occurrence of seizures such as (e.g., febrile, withdrawal, acute stimulant intoxication, etc.) were also viewed as eligible.

**Study Objectives**

The main objective for this study is the replication of results that completing the Stroop Word-Color Task is a primary predictor of treatment completion for cocaine and MA abusing female and male study participants. Neuropsychological studies of substance abuse demonstrate that when addicted individuals respond to drug associated cues, this could indicate frontal lobe dysfunction and difficulty with response inhibition to change the behavior. Measuring internal thought processes is impractical for the scope of this study, therefore, a number of cognitive measures have been utilized to response inhibition, the Stroop Word Color Task is considered to very useful in selective attention by interference trials. A second objective is to assess performance on a variety of neurocognitive measures, including the Stroop Word-Color Task, Rey Auditory-Verbal Leaning Test (RALVT), Wisconsin Card Sorting Task (WCST), the Iowa Gambling Task (IGT), the Barratt Impulsiveness Scale-11 (BIS-II), and the Frontal Systems Behavior Scale (FrSBE) as predictive of treatment attrition for females and males.

**Analysis:** In this study, the analysis of a single primary test, the Stroop Word Color Task and multiple secondary measures (Stroop Word Color Task, FrSBE, RALVT, WCST and BIS-11), and will utilize logistic regression. Statistical tests for this study will be two sided at a 5% level alpha Type 1 error rate.

**Power Analysis**: For estimation of power for the logistic regression using the Stroop RT to predict treatment completion, I assume the following: (1) a 30% non-completion rate among participants, (2) a sample size of 164 and (3) the Stroop RT test split at the median (giving 82 per arm) then using the formula due to Fleiss (Fleiss 2003) this design is powered to detect an odds ratio of 2.45. If I approach the problem in the more familiar standardized effect size, power is approximately equal to that found by Street et al. (2007), who used this RT to differentiate completers from non-completers in a cocaine and MA dependent sample (effect size = .53). Based on these assumptions, a sample size of 164 is expected to yield power of less than the 90% (.894) expected from the CTN-0031A data. The anticipated sacrifice of some power in the analysis is due to the fact that we separate the date according to the gender.

**Missing Values:** Missing values are common in studies of drug abuse, and estimation in the presence of missing values may lead to biased and underpowered estimates and hypothesis testing. In the analysis proposed here, the amount of missing values should be minimal. First, participants ideally will be tested within a short session and will be consented and will agree to that session. Second, missing values on the outcome variable (completion rates), will indicate the participant’s failure to complete. However even minimal missing values across study variables may compound in the presence of list-wise deletion procedures. If this list-wise deletion is greater than 5%, the covariance model will be developed using bootstrap techniques as implemented under SAS PROC MI.

**Post-hoc Analysis:** Given that there are only a limited number of variables extracted from the CTN-0031-A study, and there are only two research questions, it is not expected that a post-hoc analysis will be merited.

**Confidentiality of data: Study Staff**

In conjunction with state and federal guidelines, NIDA has required that each Community Training Program (CTP) engaged in any aspect of the CTN-0031 and CTN-0031-A study have established protocols for the supervision and management of medical and psychiatric emergencies (NIDA, 2013). All study staff were trained in all procedures and standards according to these protocols. In addition, NIDA provided a medical monitor to the CTN-003-A study to independently review the safety data and present it to the Data Safety and Monitoring Board (DSMB) for periodic review. Investigators were required by NIDA to make periodic visits by contract monitors to audit data quality, protocol adherence, and audit and evaluate the study safety and progress. These monitoring visits allowed for independent evaluation of study progress and identification of potential problems at the study sites (NIDA, 2013).

**Data and Safety Monitoring Board:** An independent CTN-DSMB was responsible for examining accumulating data to assure protection of participant’s safety while the study’s scientific goals were being met. The CTN DSMB was responsible for conducting periodic reviews of accumulated safety and efficacy data. Support for the continuation of the trial, or evidence that study procedures were being followed, should have been changed, or if the trial required halted, for reasons including the safety of the study participants or inadequate trial performance (NIDA, 2013).

