A COMPARATIVE ANALYSIS OF REPRESENTATIONS FOR EXECUTIVE FUNCTION IN THE CONTEXT OF HIV MEDICATION ADHERENCE AND METHAMPHETAMINE USE

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Abstract

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By

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The current research seeks to clarify the relationship between executive function and the behaviors of medication adherence and methamphetamine use in HIV+ men who have sex with men. Executive function is impaired by HIV, and those impairments are associated with difficulties in adherence. Difficulties in adherence lead to greater disease burden and more impairment. Methamphetamine contributes to the problem by exacerbating executive function directly, and by impacting executive function indirectly through disease progression related to poorer adherence, less effective treatment, and by directly increasing the replication rate of HIV.

Executive function is the process by which distinct cognitive functions are coordinated in order to direct behavior towards a goal. The construct of executive function and many of the neuropsychological tests used to measure it are multifaceted in nature, making it difficult to delineate specific components of executive function. This inability to accurately differentiate components creates a barrier to targeted intervention development for impacting executive function problems that may lead to nonadherence and methamphetamine use.

The present study operationalized executive function in three ways: a) by using individual neuropsychological test variables; b) by averaging individual variables to create a executive domain NPZ score, the standard for the current literature; and c) by using factor scores

created through exploratory factor analysis of the individual neuropsychological test variables. These three methods were compared in their association with demographic variables, methamphetamine-use characteristics, disease progression, and adherence variables.

The factor analysis yielded a six-factor solution: Executive Inhibition, Decision Making/ Reinforcement Processing, Wisconsin Card Sorting Test Performance, Motor Impulsivity, Slowness of Processing, and Sustained Attention.

All three methods for operationalizing executive function predicted adherence behavior while controlling for methamphetamine dependence severity. However, the comparison of the three representations of executive function demonstrated the strengths and weaknesses of each approach. Analyzing the relationship between executive function and HIV-related health behaviors using neuropsychological test variables individually retained specificity, but lacked statistical predictive power. The executive domain NPZ score was a powerful predictor, demonstrating a relationship between executive function and adherence even when controlling for demographic factors. However, this method lacked specificity and was sensitive to misinterpretation. The factor scores were not as powerful, but greatly added to the interpretability of function associated with HIV-related health behavior.

These three methods for operationalizing executive function all retain some value for predicting HIV-related health behaviors. The factor scores provide an intermediate level of power between individual scores and an executive domain NPZ score. Most importantly, the convergent and divergent evidence provided by the factor loadings increases the confidence that the factor scores are measuring specific delineated functions than. Clarifying the relationship between specific functions and health behavior is the first step in paving the way to targeting executive function difficulties for intervention development in HIV+ persons.

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Chapter 1:

Background and Introduction

The management of HIV infection and the control of further transmission requires HIV+ individuals to exhibit behavioral control to maintain almost-perfect medication adherence in order to avoid disease progression and/or the development of a treatment resistant strain of the virus (Bangsberg et al., 2003). Behavioral control is even more difficult among substance using individuals. Substance intoxication can lead to attention deficits and memory difficulties (Simon et al., 2000), which in turn can lead to poor HIV medication adherence. Compounding the problems caused by nonadherence is the fact that dopamine agonist drugs, such as cocaine and methamphetamine, speed up viral replication and increase viral load (VL), leading to accelerated disease progression (R. Gonzalez & Cherner, 2008). Because of their vital and intersecting impact on the health of HIV+ adults, adherence and substance use must be examined together in the hope of developing comprehensive interventions for treatment.

Executive function is the cognitive ability that allows for the behavior control necessary to maintain antiretroviral therapy (ART) adherence. Executive function is required for any behavior that includes the *planning, initiation, sequencing, and modifying* of complex behavior in the face of multiple or novel cues (Duncan, Emslie, Williams, Johnson, & Freer, 1996; Hester, Lubman, & Yucel, 2010; Miller & Cohen, 2001; Pickens, Ostwald, Murphy-Pace, & Bergstrom, 2010; Royall et al., 2002). Executive function is involved in goal-directed behavior as it allows for setting rules to achieve a desired goal and *maintain* behavior, even when there are prepotent responses or more salient cue*s* (Miller & Cohen, 2001). ART adherence requires all of these

considerations. HIV+ persons must *plan* for how they will take their medications. They must *initiate* that behavior when first prescribed treatment. They must deal with the *sequencing* of behavior when food or water is required before or after a medication. They must deal with the *modification* of their behavior when a new regimen is required or when dealing with daily routine changes, such as on weekends or on vacation. And perhaps most important, they must *maintain* these behaviors despite treatment fatigue, negative side effects and a desire to simply not be reminded that they have a stigmatized disease.

Considering the importance of executive function to ART adherence, it is troubling that HIV infection has been associated with deficits in executive function tasks. These deficits include problems with decision making (E. M. Martin, Sorensen, Edelstein, & Robertson, 1992), working memory (E. M. Martin et al., 2003), and cognitive flexibility (Basso & Bornstein, 2003; E. M. Martin, Novak, et al., 2004). Not surprisingly, the same deficits in executive function are associated with problems remaining adherent to HIV medications (Barclay et al., 2007; Ettenhofer, Foley, Castellon, & Hinkin, 2010; Hinkin et al., 2004). Thus, HIV presents escalating barriers to its own treatment.

The relationship between HIV, executive function deficits, and medication adherence is complicated by substance use, as substance dependence has also been associated with deficits in executive functioning (Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2006), including problems with decision making (Bechara, 2003a; Bechara & Damasio, 2002), working memory (E. M. Martin, et al., 2003), sensitivity to future consequences (Bechara & Damasio, 2002; Bechara, Dolan, & Hindes, 2002), and impulsivity (Kirby & Petry, 2004). Beyond directly affecting executive function, there is

evidence that substance use itself is a barrier to adherence (Altice, Kamarulzaman, Soriano, Schechter, & Friedland, 2010; Carrico, 2010; French, Tesoriero, & Agins, 2011; Friedman et al., 2009; A. Gonzalez, Barinas, & O'Cleirigh, 2011; Hinkin et al., 2007; Ingersoll, 2004; Lehavot et al., 2011; Sharpe, Lee, Nakashima, Elam-Evans, & Fleming, 2004). At this lower level of adherence, higher viral loads are more likely, and there is more of an opportunity for HIV-related executive dysfunction to occur. Methamphetamine use is particularly insidious for this indirect path to executive function impairment, because in addition to being a barrier to adherence, methamphetamine directly increases the rate of HIV replication (Gavrilin, Mathes, & Podell, 2002; Toussi et al., 2009). Thus, to effectively intervene on the health of HIV+ persons it is important to examine the nature of executive dysfunction in HIV+ nonadherent substance users and in specific, methamphetamine users.

Despite the interest in executive function and its relative importance to behavior, the construct of executive function is often poorly operationalized. Researchers operationalize executive function differently from study to study. Executive function is, at times, operationalized with one test (Solomon & Halkitis, 2008), and more often, with many tests (Ettenhofer, et al., 2010; Hinkin, et al., 2004; Waldrop-Valverde, Jones, Gould, Kumar, & Ownby, 2010). Some researchers have argued that executive function is a unitary construct, while others suggest it consists of multiple functions that share a similar brain region (Miyake et al., 2000). The tasks used to measure executive function often correlate poorly with one another, suggesting that executive function is more likely executive function**s**. Studies that have examined factor structures of executive function tasks have yielded results ranging from a single to multiple factors (Royall, et al., 2002).

Even within a single executive function task, multiple factors can sometimes be derived from different variables within that task (Greve, Ingram, & Bianchini, 1998). Despite the apparent diversity of executive function, researchers often simply average the scores across different tasks making a composite score (Ettenhofer, et al., 2010; Hinkin, et al., 2004; Waldrop-Valverde et al., 2006). Complicating matters further is the issue of task impurity. Performance on executive function tests often requires lower-level functioning to be intact. Thus, two people with dysfunction in different domains may look the same on an executive function test (Miyake, et al., 2000). For example, many executive function tests require decisions to be made based on past feedback. A participant who makes those decisions poorly may do so by improper calculation of information from earlier in the task, or s/he may make those same decisions due to an inability to remember the past input. These two people have distinctly different deficits, but may receive similar test scores.

Considering the complexities that exist in relation to executive function measurement and the importance of executive function to ART adherence behavior, it is surprising to find that within the HIV literature many researchers simply standardize and average scores across multiple tests, yielding a blanket domain score. The treatment of executive function as a homogenous construct ignores the fact that specific aspects of executive function may be driving the relationship with missed medication. As mentioned earlier, there are aspects of planning, initiation, sequencing, modification and maintenance that are necessary for successful ART adherence. Any one of these individual issues may be driving the relationship between adherence and executive function, but without careful consideration of the representation of executive function

measurement, those relationships will remain a mystery. This dumping of all functions into a single construct is problematic, because interventions that will effectively improve ART adherence will require the accurate identification of executive function deficits that are most likely to: 1) lead to poor ART adherence, 2) be associated with HIV disease progression and methamphetamine use, and 3) be associated with the interaction of ART adherence, HIV disease progression and methamphetamine use.

In summary, HIV+ persons must maintain ART adherence to stave off disease progression. Adherence is a complex behavior that requires goal-directed action, and executive function is used in order to successfully maintain high levels of adherence. HIV+ methamphetamine users have an uphill battle to maintain ART adherence, as both HIV and methamphetamine use have been shown to impair executive function. The measurement of executive function is complicated, which leads to issues of poor operational definitions. When these poor operational definitions are used in the study of HIV and ART adherence, they obfuscate the specific neurocognitive functions that could be used for intervention development. In order to clearly understand the relationship between the neuropsychological construct of executive function and the health behaviors of nonadherence and methamphetamine use, we need to employ methods that compare different approaches to defining executive function. These methods need to allow for the diversity of executive function, as well as addressing task impurity. The current proposal seeks to contrast three methods of examining executive function (single variables from tasks, domain NPZ score, and factor scores) in predicting the associations between dysfunction and both medication nonadherence and methamphetamine use in a population of HIV+ men who have sex with men (MSM).

In order to set the stage for the present study, this introduction will review past research on the intersection of methamphetamine use, adherence, and neuropsychological dysfunction among HIV+ persons. The review will begin with a section on HIV. This section presents the particular importance of medication adherence in treating HIV and the rationale for the specific population being studied (MSM in New York City). In order to offer evidence that executive function is necessary to maintain adherence behavior, it is necessary to briefly define executive function, and demonstrate the complexity of adherence behavior. What follows is a summary of the existing knowledge regarding neuropsychological deficits associated with HIV. This section will distill the present body of literature suggesting that HIV presents executive function barriers to ART adherence.

The next section will then explain how methamphetamine use complicates the intersection of HIV, medication adherence and neuropsychological function. In order to do this, there will first be a presentation of background information on methamphetamine and key studies of the neuropsychological consequences of methamphetamine use. Following will be a section demonstrating methamphetamine's association with HIV infection among MSM, as well as its impact on adherence behavior. This section will discuss two pathways through which methamphetamine impacts executive function, both directly, as well as indirectly through methamphetamine's association with poor adherence. Having reviewed adherence and methamphetamine use, the stage is set to review the scientific literature addressing the neuropsychological effects of methamphetamine use combined with HIV infection. Following will be a section demonstrating the significant difficulties posed by the operationalization of executive function. In response to these difficulties, the literature that addresses factor analytic

methods within studies of executive function will be presented, along with a discussion of the barriers for accurate identification of executive function as it relates to HIV and adherence. In this last section, having presented the context of difficulties defining executive function, the neuropsychological deficits associated with adherence will be revisited, with a focus on the methods of operationalizing deficits.

HIV and Antiretroviral Therapy

HIV, Prevalence and ART Therapy. Since the first diagnoses in 1981, AIDS has been a significant public health problem in the United States and in the world. The virus which leads to AIDS, the Human Immunodeficiency Virus (HIV), remains an issue in the United States, with the Centers for Disease Control and Prevention (CDC) estimating that 1,178,350 people were living with the virus in 2008 (CDC, 2011b). Alarming is that it is believed that 20% of HIV+ individuals are undiagnosed (CDC, 2011b). While the incidence rate of HIV fell after the 80s, it has remained relatively constant since 1990 with between 40,000 and 50,000 new infections each year (Hall et al., 2008; Prejean et al., 2011).

HIV has particularly affected men who have sex with men (MSM) in the United States. Of new infections in 2009, 59% were transmitted via male-to-male sexual contact (CDC, 2011a) and 61% of all new infections were among MSM (Prejean, et al., 2011). A recent CDC study in which MSM were tested for HIV, revealed a prevalence of HIV among MSM at 19%, with 44% of those infected unaware of their status (CDC, 2010). In this study of 21 cities in America, New York had the second highest HIV prevalence, with 29% of MSM studied testing positive, and of those, 52% were unaware of infection

(CDC, 2010). Based on these prevalence rates, HIV infection and treatment in the MSM community in New York City (NYC) should be made a priority.

While incidence rates have remained consistent over the last two decades, prevalence rates of HIV have increased, partially due to the development of antiretroviral therapy (ART). Although contracting the virus was once considered a fatal condition, ART has made infection a lifelong chronic disease. In response to its rapid replication and high likelihood of mutation, HIV is treated with a combination of different classes of ART medications which interrupt the replication process of the HIV life cycle at different stages. The HIV replication process is the point of intervention for ART. Disrupting replication stops the virus from spreading inside the body and limits the possibility of mutation, which can lead to new strains of the virus.

The Importance of Adherence. HIV medications are given in "cocktails" that combine multiple classes of ART. These combinations of medications are given to insure that any virus that undergoes a single mutation will still be unable to replicate. This constant battle against replication and mutation makes it essential to take each and every medication as prescribed if long-term viral suppression and immunological benefits are to be achieved (Safren, Hendriksen, Desousa, Boswell, & Mayer, 2003; Sherer, 2003). The construct defined by level of medication taken as prescribed is referred to as adherence. Studies have shown that adherent patients demonstrate significant increases in CD4 counts and are more likely to have undetectable viral loads compared to nonadherent patients (Kitahata et al., 2004; Kobin & Sheth, 2011; Safren et al., 2005).

Early studies found that a 90 to 95 percent rate of adherence was necessary to achieve undetectable viral loads (Paterson et al., 2000; Read, Mijch, & Fairley, 2003),

slow disease progression, and prevent resistance (Piacenti, 2006). In recent years, the development of new, more potent medications has allowed for regimens that are more forgiving of nonadherence. For example, the level of adherence necessary to achieve positive outcomes such as viral suppression and prevention of resistance depends to a certain degree on the pharmacokinetic profile of the particular medications taken (Kobin & Sheth, 2011). Studies of protease inhibitors have shown distinct differences based on whether the regimen is boosted by a protease inhibitor that slows the metabolism of other ART medications, such as Ritonavir. Studies of unboosted regimens of protease inhibitors continue to show that 90 to 95 percent adherence is still necessary for adequate viral suppression (Maggiolo et al., 2007; M. Martin et al., 2008). Boosted regimens of protease inhibitors require far lower rates of adherence to achieve viral suppression, with most studies suggesting that 80 percent adherence is sufficient (Maggiolo, et al., 2007; M. Martin, et al., 2008; Parienti et al., 2010; Shuter, Sarlo, Kanmaz, Rode, & Zingman, 2007). These boosters create other problems despite making ART regimens more effective. Ritonavir, the medication most often used and studied as a protease inhibitor booster, boosts levels of other protease inhibitors through its potent cytochrome p450 inhibition. Different cytochrome p450 enzymes break down various medications and foods. Thus, their disruption can create problematic interactions for other substances. Most important for the research at hand, Ritonavir has potentially deadly interactions with methamphetamine-based substances of abuse (Hales, Roth, & Smith, 2000; Harrington, Woodward, Hooton, & Horn, 1999; J. A. Henry & Hill, 1998).

Studies of the adherence levels necessary for viral suppression using non-nucleoside reverse transcriptase inhibitors (NNRTI) have yielded equivocal results. Some

studies have reported that an adherence rate as low as 55 percent is adequate for viral suppression (Bangsberg, 2006; Maggiolo, et al., 2007). Others have reported an 80 percent threshold for viral suppression (M. Martin, et al., 2008) and still others report 95 percent adherence as necessary to maintain an undetectable viral load (Bangsberg et al., 2006). An explanation for this wide range of adherence thresholds can be found in the pharmacological profile of NNRTIs. NNRTIs have long half-lives and can be active in the body weeks after discontinuation, making the concerns related to NNRTI adherence not one of percent medication taken, but one of continuous gaps in treatment (Bae, Guyer, Grimm, & Altice, 2011). A single day of NNRTI treatment missed once a week over a three-month period would be less likely to lead to virological failure than a 12-day continuous gap in treatment over that same three-month time frame, despite the fact that the percent adherence would be the same (Parienti et al., 2008). This emerging field of medication research examines medication persistence, or a sustained interruption in treatment. There is still much research needed to determine what length of disruption is predictive of poor outcomes, both for viral rebound and resistance (Altice & Bae, 2011).

The Measurement of Adherence. The way adherence is measured also impacts determinations of adherence levels necessary for maintaining viral suppression. Although measuring drug levels in the blood would be the most direct way to determine whether a participant had taken his or her medication, this method is extremely costly and ignores the many individual metabolic factors that change a medication's pharmacokinetics. In addition, for drugs with shorter half-lives one would need to monitor drug levels on an almost daily basis to track adherence, which is not feasible in either a research or a

clinical setting. For these reasons, many alternative methods have emerged, ranging from subjective self-report measures to electronic objective monitoring.

Adherence is most often measured using self-report (K. M. Berg & Arnsten, 2006; M.A. Chesney, Morin, & Sherr, 2000; Liu et al., 2001; Nieuwkerk, de Boer-van der Kolk, Prins, Locadia, & Sprangers, 2010; Nieuwkerk & Oort, 2005; Ortego, Huedo-Medina, Vejo, & Llorca, 2011; Wilson, Carter, & Berg, 2009) as this method is cost effective, has a moderate correlation with virologic outcomes, and is easy to administer for the participant, clinician and researcher (K. M. Berg & Arnsten, 2006; Ortego, et al., 2011; Parsons, Golub, Rosof, & Holder, 2007; Wilson, et al., 2009). Self-reported adherence takes a variety of forms. In a common version, the participant is asked how many doses s/he missed within a specific time frame, and the time frames most frequently offered include "yesterday,""the last three days,""the last seven days," and "the last 30 days"(Hansen et al., 2009; Simoni et al., 2006; Wilson, et al., 2009). The response options vary from study to study, with some obtaining an exact number of missed doses, some using a Likert scale, and still others using a visual analogue scale (Dobbels et al., 2010; Rao et al., 2011; Simoni, et al., 2006). A visual analogue scale asking about the last thirty days has been validated against unannounced pill counts, suggesting it is a very good method for assessing adherence (Kalichman et al., 2009). Another method for obtaining adherence data is the Timeline Follow Back (Sobell & Sobell, 1992). The Timeline Follow Back is a well-validated measure that uses a calendar to guide participants through recall. In addition, it allows for the examination of behavioral determinants of adherence in a time-dependent manner (Ingersoll et al., 2011; Meade, Conn, Skalski, & Safren, 2010; Parsons, Rosof, & Mustanski, 2008b; Parsons,

Rosof, Punzalan, & Di Maria, 2005). More broadly, another advantage of these self-report measures is that they provide immediate opportunities to examine reasons for nonadherence with participants (K. M. Berg & Arnsten, 2006; Garvie, Wilkins, & Young, 2010; Johnson, Dilworth, Taylor, & Neilands, 2011). The initial obvious drawback to self-report is that these measures rely upon the ability of participants to remember something they forgot. In addition, as patients have been reminded by their doctors of the importance of adherence, there is also concern that social desirability plays a factor in self-reported adherence, especially when reporting directly to the medical staff that supplies or prescribes the medication. It is widely believed that self-report measures, in general, produce overestimated adherence rates (Arnsten et al., 2001; K. M. Berg & Arnsten, 2006; Nieuwkerk & Oort, 2005; Simoni, et al., 2006), but this overestimation can be diminished by permitting a participant to answer without a researcher present (Cohen, Harezlak, Gongvatana, et al., 2010; Harezlak et al., 2011; Kalichman, et al., 2009). Overestimation of adherence may lead to overestimating the level of adherence necessary for viral suppression. In summary, although the self-report methods are not perfect, they are associated with biological outcomes, they are relatively cost-effective, and their flaws can be minimized with simple techniques.

Though self-report is the most common measure for ART adherence, for quite some time electronic drug monitoring through the use of devices such as the Medication Event Monitoring System, or MEMS caps, was considered the gold standard in the adherence literature. MEMS caps electronically monitor the opening of a pill bottle. Although MEMS data has the highest correlation with biological outcomes, it is not without problems (K. M. Berg & Arnsten, 2006; Christensen, Osterberg, & Hansen, 2009;

Hawthorne et al., 2011; Pearson, Simoni, Hoff, Kurth, & Martin, 2007). MEMS records the opening of a bottle, but an open bottle does not always mean a taken pill. Furthermore, the MEMS cap places an added barrier between a person and his/her medication. Some standard adherence techniques, such as using a pill box, are not compatible with MEMS caps. Removing people who use pill boxes can lead to a biased sample of participants who are more likely to be nonadherent (Kalichman, Cain, Cherry, Kalichman, & Pope, 2005; Ruddy, Mayer, & Partridge, 2009; Schneider, Hess, & Gosselin, 2011). Participants who like to have an extra pill with them in case they need it, will often pull out several pills at a time. These "pocket doses" may lead to an underestimation of adherence (Bangsberg, Hecht, Charlebois, Chesney, & Moss, 2001; Becker, Thames, Woo, Castellon, & Hinkin, 2011; Ettenhofer et al., 2009). The barrier to adherence that MEMS caps create, and these pocket doses may lead to underestimation of adherence, which may in turn lead to underestimating the adherence levels necessary to achieve viral suppression. The financial cost of MEMS to the researcher and the burden this method places on participants (barrier to medication, bulky bottles, frequent trips to download data) makes electronic drug monitoring impractical for widespread use.

There are several other methods to objectively measure adherence. One common objective measure is the pill count, which may take one of two forms. The first is an announced pill count, in which a participant brings his/her medication bottles to the researcher who then counts the medication. These counts have only a moderate correlation with viral load, as the pill count is sensitive to "pill dumping" (K. M. Berg & Arnsten, 2006; Kalichman, Amaral, et al., 2010; Kalichman, et al., 2009). The second method involves unannounced pill counts, where the researcher visits a participant's

regular place of residence and counts his/her medication. The latter method has proven as, or more effective than, electronic drug monitoring at predicting viral load (Bangsberg, et al., 2001; Haberer et al., 2011; Kalichman, Cherry, et al., 2010; Moss et al., 2004). To limit the burden on participant and researcher, studies now will call participants and count their medication with them over the phone (Kalichman et al., 2008; Kalichman et al., 2007). Despite this advancement, unannounced pill count methods are still time consuming for both researcher and participant, and have not replaced other measures of adherence.

Pharmacy refill patterns provide another source for obtaining objective adherence data. Although pharmacy refill data can be difficult to obtain due to HIPPA laws, it is free from tampering and provides a unique opportunity to examine the effects of population level adherence (Wood et al., 2004). However, it does not allow for daily assessment of behavior, and cannot be used for finer discrimination of reasons for nonadherence. For example, a participant whose insurance company has denied coverage, a participant whose doctor forgot to call in a prescription, and a participant who is simply nonadherent might all have the same "adherence" level, despite having very different problems. The many methods for adherence measurement have an impact on the level of adherence necessary for a particular outcome, but should not fundamentally change that relationship. As different types of adherence measurement have different strengths and weaknesses, and may over- or underestimate adherence, it is generally accepted that the best way to measure adherence is to use multiple techniques (Carrico, 2010; Garvie, et al., 2010; Kunutsor et al., 2010; Pearson, et al., 2007).

The Relationship of Adherence to Resistance. Another common outcome examined in adherence studies is the development of ART resistance. Resistance develops when the virus mutates at the site of therapeutic action rendering a medication, or class of medications, ineffective. In the presence of ART, a mutation that allows the virus to replicate will be selected for, and thus a treatment resistant strain emerges. Given no drug, there is no force on the system to select for treatment resistant strains, and at perfect adherence the virus cannot mutate because replication is most likely being successfully suppressed (Gardner, Burman, Steiner, Anderson, & Bangsberg, 2009). Therefore, for resistance, unlike virologic outcomes, there is a peak level of adherence where resistant mutations are likely to develop. With regard to optimal adherence for resistance, differences again emerge by medication regimen type, especially with regards to potency. Unboosted protease inhibitor and NNRTI regimens are most likely to develop resistance at relatively higher levels of adherence (~80 percent), boosted protease inhibitors are most likely to develop resistance at about 50 percent adherence (though resistance to boosted protease inhibitors is relatively unlikely to occur at all), and NNRTIs develop resistance optimally at low rates of adherence (~20 percent) (Bangsberg, Moss, & Deeks, 2004; Gardner, et al., 2009). Despite the discussion in the academic community of how to measure adherence, and the differences in adherence levels adequate for viral suppression or to stave off resistance, perfect adherence is the best way to ensure a patient's health.

Executive Function: The Basis of Cognitive Control

It is important that HIV+ individuals maintain high rates of adherence to HIV medication in order to keep viral load low and CD4 levels high. HIV+ individuals must

engage in safe sex practices to avoid transmission and infection with other sexually transmitted diseases. They must also maintain a healthy lifestyle: eating well, avoiding substance use, and exercising in order to keep their immune system functioning well. To achieve these behaviors, the HIV+ individual must exhibit cognitive control, focusing on the goal of long life over immediate pleasures. The neuropsychological function primarily responsible for the ability to control behavior in such a manner is referred to as executive function.

Executive function is loosely defined as the cognitive process by which other cognitive functions are organized, sequenced and controlled. Executive function is necessary in any task that requires goal-directed behavior, and includes the planning, initiation, sequencing, and modifying of complex behavior in the face of multiple, more salient, or novel cues (Duncan, et al., 1996; Hester, et al., 2010; Miller & Cohen, 2001; Pickens, et al., 2010; Royall, et al., 2002). As discussed in their review article, Miller and Cohen (2001) argue that the prefrontal cortex drives behavior through top down executive processes. These processes make possible behavior that adheres to rules that are set to achieve the desired goal, despite prepotent responses or more salient cues. Executive function is necessary to continue goal-directed behavior through intervening, irrelevant, interfering and distracting events.

Higher cognitive functions have long been localized to the frontal lobes. Since the case of Phineas Gage (Harlow, 1999) in 1848, "higher level" functions have been related to the frontal lobes. It is only since the cognitive revolution that executive function has been studied in its present form. The work of Alexander Luria, carefully detailing head injuries in soldiers from World War II (Royall, et al., 2002), as well as the concept of the

central executive developed by Norman and Shallice and adapted to working memory by Baddeley (1986), has brought us to the modern-day concept of executive function. Since the 80s, many studies have examined the effects of focal frontal lesions on a wide array of neuropsychological functions (Picton et al., 2007; Shallice, Stuss, Picton, Alexander, & Gillingham, 2007; Stuss & Alexander, 2000; Stuss et al., 2005; Stuss & Levine, 2002), clearly demonstrating the importance of the frontal lobes in tests of executive function. Because executive function is regarded as a higher-level function that coordinates lower level abilities, the frontal lobes are not alone in their importance. The prefrontal cortex is uniquely situated with connection to virtually every brain region. There are inputs to the prefrontal cortex from sensory and motor regions, as well as reciprocal connections throughout the frontal lobes, anterior cingulate, and midbrain structures (Miller & Cohen, 2001). These extensive connections make the frontal cortex the only region of the brain receiving somatosensory, external sensory, emotional, and motivational information (Royall, et al., 2002). Therefore, this region of the brain is uniquely capable of integrating that information into complex action.

Measures of Executive Function. A wide variety of abilities are tested as executive function, including cognitive flexibility, planning, response inhibition, decision making, and working memory. Two commonly used measures are the Wisconsin Card Sorting Test (WCST: E. A. Berg, 1948) and the Stroop color-word interference task (Stroop, 1935). Both of these tests were developed long before the modern concept of executive function was being studied. In the WCST, participants are asked to sort cards based on one of three rules. After 10 correct trials, the rule changes and the participant must shift her or his set in order to sort the cards correctly. This test is thought to measure

cognitive flexibility, or the ability to adapt to a new set of rules. The WCST has been used extensively for more than 60 years to examine executive function through cognitive flexibility in both research and clinical populations. Other similar tests have been developed to study these same concepts verbally, such as the Category Test. The second classic test of executive function is the Stroop test. In the Stroop, participants are presented with a list of color words to read. Then they are presented with another list of color words, but the words are printed in different colored ink. The participant is instructed to not read the word, but instead to say the color of the ink the letters are printed in. Thus a participant may see the word "green" but have to say "red" because the word is printed in red ink. This test is most commonly thought of as measuring executive function through inhibition, as the participant must inhibit his or her natural reaction (reading the word) in order to answer correctly (naming the color).

Numerous other tests have been developed to assess individuals' executive function capacity. The Trails AB (Reitan, 1958) is often described as an inhibition task but is also described as a task of cognitive flexibility (Barry & Petry, 2008; Sanchez-Cubillo et al., 2009). In a way, it bridges both the concepts being tested by the WCST and the Stroop. Participants are asked to connect numbers in order and then asked to connect numbers to letters to numbers in order (1, then A, then 2, then B, and so on). To perform well, participants must switch between ordered sets of stimuli (cognitive flexibility) while inhibiting the more natural response of staying within a set (inhibition). Another means of tapping executive function is the dual task, which is simply having a participant performing two tasks at once. For example, a participant could first be asked to complete mazes as quickly as possible. Then the participant could be asked to complete a verbal

fluency test and generate as many words as possible using different letters. Finally, the participant is asked to do both tasks simultaneously. The difference between performance on the two tests when they are performed at the same time is calculated and used as a measure of executive function (Miyake, et al., 2000). Interestingly, many researchers use the verbal fluency test in a dual task design, despite the fact that verbal fluency is often considered a test of executive function in its own right (Royall, et al., 2002).

There are also tests of planning, such as the Tower of London (Shallice, 1982), that measure executive function by examining a participant's ability to plan a visual spatial strategy. Based on a classic puzzle, the Tower of Hanoi, this test requires a participant to make a series of planned moves in order to transfer a set of disks from one peg to another in the fewest moves possible. Recently, several tasks have been developed to look at executive function through decision making. Tasks such as the Iowa Gambling Task (Bechara & Damasio, 2002) and the Columbia Card Task (Figner, Mackinlay, Wilkening, & Weber, 2009) ask participants to try to win money based on the decisions they make in a card game. These tests are designed to test whether a participant can make decisions that are consistent with optimizing long term success. These tests reveal a participant's ability to understand the net outcome of consequences (both for rewards and punishment). Another executive function task is the Random Number Generation Task, or the Random Letter Generation Task, which is thought to tap directly into Baddeley's central executive of working memory (Miyake, et al., 2000). In this test, the participant is asked to create a random list of single-digit numbers or letters. The participant is instructed to avoid repeating the same letter or number sequences, to avoid ordered sets (e.g. 2-3-4-5, L-M-N-O), and to use each number or letter with the same frequency (Fisk

& Sharp, 2004). This test produces a series of variables for researchers to examine central executive ability, including a randomness score, the median number of items between repeats, and the number of times each character occurs in the complete set.

Adherence Requires Executive Function. The management of ART adherence is a behavior that requires executive control processes to work towards the goal of continuous undetectable viral loads and normal CD4 levels. Maintaining the goal of near-perfect levels of adherence requires the ability to plan, initiate, modify, and maintain behavior. Behavior must be initiated when ART is prescribed. Planning for how one will take his/her medications must be made during initiation and maintenance of ART. Behavior must be maintained despite changes in routine, the distractions of daily life, or in the face of negative side effects. Of particular importance for adherence is the repression of an immediately salient possible outcome in favor of an outcome far off into the future. This issue is similar to that faced by a dieter who passes up a donut by considering the upcoming bathing suit season, or the smoker who considers the long term consequences of smoking before lighting up a cigarette. The cognitive control necessary to maintain adherence involves the ability to inhibit acting on immediate desires in favor of acting in a manner that, while not immediately rewarding, is more in accordance with some future goal. For the HIV+ individual, this cognitive control for adherence is particularly difficult because it is a life-long struggle. While an occasional slip in behavior may not have significant consequences, the necessity of the goal (limiting the impact of HIV on health) is not one that will change for the duration of the person's life.

Supporting the idea that executive function is necessary for adherence is that executive function is the neurocognitive domain most frequently associated with ART

adherence. Executive function deficits as measured by the trails B (Avants, Margolin, Warburton, Hawkins, & Shi, 2001; Barclay, et al., 2007; Ettenhofer, et al., 2010; Ettenhofer, et al., 2009; Hinkin et al., 2002; Hinkin, et al., 2004; Solomon & Halkitis, 2008; Wagner, Remien, Carballo-Dieguez, & Dolezal, 2002), the Stroop Color-Word Interference Test (Barclay, et al., 2007; Ettenhofer, et al., 2010; Ettenhofer, et al., 2009; Hinkin, et al., 2002; Hinkin, et al., 2004), the Short Category Test (Barclay, et al., 2007; Ettenhofer, et al., 2010; Ettenhofer, et al., 2009; Hinkin, et al., 2002; Hinkin, et al., 2004), the Rey Complex Figure (Meade, et al., 2010; Waldrop-Valverde, et al., 2010), the Tower of London (Waldrop-Valverde, et al., 2010), and the WCST (Ettenhofer, et al., 2010; Ettenhofer, et al., 2009) all have shown that executive function impairment is associated with nonadherence. The executive function component is a particularly robust finding throughout examinations of neurocognitive correlates of nonadherence. However, the meaning of the relationship between executive function and adherence is hard to determine as executive function itself is difficult to operationalize. The nature of this issue will be fleshed out in subsequent sections, as the purpose of this dissertation is to better characterize this relationship.

The Neuropsychology of HIV

Neuroanatomical damage associated with HIV. Insidiously, once infected with the virus, one of the factors impeding medication adherence is the neurodegenerative effects that HIV has on the brain. These neurodegenerative effects lead to an array of neurocognitive deficits, including executive function deficits. HIV infects the brain by crossing the blood brain barrier inside infected monocytes, CD4 cells, or via cell-independent entrance (Hult, Chana, Masliah, & Everall, 2008). Once inside the brain,

HIV predominantly infects microglia and, to a lesser extent, astrocytes (Anthony & Bell, 2008; Hult, et al., 2008). Neurotoxicity and neuronal apoptosis occurs in a variety of ways, including excitotoxicity from overexcitation of NMDA coupled ion channels. HIV infected cells also release neurotoxins such as cytokines and chemokines leading to inflammation and stimulation of uninfected glia. This process may produce further damaging factors such as TNF-α, IL-1β, and IL-6, as well as viral proteins shed by infected cells such as Tat, gp120, and gp41 (Hult, et al., 2008).

The damage done by HIV has been shown to differentially affect several structural and functional systems in the brain. Neuroimaging and autopsy studies have revealed that patients with HIV in varying stages of the disease exhibit neuroanatomical abnormalities, and neuronal loss. HIV infection, even before symptoms or neurocognitive impairment occur, is associated with a decrease in the blood flow to the brain (Ances et al., 2009; Ances et al., 2011) and with grey matter cortical thinning in regions from the frontal eye field to primary sensory and motor cortex (Thompson et al., 2005). Studies have found corresponding decreases in brain volume (Cardenas et al., 2009; Cohen, Harezlak, Schifitto, et al., 2010; Towgood et al., 2011) and increases in ventricular volume (Thompson et al., 2006). White matter tract damage has been shown in the internal capsule, longitudinal fasciculus and the corpus callosum (Gongvatana et al., 2009; Tate, Sampat, et al., 2011; Thompson, et al., 2006). These neuroanatomical abnormalities in the cortex are associated with clinical indicators of HIV including nadir CD4, current CD4 count, and RNA viral load (Cohen, Harezlak, Schifitto, et al., 2010; Thompson, et al., 2005). Neuroimaging studies also consistently find damage to regions of the basal ganglia-- both the caudate (Ances et al., 2006) and putamen (Castelo, Courtney, Melrose,

& Stern, 2007), which could explain the often seen motor slowing in HIV+ individuals. Magnetic resonance spectroscopy has revealed abnormal quantities of metabolites in HIV+ individuals that correspond to the existence of different pathological conditions in the cortex and basal ganglia. Decreased levels of *N*-acetylasparate, indicating neuronal injury or cell loss, have been found in the basal ganglia, the mid frontal cortex and the white matter of the frontal cortex (Harezlak, et al., 2011). Differences in these same brain regions were found with increases in choline-containing compounds and *myo*-inostitol, which indicate inflammation and the breakdown of cell membranes (Harezlak, et al., 2011). These changes in brain metabolites are directly associated with differences in brain volume (Cohen, Harezlak, Gongvatana, et al., 2010). In summary, HIV infection is associated with diffuse white matter loss, cortical thinning, especially in primary and association sensorimotor cortex, as well as damage to the basal ganglia (Tucker, Robertson, et al., 2004).

Neuropsychological deficits associated with HIV. The neuroanatomical abnormalities described above are implicated in the neuropsychological dysfunction seen in HIV (Castelo, et al., 2007; Gongvatana, et al., 2009; R. H. Paul et al., 2008; Thompson, et al., 2005). It is estimated that 40 to 50 percent of HIV+ individuals show impairment on neuropsychological tasks (Harezlak, et al., 2011; R. Paul, Cohen, Navia, & Tashima, 2002; Thompson, et al., 2005). HIV has been shown to be associated with: working memory deficits using auditory (Farinpour et al., 2000; E. M. Martin et al., 2001) or visual cues (Chang et al., 2001; E. M. Martin, et al., 2003); difficulties in verbal learning and memory (Hardy, Hinkin, Levine, Castellon, & Lam, 2006); and attention deficits (Chang, et al., 2001; Hardy, Castellon, Hinkin, Levine, & Lam, 2008).

Presumably due to the opportunistic damage HIV inflicts on the basal ganglia, white matter and sensorimotor cortex, often the first deficits that are clinically distinguishable are that of motor control, or motor slowing (McArthur, 2004; Nath et al., 2008). While there are clearly deficits seen in seropositive individuals, the simple examination of population means may not describe the patterns of deficits seen in individual persons. Recent cluster analyses indicate that neuropsychological impairments are not found in all HIV+ individuals, affect variable domains at the individual level, and are relatively stable over time (Dawes et al., 2008; Lojek & Bornstein, 2005).

Of greatest interest for the present study, however, is the neuropsychological domain of executive function. Indeed numerous studies have documented executive dysfunction in HIV+ participants. In an early study of HIV related neurocognitive dysfunction, Sahakian and colleagues (1995) tested HIV-, HIV+ asymptomatic, and HIV+ symptomatic men on a battery of tasks. HIV+ participants showed distinct impairment in the executive function factor of their battery regardless of whether or not they were symptomatic. These data suggest that executive function impairment may exist prior to the development of other symptoms. In more recent studies, impairment has been demonstrated in: decision-making on the Iowa Gambling Task (Hardy, et al., 2006; E. M. Martin, Pitrak, et al., 2004); cognitive flexibility on the WCST (Basso & Bornstein, 2003); multitasking (Scott et al., 2011); and on interference tasks such as the Stroop Color Word Interference (Hardy, et al., 2006) and Trails B (Basso & Bornstein, 2003; Solomon & Halkitis, 2008). As executive function deficits have been shown to be associated with poorer adherence, and HIV has been shown to be associated with poorer

executive function performance on many of the same tests, one would likely conclude that HIV presents executive function barriers to its own treatment.

It is this synergistic relationship between HIV, neurocognitive deficits and adherence that makes research into these issues so important. The neurocognitive barriers HIV presents to its own treatment lead to a snowballing effect of neurocognitive deficits relating to nonadherence behaviors that increase the likelihood of that very same array of neurocognitive deficits. This snowball effect can be seen in the work of Ettenhofer and colleagues (Ettenhofer, et al., 2010). Using path modeling, researchers demonstrated that global neurocognitive functioning (driven by measures of executive function, learning and memory) at baseline predicted the next 6 months of adherence behavior. In addition, they showed that the very same adherence behavior over the course of 6 months, while controlling for global neurocognitive functioning at baseline, was an independent predictor of global neurocognitive functioning at follow-up. This second effect was driven by predictions of processing speed, attention, motor function, and most importantly, executive function. This work clearly shows that if unchecked, neurocognitive deficits can lead to adherence difficulties, which can lead to further deficits.

Clinical neuropsychological diagnoses associated with HIV. Though not specifically addressed in the present study, the clinical neuropsychological diagnoses for the HIV-Associated Neurocognitive Disorders (HAND) provide important background information for understanding the scope of HIV related cognitive impairment. HIV Associated Dementia (HAD) is the most severe diagnosis, but HAND is further broken down into mild neurocognitive disorder (MND) and asymptomatic neurocognitive

impairment (ASI) (Antinori et al., 2007). While some of the neuropsychological deficits are clearly cortical in nature, HAD is considered a form of subcortical dementia (Nath, et al., 2008). HAD is associated with a variety of neurocognitive symptoms. Early indicators of HAD include short-term memory loss, mental slowing, reading and comprehension difficulties, motor slowing, postural tremor and executive dysfunction. Prior to ART therapy, the lifetime incidence of HAD in HIV+ persons was about 5-20%, but post-ART incidence rates have fallen (McArthur, 2004; Nath, et al., 2008). However, prevalence of these HIV-related cognitive disorders has risen in the post-ART era, as people live longer with HIV (Dore, McDonald, Li, Kaldor, & Brew, 2003; McArthur, 2004; Nath, et al., 2008). Once diagnosed, HAD was rapidly progressive in the pre-ART era, with studies indicating survival times of 6 months (Nath, et al., 2008) to 12 months (Dore, et al., 2003). Post-ART, these disorders are still independent predictors of fatality (Sevigny et al., 2007), but the survival time with these disorders is greatly increased (Dore, et al., 2003). Another curious effect of ART, is that post-ART HAD is now diagnosed at far higher CD4 levels (Dore et al., 1999; Nath, et al., 2008), which could explain some of the increases in survival time. Diagnoses at higher CD4 levels could be due to differential permeability of the ART medications, such that HIV replication which may be suppressed in many places of the body is not being halted in the brain (Letendre et al., 2008). Thus, viral load may be higher in the nervous system than in the rest of the body. MND and ASI are defined by performance one standard deviation below age and education adjusted means on standardized neuropsychological instruments in at least two domains (Antinori, et al., 2007). What separates the two is that MND is associated with impairment in everyday functioning while ASI is not (Letendre et al., 2009). These

milder forms of cognitive impairment have been shown to be somewhat retractable with the use of ART (Clifford et al., 2002; Cohen et al., 2001; Cysique et al., 2009; Sacktor et al., 2000) despite the fact that neuroanatomical abnormalities persist in participants on ART (Gongvatana, et al., 2009; Thompson, et al., 2005).

In summary, HIV has a distinct impact on the brain, which has been shown through studies of neuroanatomy as well as performance on clinical neuropsychological measures. Included in these deficits is executive function, as well as deficits in memory, attention, and motor speed. These deficits are also implicated in adherence, and thus HIV presents barriers to its own treatment. As these deficits mount, patients manifest illnesses such as HAD, which is an independent predictor of fatality.

The Complication of Methamphetamine

Methamphetamine and its association with risk behavior and HIV. Beyond the barriers presented by HIV-related neurocognitive deficits, substance use is common among HIV+ individuals, presenting another set of barriers to adherence and positive health behaviors. Over the past 10 years, methamphetamine has proved to be exceptionally problematic for HIV+ persons. Methamphetamine is a powerful central nervous system stimulant with a long half-life (8-12 hours) compared to other stimulants. It has high abuse potential and is commonly taken orally, smoked, snorted, or injected. Methamphetamine acts as an agonist of dopamine (primarily), noradrenalin, and serotonin by facilitating their release and by blocking their reuptake (Cruickshank & Dyer, 2009). Methamphetamine administration has been shown to produce arousal, euphoria, anxiety, increased heart rate, increased blood pressure and decreased appetite amongst a myriad of other subjective and physiological effects (Cruickshank & Dyer,

2009). Long term consequences of methamphetamine use can include drug-induced psychosis, cardiovascular problems, and dental issues (Gonzales, Mooney, & Rawson, 2010). Methamphetamine is not as common as many other drugs of abuse, with only 0.2% of the US population reporting past month use in the 2009 national survey on drug use and health (Substance Abuse and Mental Health Administration, 2009). However, methamphetamine is used at much higher rates among men who have sex with men (MSM). Gay and bisexual identified young men in New York were significantly more likely to use methamphetamine than heterosexual identified men (Parsons, Grov, & Kelly, 2009). A study of MSM in Chicago found that 18-30 year olds had rates of past month methamphetamine use of 10% (Mackesy-Amiti, Fendrich, & Johnson, 2008), while the CDC found rates of past year use in MSM to be 22% in San Francisco, 16% in Los Angeles, and 14% in NYC (CDC, 2006).

Methamphetamine is consistently demonstrated to be a risk factor for contracting HIV. Within the MSM community, the relationship between methamphetamine and HIV infection may be in part due to the close connection between methamphetamine use and sexual behavior. Sexual situations are consistently discussed in qualitative research regarding the motivations for methamphetamine use in MSM populations (Parsons, Kelly, & Weiser, 2007; Semple, Patterson, & Grant, 2002). In the Semple and colleagues study (2002), participants reported that their motivation for methamphetamine use included making sex more pleasurable, reducing anxiety associated with sex, or making sex more adventurous. Indeed, psychopharmacological studies have noted that stimulants have the ability to increase sexual desire (Volkow et al., 2007). Methamphetamine also dries the mucosa and reduces the sensitivity of rectal and genital areas, allowing for more

extended and forceful sexual behavior. This rougher sexual behavior increases the likelihood of breaking the skin and transmitting the virus (Shoptaw & Reback, 2007). Further increasing the risk for transmission, is the fact that methamphetamine is occasionally administered through anal insertion, or a "booty bump" (Shoptaw, 2006). Consistently, methamphetamine has been found to be related to sexual risk behavior. In NYC, MSM who used methamphetamine recently (i.e., in the past 90 days) reported 2.8 times greater odds of having had recent unprotected anal intercourse than not, and 4.8 times greater odds of having had receptive unprotected anal intercourse than not (Grov, Parsons, & Bimbi, 2008). In addition, studies have found that MSM who specifically take on the identity of someone who doesn't use condoms, or a barebacker (a sexual identity indicating the non-use of condoms for anal sex), has 3.8 times greater odds of using methamphetamine than someone who does not identify as a barebacker (Parsons & Bimbi, 2007). A study of MSM in the Miami area found that methamphetamine users, regardless of HIV status, engaged in significantly more sexual risk behavior as defined by number of non-main partners, having multiple unprotected partners, or engaged in unprotected anal intercourse at their last sexual act than both non-drug users and users of other drugs (Forrest et al., 2010). Thus, methamphetamine poses a risk for transmission through increased risk behavior, by biologically increasing the likelihood of transmission through that behavior, and by attitudes and motivations for methamphetamine use.

Likely through the association methamphetamine use has with sexual risk, studies have identified high rates of HIV seroprevalence within samples of methamphetamine using MSM and high rates of methamphetamine use among HIV+ MSM (Halkitis, Fischgrund, & Parsons, 2005; Halkitis, Shrem, & Martin, 2005; Schilder, Lampinen,

Miller, & Hogg, 2005; Vaudrey et al., 2007). For example, depending on the intensity of use, HIV prevalence ranged from 23% to 86% among MSM methamphetamine-users, with HIV infection rates increasing with increased intensity of methamphetamine use (Shoptaw & Reback, 2006). In San Francisco, surveys found between 33.7% (CDC, 2007) and 40% (Mitchell, Morris, Kent, Stansell, & Klausner, 2006) of HIV+ MSM reported recent methamphetamine use. A survey at the Los Angeles Gay and Lesbian Center (LAG&LC, 2007) found rising rates of methamphetamine use (with lifetime use increasing from 18% to 25% between 2005 and 2006 and recent use increasing from 9% to 13%). Their survey also found that gay men who used methamphetamine in the last year were five times more likely to test positive for HIV. In Miami, methamphetamine using MSM were 3.8 times more likely to be HIV+ than non-drug users, and two times more likely to be HIV+ than those drug users who did not report methamphetamine use (Fernández et al., 2007). A study conducted in NYC, found that HIV+ MSM were 2.8 times more likely to have recently used methamphetamine compared to HIV- MSM (Parsons, 2006). Additionally, the National HIV Behavioral Surveillance System reported that in NYC, 22% of HIV+ MSM recently used methamphetamine (compared to only 12% of HIV- MSM). These statistics clearly demonstrate the connection between methamphetamine use and HIV infection within the MSM community.