**Confidentiality of data**: By signing the protocol the investigator affirms to NIDA that information furnished to the investigator by NIDA was maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committee; affiliated institution, and employees only an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

**Confidentiality of participant records:** One of the most challenging issues associated with substance abuse research is predicated on the fact that the abuse of cocaine and methamphetamine in the United States is illegal, and fully punishable by law; therefore, those who conduct research in this area must be especially cognizant and compliant with legal and ethical protocols of working with active substance abusers (Bersoff, D., 2008; Department of Justice, 2013; NIDA, 2013).

Confidentially is paramount in neuropsychological testing, and for those who are substance abusing study participants, the protection of their privacy is especially critical in supporting the goal of credible, viable and ethical addiction research. In order to maintain strict participantconfidentiality, all Case Report Forms (CRF’s) and other related reports will be identified only by a coded participant number. NIDA provided that no participant study information will be available for release without written permission, except as required for monitoring.

**Safety Reporting**: Given that the CTN-0031-A study included participation in a single research visit and did not entail treatment intervention, required safety reporting was limited to reporting any complications directly requiring medical attention of participants. All safety data reported were expected to occur within local, state and federal guidelines and in accordance with NIDA medical intervention protocol.

**Operationalization**

**Outcome Variable**

The primary objective of the cognitive interference and executive function portions of the study focuses on the ability of neurocognitive measures to predict treatment completion by female and male participants. The outcome variable tested in this study is treatment completion by participants. Treatment completion is defined as whether or not a participant successfully completed treatment over an 8-week intervention period. For this study, participants who attended at least 5 weeks of treatment with no more than 2 consecutive absences were considered as treatment completers. A participant who attended the first 4 weeks of the program and failed to attend the fifth week could be a completer, if the individual attended in week 6 of the intervention period. Certification of each participant’s attendance is the responsibility of CTN-0031-A clinic staff.

**Independent Variables**

Cognitive and Executive Function performance on a battery of neuropsychological tests.

**Control Variable**

Gender (Male and Female)

**Recruitment, Participation and data associated with main study**

Participants for this study were taken from a sample of randomly selected males and females from the CTN-0031-A study who also met the DSM-IV requirements from current cocaine and/or MA abuse. Potential candidates were provided information concerning the CTN-0031-A study, allowed to review, ask questions and sign the informed consent form. Participants who were willing to participate in the study yet demonstrated problems in comprehending the scope of the study information, or the informed consent material were asked to review any sections that were misunderstood and discuss these section with a research staff member until the candidate exhibited a complete comprehension of the information and could willingly provide full and signed consent for participation.

Once all mandatory components of initial review and consent were completed, and a consent form was signed, each participant was directed to complete a minimal screening to determine if the participant had a history of stroke and/or recurring seizure disorders and if he or she could visually distinguish the colored stimuli on the Stroop word color task. If deemed eligible, each participant completed a research visit, the single visit was estimated to take approximately 1 and ½ hours to finish. For practicality, these visits occurred within the first one to two weeks of study participant randomization.

**Treatment Attendance**: In the CTN-0031-A study, clinic staff recorded each participant’s treatment attendance, including the dates, number of treatment hours (individual and group) sessions during the entire 8-week intervention phase of CTN-0031.

**Participant Reimbursement**: Participants received compensation for their travel, inconvenience and time. These compensations were provided via cash, vouchers or retail scrip at the direction of each study site. It was suggested that each participant receive $50 for the completion of the research site visit, including providing. It was also advised that participants who did not complete the entire research visit (due to ineligibility or other circumstance) receive the cash amount of $10.00 at the direction of perspective sites and IRB guidelines.

**Gaining access to the data**: The NIDA data-share website is an electronic environment that permits data from published clinical trials to be disseminated to researchers and the public in order to promote new research, support further analysis and distribute information to the community. The protection of human subjects in sharing data is of the utmost concern for NIDA, thus data on this site has been completely de-identified to prevent any links to actual research participants. De-identification includes the removal of all Personal Health Information (PHI) and other de-identifiers that are not contained in PHI but could potentially lead to “deductive disclosure” including comment fields and site participation numbers. De-identifiers specific to the study methods are documented in the research protocols (NIDA, 2013).