Methamphetamine and the health of HIV+ persons. In addition to being a risk factor for sexual behavior and transmission of HIV, many reports exist implicating stimulants as a barrier to effective ART adherence (Halkitis, Kutnick, & Slater, 2005; Hinkin, et al., 2007; Ingersoll, 2004; Sharpe, et al., 2004). Regular stimulant use, defined as 1 or 2 times a week, has been shown to be associated with poorer adherence (Carrico,

Johnson, Colfax, & Moskowitz, 2010; Carrico et al., 2007), and with prolonged interruptions in ART treatment, resulting in poorer medication persistence (Carrico et al., 2011). This effect is not simply an effect of drug use, as stimulant users have been shown to be less adherent than users of other drug classes (Hinkin, et al., 2007).

Recent reports have begun to document the specific negative impact of methamphetamine, rather than amphetamines or stimulants as a broader class of drugs, on adherence. A study of drug-using HIV+ MSM found that methamphetamine users were significantly less likely than users of other drugs to achieve optimal adherence (Halkitis & Parsons, 2001). A study by Reback and colleagues (2003) conducted qualitative interviews with HIV+ MSM enrolled in a drug treatment program and found that methamphetamine use and abuse negatively affected HIV medication adherence. Participants discussed consciously choosing to not take their medication, because it's their "time off," because they wanted to focus on the sexual aspects of methamphetamine, or because they feared interactions with their medications and methamphetamine or other substances of abuse. There was also discussion of unplanned nonadherence that centered on the disruptions in schedule and sleep patterns that accompany such a long acting stimulant that is often used in binge patterns. An ethnographic investigation of medication adherence among young HIV+ methamphetamine users found that methamphetamine use presented a challenge to medication adherence as well as access to health care (Carroll, 2006). Beyond predicting nonadherence behavior, methamphetamine use was also associated with being less likely to be prescribed ART (Marquez, Mitchell, Hare, John, & Klausner, 2009).

In addition to methamphetamine's connections to nonadherence, the biological manifestations of methamphetamine use are a critical factor to consider for HIV+ persons whose immune systems may already be ravaged by the virus (Shernoff & Sussman, 1995). The effects of methamphetamine use on HIV as well as potential interactions between methamphetamine and HIV medications make methamphetamine use by HIV+ individuals especially problematic. Methamphetamine has been shown to weaken the immune system, leaving a person more susceptible to infection (Ellis et al., 2003; R. Gonzalez & Cherner, 2008). Methamphetamine can activate the immune system leading to the depletion of tryptophan (Carrico et al., 2008) an amino acid necessary in the production of serotonin, a neurotransmitter affecting mood. There is also evidence that methamphetamine damages the brain in a manner that makes it more susceptible to mood disorders (London et al., 2004). These findings are concerning as negative affect has been shown to be associated with more frequent stimulant use and lower adherence in HIV+ stimulant users (Carrico, et al., 2007, 2010).

Stimulant use (including methamphetamine) is associated with increases in viral load above and beyond its association with nonadherence (Carrico, et al., 2007). There are two lines of research explaining this association. One, methamphetamine is believed to speed up the replication of HIV (Toussi, et al., 2009), which can lead to higher viral loads and a greater likelihood for mutation and resistance. Second, there is evidence that increases in viral loads associated with methamphetamine use can be explained by decreased efficacy of ART (Ellis, et al., 2003). Together, the increased rate of replication and the decreased efficiency of ART explain how stimulants can increase viral load independently of adherence. Beyond associations with viral load, methamphetamine

complicates ART treatment. Frequent methamphetamine use has been associated with an increased rate of resistance to one class of ART medications, NNRTIs (Colfax et al., 2007). In addition, there is also concern that the interaction of methamphetamine and certain ART medications could lead to potential overdoses due to CYP2D6 enzyme inhibition (Hales, et al., 2000; Pham & Dunning, 2005; Urbina, 2006).

In sum, methamphetamine is consistently associated with increases in risk behavior and HIV infection. Methamphetamine has been demonstrated to be a barrier to adherence to ART, through both a failure to take medication and through a lifestyle that is inconsistent with good ART adherence or a healthy lifestyle. Methamphetamine is also associated with a host of other health consequences (e.g. increased rate of viral replication, weakened immune system, greater likelihood of further sex risk and secondary infection) that can complicate the lives of HIV+ individuals.

Neuropsychological consequences of methamphetamine use. Methamphetamine is a neurotoxic substance known to cause neuronal cell loss (Berman, O'Neill, Fears, Bartzokis, & London, 2008; Cruickshank & Dyer, 2009; McCann & Ricaurte, 2004; Thrash, Thiruchelvan, Ahuja, Suppiramaniam, & Dhanasekaran, 2009). In humans, research on neuroanatomical damage is far from complete, but studies using a variety of imaging techniques have uncovered several regions of interest. The first controlled examination of methamphetamine use on brain volume revealed a reduction in grey matter in the temporal lobe for methamphetamine users as compared to controls (Bartzokis et al., 2000). Thompson and colleagues (2004) found grey matter deficits in the cingulate cortex and limbic structures, a significant decrease in hippocampal volume, and a white matter hypertrophy especially in the regions around the hippocampus. This is

a pattern of deficit that is concerning because it mimics what is seen in patients with schizophrenia. In studies of abstinent methamphetamine users neuroanatomical abnormalities still exist. Studies have shown a decrease in dopamine binding (McCann et al., 2008; Volkow, Chang, Wang, Fowler, Ding, et al., 2001) in the striatum that is lessened with length of time abstinent (Volkow, Chang, Wang, Fowler, Franceschi, et al., 2001). There is also evidence of enlargement in the striatum (Chang et al., 2005; Jernigan et al., 2005), suggesting a compensatory mechanism to the damage done by methamphetamine to dopaminergic neurons (Thrash, et al., 2009).

Of particular importance for executive function are studies showing abnormalities in the frontal lobes. Studies have shown decreases in grey matter throughout the frontal lobes, bilaterally in the middle frontal gyrus, the left medial frontal gyrus and the right post central gyrus (S. J. Kim et al., 2006), as well decreased white matter integrity in the right frontal lobe (Chung et al., 2007). Magnetic resonance spectroscopy indicates that there is dose dependent damage to both the white and grey matter in the frontal lobe gyri (Sung et al., 2007). There is evidence that some of the loss in grey matter may partially recover with abstinence, particularly in the right middle frontal gyrus (S. J. Kim, et al., 2006; Sung, et al., 2007). Diffusion tensor imaging has shown structural abnormalities in the white matter tracts connecting the frontal lobes to midbrain structures (Tobias et al., 2010). These findings are consistent with research showing hypoactivation of the orbital frontal cortex and hippocampus in response to an empathy task, suggesting that one of the difficulties caused by this white matter tract damage is the integration of emotional information (Y. T. Kim et al., 2010).

These structural abnormalities may underlie the neuropsychological functioning deficits seen in methamphetamine users. In studies of methamphetamine dependent individuals in various stages of abstinence (minimum two weeks to three months), there is a consistent pattern of deficit. Methamphetamine dependent individuals show deficits in memory recall (Dore, et al., 1999; J. D. Henry, Mazur, & Rendell, 2009; Hoffman et al., 2006; Johanson et al., 2006; McCann, et al., 2008; Rendell, Mazur, & Henry, 2009) and those deficits have been demonstrated to be correlated to decreased dopamine binding in the striatum (Dore, et al., 1999; Johanson, et al., 2006; McCann, et al., 2008; Volkow, Chang, Wang, Fowler, Ding, et al., 2001). Dependence on methamphetamine is also associated with impairment on tasks of verbal learning (Dore, et al., 1999; J. D. Henry, et al., 2009; Hoffman, et al., 2006; Johanson, et al., 2006; Rendell, et al., 2009) and prospective memory (Rendell, et al., 2009). Other areas of impaired neuropsychological functioning include motor speed (Dore, et al., 1999; Hoffman, et al., 2006; Johanson, et al., 2006), attention (Dore, et al., 1999; Johanson, et al., 2006; Salo et al., 2005), and social cognition (J. D. Henry, et al., 2009; Y. T. Kim, et al., 2010).

Methamphetamine and executive function. We propose that methamphetamine has two pathways to executive function deficits. The first is a direct pathway where methamphetamine use is associated with executive dysfunction. Much of the work on executive function deficits in methamphetamine users shows deficits in executive function on tests that require the inhibition of a more salient response, or some other inhibitory mechanism. Many studies have demonstrated impairment on the Stroop in participants with methamphetamine dependence (McCann, et al., 2008; Salo, Nordahl, Buonocore, et al., 2009; Salo, Nordahl, Galloway, et al., 2009; Salo et al., 2007; Salo,

Ursu, Buonocore, Leamon, & Carter, 2009; Simon, et al., 2000; Simon et al., 2002). These executive function deficits have been directly associated with brain activity using fMRI (Salo, Ursu, et al., 2009) and brain metabolites levels using diffuse tensor imaging (Salo, et al., 2007). Inhibitory control has also been shown to be impaired in participants with methamphetamine dependence on the Hayling Sentence Completion Test (J. D. Henry, et al., 2009; Rendell, et al., 2009). Methamphetamine users have been shown to commit more perseverative errors on the WCST (Chung, et al., 2007; S. J. Kim, et al., 2006; S. J. Kim et al., 2005; Y. T. Kim et al., 2009; Simon, et al., 2002). Methamphetamine dependent individuals also have decision-making impairments as indicated by poorer scores on the IGT (Boileau et al., 2008) and more impulsivity on a test of monetary delay discounting (Hoffman, et al., 2006; Monterosso et al., 2007). The majority of these studies have been completed using methamphetamine dependent participants in various states of abstinence. Despite that fact, there is evidence that these deficits lessen as abstinence time increases. Participants who had been abstinent for less than six months were more impaired than participants with at least six months of abstinence on both the WCST (S. J. Kim, et al., 2006) and Stroop (Salo, Nordahl, Galloway, et al., 2009). In fact, for the Stroop, participants abstinent for at least one year were indistinguishable from control participants.

Though these studies show a pattern of executive function deficits, they are not without caveat. While many studies found in executive function deficits in methamphetamine users, some either found none (Chang, Cloak, et al., 2005; Simon, Dean, Cordova, Monterosso, & London, 2010), or the results were mixed with some executive function tests showing effects and others not (Boileau, et al., 2008; Hoffman, et

al., 2006; S. J. Kim, et al., 2006; McCann, et al., 2008). Many of these studies of executive function either did not control for other substance use, or had differences between the methamphetamine group and controls in education (Hart, Marvin, Silver, & Smith, 2012). These flaws do not exist in all studies, and while some question the legitimacy of this direct relationship between executive function and methamphetamine use, it is generally accepted (Iudicello et al., 2010; Scott et al., 2007).

The second pathway by which methamphetamine use can lead to executive function deficits among HIV+ persons is indirect. Evidence was presented earlier that methamphetamine is a barrier to adherence, and that the increases in disease progression associated with poorer adherence could lead to executive function deficits. In addition, as methamphetamine has been shown to exacerbate HIV outcomes even when controlling for its effect on adherence, methamphetamine could act through HIV to increase executive dysfunction. Thus, through interfering with adherence and directly advancing HIV disease progression methamphetamine has an indirect path to increasing executive function deficits.

The intersection of HIV, methamphetamine use and neuropsychological function. Considering the wealth of research that has connected HIV, neuropsychology and methamphetamine, it is no surprise that there is some research on the intersection of these three topics. There is evidence that for the HIV+ individual, methamphetamine may pose an even greater risk for neurological damage. Methamphetamine weakens the blood brain barrier making it easier for HIV to gain entry into and infect the brain (Ramirez et al., 2009). Both HIV and methamphetamine are neurotoxic substances leading to neuronal cell loss. They preferentially affect the dopaminergic regions of the brain, and

their neurotoxic effects are not merely additive. There is evidence that at the cellular level methamphetamine combines with the HIV proteins, tat and gp120, causing a synergistic neurotoxic effect (Cadet & Krasnova, 2007; Theodore, Cass, & Maragos, 2006; Theodore, Stolberg, Cass, & Maragos, 2006). In vivo, both methamphetamine and the HIV proteins tat and gp120 were shown to cause the death of about 1% of the fetal neuronal tissue to which they were exposed. The combination tat, gp120 and methamphetamine caused 8% neuronal death (Nath et al., 2000). This synergistic damage is likely caused through dysregulation of calcium channels in neuronal mitochondria (Langford et al., 2004).

These findings of cell loss have been verified in neuroanatomical post-mortem studies. Post-mortem analyses have shown similar synergistic effect on brain cell loss (Chana et al., 2006; Langford et al., 2003) that was associated with clinical ratings of cognitive impairment (Chana, et al., 2006). Analyses of cerebral blood flow indicate that there is an additive effect of HIV and methamphetamine dependence in abstinent users decreasing brain activity at rest, but there is no interaction between HIV and methamphetamine (Ances, et al., 2011).

A volumetric neuroanatomical study of the combination of HIV and methamphetamine yielded some surprising results. Specifically, HIV and methamphetamine have opposing volumetric effects on the striatum and areas of the cortex, such that HIV infection decreases their volume and methamphetamine increases their volume. Most interesting is in the caudate nucleus of the basal ganglia, where the combination of these two opposing effects make HIV+ methamphetamine users' caudate volumes appear normal (Jernigan, et al., 2005). It seems unlikely that this finding means

that HIV and methamphetamine counteract their neuroanatomical effects, as clinically rated cognitive impairment in methamphetamine users was associated with brain volume increases, while clinically rated cognitive impairment in HIV+ participants was associated with brain volume decreases (Jernigan, et al., 2005). These opposing effects may explain the relative lack of a methamphetamine by HIV effect on metabolites associated with neuronal death or inflammation in magnetic resonance spectroscopy (M. J. Taylor et al., 2007). Interestingly, decreased levels of *N*-acetylasparate have been found, indicating neuronal injury or cell loss, in the anterior cingulate gyrus of HIV+ meth users. The anterior cingulate is involved in many functions, but of interest to executive function, it is a key contributor to response inhibition.

Though neuroanatomical evidence points to synergistic brain damage, studies of neuropsychological function suggest merely an additive relationship. Rippeth and colleagues (2004) examined a sample of participants stratified on HIV serostatus and methamphetamine dependence. They administered a comprehensive neuropsychological battery including processing speed, learning, memory, executive function, attention, working memory, and motor speed. The researchers examined the percent of participants impaired in each group, finding that the HIV- non-dependent group was less likely to be impaired than any of the other groups. Carey and colleagues (2006) examined a sample of participants stratified on methamphetamine dependence and disease severity (CD4 count greater or less than 200) using a similarly extensive neuropsychological battery. In this study, participants who were methamphetamine dependent and had CD4 counts lower than 200 were more likely to have neuropsychological impairment than any other group, and the dependent participants with CD4 counts above 200 were more likely to

have impairment than the participants without dependence and CD4 counts above 200. Results from these two studies were replicated in a third study examining the intersection of methamphetamine and HIV on neurocognitive function (Sadek, Vigil, Grant, &Heaton, 2007). Analyses within all these studies concluded that while there are differences between the groups of participants who are HIV+, use methamphetamine, and are HIV+ methamphetamine users, the magnitude of difference does not rise beyond an additive level. Thus, despite the research indicating synergistic damage to neurons by the combination of HIV and methamphetamine abuse, their effect on neuropsychological functioning is more likely additive than synergistic.

Additive neuropsychological damage is still a concern for ART adherence and HIV disease progression. There is evidence that neurocognitive deficits contribute both directly to poorer ART adherence and to the relationship between substance use and ART adherence. Global neurocognitive impairment (including tests of executive function) has been shown to be associated with nonadherence directly, while also partially mediating the effect of cocaine dependence on nonadherence (Meade, et al., 2010). While this study was completed with cocaine users and not methamphetamine users, both drugs are central nervous stimulants and dopamine agonists; thus it is likely that similar effects would be seen in methamphetamine dependent individuals.

The importance of studying executive function in HIV+ methamphetamine users. Studying executive function within HIV+ methamphetamine users could provide a useful target for intervention to increase adherence, slow disease progression and decrease methamphetamine use. The association of executive function deficits with ART nonadherence, HIV disease progression, and methamphetamine use provides an untapped

intervention target. If researchers could accurately define the executive function deficits associated with adherence, HIV disease, methamphetamine use, and their interaction, one could intervene on those specific executive function deficits. Either reversing or compensating for those deficits could lead to positive changes in methamphetamine use, adherence and HIV disease progression.

Issues of the Definition and the Measurement of Executive Function

The varied definitions, operationalizations, and measurements of executive function make accurate assessment difficult and they obscure associations with behavior. There is confusion as to an accepted definition of executive function, which stems from both the complexity of behavior it is reported to be involved with and the conflation of language from similar lines of study. These definitional issues are compounded by arguments about whether executive function is a unitary construct or made up of many "executive functions." This argument fractures even more, as those who believe that there are many diverse functions that make up executive function cannot agree on what those functions are. To some degree, these many different perspectives on executive function simply represent the multitude of functions the brain is capable of. However, for those seeking to apply the study of function to health behaviors, concise definitions of function would be optimal.

One method to objectively determine the functions that comprise executive function is factor analysis. However, problems with factor analysis of executive function have emerged in the literature. The choice of which tests to include and the population being studied can greatly affect the domains uncovered through factor analysis. A final difficulty is task impurity. Task impurity refers to the fact that executive function is a top

down process, where lower-level functions (i.e. declarative memory, attention, perception) are controlled. Thus, measurement of executive function tests is often sensitive to impairment in both executive function itself and impairment in the lower-level functions being controlled. Controlling for impairment in these lower-level functions must be considered to accurately assess the domains of executive function. Below, each of these barriers is discussed in greater detail. While there are many issues impeding the accurate assessment of domains of executive function, the use of careful factor analytic approaches can minimize or eliminate many of them.

Conflation with frontal functions. The first issue of defining executive function stems from the unique relationship between these highest of cognitive functions and the most evolutionary modern brain region. Because of this compelling relationship, the term "frontal functions" has become conflated with executive functions. In their review, Stuss and Alexander (2000) warn:

> While the study of the effects of damage to the frontal lobes has been the most common way to study frontal lobe functions, many researchers still use the term "frontal functions" as a synonym for "executive function", without objective reference to anatomy. Yet the relationship between "executive" or "supervisory" functions to the "frontal lobe" functions is not clear. Even those who research the effects of frontal lobe damage have not clearly defined the anatomical limits of pathology (p. 289).

Though executive function and frontal lobe function are closely related, this conflation is problematic for several reasons. Participants with frontal lobe pathology are not necessarily impaired upon tests of executive function (Miyake, et al., 2000). Second,

performance on executive function tasks is not sensitive only to frontal lobe pathology, but it is also sensitive to damage in the systems underlying the "executive" controls. Studies of executive function that lack lesions or brain imaging are particularly sensitive to the difficulties presented by the lack of localization. On performance based measures it is hard to tell the difference between a participant who has difficulty due to frontal dysfunction, and a participant who has deficits in the lower level systems being coordinated by the top down control of frontal function. These two neuroanatomical regions of deficits may present different challenges clinically, as these functional deficits may express themselves in different behavioral difficulties.

The unity or diversity of executive function. There is debate extending back to the early research by Hans-Lukas Teuber as to whether the nature of executive function was unitary or contained multiple factors (Teuber, 1972). Some researchers believe there is a single common element, a "g," or an "executive," in executive function, while others believe that a series of "executive functions" make up executive function (Royall, et al., 2002). Tests of executive function often correlate poorly with each other (Huizinga, Dolan, & van der Molen, 2006; Miyake, et al., 2000; Packwood, Hodgetts, & Tremblay, 2011; Royall, et al., 2002) suggesting that executive function is not a simple unitary construct, but these correlations are not sufficient evidence to claim that executive function has multiple components. The lack of correlation between executive function measures is partially due to the fact that tests of executive function often have poor reliability. It has been suggested that a reason for this lack of reliability stems from the concept that the executive system will only achieve peak activation in novel situations (Rabbitt, 1997). Thus, upon any second administration, the nature of what is being

studied is different. A participant's familiarity with what he or she is being asked to do can contribute to whether or not executive systems are activated to complete the task. In order to better characterize the unity or diversity of executive function and work around the difficulties with measurement, researchers have been regularly employing principal components analysis and factor analysis on executive function tests and batteries for the last 20 years (Royall, et al., 2002). The reports of researchers have varied from a single construct (Ettenhofer, Hambrick, & Abeles, 2006) to as many as six different factors (Fournier-Vicente, Larigauderie, & Gaonac'h, 2008) that make up executive function. Careful examination of executive function through factor analysis is needed in order to accurately identify domains of executive function.

One of the most comprehensive and thoughtful examinations of this issue concluded that there is a diverse set of functions that make up executive function, but that these functions overlap sharing common variance. Miyake and colleagues (2000) designed a confirmatory factor analysis built around three possible (but not comprehensive) executive control factors. The factors they examined were shifting between tasks or mental sets, updating information in working memory, and inhibiting prepotent or dominant responses. Using confirmatory factor analysis the authors examined the performance of 137 undergraduate students on three tests they believed exclusively measured these factors, and examined whether a three-factor, two-factor or single-factor solution best fit the data. Their results indicated that the three-factor solution fit the data best, indicating that they were indeed measuring three distinct components. This solution worked best only when allowing those three factors to correlate, suggesting that only when one accounts for the common shared variance among tests does the best

representation of executive function emerge. Thus, this study provides evidence that executive function tests contain multiple factors, yet there is common variance shared, harkening back to Teuber's original hypotheses that frontal functions can be represented by both unitary and diverse constructs (Teuber, 1972).

Defining the functions of executive function. There is little agreement as to which factors make up executive function. For studies using confirmatory factor analysis, such as that performed by Miyake and colleagues (2000), proposed factors of executive function are determined *a priori*. For other forms of factor analysis, researchers simply name the factors based on their own judgment, or referencing previous research (Latzman & Markon, 2010; Verdejo-Garcia & Perez-Garcia, 2007). There has been so much speculation that a recent article identified 68 different subcomponents that have been theorized by studies for executive function (Packwood, et al., 2011). Often two researchers describe a function with subtly different labels for what is essentially the same thing, or even use the same label to mean something different. Part of the problem stems from an inability to come to a consensus on what domain a single test measures. For example, while the Stroop task is commonly thought of as a measure of inhibition, it has also been described as measuring working memory, selective attention, cognitive flexibility, and concentration, to name a few (Packwood, et al., 2011). The WCST similarly has been described as conceptually measuring cognitive flexibility, mental set shifting, inhibition, categorization and problem solving (Miyake, et al., 2000). These issues are in part due to the multifaceted design of neuropsychological measures. Because of the unique nature of complex executive function tasks, all of these different processes

may be captured in performance, but both convergent and divergent evidence is needed to make those claims.

The variables and tests selected for inclusion can greatly affect the outcome of factor analysis. Often factor analyses using the WCST will use two variables: the number of perseverative errors (or number of perseverative responses) and the number of categories completed. These two variables consistently load onto the same factor (Ardila, Galeano, & Rosselli, 1998; Ardila & Pineda, 2000; Bamdad, Ryan, & Warden, 2003; Burgess, Alderman, Evans, Emslie, & Wilson, 1998; Dawes, et al., 2008; Goldman et al., 1996; Greve, et al., 1998; Huizinga & van der Molen, 2007; Nagahama et al., 2003) and are the variables most consistently used clinically. When other variables are examined, the picture often changes. Two factor or three factor solutions can emerge when the variables failure to maintain set, and non-perseverative errors are examined (Ardila & Pineda, 2000; Goldman, et al., 1996; Greve, et al., 1998; Greve, Stickle, Love, Bianchini, & Stanford, 2005; Huizinga & van der Molen, 2007; Nagahama, et al., 2003). Thus, the decision of which variables are entered into the model can greatly affect the relationships uncovered by factor analysis, even for a single test.

Another consideration for factor analysis is the population being studied. There is evidence that the factor scores created with unimpaired populations may differ from those arrived at for impaired populations. In their 1996 study, Goldman and colleagues examined the factor structure of the WCST in 343 participants with brain lesions and 356 normal controls. For the control population, the 5 variables examined (total errors, perseverative responses, non-perseverative errors, failure to maintain set and percent conceptual level responding) all loaded on a single factor. For the sample with

neurological damage these variables loaded on two factors. The first factor loaded perseverative responses, total errors and percent conceptual level responses and was labeled problem solving/perseveration by the authors. The second factor loaded with failure to maintain set and non-perseverative errors, but was labeled failure to maintain set because the loading for that variable was stronger. These results have been replicated consistently with non-clinical populations showing a single factor structure (Ardila, et al., 1998; Huizinga & van der Molen, 2007) and clinical populations showing a two-factor (Busch, McBride, Curtiss, & Vanderploeg, 2005) or a three-factor (non-perseverative errors loading on its own factor) structure (Greve, et al., 1998; Greve, et al., 2005). Norms are used to adjust a score in reference to a specific population, allowing comparisons to be made within a particular population, or to be made between the population in question and a more general population. However, there is often an assumption that what is being measured by a neurocognitive test across populations is the same. These factor analyses suggest that in some cases, not only might scores be lower or higher in a given population, but the constructs measured by a test can vary in different populations. Clarity of construct within a population is one of the primary benefits of factor analysis of this type.

As different populations can have different factor structures, mixing different populations can cause problems in factor analysis. A study examined the factor loadings of executive function tests in a sample of substance (cocaine and heroin) dependent individuals (n = 81) and a group of controls (n =31) (Verdejo-Garcia & Perez-Garcia, 2007) using a large battery of executive function tests with the added component of two decision making tasks, the Cognitive Bias Test and the Iowa Gambling Task. Their

analysis yielded a four-factor model that they labeled updating, inhibition, shifting and decision making. However, there was no attempt to clarify whether the model was the same if examined in the substance dependent participants or the control participants (likely due to the small n in the control group). There was a large variety of tasks that loaded on what researchers called the "updating" factor (i.e., fluency tests, working memory spans, arithmetic, and cognitive bias test). All of the measures loading on the updating factor were the variables in which cocaine and heroin dependent groups were different than the controls. An alternative hypothesis is that this factor analysis was sensitive to differences between groups rather than similarities between tests. In other words, the updating factor could be reinterpreted as a factor of deficits in substance dependent individuals. To avoid issues of interpretation like the one presented here, it is important to examine that structure for each group being studied.

The problem of task impurity. In testing executive function, there is a problem of task impurity. The direction of complex behavior towards a goal requires coordination of many 'lower' cognitive abilities. Depending on the specific task, different aspects of cognitive function outside of the realm of what is normally thought of as executive function are required. The cognitive processes necessary for any well-made decision are many: one must be paying attention to all the factors that go into the decision; one must have episodic memory for how similar decisions turned out; one must have simple working memory intact to hold the different options in mind; one must be functioning emotionally to understand how the different possibilities might make them feel; and so on. Thus, in order to perform well on any task that measures executive function many other cognitive abilities must also be intact.

Task impurity is a problem for many neuropsychological measures in general. Neuropsychological tasks are multifaceted in nature and require multiple aspects of function to perform well. Careful test construction allowing for the subtraction of test scores to create variables that represent a specific function can help negate the multifaceted nature of neurocognitive tests. These tests are created so that a participant completes successive versions of the same task, but with each version having one new element added. Then the old score is subtracted from the new score, giving the researcher a score that presumably only represents the new addition. Even for the most well designed tests, the subtraction method is not without its own set of problems. The subtraction method relies upon the assumption of pure insertion, the idea that addition of each successive element of a test does not change the nature of the elements already in the test. In statistical terms, this means that the interaction between the elements is negligible. With only cognitive variables it is difficult to examine this interaction, and using neuroimaging techniques this assumption has been shown to be occasionally faulty (Friston et al., 1996). While some transformations have been developed to account for the assumption of pure insertion, factor analysis provides another means to examine the issue of task impurity.

Another method of addressing the issue of task impurity is the use of factor analysis. If factor analytic methods are employed in examining executive function tests along with multiple other neuropsychological measures, researchers should be able to parcel out the portion of the variance in executive function tests associated with lower-level function, reducing the task impurity problem. For example, motor speed tests or processing speed tests are used to parcel out the variance associated with reaction time

from executive function tests (Huizinga, et al., 2006). Despite commonly using procedures for reducing reaction time variability in executive function, studies of a comprehensive battery on enough participants to truly parcel out the variance associated with other lower functions has rarely been attempted.

Clearly delineating the dysfunction of different populations will allow for more targeted intervention approaches (Royall, et al., 2002). Barriers exist to accurate identification of the executive function deficits associated with poor ART adherence, methamphetamine use, HIV disease progression and their interaction. Poor operationalization of executive function helps to create these barriers. Factor analysis can help to identify specific executive function impairments. However, while examining executive function one must carefully consider the tests and variables chosen, populations being studied, and the issue of task impurity to accurately interpret the results of those factor analyses.

Methods Used in Studying the Neurocognitive Correlates of ART Adherence

The methods used in examining neurocognitive deficits and ART adherence stand in stark contrast to the issues presented above in defining accurate domains of deficit. The most common method to examine the relationship between neurocognitive variables and ART adherence is to conduct an extensive battery of multiple tests from multiple domains of function. From these extensive batteries, studies create a global functioning score by using published standardized norms to transform raw data into T scores (mean of 50 standard deviation of 10) or Z scores. Those scores are then either averaged across all variables to create the global score (Applebaum et al., 2009; Barclay, et al., 2007; Becker, et al., 2011; Clifford, et al., 2002; Ettenhofer, et al., 2010; Meade, et al., 2010) or

averaged within a domain and the domain score is averaged to achieve a global score (Hinkin, et al., 2002; Hinkin, et al., 2004; Levine et al., 2005). Poorer global scores have been found to be associated through logistic regression with being less than 95% adherent as measured by MEMS caps (Barclay, et al., 2007), and to be associated with poorer adherence measured over six months of continuous MEMS data through linear regression (Ettenhofer, et al., 2010). Of particular interest, Ettenhoffer and colleagues (Ettenhofer, et al., 2009) conducted a confirmatory factor analysis on average domain T-scores and found that a single cognition factor was associated with an adherence factor (comprised of MEMS, Qualitative, 1-day and 30-day self report) for participants over 50, but not for younger participants. There was not, however, an exploration of whether or not a different factor structure would have better fit the domain T-scores, nor a factor analysis to determine if the domain scores themselves were made from related tests. These global scores lack any specificity. The concept of intervening on global neuropsychological functioning seems a daunting task. Intervening on global functioning would be analogous to designing an intervention for **all** health risk behavior (instead of specifically focusing on ART adherence) when dealing with a population of drug users with poor ART adherence.

Many studies take the global score a step further and convert their global score into an impairment score. The creation of impairment scores is done most frequently by converting the T-scores for each domain or for each neuropsychological variable to a deficit score, with a score of ≥ 40 being not impaired, 39 - 35 = 1, 34 - 30 = 2, 29 - 25 = 3, 24 - 20 = 4 and $\leq 19 = 5$. Essentially this process converts anything one standard deviation below the mean to a one, and adds a point for each half a standard deviation

decrease with a maximum of five. These deficit scores are then averaged across each domain (Hinkin, et al., 2004; Levine, et al., 2005) or across each variable (Becker, et al., 2011; Meade, et al., 2010) to create a global deficit score. The diagnostic cut off for impairment is generally placed at .5 for average deficit score. This method has shown good predictive validity with regard to the clinical ratings of HIV neuropsychological impairment (Carey et al., 2004) and participants' levels ART adherence (Becker, et al., 2011; Hinkin, et al., 2004; Levine, et al., 2005; Meade, et al., 2010). Other studies employed more unique methods to create a global functioning impairment score that was predictive of ART adherence (Hinkin, et al., 2002; Waldrop-Valverde, Jones, Weiss, Kumar, & Metsch, 2008). While these impairment scores have much predictive power, like the global functioning score they lack specificity for which interventions would be most efficient.

In order to better describe the relationship between specific neurocognitive deficits and adherence, researchers have made efforts to examine specific domains of function. Similar to global functioning scores, researchers often use established norms to transform raw scores into Z or T scores and average them into domain specific scores. Using these techniques, studies have found relationships with adherence and the domains of learning and memory (Becker, et al., 2011; Ettenhofer, et al., 2010; Hinkin, et al., 2002; Hinkin, et al., 2004; Levine, et al., 2005), attention (Becker, et al., 2011; Hinkin, et al., 2002; Levine, et al., 2005), psychomotor speed (Becker, et al., 2011; Ettenhofer, et al., 2009; Hinkin, et al., 2004; Waldrop-Valverde, et al., 2006), and processing speed (Becker, et al., 2011; Ettenhofer, et al., 2009).

Not surprisingly, the domain most consistently associated with adherence behavior is executive function. A few studies have examined individual executive function task performance on adherence. Several studies have shown that increased time on Trails B is associated with poorer adherence (Avants, et al., 2001; Solomon & Halkitis, 2008; Wagner, et al., 2002). Another study demonstrated that impairment on the Rey Complex Figure Copy was also associated with poorer adherence (Meade, et al., 2010). While examining specific tasks does offer some specificity for determining targets for intervention, it lacks the convergent and divergent evidence that a factor analysis would offer for characterizing that deficit.

Most studies examining the executive function adherence relationship have used the domain score approach to operationalizing executive function. Studies examining an executive domain score for executive function have found that executive dysfunction is associated with poor MEMS adherence (Ettenhofer, et al., 2010) and this relationship is stronger in participants with more complex regimens (Hinkin, et al., 2002). Decline in executive function impairment was also associated with MEMS adherence (Becker, et al., 2011). For older HIV+ adults (over 50) executive function was associated with a factor made up of objective, subjective and qualitative measures of adherence (Ettenhofer, et al., 2009) as well as predicting less than 95% adherence on MEMS measures (Barclay, et al., 2007; Hinkin, et al., 2004). These executive domain scores can be called into question as they often include tests that would not normally load together in a factor analysis of executive function. For example most of these studies create an executive function score from the Trails B, Stoop Color Word Interference Trial, and perseverative errors on either the Short Category Test (Barclay, et al., 2007; Ettenhofer, et al., 2009; Hinkin, et al.,

2002; Hinkin, et al., 2004) or the WCST (Becker, et al., 2011; Ettenhofer, et al., 2010; Ettenhofer, et al., 2009). However, in several factor analyses of executive function, perseverative errors did not load together with Trails B (Bamdad, et al., 2003; Dawes, et al., 2008; Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996) or the Stroop task (Bamdad, et al., 2003; Dowler et al., 1997; Miyake, et al., 2000; Robertson, et al., 1996). So while these studies are examining the domain of executive function they are ignoring the diverse nature of executive functioning.

Another weakness of the domain score approach for executive function is that it does not address the task impurity issue. Factor analytic methods have shown that Trails B and the Stroop load with Trails A on a motor or processing speed factor (Bamdad, et al., 2003), even in examinations of neurocognitive predictors of adherence (Contardo, Black, Beauvais, Dieckhaus, & Rosen, 2009). Despite this fact, numerous studies list the Trails A time as a processing speed component and trails B time as an executive component (Barclay, et al., 2007; Becker, et al., 2011; Contardo, et al., 2009; Ettenhofer, et al., 2010; Ettenhofer, et al., 2009; Hinkin, et al., 2002; Hinkin, et al., 2004) without addressing the fact that scores on these tests are related. To examine the variance associated with executive function for Trails B and the Stroop, some adjustment for speed of processing should be made. This adjustment can be a simple subtraction, a transformation or, most effective, including both scores in a hierarchical model. The executive domain scores that are used in ART adherence research ignore both the diversity of executive functions, and task impurity associated with the tests.

Studies have begun to use a more comprehensive factor analytic approach to examine the relationship between neurocognitive factors and ART adherence. A recent

study by Waldrop-Valverde and colleagues (Waldrop-Valverde, et al., 2010) used a factor analytic approach on a neurocognitive battery in 191 HIV+ adults to demonstrate a relationship with neurocognitive function and performance on the Columbia Medication Management Test. While not directly measuring adherence, the Medication Management Test is a performance-based test of medication management that has been validated by distinguishing nonadherent participants from adherent ones (Albert et al., 1999). The neurocognitive battery included tests designed to measure memory (WHO/UCLA Auditory Verbal Learning Test; Maj et al., 1993), executive function (Color Trails; D'Elia & Satz, 1989, Rey Complex Figure; Corwin & Bylsma, 1993, Tower of London; Shallice, 1982), psychomotor speed (Purdue Pegboard; Tiffin, 1968), numeracy (Applied Problems Test; Woodcock, McGrew, & Mather, 2001), and Reading Comprehension (The Reading Comprehension subtest of the Test of Functional Health Literacy; Parker, Baker, Williams, & Nurss, 1995). When examined using exploratory factor analysis, these tests yielded four factors labeled as executive, planning, psychomotor, and verbal memory. Reading comprehension, the Applied Problems Test, the Rey Complex Figure, and Color Trails loaded on the executive factor. The Tower of London, another traditional executive function test, loaded on its own factor: planning. The psychomotor and verbal learning factors contained the variables designed to measure those domains. The executive factor was the most highly associated with performance on the Medication Management Test, while the planning factor was also associated. This study marks an interesting turn from grouping tests based on what they are *expected* to measure to grouping tests based on their statistical similarity. In order to have a clearer concept of where one might intervene with cognitive remediation to improve adherence, more work

that clearly delineates the specific types of executive function associated with adherence is needed.

In summary, the use of global scores or executive function domain scores containing only a few tests offer some predictive power to show that cognitive issues are related to ART adherence. These methods do not take into account the specificity that will be needed to create targets for intervention. Examining executive function using factor analytic methods should increase the ability to accurately define domains of functioning.

Theoretical Framework

The current proposal seeks to unite a neuropsychology approach and a health psychology approach. While neuropsychology is often concerned with brain – behavior relationships, health psychology is often concerned with the etiology of behaviors that lead to problematic health outcomes. What constitutes "behavior" for these two fields of psychology can be disparate. In neuropsychology, the "behavior" in brain – behavior relationships is often a discrete abstract representation of a cognitive function (e.g. digit span score to assess working memory), while the "behaviors" health psychologists study are usually concrete, complex events with multiple antecedents (e.g. smoking, or eating at McDonalds). At times, neuropsychologists bridge these two concepts, adding a link to the chain, and examine brain – function – behavior relationships. What makes these two fields of psychology important to examine together is that impairment in neurocognitive function may make complex health behaviors more or less probable. The relationship of the complex health behavior to neuroanatomy can then be traced back through the brain - function relationships. This method is being used in the examination of neurocognitive

function and ART adherence. However, as there are only a small number of executive function tests being examined in these studies, that brain – function – behavior relationship may be skewed as scientists are not accounting for the wide range of possibilities for executive function. To provide clear targets for new interventions, it is the clarity of function – behavior relationships that are key, as putting every HIV+ client into a scanner is not feasible.

In neuropsychological research, a link has been made between HIV infection and deficits in tasks of executive function, including problems with decision making (E. M. Martin, Sorensen, Edelstein, et al., 1992), working memory (E. M. Martin, et al., 2003), and cognitive flexibility (Basso & Bornstein, 2003; E. M. Martin, Novak, et al., 2004). These same deficits in executive function are associated with problems remaining adherent to HIV medication regimens (Barclay, et al., 2007; Ettenhofer, et al., 2010; Hinkin, et al., 2004). Thus, HIV presents escalating barriers to its own treatment. This relationship is complicated by substance use, as substance dependence has also been associated with deficits in executive functioning (Verdejo-Garcia, et al., 2006), including problems with decision making (Bechara, 2003a; Bechara & Damasio, 2002), working memory (E. M. Martin, et al., 2003), sensitivity to future consequences (Bechara & Damasio, 2002; Bechara, et al., 2002), and impulsivity (Kirby & Petry, 2004). Methamphetamine, in particular, presents a plethora of problems specifically for the HIV+ individual, including barriers to adherence, neurocognitive deficits, synergistic brain damage, and HIV-related health difficulties. Thus, to intervene adequately, it is important to examine the nature of executive dysfunction in HIV+ nonadherent methamphetamine users.

For studies of medication adherence in HIV, the most consistent domain of function that is associated with nonadherence behavior is executive function. Studies of executive function have demonstrated that there is a plethora of sub-functions that make up executive function. In addition, one must account for task impurity in measurement as executive function coordinates lower-level functions. In the adherence literature, executive function has been studied most often by simply placing a couple of tests together and averaging standardized scores, which is not sufficient for describing the diversity of abilities necessary for directing an individual to the goal of a healthier lifestyle.

In order to examine the relationship between executive functions with adherence and methamphetamine use, it is important to consider how impairment on various types of executive function tasks might affect behavior. As mentioned before, there is a strong need for behavioral control to achieve the levels of adherence necessary for viral suppression. Substance use and HIV infections may impede this behavioral control at least partially through neurocognitive deficits. Deficits in *decision making* could impede the goal of adherence and less methamphetamine use through inaccurate processing of reward and punishment. These deficits could lead one to value the short term pleasure of forgetting about medication and taking methamphetamine over the long term consequence of further infection leading one to skip a medication in order to avoid the immediate side effects while ignoring the long term consequence of higher viral load. Deficits in *cognitive flexibility* could impair a person's ability to take medication when on vacation, or on the weekends when routines change. *Impulsivity* or a lack of *response inhibition* by definition could lead people to act without thinking, and could lead to more

substance use or more missed medication. Lastly at the most basic level, *attention* and *working memory* are needed to complete any task, and impairments in either could lead to being unable to remember to take medication. The accurate measurement of specific deficits that are present in an individual, or the specific deficits that are most likely to be associated with the behaviors in question, can inform what specific areas a client can work on to improve their situation.

While the relationship between these deficits and adherence and methamphetamine use behavior may seem intuitive, a lack of clear concise measurement of executive function obscures the details of these relationships. Current research consistently lumps all neurocognitive measures into a global score. At best, research lumps a few executive function scores that are unrelated in factor analyses into an executive domain score. But even these domain scores treat executive function as a unitary construct combining different functions together. Thus, current research leaves us without a clear understanding of what specific deficits are related to nonadherence behavior and methamphetamine use. There is a gap in intervention targets for these behaviors because an intervention for decision making would not be the same as an intervention for working memory issues. Simply intervening on all domains of dysfunction would not be practical.

In order to understand the relationship between the neuropsychological construct of executive function and the health behaviors of nonadherence and methamphetamine use, we need to employ methods that compare different approaches to defining executive function within the same population. Key to this examination is determining the factor structure of executive function in this population. To date, research has not carried out factor analysis on an extensive battery of executive function tests in a population of HIV+

methamphetamine users. This analysis will allow us to compare the methods that are used with high predictive power (executive domain scores) with methods designed to single out specific executive function issues (factor scores, individual test scores). Understanding the specific executive functions that are impaired in this population will give us a lead on interventions for increasing adherence and lowering methamphetamine use.

Having new intervention targets for increasing adherence could lower the probability of poor disease outcomes and increase the length of HIV+ individuals' lives. Likewise, it could reduce methamphetamine use removing the negative health effects directly caused by methamphetamine use (e.g. depression, heart problems, HIV disease progression and neurocognitive deficits), as well as the barrier it presents to adherence. Reducing methamphetamine use and nonadherence could also have an impact on HIV transmission, as methamphetamine is a known risk factor for transmission both sexually and through the sharing of needles, and new data suggest that ART treatment lowers the probability of HIV transmission (HPTN-052, 2011; Montaner, 2011; Montaner et al., 2010). The only way to achieve these new interventions is to accurately identify executive function targets.

The current proposal seeks to contrast three methods of examining executive function in predicting the association between dysfunction and both medication nonadherence and methamphetamine use in a population of HIV+ men who have sex with men (MSM). Specifically this dissertation seeks to:

1. **Describe the distributional properties of three methods of conceptualizing executive function; composite scores, individual scores, and factor scores.**

2. **Compare each of three representations of executive function test data on their association with demographic and mental health variables.**
3. **Compare each of three representations of executive function test data on their association with methamphetamine use variables.**
4. **Compare each of three representations of executive function test data on their association with HIV disease progression and medication adherence.**
5. **Compare each of three representations of executive function tests on their ability to predict adherence controlling for methamphetamine use characteristics.**

Chapter 2:

Methods

Participants

Participants were recruited from a NIDA-funded, R01, randomized controlled trial of a motivational interviewing/cognitive behavioral skills building intervention for methamphetamine use and nonadherence for HIV+ MSM called Adherence Counseling and Education (ACE; R01DA023395; J.T. Parsons, PI). Participants in the study met the following inclusion criteria: 1) HIV+, confirmed with HIV RNA viral load test; 2) take ART medication; 3) report missing an ART med on at least 3 of the last 30 days; 4) use methamphetamine on at least 3 days in the last 90 and 1 day in the last 30; 5) report that they have sex with men; and 6) are able to communicate with staff and complete a survey written in English. Participants were excluded if they: 1) were concurrently enrolled in another adherence intervention; 2) had unstable serious psychiatric symptoms, as measured by the psychotic screen section of the Structured Clinical Interview for DSM-IV-TR (First, Spitzer, Gibbon, & Williams, 2002); 3) used methadone; 4) had evidence of gross cognitive impairment, as measured by a Mini Mental State-Examination (MMSE; Cockrell & Folstein, 1988) score of less than 24; and 5) were currently suicidal or homicidal.

ACE recruited participants from the NYC area using both active and passive methods. Participants were actively recruited at bars, clubs, AIDS Service Organizations, Community Based Organizations, and gay related public events. Passive recruitment included leaving cards and tear-off flyers, as well as the production of print and internet

advertising. Following initial contact the participants completed a telephone interview to verify that they met study criteria.

Procedures

All appointments took place at the Center for HIV Educational Studies and Training (CHEST). Participants enrolled in ACE completed a baseline assessment, 8 sessions of the intervention or educational control, and follow ups at 3, 6, 9, and 12 months. Enrollment in the neuropsychological battery was completed with participants at their baseline assessment. Participants were presented with a second consent form which they reviewed with a research assistant. Participation in the neuropsychological assessment was voluntary, as it was important that the neurocognitive assessment not impact participation in ACE in any way. At the baseline assessment for ACE, participants were required to provide proof of age and HIV status. Participants then were consented into the study, at which point they were given the option to sign an additional consent for the neuropsychological battery. The baseline assessment for ACE consisted of an hour long set of interview measures, followed by a one to two hour long audio assisted self-administered survey (ACASI). Demographic information collected in these surveys was used in subsequent analyses for this study. Participants also had their blood drawn by a licensed phlebotomist for the purpose of gathering HIV RNA viral load and CD4 counts. Participants then completed the first session of intervention or education.

Once consented for the neuropsychological battery, the participant was required to complete the battery before his third session of the experimental intervention or educational control. Because this project was conceived of as a supplement to ACE, it was necessary to ensure that participation in the neuropsychological battery would have

no impact on participation in ACE. Although it would have been ideal to conduct this battery before any intervention was delivered, there is little reason to think that one or two sessions of motivational interviewing, or of educational material would have any significant impact on neuropsychological functioning. The battery itself took two and a half to three hours to complete. Participants first completed a urine drug screen with 27 testing positive for methamphetamine, 29 testing positive for cocaine, 35 testing positive for marijuana and four testing positive for opiates. Participants then completed brief interview about recent medical and recreational drug use. Then participants completed a pair of one hour long sets of neurocognitive tasks (which of the 2 sets came first was randomly determined), separated by a 10-25 minute break. At the completion of the battery the participants were paid $40. All procedures have been approved by the Institutional Review Boards of Hunter College and the Graduate Center of the City University of New York (CUNY).