Shared data files are found on the clinical trial network site of NIDA and are available for download in two formats: SAS (transport files or. sas7bdat) and ASCII(CSV). Documentation regarding the data and corresponding study that generated the data are also available under each completed protocol page. Users are prompted to complete a registration agreement before downloading or gaining access to data. User registration requires a name and a valid email address in order to download data and to accept all responsibility of data use in accordance with the NIDA Data Share Agreement.

As part of the NIDA Registration Agreement, the user also acknowledges that, (1) the data will not use any information to establish identities of any of the subjects from whom study information was obtained; (2) to retain control over the received data, and not to transfer any portion of the received data with or without charge to any other entity; (3) to notify the user’s Institutional Review Board (IRB) operating under an Assurance approved by the Office of Human Research Protections (OHRP) as required by the recipient’s affiliated university, and in accordance with the Department of Health and Human Service regulations are 45 CRF Part 46 of any new research projects based on the NIDA data; (4) to acknowledge that the NIDA database and the specific trials accessed in all oral and written presentations and publications resulting from analyses of the received data; (5) to maintain security and privacy of the received data for as long as necessary per local and federal requirements; and (6) that NIDA or its affiliates may contact the recipient concerning publications of other issues regarding the use of the data.

**Measures: Predictor Measures**

The Comalli-Kaplan Version of the Stroop Word Color Task

The Stroop Color Word task (SWC), considered to be one of the most reliable psychometric tests of cognitive control has been a standard in neuropsychological assessment since the Stroop effect was first described in 1935 by John Ridley Stroop. The Stroop effect refers to the difficulty observers have in eliminating meaningful but conflicting information from a task, even when that information is irrelevant or counterproductive in that task. The Stroop effect can be manifest as either “interference”, that is when one mental operations degrades the performance of another, or as “facilitation”, that is, when one mental operation enhances the performance of another (Fogelson & Schluntz, 2016).

The Stroop Word Color task addresses key cognitive processes with resistance to interference from outside stimuli, cognitive control and goal oriented behavior. It is also a test of executive functioning requiring the inhibition of an over-learned concept in favor of a novel concept. The Comalli-Kaplan version described in 1962, utilizes timed trials, in which three stimulus cards are presented in a standard order. Card 1 presents blocks of color and asks the participant to name the color of each block. Card 2 involves asking the participants to read text of color names that are printed in black and white. Card 3 is an interference task which the color names are printed in incongruently-colored ink, and the participant is asked to name the ink as correct responses. Study staff will record the time required and the number of errors for each trial, yielding three summary scores and a derived interference score. The derived interference reaction time (RT) will be utilized as the primary predictor measure.

**Secondary Predictor Measures**

TheRey Auditory-Verbal Learning Test(RALVT), is widely used to assess verbal learning and various forms of memory, including episodic memory, proactive inhibition, retention, encoding versus retrieval and subjective organization. The measure has evolved over the years and several variations of the test have emerged. The standard RALVT format starts with a list of 15 words (list A), which an examiner reads aloud at the rate of one per second. The participant’s task is to repeat all the words he or she can remember, in any order. This procedure is carried out a total of five times (i.e. Trials I-V). The examiner presents a second list of 15 words (list B), allowing the participant only one attempt to recall, this is referred to as the Interference trial. Immediately following this event, the participant is asked to remember as many words as possible from the first list, which is referred to as Trial VI.

The results yielded by the RALVT include learning, which is the total number of words recalled during trials I-V, interference recall, which is the number of words recalled from the Interference Trial, and immediate recall, which is the number of words recalled during Trial VI. Interference recall has been found to be significantly worse in methamphetamine-dependent patients, compared to normal controls (Hoffman et al., 2006). In addition, interference recall is significantly correlated with striatal dopamine transporters in methamphetamine-dependent patients (Volkow et al. 20011). Consequently, the interference recall will be used as the RALVT secondary predictor measure; the other measures yielded by the RALVT (i.e. learning and immediate recall) will be evaluated in exploratory analysis. Ideally the RALVT administrations will be audiotaped, this will allow assessors to double check their work to ensure correct coding.

The Iowa Gambling Task

The Iowa Gambling Task is a gambling exercise that simulates real life decision making. Developed by Bechar and colleagues in 1994 and computerized in 3001, the task probes for deficits in judgement and decision making. Four decks of cards are displayed, labeled “A”, “B”, “C”, and “D.” Participants are instructed to click the mouse in order to pick a card and then proceed in a way that will allow them to obtain the overall highest “winnings.” Each card carries an immediate reward but some cards carry a penalty. Two decks pay higher amounts but come with higher penalties, leading to an overall loss (disadvantageous decks). The other two decks pay less but have lower penalties, leading to an overall gain (advantageous decks). The amount of reward and penalty, along with the net gain or loss, is displayed on the screen for the participant. In all, participants are allowed to select 100 cards across 5 blocks of 20 trails. Performance will be measured by the number of cards selected from the advantageous vs. the disadvantageous decks (Garcia et al. 2007).

The Wisconsin Card Sorting Task

In the electronic version of this test, participants are positioned in front of a computer and instructed to match 128 response cards, one at a time, to four stimulus cared by clicking a mouse. The cards can be sorted along three dimensions (color, form and number) and participants must utilize feedback following each selection to modify their responses and successfully sort cards. The participant must utilize feedback following each selection to modify their responses allowing for assessments of preservative responding and cognitive flexibility (i.e., the preservative errors will be used as the WCST secondary predictor measure; the other measures yielded by the WCST (i.e., preservative responses, failure to maintain set and categories completed) will be evaluated in exploratory analysis.

Barratt Inventory Scale-11

The BIS-11 consists of 30 self-report items with responses in a four point Likert type scale ranging from “Rarely/Never” to “Almost Always/Always” and comprises three domains: Attentional impulsiveness (AI), Motor Impulsiveness (MI) and Non-Planning impulsiveness(NP), these three domains are summed to yield a total score. The total score will be utilized as the BIS-11 secondary predictor measure while the individual scales (i.e., AI, MI, NP) will be evaluated in exploratory analysis.

Frontal Systems Behavioral Scale

Past research indicates that traditional neurocognitive assessments can fail to detect deficits in individuals with frontal lobe damage whose behavior in natural settings is clearly impaired. The FrSBE is a brief, valid and reliable assessment of three areas of functioning associated with the pre-frontal cortex: apathy, disinhibition and executive dysfunction. The FrSBE scores of both cocaine and MA addicted individuals, suggests that there are significant behavioral problems associated with the areas of the pre-frontal cortex. Since the FrSBE is a 10-minute self-administered assessment, it is an instrument that could be utilized by substance abuse community treatment programs. The FrSBE is written at a 6th grade reading level and consists of 46 self-report items with responses in a five point Likert-type scale. The FrSBE assesses three domains: Apathy (14 items), Disinhibition (15 items) and Executive Dysfunction (17 items), these three domains are summed to yield a total score. The total score will be utilized as the FrSBE secondary predictor measure while the individual scales (i.e., Apathy, Disinhibition and Executive Dysfunction) will be evaluated in the exploratory analysis.

For each of the three domain, two measures were taken (before and after). To facilitate the analysis , three outcomes were coded: increase, no change, and decrease. The test data were used for separate domains or combined of three.

**Assessment of Instruments:** The concept “executive function” is an umbrella term comprising a wide range of cognitive processes and behavioral competencies which include verbal reasoning, problem solving, planning, sequencing, the ability to sustain attention, resistance to interference, utilization of feedback, multitasking, cognitive flexibility and the ability to deal with novelty (Streeter et al. 2008).

These functions have been called the “cold” components of executive function because their corresponding cognitive processes tend not to involve much emotional arousal and are relatively mechanistic or logically based. In addition, executive functions involving more emotional, belief or desire such as the experience of reward or punishment, are regarded as “hot” components. Studies have shown that impairments in either the “hot” or “cold” components of executive function may have devastating effects on people’s everyday life activities, including the ability to work, and attend school, function independently at home, or develop and maintain appropriate social relevance (Hagen et al., 2016).