Sample Creation

A total of 203 participants were recruited for ACE and were eligible to complete the neuropsychological battery. Thirty-eight participants did not complete the neurocognitive battery for the following reasons: missing the window within their sessions to run the battery, $n = 20$; enrolled before the battery was funded, $n = 16$; withdrawn participation in the neurocognitive battery, $n = 1$; and poor eyesight, $n = 1$. Another nine participants' data are not included in the analyses due to computer error, causing missing neurocognitive data, $n = 4$, and inconsistencies in reporting inclusion criteria, $n = 5$. The final sample consisted of 156 participants. The 47 participants who

did not complete the neurocognitive battery did not differ from those who did on demographic, adherence, HIV disease severity or methamphetamine use variables.

Measures

Participant characteristics. *Demographic* variables were extracted from the ACASI administered during the ACE baseline appointment. These demographic variables were administered using a locally developed demographic questionnaire.

Sample characteristics are presented in Table 1 (continuous variables) and Table 2 (discrete variables). Participants' ages ranged from 24 to 63, M = 41.1, SD = 8.7, and ranged in years of education from 5 to 20, M = 14.4, SD = 2.4. Seventy-five percent of the sample had at least a high school diploma or GED and 41% of the sample had a bachelor's degree. This level of education is commensurate with an analogous population of urban, HIV+, methamphetamine-using MSM (Carrico, et al., 2010); however the sample has more education than samples of HIV+ stimulant users in general (Carrico, et al., 2007; Reinhard et al., 2007). Consistent with racial/ethnic distributions among MSM in NYC, the sample was 33% Black, 32% White, and 28% Latino. The sample reported lower income levels than similar samples of HIV+ methamphetamine-using MSM (Carrico, et al., 2010), with 69% of the sample earning less than $20,000 a year.

A locally developed questionnaire, the *Methamphetamine Use History,* was used to examine years since initial methamphetamine use. Participants were asked what age they first used methamphetamine, and this information was used to calculate years of methamphetamine use.

The *Composite International Diagnostic Instrument, Substance Abuse Modules*: (CIDI-SAM: WHO, 1990) is a diagnostic instrument designed by the World Health

Organization based on the DSM. The measure is used frequently to assess dependence on a variety of substances including methamphetamine. The short form used in the present study consisted of 11 items and was administered via ACASI software. Seven of the items mirror the criteria for dependence according to the DSM-IV-TR (i.e., In the past 3 months, did you have a period of a month or more when you spent a great deal of time using meth or getting over the effects of it?) and were answered with a yes no response. These seven responses were added to create a dependence score. This score can be used to dichotomize into likely dependent with a fair degree of accuracy. Those who receive a score of three or higher have a 76% chance of meeting criteria for dependence, while all participants who scored a four or higher met criteria for substance dependence (WHO, 1990).

The CIDI-SAM has been widely used (Darke, 2010), and this short form has been used to categorize methamphetamine dependence in populations of MSM (Irwin & Morgenstern, 2005; Parsons, et al., 2009). The current DSM lists dependence as a discrete category, the proposed DSM-V will change the substance disorders from discrete to continuous in part in response to the determination that criteria for abuse and dependence load onto one factor (Hasin, 2010). In order to more accurately reflect the future of substance use diagnosis, we will examine dependence score continuously.

The *Severity of Dependence Scale* (SDS: Gossop et al., 1995) is a five-item scale that was used to provide a second continuous measure of problematic drug use. Items include "Did you think your use of meth was out of control?" and "How difficult did you find it to stop, or go without meth?" These items were answered on a four-point scale, from 0 to 3, with options ranging from "never/almost never" and "not difficult at all" to

"always/almost always" and "impossible." These responses were added to create a continuous measure that is sometimes used to categorize participants with clinical dependence, and it has been validated among amphetamine users (McKetin & Mattick, 1998; Topp & Mattick, 1997). Factor analytic methods have confirmed that these five items load on a single construct (Gossop, et al., 1995). What separates the SDS from other scales, beyond its brevity, is that the SDS focuses exclusively on compulsive use. This focus on compulsive use excludes the dependence criteria that are based solely on pharmacological aspects, tolerance and dependence, and leaves a clearer picture of the impact of substance use on the behavior of the participant. Despite the focus on just the behavioral aspects, higher scores on the SDS are associated with greater frequency of drug use, longer duration of drug use, and greater dose per drug instance (Gossop, et al., 1995). In addition, the SDS has been used several times in the present population, specifically measuring the extent of problematic methamphetamine use in HIV+ MSM (Marquez, et al., 2009; Mitchell, et al., 2006).

The *Center for Epidemiological Studies-Depression Scale* (CES-D: Radloff, 1977) contains 20 items that measure the occurrence of depressive symptoms during the past week on a four-point scale. Participants indicated how often they experienced each symptom (e.g., "I did not feel like eating; my appetite was poor") on a four-point scale from 0 "Rarely or none of the time" to 3 "Most or all of the time." Items were summed resulting in a scale ranging from 0 to 60, with higher scores indicating more depressive symptomatology. The CES-D is a reliable measure for depression with Cronbach's alpha of 0.89 (USDHHS, 2004) and has been used with regularity in populations of MSM (Perdue, Hagan, Thiede, & Valleroy, 2003; Reisner et al., 2009), methamphetamine users

(Williams et al., 2008), methamphetamine-using MSM (Colfax et al., 2005; Mimiaga et al., 2010), and HIV+ MSM. A score of above 16 on the CES-D is generally considered indicative of depression (Mimiaga, et al., 2010; Radloff, 1977). It is important to note, however, that some symptoms of HIV (e. g., fatigue) can mimic symptoms of depression. To avoid overestimation of the percentage of the sample that is depressed, the CES-D will be used as only a continuous measure.

The trait anxiety portion of the *State Trait Personality Inventory* (STPI-TA; Spielberger, 1986) was used to assess anxiety in the present population. This measure is a 10-item scale modified from the State Trait Anxiety Inventory comprised of questions that ask how participants generally feel with regards to anxiety (Spielberger, Gorsuch, & Edward, 1970). Items such as "Generally, I feel nervous and restless." are scored on a four-point scale from 1 to 4, with response options being almost never, sometimes, often, almost always. Other items such as "Generally, I feel secure." are reverse scored using the same scale. The 10items are summed yielding a total score ranging from 10 to 40. The many different versions of trait anxiety have been used extensively in HIV+, MSM, and drug using populations (Amirkhanian, Kelly, & McAuliffe, 2003; M. A. Chesney, Chambers, Taylor, Johnson, & Folkman, 2003; Crepaz et al., 2008; Yoon, Kim, & Kim, 2007).

Disease progression variables. Two biological indices were collected to examine disease progression. Blood was collected by a certified phlebotomist and prepared as follows for each test.

Blood (5mL) was collected for *HIV RNA viral load* in plasma K_2 EDTA tubes and spun via centrifuge. The plasma was then frozen and an HIV-1 RNA Quantitation, using

a real-time polymerase chain reaction, was conducted by Specialty Laboratories (Valencia, CA).

Over the course of the experiment, the sensitivity of the chemical assay used to measure HIV RNA increased. At the beginning of the study, all participants with a viral load of less than 48 copies/mL were considered undetectable. However, over the course of the project the undetectable level dropped to 20 copies/mL. All participants detectable at this higher sensitivity but below 48 copies/mL were treated as undetectable for categorical analyses. In continuous analyses the absolute values were used wherever possible. In the case of undetectable participants, their viral load was considered the highest level possible. Therefore, when calculating the mean for viral load, participants with an undetectable viral load at the threshold level of 48 copies/mL were considered to have a viral load of 47 copies/mL. Similar transformations were completed for log viral load.

Blood was collected for *CD4 count* in plasma K_2 EDTA tubes (5mL) and Acid Citrate Dextrose tubes (7mL). A calculation was performed on lymphocyte counts to determine absolute CD4 values by Specialty Laboratories (Valencia, CA).

Behavioral measures. The *Timeline Followback* (TLFB: Sobell & Sobell, 1992) is a semi-structured interview in which participants were presented with a calendar and guided through recall of a variety of behaviors. Originally developed to examine alcohol use behaviors, the TLFB has become a standard way of collecting behavioral data. A variety of behaviors have been measured using the TLFB, including methamphetamine use and sexual behavior in substance-using, MSM populations (Golub, Kowalczyk, Weinberger, & Parsons, 2010; Morgenstern et al., 2009; Parsons, et al., 2009). The TLFB

procedure has demonstrated excellent psychometric properties when measuring substances of abuse, including correlation with urine drug screens (Fals-Stewart, O'Farrell, Freitas, McFarlin, & Rutigliano, 2000). The TLFB has been used to measure adherence in substance-using MSM populations (Ingersoll, et al., 2011; Meade, et al., 2010; Parsons, Rosof, & Mustanski, 2007; Parsons, et al., 2008b) and has been shown to be moderately correlated with HIV biological markers (Parsons, Rosof, & Mustanski, 2008a).

For the present study, the TLFB allowed us to capture adherence behavior for 14 days. In the adherence portion of the TLFB, information was gathered regarding which doses of participants' medications were missed and which doses of their medications were taken suboptimally (taken more than two hours from scheduled dosing time). Percent dose adherence was calculated using the missed medication data and these data will be dichotomized splitting the sample into participants who maintain at least 80% dose adherence. This cut point was chosen as studies show that 80% adherence is sufficient for viral suppression using newer classes of medications (Maggiolo, et al., 2007; M. Martin, et al., 2008; Parienti, et al., 2010; Shuter, et al., 2007). While a few studies show that an even lower level of 55% may be sufficient for viral suppression, this is only with regimens containing an NNRTI (Bangsberg, 2006; Maggiolo, et al., 2007). The TLFB was also used to collect methamphetamine use for the last 30 days. These behavioral measures were collected at the baseline assessment for ACE and were extracted for the present analysis.

Data were also collected using a *visual analogue scale* (VAS: Walsh, Mandalia, & Gazzard, 2002) giving the study a second measure of ART medication adherence.

Participants were given a sheet of paper with a 100mm line on it. Anchored on either side was 0% and 100%, with tick marks representing each 10% increase. Participants were asked to place a mark crossing the line indicating the level of medication taken properly over the last 30 days for each medication they took, up to four medications. Percent dose adherence was calculated by weighting the scores for each medication based on the numbers of doses taken per day. A dichotomous score for adherence of at least 80% was also created. The VAS has been used extensively to measure ART adherence and has moderate associations with viral outcomes (K. M. Berg & Arnsten, 2006) and other measures of adherence (Kalichman, et al., 2009). The VAS has been used specifically in methamphetamine-using, MSM populations to measure ART adherence (Carrico, et al., 2010).

Executive function measures.

Decision-making. The *Iowa Gambling Task* (IGT: Bechara & Damasio, 2002) was used to examine decision-making ability and deficits. The IGT is a test of judgment and decision-making designed to identify patients with lesions of the ventromedial prefrontal cortex, but which demonstrates sensitivity to neurocognitive deficits among substance dependent individuals (Bechara, 2003a; Bechara, et al., 2002) and HIV+ persons (Bechara & Martin, 2004). In the IGT, participants were presented with 4 decks of cards, and told that their job was to win as much money as they could. They were also informed that some of the decks were worse than others and to win they should stay away from the "bad" decks. Upon choosing a card the participant was always initially presented with a monetary reward, and occasionally that reward was followed up with a monetary punishment. There were two decks with higher rewards ($80-$130) and two decks with

lower rewards ($40-$60). The higher reward decks had higher punishments than did the low reward decks, such that choosing from the high reward decks resulted in a net loss, and choosing from the low reward decks resulted in a net gain. Thus, to perform well at the task, participants were required to forgo greater initial rewards in order to avoid larger punishment. Participants who fail in this task by choosing more cards from the high reward decks are considered hypersensitive to reward.

Consistent with procedures used in other studies (Bechara, 2003a; Bechara, et al., 2002), participants were also presented with a punishment *Variant* of the IGT. This variant is similar to the original IGT in most respects except that in this task participants always suffer an initial loss, followed by occasional rewards. In the variant, there were two decks with higher initial punishments, but greater occasional rewards that yield a net gain. There were also two decks with smaller initial punishment, yet smaller rewards that yield a net loss. To perform well in this task, participants were required to accept greater initial punishment in order to receive greater rewards. Participants who performed poorly on the variant task, by choosing more cards from the low punishment decks, were considered hypersensitive to punishment.

Standardized instructions were read to participants before administration of the task (Bechara, et al., 2002). In order to control for the effect that these two versions of the task might have on each other, the order in which participants received them was randomized. Both versions of the task were completed on the computer. Participants selected from the four decks of cards until 100 cards were selected. Each deck contains 60 cards, so it was possible for a participant to run out of cards. Data were gathered for each set of 20 trials.

Two variables were used from each of these tasks. One was the simple raw score calculated by subtracting the number of cards selected from the "bad" decks from the number of cards selected from the "good" decks. Because normative data only exist for the original IGT, raw scores were used for both the original and the Variant. In addition, as this test is also used to examine implicit learning, a learning variable was calculated by subtracting the number of cards chosen from the "good" decks in peak performance for the 3rd through 5th quintile from the number of cards chosen from the "good" decks in the 1st quintile. This measure assesses whether a participant can learn the task regardless of total score. A participant may perform poorly through the first 80 cards, and then learn the task. While another participant who randomly chooses from the decks would likely score better on the total score, they would score worse on this learning variable. Past studies have measured implicit learning by subtracting the 3rd quintile (R. Gonzalez, Wardle, Jacobus, Vassileva, & Martin-Thormeyer, 2010), 4th quintile (Ownby, Berry, & Waldrop-Valverde, 2011), or the 5th quintile (R. Gonzalez, et al., 2010) from the first.

The IGT has been effective in examining differences in substance dependent populations and HIV+ populations. In one study, HIV+ participants with a history of substance abuse were shown to perform more poorly on the IGT when compared with HIV- control participants with a similar history of substance abuse, as well as demonstrating that HIV+ participants on combination antiretroviral therapies performed better on the IGT than a group of participants who were untreated or taking just an NNRTI (E. M. Martin, Pitrak, et al., 2004).

Studies using lesion methods have shown that those with ventromedial prefrontal cortex lesions consistently perform poorly on the IGT, while damage to the dorsolateral

prefrontal cortex has yielded more equivocal results (Bechara, 2003b; Bechara & Damasio, 2002; Fellows & Farah, 2005; Manes et al., 2002). Consistent with the somatic marker hypothesis, these lesion studies often indicate that the right hemisphere is more important for IGT performance (Clark, Manes, Antoun, Sahakian, & Robbins, 2003; Tranel, Bechara, & Denburg, 2002). Studies of activation using PET and fMRI have shown wide swaths of activity across the frontal lobes when completing the IGT (Li, Lu, D'Argembeau, Ng, & Bechara, 2010; Lin, Chiu, Cheng, & Hsieh, 2008), with regions such as the medial orbital frontal cortex (Bolla et al., 2003) and the medial and superior frontal gyri being correlated with performance (Tucker, Potenza, et al., 2004). Recent research in pathological gamblers suggests that these same brain regions are activated for good decks in those who perform well and for bad decks in those who perform poorly (Linnet, Moller, Peterson, Gjedde, & Doudet, 2011; Power, Goodyear, & Crockford, 2011).

To date, few studies have examined the neuroanatomical correlates of the Variant IGT task. In their original work with the variant, Bechara, Tranel and Damasio (2000) demonstrated that those with VM prefrontal cortex lesions performed poorly on the task. To date, the only study to image performance on the variant concluded that the differences in brain activation between the IGT and this variant were minimal enough to combine the imaging data for analysis (Li, et al., 2010).

Cognitive flexibility. The *Wisconsin Card Sorting Test* (WCST: E. A. Berg, 1948) is a test of executive function that requires the participant to shift his/her rule set. A series of cards were presented via computer to the participant with a certain color, shape, or number of objects. The participant was required to sort the cards by learning the sorting

rule. Once a participant had sorted 10 cards in a row correctly, the rule changed, forcing the participant to learn a new rule. The participant continued to sort cards until he completed 6 categories (that was 10 cards in a row for each of 6 rules) or sorted a total of 120 cards.

The WCST provides a series of age- and education-normed variables to be examined. However, because much of the executive function battery in this study does not have published norms, the raw form of these scores was used in the analyses. Consistent with many published factor analyses of the WCST (Ardila, et al., 1998; Greve, et al., 1998; Greve, et al., 2005), four variables were used in the analyses: perseverative errors, non-perseverative errors, categories completed, and failure to maintain set. Perseverative errors were errors for which a participant sorted a card into the category that has been established as the perseverated to principal. For the first category, the perseverated to principal was established the first time a participant made an unambiguous error, or an error in which there was no question as to which category he intended to sort by. For subsequent category sets, the previous correct category served as the perseverated to principal. Non-perseverative errors were simply any error made to a category that is not the perseverated-to category. The number of categories completed is the number of sets of ten correct responses made in a row by the participant, and it ranges from zero to six. A failure to maintain set occurs when a participant makes five correct responses in a row followed by an error (Heaton & Psychological Assessment Resources Inc., 1993).

The WCST has been used to examine executive function differences between methamphetamine users and control subjects, with some studies showing differences

(Chung, et al., 2007; S. J. Kim, et al., 2006; Y. T. Kim, et al., 2009) and some not (Simon, et al., 2010; Simon, et al., 2000). HIV+ individuals also have been shown to make more errors on the WCST when compared to control HIV- participants (Basso & Bornstein, 2003).

The WCST has long been thought of as the standard for assessing executive function, but the degree to which the test can distinguish patients with frontal lesions from those with more rostral lesions is debatable (Nyhus & Barcelo, 2009). This finding underscores the need to understand that frontal function is not identical to executive function (Stuss & Alexander, 2000). Functional neuroimaging studies have shown that the WCST activates a wide network of brain regions bilaterally across all of the lobes of the brain (Graham et al., 2009; Nyhus & Barcelo, 2009) with particular importance in the frontal lobes (Konishi, Jimura, Asari, & Miyashita, 2003; Konishi et al., 1998; Lie, Specht, Marshall, & Fink, 2006; Nyhus & Barcelo, 2009; Specht, Lie, Shah, & Fink, 2009). Due to the specificity of the various components of the WCST, the brain regions that have been found to be associated with the various types of errors or stages of the task have been examined, but the findings have not been uniform (Graham, et al., 2009; Konishi et al., 2008; Monchi, Petrides, Petre, Worsley, & Dagher, 2001). Of interest to the present study is the specific association that has been found in fronto-striatal circuitry in WCST performance (Graham, et al., 2009; Monchi, et al., 2001; Monchi, Petrides, Strafella, Worsley, & Doyon, 2006; Simard et al., 2011) as well as the association with errors and an increased capacity for dopaminergic binding (Lumme, Aalto, Ilonen, Nagren, & Hietala, 2007).

Response inhibition / interference. The *Trail Making* portion of the *Delis-Kaplan Executive Function System* (D-KEFS; Delis, Kaplan, & Kramer, 2001) is a test of executive function involving cognitive flexibility, interference, attention, and psychomotor speed. Trail making is a series of timed pen and paper sets, which are subtracted from one another to create composite scores. The first and second tasks are the number and letter trails, respectively. In these two tasks participants were asked to connect all the numbers, or all the letters in order on an 11" x 17" page. For the numbers trail, letters serve as a distracter, and for the numbers trail letters serve as a distracter. The third trail was the switching task, and was the executive function component of the task. In the switching trail condition, participants were asked to switch between connecting numbers and letters in order. In other words, the participant was required to draw a line from the "1" to the "A" to the "2" to the "B" and so on. Errors from this trail were also included in these analyses. There are three possible types of error in the switching trial: 1) set loss errors, or errors where a participant draws a line from a number to a number or a letter to a letter ("1" to "2"); 2) sequencing errors, or errors where a participant successfully switches from a number to a letter, or a letter to a number but does so out of sequence ("1" to "A" to "3"); and 3) time discontinue errors, or any stimulus a participant does not complete because the allotted 4 minutes for the task has expired. Lastly, the fourth trail was a motor speed component in which the participant was required to trace a dotted line (which is the mirror image of the correct switching trail) connecting all the circles in the path. The time to complete each of these four trails was recorded.

The time to complete four of the trails was used to create three variables, the average of number trail and letter trail, switching trail, and motor speed trail were used in

the present analyses. Having these scores in the factor analysis should allow us to extract the variance in the switching trial that is associated with performance on both a simpler trail and the variance associated with motor speed. In addition, a sum of the three types of errors in the switching trial will also be used, as errors could be indicative of dysfunction in interference despite time to complete the switching trail.

Reitan's original trails, the Trails AB (Reitan, 1958), has often been employed successfully in HIV+ populations to study executive function test-retest generalizability (Levine et al., 2007) and to relate level of adherence to HIV medications with executive function (Applebaum, et al., 2009; Avants, et al., 2001; Ettenhofer, et al., 2009; Solomon & Halkitis, 2008). It has also been employed to show differences in executive function in regular methamphetamine users compared to controls (Simon, et al., 2000).

While the traditional Trails AB has been examined neuroanatomically, only a single study has examined the D-KEFs version. Participants with left prefrontal cortex lesions performed more poorly on the switching trial of the D-KEFs trails (Yochim, Baldo, Nelson, & Delis, 2007). Consistent with those findings, studies examining Trails AB have found consistent activation across much of the left frontal lobes when comparing activation in the switching trial to the non switching trial (Jacobson, Blanchard, Connolly, Cannon, & Garavan, 2011; Moll, de Oliveira-Souza, Moll, Bramati, & Andreiuolo, 2002; Zakzanis, Mraz, & Graham, 2005).

Response inhibition / impulsivity. In order to examine motor impulsivity, a computerized version of the *Go-Nogo* (Leland, Arce, Miller, & Paulus, 2008b) was used. The Go-Nogo works by creating a prepotent response, then requiring inhibition of that response. Go-Nogo tasks can be presented in a variety of ways; in the present task visual

stimuli consisting of 5 letter strings were used. The letter strings displayed on the screen were BBBBB, DDBDD, DDDDD, and BBDBB. Participants were instructed to press the space bar when they saw a "B" in the center of the stimuli (the "go" stimulus), and not respond when they saw a "D" (the "no-go" stimulus). The Go-Nogo was broken into three blocks separated by 30-second breaks. To create the prepotent response "Go" stimuli were presented in 80% of the trials and the initial 15 stimuli in each block were "go" stimuli. The impulsivity variable obtained was false alarms, or hitting the space bar when a "no-go" stimulus is presented. Other variables that were included in the analysis were missed opportunities, or not hitting the space bar when the "go" stimulus is presented, and reaction time on correctly identified "go" trials. Missed opportunities are theorized to measure inattention (Bezdjian, Baker, Lozano, & Raine, 2009; Halperin, Wolf, Greenblatt, & Young, 1991). The reaction time on go trials was included in the analysis to account for the speed-accuracy trade-off in response inhibition.

Relevant to this study, the Go-Nogo has been used to differentiate HIV+ participants (Schroeder et al., 1994) and MA-users (Leland, et al., 2008b) from control participants. Behavioral data are often used to study clinical populations, such as polysubstance users (Fillmore & Rush, 2006).

The Go-Nogo has been used extensively to study the functional neuroanatomy of response inhibition. Response to "nogo" stimuli has long been known to include regions of the cingulate cortex, which are known to monitor response conflict and errors (Hester, Fassbender, & Garavan, 2004; Mathalon, Whitfield, & Ford, 2003). Within the frontal lobes, successful inhibition of "nogo" stimuli have been localized to the right hemisphere, and include the insula, and the middle and inferior frontal gyri with greater activation

associated with faster responding on the go trials (Garavan, Ross, & Stein, 1999; Konishi et al., 1999). The Go-Nogo has been used specifically to examine differences in brain function among users of different stimulants (Leland, Arce, Miller, & Paulus, 2008a). Compared to controls during, studies have shown that ecstasy users have hyperactivity of the right middle and inferior frontal gyri in response to successful inhibitions (G. M. Roberts & Garavan, 2010) and cocaine users have hypoactivity in the right cingulate cortex and insula (Kaufman, Ross, Stein, & Garavan, 2003). These findings can be explained by the fact that ecstasy users had equivalent performance to controls, while cocaine users performed more poorly.

Working memory. To examine working memory the *Counting Span* (Case, Midian, & Goldberg, 1982) will be given. The Counting Span is a measure of complex working memory. Though used mostly with school age children (Conway et al., 2005), it has also been adapted for use with adults (Engle, Tuholski, Laughlin, & Conway, 1999). The participant was shown various screens filled with shapes and colors, with instructions to count and remember the number of dark blue circles. Following the counting, participants were required to hit the space bar to advance to the next screen. Again the participant had to count the number of dark blue circles. After all screens were presented, the participant used the keyboard to enter the number of dark blue circles from each screen in the order those screens were shown. The number of screens the participant must remember ranged from 2 to 8, with each range being displayed 3 times. A working memory span score was produced by the Counting Span. This score was calculated by adding the number of screens in trials where all screens were correctly identified. So if a participant correctly identified each screen in all three trials of two screens, two of the trials of three screens,

and one of the trials of four screens, their Span Score was calculated as 16, or 2+2+2+3+3+4.

Although working memory processes are often linked to functioning in the dorsolateral prefrontal cortex, research suggests activation in multiple cortical areas (Linden, 2007; Muller & Knight, 2006; Schlosser, Wagner, & Sauer, 2006). Complex span tasks are associated with multiple higher order cognitive abilities, and are believed to better reflect general working memory capacity (Kane et al., 2004) though they are harder to localize neuroanatomically due to the multiple components that make up such tests. To date, no study has examined the neuroanatomical correlates of Counting Span performance.

Preliminary Data Analysis Plan

Because only some of the executive function tests have age or educations adjusted norms all analyses used raw scores. Standard techniques from exploratory data analysis were used to investigate the distributional characteristics of all neurocognitive and outcome measures. Neurocognitive measures were reverse scored if the measure was designed so that higher scores were indicative of dysfunction. These measures included: 1) WCST perseverative errors; 2) WCST non-perseverative errors; 3) WCST failure to maintain set; 4) Go-Nogo false alarms; 5) Go-Nogo missed opportunities; 6) Go-Nogo reaction time; 7) Time to complete the switching trail; 8) number of errors on the switching trail; 9) average time to complete the number and letter trails; and 10) time to complete the motor speed trail. This reverse scoring was done to ease interpretation, creating scores for all neurocognitive variables such that a greater score is indicative of better performance. Distributional properties were examined using standard summary

statistics (means, standard deviations, medians, skewness, kurtosis) in addition to graphical summaries (boxplots and density plots), and these were compared to distributional characteristics found in literature with similar HIV+ and/or substance-using populations. Pearson product moment correlations were conducted to examine relationships between neurocognitive measures, allowing us to examine any issues with collinearity in further analyses.

Preliminary analyses uncovered several skewed variables. In cases of extreme skewness, the variables were transformed into meaningful ordinal variables. The number of missed opportunities on the Go-Nogo and the number of errors on the trails switching were transformed into ordinal variables. Other skewed variables were truncated at three standard deviations above and below the mean. This truncation process allowed for the use of parametric statistical analysis and preserved data from participants who were particularly impaired while limiting the impact of these outliers on the results. Because of the neurocognitive deficits associated with the inclusion criteria, profound impairment in tasks was to be expected for some participants. In fact all truncation occurred below the mean, with no participant exceeding three standard deviations above the mean. Eight variables were truncated: IGT variant raw score, WCST perseverative errors, non-perseverative errors, failure to maintain set score, Go-Nogo reaction time, and all three trails time to completion. The number of participants truncated within each variable ranged from one to four. Ten participants were truncated in one variable and four were truncated on two variables. No participant needed truncation on more than two variables. The truncated and categorical variables were used for all subsequent analyses.

Multivariate outliers were examined using Mahalanobis distance but after truncation no participant had Mahalanobis distance exceeding the criterion value of $p < .005$. Examinations of scatter plots yielded no violations of linearity.

Errors in data collection led to missing data for several measures. In order to preserve the measures with missing data, analyses using these measures were calculated with a smaller *n*. Two participants made errors in entering CIDI-SAM data into ACASI that made it impossible to score. One participant did not provide a year of initiation for methamphetamine use and two participants did not provide a year of HIV diagnosis. Lastly, because one participant refused to disclose his income, the analyses involving income use a smaller *n* of 155.

Specific Aim 1: Describe the distributional properties of three methods of conceptualizing executive function: composite scores; individual scores, and factor scores

Specific Aim 1 laid the groundwork for subsequent analyses. The sample is characterized to insure that it is representative and similar to other populations of HIV+ methamphetamine using MSM. In addition, the distributional properties of each representation of executive function are presented, allowing for the comparison of each method.

Hypothesized factor structure. Of particular importance within Aim 1 was the creation of factor scores. The variables used in this factor analysis suggested a six factor solution. The four variables from the IGT were expected to load together onto a Decision Making/Reinforcement Processing factor. While these four variables were expected to load together strongly, it is conceivable that variables from any other test (save the motor

speed variables) could contribute because the processes measured using other executive function tests are necessary for decision making. For example, if a participant is stuck in set he may not explore the four decks enough to discern the effectiveness of each deck. Also, a participant with poor working memory would be unable to hold all four options in mind.

A second factor, Cognitive Flexibility, was expected to be comprised of perseverative errors and categories completed from the WCST as well as time to complete the switching trails and the number of errors on the switching trail. While a third, Inhibition, was expected to similarly load the switching trail scores, the number of false alarms and perhaps the perseverative errors as all three of these variables are believed to measure some aspect of inhibition. Studies have described both the WCST and the switching trail as tests of set shifting and inhibition. Neuroanatomically, the right inferior prefrontal cortex has been linked to the processes common to set shifting in the WCST (Konishi, et al., 1998; Konishi, et al., 1999), inhibition in the Go-Nogo (Garavan, et al., 1999; Konishi, et al., 1999), and performance on the switching trail (Jacobson, et al., 2011). These studies suggest that the common process to all of these tests is inhibition of a more salient response. While each of these tasks involves inhibition, the degree to which inhibition may be the sole arbiter of success changes. After inhibiting a response, the Go-Nogo requires no further action, the switching trail requires the participant to make an alternative response to what was inhibited, and the WCST requires the participant to test hypotheses to learn what the appropriate alternative response could be. This increasing degree of post inhibition difficulty suggests that these variables would load onto multiple factors that overlap.

A fourth factor was hypothesized to consist of only the span score and would represent working memory. This factor may have weak loadings from other tests as working memory is thought to be important for nearly all executive function tests, but should primarily load span score alone.

The last two factors hypothesized were believed to represent neurocognitive function that is not regularly considered executive in nature. One factor, Attention, was expected to consist of WCST failure to maintain set and Go-Nogo missed opportunities. Both of these variables are considered to represent a degree of distractibility and thus, it is theorized that they would load together. A final factor representing Motor Speed was expected, and was theorized to consist of all the timed variables from the D-KEFS trails as well as reaction time on the Go-Nogo.

Specific Aim 2: Compare each of three representations of executive function test data on their association with demographic and mental health variables

Specific Aim 2 allowed for the comparison of executive function representations on well-characterized independent variables. The use of both bivariate and multivariate analyses allowed for the examination of both unique and complex associations between the different executive function representations and demographic and mental health variables. The main goal accomplished within this aim is the examination of which executive function representations best match what has been found in the existing literature. It was hypothesized that the composite NPZ score will have powerful associations, but that due to the means of construction, the NPZ score will be more susceptible to misinterpretation. The factor scores and individual scores were

hypothesized to have less power for detection, but due to the more narrow scope of these variables, the nature of the relationships that are found will be easier to interpret.

Specific Aim 3: Compare each of three representations of executive function test data on their association with methamphetamine use variables

Specific Aim 3 considers how methamphetamine use may impact executive function. It is hypothesized that within all three representations, deficits will be found in association to increased use, and increased problems related to methamphetamine use. In addition given the dopaminergic action of methamphetamine, motor issues were also expected in those who use more methamphetamine. The nature of the representations was expected to allow for finer examination of specific problems when using factor scores or individual variables when compared to the NPZ.

Specific Aim 4: Compare each of three representations of executive function test data on their association with HIV disease progression and medication adherence

Specific Aim 4 considers how methamphetamine use may impact executive function. It is hypothesized that within all three representations deficits will be found in association to greater disease severity, and poorer adherence. Again the nature of the representations was expected to allow for finer examination of specific problems with executive function when using factor scores or individual variables as opposed to the NPZ score.

Specific Aim 5: Compare each of three representations of executive function tests on their ability to predict adherence controlling for methamphetamine use characteristics

Specific Aim 5 was created to examine the effect of executive function on adherence while controlling for issues specifically related to methamphetamine use. This

examination was constructed to be similar to previous studies that have examined ability of neurocognitive factors to predict whether participants had adequate adherence for viral suppression (Avants, et al., 2001; Barclay, et al., 2007; Hinkin, et al., 2002; Hinkin, et al., 2004; Levine, et al., 2005; Solomon & Halkitis, 2008; Wagner, et al., 2002). While some previous studies have failed to show such effects in multivariate models examining the effect of executive function on adherence controlling for substance use (Applebaum, et al., 2009; Contardo, et al., 2009; Waldrop-Valverde, et al., 2008), studies have shown general neurocognitive effects in such models (Waldrop-Valverde, et al., 2008). Therefore, it is hypothesized that the NPZ will be associated at the multivariate level controlling for methamphetamine use characteristics, but it is unlikely that the less powerful methods (factor scores, individual variables) will show this effect.

Chapter 3:

Specific Aim 1. Describe the distributional properties of three methods of conceptualizing executive function: individual scores, composite score, and factor scores

Results

Participant characteristics. Participants' average score on the CES-D was 24.9, *SD* = 11.1. This average is well above the cutoff of 16, which is usually used to identify individuals with clinical depression (Radloff, 1977). In fact, 74% of patients scored above 16 on the CESD at baseline. This high percentage of the sample meeting the clinical cutoff may be inflated due to the fact that HIV symptoms and medication side effects can mimic some symptoms of depression, such as psychomotor retardation. While 16 is considered the cutoff for the general population, a more stringent cutoff of 27 has been found more useful for screening patients with medical conditions for depression (Ensel 1986; Zich, Attkisson et al. 1990; Logsdon, McBride et al. 1994; Geisser, Roth et al. 1997). Even using this more conservative cutoff score, 48.1% of the sample would be considered depressed. In contrast to the results for depression, the sample averaged 19.9, *SD* = 6.1, on the trait anxiety subscale of the STPI. This mean aligns with scores found in national norms using the traditional State-Trait Anxiety Inventory (Darke, 2010) and other samples of HIV+ MSM participants using the STPI (Pantalone, Hessler, & Simoni, 2010).

All sample participants used methamphetamine at least once in the last 30 days. The mean number of methamphetamine-use days in the last 30 was 5.5, *SD* = 5.3, and the range was 1 to 30. Years since initiation of methamphetamine use ranged from less than 1 to 41 years, *M* = 9.9, *SD* = 7.8. Scores on both the CIDI-SAM, *M* = 3.7, *SD* = 2.1, and severity of dependence scales, *M* = 5.2, *SD* = 3.1, indicated that methamphetamine was a significant problem in the lives

of participants. Two-thirds of the sample had CIDI-SAM scores at or above the criterion of three, indicating a high probability of a substance dependence diagnosis (Ustun et al., 1997).

Participants' years since HIV diagnosis also ranged widely, from less than 1 to 26 years, M = 11.8, SD = 7.2. Participants reported a mean number of 7.8 years on ART treatment, SD = 5.8, and reported having been placed on a mean of 3.2 different regimens, SD = 2.8. This large number of different regimens suggests a population challenged by adherence and one that has developed resistance to some ART medications (Eron, 2008). Measures of percent dose adherence from both the TLFB, M = 68.9, SD = 30.7, and VAS, M = 67.3, SD = 24.5, indicated poor adherence levels; however, percent dose adherence still exceeded levels known to be effective for newer ART medications (Bangsberg, 2006; Maggiolo, et al., 2007). There was also a wide range of adherence scores, with the TLFB yielding a range from 0 to 100% adherence in the past 14 days and the VAS a range from 0 to 99%. The range in adherence may explain some of the variance seen in the biological indices of HIV disease progression. The mean HIV RNA viral load was 34,258, SD = 112,733, yet over half the sample, 53.8%, had an undetectable viral load. The mean absolute CD4 count was 458.7, SD = 24.5, and although this number is below the normal range (500 – 1,500), it is well above the level that defines AIDS (200). Only 18.6% of the sample had CD4 levels below the AIDS-defining level, while 41% of the sample had CD4 counts in the normal range.

Individual scores and comparison with standard samples. Participants' performance on each of the 16 neuropsychological test variables are displayed in Tables 3 (continuous scores) and 4 (categorical scores). Participants' raw scores for the IGT averaged 7.4, SD = 27.6. Because this mean falls within the range of IGT scores earned by persons with ventromedial prefrontal cortex damage, it suggests impairment (Bechara, et al., 2002). However, participants' standard

T-scores, adjusted for age and education, averaged 46.1, *SD* = 9.2. Because T-scores were standardized to have a mean of 50 and a standard deviation of 10, this average is considered unimpaired, but is slightly below population norms (Bechara & Psychological Assessment Resources Inc., 2007). Participant average on the IGT variant was 12.4, *SD* = 35.7. This average fell above the range for ventromedial prefrontal cortex lesion patients (Bechara, et al., 2002), yet 79 participants (50.6%) scored below the cutoff number of eight that is considered to fall within the impaired range for the Variant.

This present sample was impaired on the WCST test. T-scores adjusted for age and education (Heaton & Psychological Assessment Resources Inc., 1993) indicated that participants in the present sample were profoundly impaired. The mean T-score for perseverative errors was 38.3, *SD* = 12.2, and for non-perseverative errors was 38.0, *SD* = 10.2. Both means are more than one standard deviation below general population means. In perseverative errors, 87 participants (55.8%) scored more than one standard deviation below the mean with only 22, 14.1%, scoring at or above the mean. A similar pattern was seen for non-perseverative errors, with 24 participants (54.5%) scoring more than one standard deviation below the mean and only 22 (15.4%) scoring at or above the mean.

Scores on the D-KEFS trails were adjusted for age using a scaled score with a mean of 10 and a standard deviation of three (Delis, et al., 2001). Scores on the D-KEFS trails were consistent with general population norms; participants' scores on number and letter composite and motor speed were 10.2, SD = 7.2, and 10.8, SD = 2.2, respectively. These results are in contrast with studies that have shown that motor slowing is the first form of impairment HIV+ persons are likely to manifest (McArthur, 2004; Nath, et al., 2008). The time to complete the switching trail, *M* = 8.9, *SD* = 3.4, was slightly below population norms. These scaled scores

suggest that the switching trail is not simply measuring the same domain as the WCST, because this sample differs so greatly from the general population on WCST but not on the switching trail.

The Go-Nogo and the Counting Span do not have standardized norms. The Go-Nogo is constructed differently from study to study, so comparisons across studies have limited utility. The Counting Span is a rarely used test of working memory. By including the distraction task of counting during the task, rehearsal is disrupted and the unique nature of the Counting Span makes it hard to compare it with other tasks of working memory such as the digit span (Wechsler, 2005) or the n-back (Kirchner, 1958).

Correlations between individual neurocognitive variables. Pearson *r* and Spearman *rho* correlations between the individual neurocognitive scores are presented in Table 5. Not surprisingly, scores within the same tests correlated with one another, but close inspection of correlations revealed other notable patterns within the data. Several patterns of correlations across tests were evident, indicating areas where tasks and variables overlapped, as well as revealing task impurity in the measurement of executive function. The span score from the Counting Span was correlated with nearly every other variable, illustrating the importance of working memory for all tasks. The two executive function tests used to measure cognitive flexibility – WCST and D-KEFS -- were associated, with perseverative errors in the WCST correlated with the time to complete and the number of errors in the switching trial in the D-KEFS trails. Associations between the IGT and tests of cognitive flexibility indicate its importance for task performance, as participants need to switch between decks in the IGT in order to learn the task. Perseverative errors on the WCST were associated with learning scores on the IGT and the IGT variant but not with either's total scores. Time to complete the switching

trail was associated with raw score on the IGT, learning on the IGT, and the IGT variant. Time to complete the switching trail was associated with time to complete the number and letter trails, the motor speed trail, and Go-Nogo reaction time.

Relationships among variables from the Go-Nogo illustrate the effect of reaction time on accuracy. As response time on the Go-Nogo became faster, the number of false alarms increased. This finding is in contrast to the positive relationship identified between response time and missed opportunities. A positive correlation between false alarms and missed opportunities was identified as well.

Creation of NPZ composite executive function score. The creation of the composite executive function score was done to mimic the methods in previous studies as closely as possible (Applebaum, et al., 2009; Barclay, et al., 2007; Becker, et al., 2011; Ettenhofer, et al., 2010; Ettenhofer, et al., 2009; Hinkin, et al., 2002; Hinkin, et al., 2004; Levine, et al., 2005; Meade, et al., 2010; Waldrop-Valverde, et al., 2006). However, as the current study examines many tests without published norms, the scores were transformed to Z-scores for all tests based on the sample, rather than published norms. Without norms, the further transformation into impairment scores (Heaton, Grant, & Matthews, 1991) was not possible. Thus, the level of impairment in the sample compared to the general population could not be explored. Where possible, however, standard scores were calculated to give an idea of the level of impairment in the sample in reference to the wider population. Standardized scores were available for the IGT (Bechara & Psychological Assessment Resources Inc., 2007), WCST (Heaton & Psychological Assessment Resources Inc., 1993), and the Trails (Delis, et al., 2001).

The composite NPZ score will be made up of the most commonly used variable in the literature for each of the 6 tests included in the study: 1) IGT: raw score (good decks – bad

decks); 2) IGT variant: raw score (good decks – bad decks); 3) WCST: number of perseverative errors; 4) Trails: time to complete switching trial; 5) Go-Nogo: number of false alarms; and 6) Counting Span: span score.

Factor score creation and labeling. Variables were selected from the various tests in order to extract the most information possible, and in order to account for task impurity where possible. Variables included in the factor score analysis were: 1) IGT: total raw score and learning score; 2) IGT Variant: total raw score and learning score; 3) WCST: perseverative errors, non-perseverative errors, failure to maintain set score, and categories completed; 4) Trails: average time to complete numbers and letters, time to complete switching trial, time to complete motor speed, and total errors on the switching trial; 5) Go-Nogo; false alarms, missed opportunities, and reaction time; and 6) Counting Span: Span Score.

In order to determine the factor structure, exploratory factor analysis was completed using SPSS software. First, linearity was examined. As there were too many pairwise comparisons to be made to examine each possible scatter plot, ten pair wise comparisons were made examining those variables most likely to break from linearity, yielding no break from linearity. After truncation there were no univariate outliers, while Mahalanobis distance indicated the lack of any multivariate outliers. The factor analysis was completed with an oblique rotation (oblimin). As we know from factor analyses of executive function, there are distinct aspects of executive functioning, but they do share common variance. An oblique rotation allows for the fact that the factors associated with executive function are correlated (Miyake, et al., 2000). Extraction was completed using maximum likelihood estimation. A criterion eigenvalue of greater than 1.0 was used to determine factor structure. Variables were allowed to load onto more than one factor as the nature of executive function makes it likely that any one variable could load onto several

factors. A random split half was run through the same procedure and yielded a similar solution. Participant scores on each factor were saved for use in subsequent analyses.

Six factors with eigenvalues greater than one were extracted, explaining 66.7% of the variance among all 16 variables. The scree plot is displayed in Figure 1. The structure matrix of the factors is displayed in Table 6. Initial examinations showed that factors were more likely to load on variables from the same test rather than loading variables from multiple tests. The one exception was the counting span; as expected, it appeared that working memory contributed to all factors, with absolute value factor loadings ranging from .270 to .405. Failure to maintain set score on the WCST was not related to any factor.

In the introduction, concerns were expressed regarding the difficulties inherent in the naming of executive functions. This challenge is due, in part, to the fact that performing well on many executive function tests requires different operations using several aspects of neurocognitive function. Factor analysis allows for a better understanding of the functions being tested through examination of the patterns of variables that load together. One of the advantages of factor analysis is that one can examine the loadings across tasks to have a better understanding of the differences in functions being studied instead of relying upon a researcher's interpretation of what an individual variable from an individual task means. However, it is important to remember that the present analysis is not exhaustive and the following categories do not necessarily represent all aspects of executive function. With a more exhaustive battery of both executive and non-executive neurocognitive function scores, labeling could be performed with more precision through convergent and divergent validation. Despite these reservations, the factor scores have been carefully named in order to characterize the specific functions being tested, giving confidence in their meaning for possible intervention.

Factor one accounted for 17.5% of the variance and was labeled "Wisconsin Card Sorting Test Performance" because the items that loaded strongly onto this factor included perseverative errors, non-perseverative errors, and categories completed, all from the WCST. The counting span score also loaded moderately onto this factor. As expected, the next highest factor loading that failed to reach the .30 criterion was trails switching, .291. This test is theorized to measure a domain of executive function (i.e., cognitive flexibility or set shifting) similar to the WCST. The label WCST Performance was used, instead of a more conceptual label, such as cognitive flexibility or set shifting, because non-perseverative errors, which may not be related to issues of cognitive flexibility (Greve, et al., 1998), loaded as strongly as perseverative errors.

Factor two accounted for 8.7% of the variance and was labeled "Motor Impulsivity" because the number of false alarms from the Go-Nogo loaded strongly in the negative direction on this factor. Items loading moderately on the Motor Impulsivity factor included reaction time and working memory through the span score. All individual neurocognitive variables were reversed so that higher scores would indicate better performance; however, the majority of factor loadings for Motor Impulsivity were negative, indicating that greater scores in this factor represent poorer performance, i.e. greater motor impulsivity.

Factor three accounted for 8.5% of the variance and was labeled "Slowness of Processing" due to the negative loadings in multiple tests that were related to speed of processing. Tests relating to processing speed that loaded onto this factor included: time to complete the number and letter trails, switching trail, and motor speed trail, as well as the number of missed opportunities on the Go-Nogo. Interestingly, Go-Nogo reaction time failed to load above the criterion of .30 (-.292), while a measure seemingly unrelated to speed—working memory—did load above .30 on Slowness of Processing. "Motor Slowness" was an alternative

name; however, the label Slowness of Processing was chosen over Motor Slowness because the pattern of loadings emphasized speed in the context of *cognitive* processing. The number and letter trails and switching trail loaded more strongly than did the motor speed trail or the Go-Nogo reaction time. Also emphasizing cognitive processing over motor speed within this factor is that working memory contributed at near the same level as did either reaction time or the motor speed trail. If this factor consisted solely of motor speed, one would not expect working memory to have contributed to the factor at all.

Factor four accounted for 8.0% of the variance and was labeled "Executive Inhibition" because it consisted of two switching variables from the DKEFS trails test: time to complete the switching trial, and number of switching errors. This label was designed to address the differences between WCST Performance and trails switching performance. Although both the switching trail and the WCST are thought to measure set shifting or cognitive flexibility (Lezak, 2004; Miyake, et al., 2000), the extent to which variables from each of these tests loaded on to different factors underscores differences in their administration and in the functions required for good performance. Set shifting and executive inhibition are similar functions, but have subtle differences. Set shifting refers to switching between different sets of rules or being able to perform a task well under different contexts. Inhibition refers to the process of not responding in a more typical manner when that response is incorrect. For example, the switching trail requires a person to inhibit a prepotent response of going automatically from A to B, and instead move a pen from the letter A to the number 2. Although the WCST also can be considered to require inhibition (one must inhibit the last rule to respond correctly when the rule changes), any given rule (e.g., sorting by color or shape) does not involve an inherent prepotent response.

Factor five accounted for 5.1 % of the variance and was labeled "Sustained Attention." Variables with strong loadings on this factor included reaction time for the Go-Nogo and number of missed opportunities on the Go-Nogo, while moderate loadings were found for time to complete the switching trail, and number and letter trails. The strong loadings for reaction time and missed opportunities suggest that this factor score will be highest for participants who have both few missed opportunities and quick reaction time on the Go-Nogo. Quick responses and few misses suggest that participants who scored well on this factor were maintaining their focus throughout the 12-minute task. This factor improves upon the simple measurement of missed opportunities as it takes into account missed opportunities while also accounting for the speed/accuracy trade off.