Neuropsychological studies of cognitive and executive functions face inherit difficulties in that there are few practical tests of brain functions that can be performed on human subjects. One of them is the accurate and valid assessment of executive functions under various conditions. Therefore, failure on executive function tests may be due to many reasons, as damage to any component process is difficult to be fully ruled out following the onset of brain lesions or psychopathologies. For example, a patient’s performance on one executive function test may have little or no predictive value for he or she performance on another test (Hagen et al., 2016). In addressing this problem, there is increasing emphasis on incorporating more complex, multifaceted and life challenges with performance measures, in other words, tasks that tap a number of executive domains at the same time.

**Participant Recruitment and Consent**

Recruitment efforts targeted participants who are randomized into the CTN-0031 study and who were found to meet DSM-IV criteria for current abuse or dependence for cocaine and MA and endorsed cocaine and/or MA as the primary drug of choice during screening baseline for CTN-0031. These candidates were provided with information about the present study and given an opportunity to review, inquire about, and to sign the informed consent form. Any participant who had difficulty understanding the information contained in the consent form was asked to review the misunderstood portion of the consent and discuss with a research staff member until he or she showed complete understanding of the information and may thus give full consent. Any participant who was unable to demonstrate understanding of the information contained in the informed consent was excluded from study participation.

**Screening/Research Visit**

After signing the informed consent form, the study participant completed a minimal screening to determine if he or she has a history of stroke and/or seizure disorder and if the participant is able to correctly distinguish the colored stimuli on the Stroop task. Based upon this eligibility, the participants then completed the research visit, which took approximately 128 minutes to complete a single visit. The timing of this visit generally occurred within the first week following the participant’s randomization into CTN-0031 but could occur as late as 2 weeks following the randomization.

**Threats to Validity**

**Content Validity**

Content validity is practical when a great deal is known about the variable that the researcher intends to measure (Gregory, 2011). Predictive validity is an area of content validity that is particularly relevant for this study in that I am seeking to predict treatment attrition rates for males and females based on their performance on various neuropsychological tests. According to Gregory (2011) when tests are used as a means of prediction, it is necessary to develop a regression equation for the data analysis. A regression equation describes “the best fitting straight line for estimating the criterion from the test” (p. 115). This research is considered to be a predictive validation study, meaning that test scores on a various neuropsychological tests are used to estimate outcome measures at a later date (Gregory, 2011). There are a number of internal and external validity threats commonly found in tests of neuropsychological testing of substance abusing populations.

Threats to validity (CTN-0031A): This is an ancillary study with data taken from a larger longitudinal study. Participants were randomly selected from six out of nine sites from the original CTN-0031 study. The neurocognitive measures included in the study yield more than a single test result. For the analyses of the data related to treatment completion, the treatment completion data will be used to classify participants as treatment completers or non-completers. There are six indicators of cognitive function derived from the interference reaction time (RT) from the Stroop Word Color Task, the interference recall score from the RALVT, 3) number of advantageous vs disadvantageous cards from the G; 4) the number of preservative errors from the WCST; 5) the total score from theBIS-11, and the total score from the FrSBE.

For the outcomes completion/non-completion, I will employ logistic regression, using a covariate adjusted model, replacing Stroop RT with the appropriate neurocognitive variables. In the latter analysis, it is possible that the distribution of the data may vary significantly from normality. Estimation in the presence of non-normality does not lead to bias in the derived estimates, however tests of significance may be impacted. It will be necessary to assess the deviation from normality of the residuals in the models, and if possible, transform the outcomes to bring about approximate normality.

Researcher bias as a threat to validity. In terms of human subject research and drug abuse, it is important that researchers maintain objectivity in the research process. One of the requirements of the research stipulates that participants had used cocaine and or methamphetamine in the past 60 days, and had a current diagnosis of cocaine or methamphetamine use or dependence (6 months) and were medically and psychiatrically stable to participate in the trial (Winhusen, 2013). In this type of study, it is important that researchers and clinic staff involved with the study participants receive appropriate training and strictly adhere to study protocols in terms of confidentiality and emergency protocol measures.