The sixth and final factor, labeled "Decision Making/Reinforcement Processing" because all four IGT variables loaded onto this factor, accounted for 5.8% of the variance. The IGT had strong loadings with raw score, .613, and learning score, .584, while the IGT variant had more moderate loading with raw score, .308, and learning score, .403. Also loading onto this factor were perseverative errors of the WCST, .338. To reiterate, this association between perseverative errors and IGT scores was not surprising because perseveration on a deck within the IGT left participants ill equipped to learn from each deck.

Correlations among factor scores and the executive domain NPZ score. Descriptive data for the executive domain NPZ and factor scores are presented in Table 7 and correlations among those variables are presented in Table 8. All factors were significantly correlated with the executive domain NPZ score. By definition, factors composed of variables used to create the NPZ were more strongly correlated with this executive domain score. Decision Making/Reinforcement Processing, WCST Performance, and Motor Impulsivity were more

strongly associated with the executive domain NPZ than those comprised of variables that were not used to create the NPZ, including Slowness of Processing and Sustained Attention. Surprisingly, one factor, Executive Inhibition, is composed of a strong loading from time to complete the switching trail, which was used to create the NPZ, but is only weakly correlated with the executive domain score. Partial correlations, controlling for all other factor scores, were run in order to examine the unique associations between factor scores and the executive domain NPZ. The relationship between both Slowness of Processing and Executive Inhibition with the executive domain NPZ was reduced below significance when run as a partial correlation, while all other factors maintained a significant correlation. Even when controlling for the other factors, Decision Making/Reinforcement Processing continued to have the strongest correlation with the executive domain NPZ score.

Correlations between factors, like correlations between individual variables, shed some light on task impurity. Slowness of Processing was negatively correlated with each of the other factors except Motor Impulsivity. WCST Performance was associated with both Executive Inhibition and Decision Making/Reinforcement Processing. Lastly, Sustained Attention was positively associated with Executive Inhibition.

Discussion

Expected factor analytic results. It was hypothesized that the solution would contain six factors: Decision Making/Response Inhibition (composed of the IGT variables), Cognitive Flexibility (composed of the WCST and the switching trail), Inhibition (composed of the switching trail, false alarms, and perseverative errors), Working Memory (composed of the span score), Attention (composed of missed opportunities and failure to maintain set), and Motor Speed (composed of trails and Go-Nogo response time). Although a six-factor solution was the

result, there were several differences as compared with the expected results. While the WCST Performance factor was similar to the results expected in the cognitive flexibility factor, the switching trail did not load onto this factor. Similarly, perseverative errors did not load with the switching trail on the Executive Inhibition factor. Inhibition was split into two factors: one, a simple Motor Inhibition factor composed of the false alarms and reaction time from the Go-Nogo, and a second Executive Inhibition composed of the switching trail time and errors. Sustained Attention was similar to the hypothesized Attention factor but did not contain a loading from failure to maintain set. Lastly, the Span score did not load onto a factor by itself, but instead loaded across all factors.

What factors represent executive function? One purpose of this factor analysis was to clarify which domains are measured by variables from executive function tests. A second purpose was to remove some of the impact of task impurity. It was therefore important to examine the loadings for each factor in order to clarify which of the factors represented executive function. This examination was important not only for the factor analysis itself, but also to contextualize subsequent analyses of the association between neurocognitive factors and demographic, HIV-related, and methamphetamine-related factors. Three factors can be clearly linked to aspects of executive function, including WCST Performance, Executive Inhibition, and Decision Making/Reinforcement Processing. Each of these factors has variable loadings believed to represent executive functions (e.g. perseverative errors and IGT score) but none that are considered representative of a lower-level function (e.g. number and letter trails and reaction time).

Two factors, Slowness of Processing and Sustained Attention, could be considered nonexecutive in nature because the pattern of factor loading indicates more basic processes.

Although both factors had strong loadings from the time to complete the switching trial, which is a traditional executive variable, this loading was likely the result of the reaction time aspect of this variable as opposed to its executive aspect. In Slowness of Processing, time to complete the switching trail in both research and clinical populations loaded along with time to complete the motor speed trail and the number and letter trails. For Sustained Attention, time to complete the number and letter trails and reaction time on the Go-Nogo loaded along with the switching trail. While some consider attention on a similar spectrum as executive function, there is no evidence from the factor loadings to confirm or deny this. Slowness of Processing clearly represents lower levels of function, and Sustained Attention may similarly represent nonexecutive function. Both these factors exemplify how variables containing a speed of processing component can cause task impurity. The loadings of these variables in this factor analysis elucidate the degree to which speed of processing contributes to a domain.

The degree to which Motor Impulsivity may represent executive function is equivocal. While it is widely accepted that the ability to inhibit impulsive behavior is an executive function (Finn, Justus, Mazas, & Steinmetz, 1999), the extent to which simple motor response inhibition measures this higher-level construct is at issue in the present analysis. While this question cannot be answered using the present design, it is important to note that the motor impulsivity factor lacks other accepted measures of inhibition within this sample. This circumstance supports the hypothesis that simple motor response inhibition is insufficient to measure the construct of impulsivity.

Task impurity. When examining the correlations seen among neurocognitive variables, issues of task impurity (i.e., the degree to which performance on a task relies upon functions that it is not being used to measure) emerge repeatedly. Task impurity is best illustrated through the

examinations of trails switching in relation to other reaction time variables. The time to complete the switching trail is often used to measure executive function. As expected, this measure's reaction time was associated with other reaction time measures not used to measure executive function (i.e. time to complete the number and letter trails, time to complete the motor speed trail, and Go-Nogo reaction time). Because participants' speed of movement affects all of these measurements, it was no surprise that all the measures were correlated. One of the neurocognitive tests most commonly used in HIV research is the Trails AB (Al-Khindi, Zakzanis, & van Gorp, 2011). When analyzing these data, most researchers examine the time to complete Trail A (analogous to the number trail in the present study) and Trail B (analogous to the switching trail in the present study) separately, labeling Trail A motor function or attention, and Trail B executive function. It is clear, however, that the Trail B relies upon motor function. Therefore, in order to accurately reflect the measurement of executive function with the Trail B, researchers must control for Trail A.

Task impurity is more than a problem of nonexecutive functions interfering with the measurement of executive functions. Task impurity can also refer to situations in which different executive functions overlap, and performance in one domain depends on performance in another. For example, one can examine the correlations with learning on the IGT and Variant to see how executive functions can be required to perform other executive functions. In order to learn which decks are the "good" decks in either IGT version, one must be exposed to the various deck options and also remember what they were. The correlation between perseverative errors on WCST and learning on the IGT demonstrates the importance of cognitive flexibility in the IGT. A participant who perseverates on any particular deck will have limited ability to distinguish between decks. The correlation between span score and learning on the IGT demonstrates the

importance of working memory capacity to one's learning the IGT. The relationships uncovered using factor analysis are a useful tool in defining the relationships between constructs being measured in neuropsychological tests.

Correlations among factor scores and the executive domain NPZ score. When examining the correlation of the factor scores and the executive domain NPZ, it is important to remember that both were created from the same set of variables. Therefore, when examining the correlations between factor scores and the NPZ, one should consider the variables that a factor score and the NPZ score consist of. Factors that loaded strongly from a variable used to create the NPZ score tended to be more strongly associated with the NPZ score.

However, the variables constituting the NPZ did not solely determine the relationship between factor and NPZ score. Decision Making/Reinforcement Processing, the factor with the lowest eigenvalue above criterion, was the factor most closely associated with the executive domain NPZ score. The strength of this relationship is not due to the NPZ being created from two variables associated with the decision-making factor (IGT raw score and variant raw score), while the other factors had, at most, one variable associated that was used to directly create the NPZ. This finding was verified by creating an NPZ score using only the original IGT score (excluding the variant score) and affirming that Decision Making/Reinforcement Processing continued to have the strongest association with the NPZ score (data not shown). Nor was the strength of this relationship related to the loading of perseverative errors onto Decision Making/Reinforcement Processing. Correlations controlling for all other factor scores (including WCST Performance) were run, and the association between Decision Making/Reinforcement Processing and the NPZ score remained the strongest. This finding bodes well for those studying

executive function using NPZ, that decision-making tests, which are arguably the end products of executive systems, have the strongest association with the NPZ.

The factor scores representing executive function are interrelated. WCST Performance is associated with Executive Inhibition. This association is likely due to the need to switch between two sets when completing the trails switching. Although differences between these two factors have been established, there is some conceptual overlap between the variables that load strongly on these factors (time and errors in the switching trail, perseverative errors). The Decision Making/Reinforcement Processing factor is only associated with WCST Performance. Not only does this association mimic findings at the individual variable level (the association of perseverative errors with IGT learning), but it provides further evidence for the dissociation of WCST Performance and Executive Inhibition.

The associations between Slowness of Processing and other factor scores demonstrate further task impurity and support the naming of other factors. Slowness of Processing was negatively associated with all other factor scores, save Motor Impulsivity. This finding--that slower participants perform more poorly on tests of executive function--again illustrates how simpler forms of function are used in tasks of executive function. In addition, the lack of association between Slowness of Processing and Motor Impulsivity supports the theory that Slowness of Processing is not limited to motor slowness. As seen on the individual variable level, slower reaction times were associated with fewer false alarms. If Slowness of Processing represented only motor slowness then the expectation would be a strong negative relationship with Motor Impulsivity. Lastly, a negative correlation with Slowness of Processing and a positive correlation with Executive Inhibition were found for the Sustained Attention Factor. One would not expect sustained attention to be significant in any of the other tasks; therefore,

these associations, and the lack of other correlations, strengthen the argument that this factor does in fact represent sustained attention.

Chapter 4

Specific Aim 2. Compare each of three representations of executive function test data on their association with demographic and mental health variables

Results

Bivariate associations of individual neurocognitive variables with demographics and mental health. Pearson *r* and Spearman *rho* correlations were run, examining bivariate relationships between neurocognitive variables and continuous measures of demographics and mental health, while univariate ANOVA and ordinal probit analyses were used to examine bivariate associations between neurocognitive variables and categorical demographic and mental health variables. Tukey's B post hoc test was used to examine pair wise differences at a p of .05 for ANOVA analyses. Bivariate associations with continuous demographic and mental health variables are displayed in Table 9 and bivariate associations with discrete variables are displayed in Table 10.

Age-related decline was apparent in many variables in the present study. Not surprisingly, age was associated with poorer working memory (i.e., counting span scores) and poorer cognitive flexibility (i.e., more perseverative errors on the WCST). Neither variable from the switching trail was associated with age, drawing further distinctions between perseveration on the WCST and the switching trail. Nor was age associated with other aspects of performance on the WCST, IGT, or the IGT variant. Age was associated with cognitive slowing, as indicated by slower reaction times to go stimuli on the Go-Nogo and longer times to completion on the number and letter trails. However, this association did not exist for time to complete the motor speed trail. These results suggest that slowing on these first two tasks was more cognitive in nature, rather than being driven primarily by motor coordination. Though age was associated

with reaction time on the Go-Nogo, it was not associated with the number of false alarms or missed opportunities.

Like age, education was associated with working memory and cognitive flexibility in the WCST. But in contrast to age, education was associated with other variables from the WCST, including categories completed and non-perseverative errors. Both measures of executive inhibition—time to complete and number of errors—were associated with education, revealing overlap between the switching trail and WCST. Education was associated with decision-making (i.e., IGT raw score) but was not associated with learning the IGT or either variable from the variant. Education was not associated with the Go-Nogo or with motor speed, but was associated with the number and letter trails.

Race and ethnicity, like education, were associated with measures of cognitive flexibility (i.e., categories completed on the WCST) and executive inhibition in the switching trail, both for the time to complete and the number of errors on the switching trail. Pair wise comparisons indicated that White participants performed better than Black participants on both switching trail variables. No two groups differed significantly in categories completed on the WCST, but if racial differences were examined using a White/non-White distinction, the effect was significant, with white participants completing more categories than non-white participants $F(1,154) = 7.7$, $p \leq .01$. No racial/ethnic effects were detected in the other measures associated with the WCST, nor with decision-making or working memory. Race and ethnicity were not associated with any measure of reaction or motor speed. However, White participants performed better on the Go-Nogo on the measure of sustained attention, missed opportunities.

Income was associated with working memory, cognitive flexibility (i.e., perseverative errors and categories completed), and with executive inhibition (i.e., time to complete and

number of errors on the switching trail). Pair wise comparisons indicated that participants whose income exceeded $19,999 scored better on working memory, both measures of trails switching, and the number of categories completed on the WCST, than participants earning less than $10,000. In addition, participants earning between $10,000 and $19,999 scored higher on the time to complete the switching trail than participants earning less than $10,000. No pair wise differences were noted for perseverative errors, but the lack of findings was due to the loss of power associated with breaking income into three groups. Participants who earned less than $10,000 scored more poorly than participants making $10,000 or more $F(1,153) = 6.3$, $p \leq .05$. Income was associated with one variable of decision-making, the IGT variant raw score. The pair wise comparisons revealed that, interestingly, those who earned between $10,000 and $19,999 scored more poorly than those who earned more or less. These specific differences between income groups could be accounted for by the different levels of willingness to gamble between participants with adequate or miniscule incomes (believing they can afford to lose or have little to lose, respectively), and participants with small but not insignificant incomes. Income was not associated with any variable from the Go-Nogo or the motor speed trail. However, an income effect was identified, with those earning more than $19,999 scoring better than those making between $10,000 and $19,999 on the number and letter trails.

There were surprisingly few associations between mental health variables and neurocognitive testing variables. The only significant bivariate association was a negative association between CES-D depression and time to complete the switching trail. No other neurocognitive variable was significantly associated with either depression symptoms or state anxiety.

Multivariate associations of demographics and mental health with individual neurocognitive variables

Linear regression and ordinal probit analyses were used to elucidate multivariate demographic and metal health associations with continuous and ordinal neurocognitive variables, respectively. In each model, variables were included if they were associated at the bivariate level at a p of at least .25 (Hosmer & Lemeshow, 2000). Due to the strong relationship between anxiety and depression, special effort was made to ensure that use of both variables did not mask the effect of mental health. If collinearity diagnostics indicated that both CES-D and trait anxiety scores loaded on a single factor at over .50, the predictor with the lower p value was dropped from the model. Results from these models are presented in Table 11.

Demographics and mental health significantly predicted 17% of the variance in working memory. Controlling for income and depression, greater education continued to predict higher scores on the Counting Span. Older and Latino participants, in comparison to White participants, scored more poorly on the Counting Span.

The results of multivariate models using demographics and mental health variables to predict decision making were equivocal. In the multivariate regression model predicting IGT performance, education and depression emerged as significant predictors while controlling for income. Taken together, these variables predicted a little over 10% of the variance in IGT scores. It is important to note that the coefficient associated with depression is positive, suggesting that higher levels of depression are actually associated with *better* performance on the task. No model was created for the raw score on the variant because only one variable, income, reached the criterion for entry into the model. Linear regression models predicting learning scores for both

IGT and variant were nonsignificant. However, controlling for education, Black participants scored lower on the learning score for the variant than White participants.

Measures of cognitive flexibility and executive inhibition yielded different patterns of results. Demographic variables predicted over 10% of the variance in perseverative errors on the WCST, with age significantly predicting more errors when controlling for a trend of education and income. Demographics and mental health predicted 12% of the variance in categories completed on the WCST, $p \leq .05$, but unlike perseverations age was not a significant predictor. The only significant predictor in the model of categories completed was Black participants completing fewer categories than White participants controlling for age, education, anxiety, and income.

When compared to measures of cognitive flexibility, executive inhibition measures were extremely sensitive to demographic factors. Demographics and mental health predicted just over 30% of the variance in the time to complete the switching trail. Quicker times on the switching trail were found for participants with more education and in higher-income group members as compared to the low-income group. Slower times were found in participants who were older, more depressed, and Black or Latino, in comparison to White participants. As with the findings for time to completion, an ordinal probit analysis found that the number of errors in the switching trail was predicted by demographics. Fewer switching errors were predicted by greater years of education and more errors were made by Black participants in comparison to White participants. Unlike time to completion for the switching trail, income was not significant in the model for number of errors, and age and depression were not entered into the model.

In order to put the time to complete the switching trail into perspective, it is important to examine simpler reaction times. Both time to complete the motor speed trail and Go-Nogo

reaction time were predicted by multivariate linear regression models that included demographic and mental health variables. Time to complete the motor speed trail was greater at older ages controlling for education, anxiety, race, and income. Go-Nogo reaction time, controlling for education, was also predicted by age. The number and letter trails, as at the bivariate level, seem to have had greater cognitive loads and more associations than these simpler reaction time measures. Demographics predicted 16% of the variance in the time to complete the number and letter trails, with less education, greater age, and middle versus higher-income, predicting greater times.

Demographic and mental health variables predicted 9% of the variance in response inhibition. Controlling for age and education, depression symptoms were associated with fewer false alarms and those who fell into the other racial/ethnic categories had more false alarms than White participants. This effect of depression is likely associated with the motor slowing seen in the model predicting Go-Nogo reaction time because slower reaction times are associated with fewer false alarms.

Demographic factors were associated with measures of attention in an ordinal probit analysis. After controlling for education, Black and Latino participants had more missed opportunities than White participants. While the multivariate regression model predicting failure to maintain set was nonsignificant, Black participants had more failures to maintain sets in the WCST when compared to White participants, while controlling for education, anxiety, and income.

Bivariate associations of demographics and mental health with neurocognitive factor and NPZ scores. Pearson *r* correlations were run examining bivariate relationships between neurocognitive factor scores, executive domain NPZ score, and continuous measures of

demographics and mental health. Univariate ANOVA analyses were used to examine bivariate associations between neurocognitive factor scores and categorical demographic and mental health variables. Bivariate associations with continuous demographic and mental health variables are displayed in Table 12 and bivariate associations with these variables are displayed in Table 13.

When examining the relationship between the factor scores and age, only those factors clearly not executive in nature had age-related effects. Slowness of Processing and Sustained Attention were positively and negatively associated with age, respectively, while Motor Impulsivity, WCST Performance, Executive Inhibition, Decision Making/Reinforcement Processing and NPZ were not. These effects are similar to the pattern of associations between individual measures of non-executive neurocognitive functioning and age. However, the associations that were seen with executive measures (i.e., perseverative errors, working memory) and age were not seen at the factor score or NPZ level.

Unlike age, education was associated with variables thought to be executive in nature. The NPZ score, WCST Performance, Executive Inhibition, and Decision Making/Reinforcement Processing were all positively associated with years of education. Slowness of Processing had a negative association with education, and Motor Impulsivity and Sustained Attention had no association with age.

Although the omnibus F-statistic indicated racial/ethnic differences on the executive domain NPZ, WCST Performance, and Decision Making/Reinforcement Processing, Tukey's pair wise comparisons revealed no individual differences between racial/ethnic groups. This lack of an association seen in pairwise comparisons is driven by the loss of power caused by splitting race into four groups. If race is examined as White/non-White, White participants scored better

on the executive domain NPZ, $F(1,154) = 8.3$, $p \leq .01$, WCST Performance, $F(1,154) = 8.1$, $p \leq .01$, and Decision Making/Reinforcement Processing, $F(1,154) = 9.8$, $p \leq .01$. For Executive Inhibition, pair wise comparisons did reveal racial differences, with White participants scoring better than Black participants. The combination of variables into factor scores appears to have made race/ethnicity more important. For example, none of the four IGT variables and perseverative errors was associated with race/ethnicity at the bivariate level, but a factor comprising those five scores, Decision Making/Reinforcement Processing, was associated with race.

ANOVA analyses revealed significant differences by income on four of the six factors, NPZ, WCST Performance, Executive Inhibition, Decision Making/Reinforcement Processing, and Slowness of Processing. In each case, Tukey's B pairwise comparisons revealed that participants who earn more than $19,999 scored better than those who earn less than $10,000 for each of these effects. In addition, participants who earn between $10,000 and $19,999 scored better than low-income participants in Executive Inhibition, but were slower than participants who earned more than $19,999 in Slowness of Processing.

Consistent with patterns of bivariate associations between task scores and mental health variables, there were few associations between factor scores and mental health. There was a small negative correlation between Executive Inhibition and depression, which is likely driven by the bivariate association between depression and time to complete the switching trial. No other associations between the NPZ or factors scores and mental health variables were observed.

Multivariate associations of demographics and mental health with neurocognitive factor and NPZ scores. Multivariate linear regressions were performed to analyze the relationship of demographic and mental health variables with neurocognitive factors and NPZ

scores, in order to determine the independent predictors of neurocognitive function. Results from these analyses are presented in Table 14.

Taken together, demographic and mental health factors accounted for 20% of the variance associated with the NPZ score, $p \leq .001$. In a model controlling for income, lower NPZ scores were found for older participants, participants with less education, and Latino participants, as compared to White participants. Interestingly, more depressive symptoms led to better NPZ scores, $\beta = .17$, $p \leq .05$. This paradoxical effect was seen for two of the variables that made up the NPZ score, IGT raw score, and false alarms on the Go-Nogo.

Demographic and mental health variables accounted for slightly more than 12% of the variance in WCST performance, $p \leq .05$. However, most variables entered into the model were not significant predictors and race (Black compared with White) was the only significant parameter. These results were similar to the findings for categories completed at the individual variable level, but differed from the findings for number of perseverative errors.

Demographic and mental health variables accounted for 23% of the variance in Executive Inhibition, $p \leq .001$. Parameter estimates yielded results similar to those seen with the two switching trails variables in earlier analyses. More years of education and higher income were associated with higher Executive Inhibition scores. Depression symptoms, as well as Black and Latino race/ethnicity, were associated with lower scores in Executive Inhibition.

Although composed of the four IGT variables, the multivariate examination of demographic and mental health predictors of the Decision Making/Reinforcement Processing factor produced results markedly different from those obtained for those same four individual IGT variables. Demographic variables accounted for just under 13% of the variance in Decision

Making/Reinforcement Processing, $p \leq .01$. More years of education were associated with better scores, when controlling for race and income.

Demographic variables accounted for 18% of the variance in Slowness of Processing scores, $p \leq .001$. Older and Latino compared with White participants, and middle-income compared with high-income participants, were associated with slower processing. Education was associated with faster processing. Sustained Attention, the other factor that strongly loaded reaction times, had only one association at the bivariate level and therefore a multivariate model was not created.

Multivariate analysis of the Motor Impulsivity factor was strikingly similar to the model for false alarms on the go-Nogo. Demographic and mental health variables accounted for 9% of the variance in Motor Impulsivity, $p \leq .05$. Controlling for age and education, depression symptoms were associated with lower Motor Impulsivity scores, and those who fell into the other category in race/ethnicity had higher Motor Impulsivity scores than White participants.

Discussion

Differences among the relationships between demographics and executive function representations. Depending on the method used to represent executive function, conclusions may vary in terms of the effects of age. Using the standard NPZ method, multivariate analyses, controlling for other demographic factors, indicated that executive function declines with age. This finding is supported by individual neurocognitive variables also found to decline with age. The executive function variables associated with age are perseverative errors, trails switching time, and span score. In contrast, using a factor analytic approach would cause one to draw a different conclusion. The only factor scores associated with age were Slowness of Processing and Sustained Attention. These factors are measures of processing speed and sustained attention

respectively, and would lead one to conclude that speed and attention are influenced by age effects, but that overall executive function is not sensitive to age.