**Empirical Validity (Neuropsychological tests used in the study)**

The Iowa Gambling Task (IGT) is another test considered to measure aspects of executive function. Performance on IGT tasks has been shown in populations demonstrating chemical dependence and thought disorder (Gansler et al. 2011). Using structured equation to test whether the IGT is an executive function task (convergent validity) and whether it is not related to other neuropsychological domains (discriminant validity). One way to consider the construct validity of a neuropsychological measure is in terms of brain behavior relationships. In terms of convergent validity, relative to two other gambling tasks, the IGT was demonstrated more sensitive to differences in decision-making capacity of pre-frontal sub-region groups. Convergent/discriminant validity, the degree to which a measurement converges with similar measurements and diverges from dissimilar measurements, is another key index of overall validity. Although some research has argued that the total difference score metric from the IGT represents a diffuse amalgam of processes, nevertheless a review of the literature indicates that the IGT is assumed to measure executive function. EF, though not necessarily considered a unitary cognitive process, has been defined as the ability to organize a sequence of actions towards a goal.

In two empirical reports, the IGT was considered more sensitive to the presence of neurologic disease than the classic executive functioning tasks (i.e. Trail Making Test, Verbal Fluency, WCST) and in another was more sensitive to the presence of serious chemical dependence. It has been reported that the last four blocks (80 trials) of the IGT are associated with a measure of EF, the WCST, and not with a measure of intelligence, the Wechsler Abbreviated Scale of Intelligence among healthy controls. Although this is a reasonable test of construct validity, it is not a stringent test, which arguable would include neuropsychological measures.

Carvalho et al. (2013) note that evidence supporting the FrSBE’s validity is growing. In their research, concurrent validity of the FrSBE has been evidenced by other measures of behavioral interference and neuropsychiatric problems (e.g. depression, anxiety, disinhibition etc.). In conjunction with other psychiatric assessments including the Neuropsychiatric Inventory (NPI). Convergent validity of the FrSBE was supported in association with the Apathy and Disinhibition in terms of measuring distinct forms of depression (Carvalho et al. 2013).

Although limited, construct validity of the FrSBE is supported in associations between the scale and neuroimaging data. An Exploratory Factor Analysis (EFA) was conducted on the FrSBE to investigate the factor structure of the instrument. Informant ratings on the FrSBE were provided for patients representing a broad range of neurological diagnosis such as mild cognitive impairment (MCI, AD, FTD, PD, and HD). Model fit indices and reliabilities (measured using internal consistency reliability) were compared in the original and in several alternative models. The original scale demonstrated a generally good fitting model, although the best fitting model (referred to as the reduced model) removed eight items from the original measure and modestly improved fit over the original FrSBE. Strong reliability was found in both versions.

**RALVT**

The Rey Auditory Verbal Learning Test (RALVT) is widely used for the assessment of episodic memory (Jardim de Paula et al., 2011). The reliability analysis is the evaluation of the stability or precision of a test measurement. One method for the analysis of the characteristic is the internal consistency, performed for this study by calculating Cronbach’s Alpha. The construct validity of the RALVT was attained through its correlations with two other neuropsychological tests (MMSE ad CDT) and an EFA, using the principal axis factoring and oblique rotation. Considering the variable gender, performance of men and women was compared by the Student’s t test, including the calculation of Cohen’s d effect magnitude.

The analysis of the psychometric properties of the RALVT conducted in de Paula’s study provides significant evidence of reliability (through analysis of internal consistency), construct validity (through the use of divergent correlations and analysis of factorial structure), besides it investigates the influence of sociodemographic variables such as age, education, and gender and the clinical variable of depressive symptom. RALVT is an instrument marked by learning processes, where each component of the test depends crucially on the previous one, which tends to increase the variance shared by each component.

These authors argue that the assessment of construct validity through correlations with other neuropsychological tests and analysis of the factorial structure is overly biased by the characteristics of the participants. In certain populations experiencing episodic memory issues is not supported by analysis. However, evidence suggests that factorial analysis can be a useful tool for construct validity when conducted in samples of adequate size and homogeneity, and preferably in combination with other similar cognitive measures.

**Stroop Word Color Task**

Neuropsychological studies involving treatment attrition and drug dependence frequently support findings from performance on computerized test to be a highly reliable measure of treatment attrition. Computerized tests such as the Stroop Word Color Task demonstrate that poor performance on these test of cognition are consistent with non-completion of drug abusing males and females in drug treatment programs. Research suggest that the ability to identify cognitive and executive function deficits in treatment participants might also improve those individuals who are most vulnerable to treatment incompletion (Streeter et al., 2008).

The Stroop Word Color Task is believed to test key cognitive processes associated with selective attention, cognitive control, and goal-oriented behavior that supports the ability to select a weaker, task relevant response in the face of competition from a potentially stronger, task irrelevant on (Streeter et al. 2008). Difficulty with the inhibitory processing is reflected by an increases in time in the interference subtest relative to the color naming or word reading subtests. Slowed performance on the interference subtest has been interpreted to reflect difficulty in resisting interference, an inhibitory function associated with frontal cortical integrity. Subjects with prefrontal impairment have difficulty with this task, suggesting that the frontally mediated processes are involved in adhering to the goals or rules of the task in the face of a competing, stronger (i.e. more salient, habitual, or prepotent) response.

The present study assessed whether performance on the Comalli version of the Stroop Task was able to predict treatment attrition in cocaine-dependent subjects. It was hypothesized that dropouts would exhibit poorer performance scores on the interference subtests than subjects who completed the course of treatment, suggesting that impairment in the ability to inhibit a proponent response is a marker for poor treatment compliance.

**Threats to construct or statistical conclusion validity**

Statistical conclusion validity, a term coined by Cook and Campbell, holds that when the conclusions of a research study are founded on adequate analysis of the data, generally meaning that adequate statistical methods are used whose small-sample behavior is accurate, besides being logically capable of providing an answer to the research question (Garcia-Perez, 2012).

Garcia-Perez (2012) discusses two types of threats to statistical conclusion validity, the first threat involves data that are subjected to inadequate statistical analyses that do not match the characteristics of the design used to collect the data, or that cannot logically give an answer to the research question. The second issue is when a proper statistical test is used but is applied under conditions that alter the stated risk probabilities. In the first case, the conclusions will be wrong except by accident; and in the second case, the conclusions will fail to be incorrect with the declared probabilities of Type I and Type II errors. Regression methods such as those used in the analysis of data in CTN-0031 and CTN-0031 A, rely on the assumption that predictor variables have fixed values and are measured without error is the standard in statistical testing, however, despite this assumption there are some precautions that must be taken pertaining to these variable measurements.

Garcia-Perez (2012) cautions that the assumption of validity can be assessed in predictor variables by correlational methods investigating bivariate relationships, this is also true in the case of psychometric functions (the six predictor measurements in the CTN-0031A study) describing the form of the relationship between physical magnitude and the performance in a detection, discrimination, or identification task. Regression or similar methods are typically used to estimate parameters of these relationships, with stimulus magnitude as the independent variable and the perceived performance as the dependent variable, in the case of the CTN-0031A study, this description is accurate in that the strength (magnitude) of associated neuropsychological tests employed in the research are expected to predict treatment completion (outcomes).

The assumption of predictive measures for the CTN-0031 A study is directly associated with the exactness of test performance from the sample population of the CTN-0031 study. Researchers in the CTN-0031A study have taken steps in the statistical analysis to ensure that irregularities or the possibility of Type 1 and Type II errors are controlled in their study by conducting appropriate two stage and regression analyses in examining the bivariate relationship of the independent and dependent variables.

Summary of Research Design

In this quasi-experimental study design, the research intention is to approach a previous study that performance on a series of neurocognitive tests from a different angle in an attempt to derive the innate association of cognitive interference and treatment completion with gender. This study specifically examines gender differences in neurocognitive test performances and treatment completion from the CTN-0031A dataset.

The researcher is fully aware that the population from the CTN-0031A is unique in that each participant must meet the criteria of cocaine and or methamphetamine abuse in addition to other study criteria. While it is hoped that in terms of study replication, there will be generalizability to other populations with similar characteristics of drug abuse and treatment outcomes, it is not expected that the results of this study analysis will be generalizable to other populations who do not possess similar characteristics.

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