While the comparison of these three methods for examining executive function may lead one to conclude that the NPZ and individual variables are more sensitive to differences in age for this population, the available literature on the association between neurocognitive function and age does not support this interpretation. The NPZ was associated with age, presumably through the significant effects seen for perseverative errors, working memory, and the time to complete the switching trail, all of which had significant effects for age. Evidence from other studies suggests that the findings for the WCST and trails switching may be related to other cognitive factors better explained by the factor analysis method. The effect of age seen in perseverative errors on the WCST is surprising, because this score is thought to be relatively stable for participants in their twenties through their fifties (Haaland, Vranes, Goodwin, & Garry, 1987; Heaton & Psychological Assessment Resources Inc., 1993). Studies have shown that age-related deficits in the WCST and other executive function tests are mediated or moderated through working memory or processing speed (Fisk & Sharp, 2004; Hartman, Bolton, & Fehnel, 2001; Salthouse, 1996). In their analysis of age-related decline in executive function, Fisk and Sharp (2004) used an oblique rotation factor analytic method to examine the relationship between executive function and age, and found a WCST performance factor similar to the one in the present analysis. This factor was associated with age, but this effect was diminished when controlling for working memory or processing speed. Likewise, there is often an effect of age seen for the time to complete a switching trail (Lezak, 2004; Tombaugh, 2004) but this effect is only evident in elderly populations older than the present sample when derived scores remove the speed of processing component from the switching trail (Drane, Yuspeh, Huthwaite, &

Klingler, 2002; C. Roberts & Horton, 2002). Therefore, the effects seen for the WCST and switching trail may be related to the processing speed variables and, in turn, would make the factor analytic interpretation of the age executive function connection more appropriate.

With respect to education, the NPZ score, factor scores, and individual variables all consistently demonstrate that education is predictive of better scores. Although all three methods suggest that education is important for executive function, examining the factor scores and individual variables can tell us something about the specific executive functions that are associated with education within this sample, including working memory, executive inhibition, and decision making. These distinctions may be important when we examine possible intervention targets.

An examination of the relationship between executive function and income using the NPZ score reveals a bivariate relationship; however, in multivariate analyses, controlling for age, race, education, and mental health, the effect of income loses significance. Therefore, using the NPZ score might produce a conclusion that the effect of income on executive function is a product of other demographic factors. At both the individual variable and factor levels, most effects seen at the bivariate level (i.e., span score, perseverative errors, categories completed, errors on the switching trail, WCST Performance, and Decision Making/Reinforcement Processing) are not significant at the multivariate level when controlling for other demographic factors. The many bivariate associations between socioeconomic status and time to complete the switching trail or Executive Inhibition continue to be significant at the multivariate level, suggesting that socioeconomic status plays a part in this specific aspect of executive function.

The literature examining the effect of socioeconomic status on executive function has focused on school-age children, with those from low socioeconomic backgrounds having lower

levels of executive function from early grade school through adolescence (Hackman & Farah, 2009; Hackman, Farah, & Meaney, 2010). Though not consistent across all studies, these findings are often explained in terms of health disparities associated with low income (Hackman, et al., 2010). This explanation is relevant here because all the participants in the present study have health issues. If health problems mediate the association between socioeconomic status and executive function, then studies that carefully exclude the unhealthy and studies including only the unhealthy, like the present study, would both have difficulty detecting differences. In a study of the predictors of neurocognitive function, a similar result was found. Executive function was related to socioeconomic status at the bivariate level but dropped out in multivariate analyses (Fazeli, Marceaux, Vance, Slater, & Long, 2011).

Another interesting effect related to income is that those with income levels in the middle of the sample perform more poorly on the IGT Variant than does either the low- or the high-income groups. At first glance this result may be spurious, but there is a logical explanation for this finding. Impairment on the IGT variant is associated with hypersensitivity to punishment or extreme loss aversion. It makes sense that participants with little to lose (i.e., those making less than $10,000) and those with a surplus of income (i.e., those making more than $19,999) would both be less averse to losing money.

Differences among the relationships between mental health and executive function representations. Recent reviews point to consistent deficits in executive function for both depression (Marazziti, Consoli, Picchetti, Carlini, & Faravelli, 2010) and anxiety disorders (Ferreri, Lapp, & Peretti, 2011). A recent meta analysis of these issues found an association with depression severity and executive function (McDermott & Ebmeier, 2009). The connection between mood disorders and neurocognitive function among HIV+ persons has been established

(Fazeli, et al., 2011). However, recent reports suggest that depression may not be important in executive function for those who are virally suppressed (Cysique & Brew, 2011). Despite this recent report, it is surprising to see so few effects of mental health variables on executive function in bivariate analyses. While bivariate associations between executive function and mental health variables were not significant, many relationships were uncovered in multivariate analyses.

Problematically, multivariate analyses revealed that depressive symptoms are associated with an increase in executive function as measured by the domain NPZ score. This finding is the result of the associations of depression with the variables that make up the NPZ score. There are three variables associated in different directions with depression, with two variables having been positively associated with depressive symptoms and one having been negatively associated. Basing results solely on the NPZ score could result in misleading and inaccurate findings. Scores on the IGT were positively associated with depressive symptoms. This association is presumably due to depression's impact on decreased sensitivity to reward, and has been addressed in the literature previously (Smoski et al., 2008). False alarms on the Go-Nogo (and at the factor score level Motor Impulsivity) were decreased as depression increased in this sample. This increase in response inhibition runs counter to the literature (Kaiser et al., 2003; Ruchsow et al., 2008) making it important to note that this effect may be partially driven by a speed-accuracy tradeoff as reaction time slowed in the Go-Nogo (at the trend level) in response to depression. Finally, the switching trail time (and at the factor score level Executive Inhibition) showed poorer performance in response to increased depressive symptoms. In contrast to the picture painted by the NPZ score, that executive function is increased by depression, a more complex picture emerges when examined carefully through individual variables or factor scores. Depression is

associated with a decrease in reward sensitivity, an increase in response inhibition (with some caveats), and a decrease in executive inhibition.

Chapter 5

Specific Aim 3. Compare each of three representations of executive function test data on their association with methamphetamine use variables

Results

Bivariate associations of individual neurocognitive variables with methamphetamine-related variables. Pearson *r* and Spearman *rho* correlations were run to examine bivariate relationships between neurocognitive variables and measures of methamphetamine use and severity. Because of collinearity, a partial correlation was run to remove the effect of age when examining years of methamphetamine use. Results are displayed in Table 15.

Very few significant bivariate associations existed for the individual neurocognitive scores and methamphetamine use variables. None of the neurocognitive variables were associated with years of methamphetamine use when controlling for the effect of age. Several variables did correlate with the dependence score on the CIDI-SAM. However, these scores were paradoxical, with higher scores on the CIDI-SAM associated with increases in Variant learning score and faster reaction time on the Go-Nogo. The one significant effect for number of methamphetamine use days was similarly paradoxical, with more methamphetamine use days associated with fewer errors on the trails.

Multivariate associations of methamphetamine variables with individual neurocognitive variables controlling for demographics and mental health. Hierarchical linear regression and ordinal probit analyses were used to examine multivariate associations between methamphetamine use and continuous and ordinal neurocognitive variables respectively, while controlling for demographic and mental health associations. For hierarchical

models, significant demographic and mental health associations identified in aim 2 were entered as step one. Step two included methamphetamine use variables that were associated at the bivariate level at a p of at least .25. Results from these models are presented in Table 16.

Methamphetamine use variables accounted for 12 % of the variance in IGT variant learning scores after controlling for demographics, $p \leq .05$. The number of methamphetamine use days was associated with poorer learning scores on the IGT variant. This finding is in contrast to models predicting Go-Nogo reaction time, $\Delta r^2 = .05$, $p \leq .05$, and number of errors on the switching trails, $\Delta \chi^2 = 7.4$, where more methamphetamine use days produced further paradoxical effects. A greater number of methamphetamine use days was associated with faster reaction time and fewer errors on the switching trails.

Bivariate associations of neurocognitive factor and NPZ scores with methamphetamine-related variables. Pearson *r* correlations were used to examine bivariate relationships between neurocognitive factor and NPZ scores, and measures of methamphetamine use and severity. A partial correlation was used to control for the effect of age when examining years of methamphetamine use. Results are displayed in Table 17.

As with individual neurocognitive variables, there were very few associations between methamphetamine use variables and neurocognitive factor and NPZ scores, and the associations were in an unexpected direction. Controlling for age, the number of years of methamphetamine use was associated with an increase in NPZ score ($r_{ab,c} = .18$, $p \leq .05$). No neurocognitive factor score was associated with years of methamphetamine use. Neither NPZ nor factor scores were associated with either measure of methamphetamine use severity. The only effect found for number of days of methamphetamine use was another paradoxical one, seen with the number of

errors in trails switching. Methamphetamine use was associated with an increase in Executive Inhibition score.

Multivariate associations of methamphetamine variables with individual neurocognitive variables controlling for demographics and mental health.

Multivariate linear regressions were performed to analyze the relationship among methamphetamine use multivariate and neurocognitive factor or NPZ scores, while controlling for demographic and mental health associations. The same stepwise method employed in examining the multivariate effects of methamphetamine variables on individual neuropsychological variables was used here. Results of these models are displayed in Table 18.

Controlling for demographic and mental health variables, years of methamphetamine use accounted for 3% of the variance after entering demographic and mental health variables at step one, $p \leq .05$. The number of years of methamphetamine use was associated with increased NPZ score. Methamphetamine use variables did not account for a significant amount of the variance after controlling for demographics and mental health. However, more methamphetamine use days predicted increases in Executive Inhibition score. Models created for WCST Performance, Decision Making/Reinforcement Processing, Slowness of Processing, and Sustained Attention revealed no increases in explained variance when methamphetamine use variables were added to the models.

Discussion

The lack of an association between methamphetamine use variables and executive function. Perhaps the most surprising finding in this dataset is the lack of consistent associations between executive function and methamphetamine use variables. The few effects that were uncovered have seemingly paradoxical relationships, with the exception of the multivariate

relationship between methamphetamine use days and IGT variant learning score. The paradoxical effects include more methamphetamine use days associated with fewer errors on the switching trail, and better scores on the Executive Inhibition factor. Higher dependence scores were associated with faster reaction times, and more years of methamphetamine use were associated with better NPZ scores. While previous research suggests that methamphetamine use is associated with poorer executive functioning (Chang, Cloak, et al., 2005; J. D. Henry, et al., 2009; Hoffman, et al., 2006; S. J. Kim, et al., 2006; Y. T. Kim, et al., 2009; McCann, et al., 2008; Monterosso, et al., 2007; Rendell, et al., 2009; Simon, et al., 2000; Simon, et al., 2002), the present research does not find an association between methamphetamine use and impairment. While some studies have found a lack of executive function differences in methamphetamine users (Boileau, et al., 2008; Chang, Cloak, et al., 2005; Johanson, et al., 2006; Salo, Ursu, et al., 2009; Simon, et al., 2010), numerous studies have found effects. The question then remains: what differences within the current study's method and sample might explain the lack of a finding?

One difference between past studies showing methamphetamine-related cognitive deficits and the present study is the basic design; most previous research has employed a between-subjects design, while the present study employs a within-subjects design. Most studies that have reported executive function deficits in methamphetamine users have done so by comparing methamphetamine users to a control population (Hart, et al., 2012; Scott, et al., 2007). Only a few studies have reported executive function differences based on the quantity of methamphetamine used and none of these dose-related impairment studies were conducted in a population of HIV+ participants. One study reported a single reaction time being associated with grams of methamphetamine used per week (Monterosso, Aron, Cordova, Xu, & London, 2005),

and a second study reported several neuropsychological differences (though none were executive function tests) between those who used methamphetamine daily and those who did not (Simon, et al., 2000). Numerous studies have shown no association between methamphetamine use characteristics and neuropsychological function (Chang et al., 2002; Cherner et al., 2010; Hoffman, et al., 2006; Johanson, et al., 2006; Rippeth, et al., 2004). The current study examines the relationship between the quantity of methamphetamine use, or the extent of methamphetamine dependence severity, and cognition. In contrast to previous studies, which sought to determine whether methamphetamine users are cognitively impaired as compared to a normal population, the present study seeks to learn whether there exists an association between the extent of methamphetamine use and extent of neurocognitive ability. The present study sets a higher bar for detecting differences.

The questions raised about the body of literature associated with methamphetamine-related executive deficits (Hart, et al., 2012) are important to consider here. Much research that has found differences between methamphetamine users and control participants has either not reported education (Volkow, Chang, Wang, Fowler, Ding, et al., 2001; Volkow, Chang, Wang, Fowler, Franceschi, et al., 2001; Volkow, Chang, Wang, Fowler, Leonido-Yee, et al., 2001), or has found differences between those two groups on education or IQ measures but failed to control for the effect (Boileau, et al., 2008; Chang, Ernst, Speck, & Grob, 2005; Hoffman, et al., 2006; S. J. Kim, et al., 2006; S. J. Kim, et al., 2005; Y. T. Kim, et al., 2009; London et al., 2005; London, et al., 2004; Salo, Nordahl, Buonocore, et al., 2009; Salo, Ursu, et al., 2009; Thompson, et al., 2004). In the few cases when researchers controlled for education or IQ the results have been mixed, with one study showing similar results with WCST impairment after adjusting for education (S. J. Kim, et al., 2005) and another showing that cognitive differences on an extensive

battery were no longer significant (Chang, Cloak, et al., 2005). If the cognitive differences between controls and methamphetamine users described in previous research were mediated by education, we would not expect to see differences in cognition within our sample, because there is no bivariate association between education and methamphetamine use days.

Another difference between the present analysis and previous studies is that the majority of studies in the literature have controlled for the length of abstinence from methamphetamine. Most studies set a minimum number of days abstinent from methamphetamine to limit effects of residual methamphetamine and withdrawal symptoms on results (Hart, et al., 2012). Some studies have looked at length of abstinence, finding cognitive differences between short term (< 6 months) and long term (> 1 year) abstinent methamphetamine users (Salo, Nordahl, Galloway, et al., 2009). The present study could not mandate abstinence because it was imbedded in a randomized controlled trial and an abstinence mandate would interfere with the natural course of treatment. Despite this limitation, those who tested positive for methamphetamine were no different on any neurocognitive variable than those who tested negative. Given the lack of a neurocognitive effect for those who tested positive for methamphetamine, it is unlikely that any residual effects of the drug are disguising cognitive differences. Withdrawal symptoms for methamphetamine peak 24 hours after last administration (McGregor et al., 2005). Therefore, the absence of an effect for those who tested positive also makes it unlikely that withdrawal symptoms are disguising any neurocognitive effects, because those who test positive are far more likely to have significant withdrawal symptoms. Differences among participants in the length of abstinence are also unlikely to lead to the lack of an effect, because the length of abstinence is limited by the inclusion criteria of the study. All participants must have used methamphetamine at least once in the last month at their initial appointment;

thus, for the baseline neurocognitive assessment the longest length of abstinence was roughly two months.

Numerous studies control for other substances of abuse in their data. Studies that examine methamphetamine-dependent participants often exclude persons who meet dependence criteria for other drugs. Some studies use oral, urine, or hair testing to exclude participants on the basis of recent drug use. The present study could not control for other drug use, a difference that could obfuscate possible associations between methamphetamine and cognitive dysfunction. In fact, of the 155 participants in this sample only one reported methamphetamine as the sole substance taken in the last 90 days. Participants' drug use was verified with a urine screen for cocaine, amphetamines, opiates, and marijuana. Although participants who tested positive were not excluded from participation, urine toxicology data were not associated with any difference in neurocognitive function. The possibility that participants' drug use histories may have a stronger relationship with neurocognitive functioning than methamphetamine use characteristics remains a concern.

While some of the issues mentioned above might explain the null findings in the data, they do not explain the paradoxical finding that dependence scores, days of methamphetamine use, and years of methamphetamine use are all associated with increases in functioning for some variables. There is a plethora of data suggesting that short-term administration of low doses of methamphetamine actually increases performance on some measures of functioning (Hart, et al., 2012). However, since there is no difference between those who tested positive for methamphetamine and those who tested negative, this hypothesis fails to explain these findings. The lack of an adequate explanation for these paradoxical findings raises other considerations that are beyond the scope of the present analysis. One possible explanation is another substance

of abuse that is dominating the data, crack cocaine in particular. Crack cocaine is prevalent among methamphetamine users. Within NYC, methamphetamine is scarce and expensive when compared to cocaine (B. G. Taylor et al., 2011; Wendel et al., 2011). For these reasons, many stimulant users may use methamphetamine when given the opportunity to do so, but may be more likely to use crack or powdered cocaine. Anecdotally, therapists and educators in the full trial commented frequently about participants' issues with other substances, specifically crack cocaine.

Chapter 6

Specific Aim 4. Compare each of three representations of executive function test data on their association with HIV disease progression and medication adherence

Results

Bivariate associations of individual neurocognitive variables with HIV disease progression and adherence. Pearson *r* and Spearman *rho* correlations were used to examine bivariate relationships between neurocognitive variables and measures of HIV disease progression and adherence. Partial correlations were run for years since diagnosis (controlling for age), years on ART (controlling for years since diagnosis), and number of different regimens (controlling for years on ART). Results are presented in Table 19.

There were no correlations between neurocognitive variables and years since diagnosis, years on ART, or number of different regimens. CD4 count was associated with variant learning score, $r = .16$, $p \leq .05$. No other variables from the IGT, the WCST, switching trail, or Counting Span were associated with biological measures of disease progression. Reaction time and number of missed opportunities were associated with CD4 count, such that faster reaction times and fewer missed opportunities were associated with increases in CD4 count, $r = .16$, $p \leq .05$; *rho* = .33, $p \leq .01$, respectively. Faster reaction times and fewer missed opportunities were also associated with lower log viral load, $r = -.17$, $p \leq .05$; *rho* = -.24, $p \leq .01$, respectively.

There were few associations between traditional executive measures and adherence. The only association between IGT and adherence was a positive association between IGT raw score and VAS adherence, $r = .17$, $p \leq .05$. Working memory and the WCST had no associations with either measure of adherence. Time to complete the switching trail was associated with TLFB adherence, with faster times associated with increased TLFB adherence, $r = .16$, $p \leq .05$. Faster

times on the number and letter trails were associated with TLFB adherence, $r = .16$, $p \leq .05$, calling into question whether the effect of the switching trail is truly executive in nature. The last variable that had an association with adherence was missed opportunities on the Go-Nogo. Fewer missed opportunities were associated with higher levels of adherence as measured by both the TLFB and the VAS *rho* = .17, $p \leq .05$; *rho* = .234, $p \leq .01$, respectively. This finding suggests that attention is important for the maintenance of adherence.

Multivariate associations of HIV disease progression and adherence variables with individual neurocognitive variables controlling for demographics and mental health. Hierarchical linear regression and ordinal probit analyses were used to examine multivariate associations between disease progression and adherence with continuous and ordinal neurocognitive variables respectively, while controlling for demographic and mental health associations. For hierarchical models, demographic and mental health associations that were found in aim two were entered as step one. Step two included HIV disease progression and adherence variables that were associated at the bivariate level at a p of at least .25. Because the two biological variables and the two adherence variables are strongly correlated, collinearity diagnostics were examined. When these variables loaded onto the same factor over .50, the variable with less predictive power was removed from the analysis. Results from these models are presented in Table 20.

HIV disease progression and adherence were not predictive above demographic and mental health variables for working memory, IGT raw score, IGT variant raw score, IGT variant learning score, and categories completed on the WCST. While adherence did not add to the percentage of variance explained, higher levels of adherence on the TLFB were associated with

faster times on the trails switching. Interestingly, VAS adherence was associated in the opposite direction, though not at a significant level.

Log viral load accounted for 3% of the variance associated with reaction time on the Go-Nogo, $p \leq .05$. Lower log viral loads were associated with faster reaction times. Controlling for demographics, HIV disease progression and adherence were associated with missed opportunities on the Go-Nogo, $\Delta \chi^2 = 15.1$. In the final model, increases in CD4 count were associated with decreases in missed opportunities. HIV disease progression and adherence did not add to the variance predicted for number and letter trails and false alarms.

Bivariate associations of neurocognitive factor and NPZ scores with HIV disease progression and adherence. Pearson *r* and Spearman *rho* correlations were used to examine bivariate relationships between neurocognitive variables and measures of HIV disease progression and adherence. Partial correlations were run for years since diagnosis (controlling for age), years on ART (controlling for years since diagnosis), and number of different regimens (controlling for years on ART). Results are presented in Table 21.

Again, the results with the factor and NPZ scores are very similar to findings at the individual variable level. No associations were found with years since diagnosis, years on ART, and number of different regimens. The only association with biological indicators of HIV disease progression was with Sustained Attention. Lower log viral loads and higher CD4 counts were associated with higher Sustained Attention scores, $r = -.21$, $p \leq .01$; $r = .24$, $p \leq .01$, respectively.

There were several associations with adherence. Better adherence, as measured on TLFB and VAS, was associated with higher NPZ scores, $r = .17$, $p \leq .05$; $r = .18$, $p \leq .05$, respectively. Better adherence as measured by the VAS was associated with higher scores on Decision Making/Reinforcement Processing, $r = .17$, $p \leq .05$. There was no association between adherence

measures and WCST Performance or Executive Inhibition. Better adherence on both TLFB and VAS was associated with faster processing, as indicated by lower scores in Slowness of Processing, $r = -.18$, $p \leq .05$; $r = -.16$, $p \leq .05$, respectively.

Multivariate associations of HIV disease progression and adherence variables with neurocognitive factor and NPZ scores controlling for demographics and mental health. Hierarchical linear regression analyses were used to examine multivariate associations between disease progression and adherence with neurocognitive factor and NPZ scores, while controlling for demographic and mental health associations. For hierarchical models, demographic and mental health associations that were found in aim 2 were entered as step one. Step two included HIV disease progression and adherence variables that were associated at the bivariate level at a p of at least .25. Issues of collinearity were addressed as described earlier. Diagnostics were examined. Results from these models are presented in Table 22.

HIV disease progression and adherence did not account for a significant amount of the variance above demographic and mental health measures. However, in the final model, better percent dose adherence as measured by the VAS, predicted increases in NPZ score, $\beta = .17$, $p \leq .05$. HIV disease progression did not account for a significant amount of the variance controlling for demographics and mental health when examining WCST Performance, Executive Inhibition, and Decision Making/Reinforcement Processing. CD4 count accounted for 7% of the variance controlling for demographics when predicting Sustained Attention, $p \leq .01$. Increases in CD4 count were associated with increases in Sustained Attention score, $\beta = .23$, $p \leq .05$. HIV disease progression and adherence did not account for a significant amount of variance controlling for demographics and mental health, when examining Motor Impulsivity and Slowness of Processing.

Discussion

Differences in the relationship to HIV disease progression between executive function representations. None of the HIV history variables were associated with executive functioning controlling for demographic factors, but there were some associations with biological and self-report markers of adherence. The associations with biological markers are surprising, as current viral load and CD4 have been shown to be poor predictors of HIV-related cognitive impairment in the post-ART era (McArthur et al., 2004). Studies have shown nadir CD4, or the lowest CD4 count in a patient's medical history (Valcour et al., 2006), and one year previous CD4 counts (Tate, Delong, et al., 2011) to be better predictors of cognitive impairment. Studies have also shown that there is no difference in neurocognitive impairment between participants with detectable viral loads and those with undetectable viral loads (Cysique & Brew, 2011). It is therefore not surprising that there was no association between executive function and biological markers that persisted through multivariate analyses regardless of how executive function was operationalized.

Despite lacking associations with executive function, CD4 count and viral load were associated with sustained attention. Reaction time and the number of missed opportunities on the Go-Nogo, and the Sustained Attention factor score, were all significantly associated with biological measures when examined in bivariate and multivariate analyses. Attention is similar to executive function in that it refers to a multitude of different processes. Measures of simple reaction time, sustained attention, vigilance, selective attention, divided attention, and even working memory are used to examine attention, often with different neuroanatomical correlates (Lezak, 2004). Interestingly, few researchers have broken down the component measures of attention and measured attention using higher-level tasks that either require components of motor

and processing speed such as the trails A, or a higher-order working memory task (Al-Khindi, et al., 2011). There have been few studies that have examined more basic aspects of attention and they have found deficits in HIV+ persons (Hardy & Hinkin, 2002; E. M. Martin, Sorensen, Robertson, Edelstein, & Chirurgi, 1992; Maruff et al., 1995). However, these studies were conducted before the modern ART era, making the findings questionable given the recent developments in HIV treatment. Considering the damage caused by HIV to frontal dopaminergic systems (Ances, et al., 2006; Ferris, Mactutus, & Booze, 2008; Melrose, Tinaz, Castelo, Courtney, & Stern, 2008; Nath, et al., 2000; Tucker, Robertson, et al., 2004), attention may be particularly sensitive to changes in biological markers of HIV and could be fertile ground for further research.

Differences in the relationship to HIV medication adherence between executive function representations. When examining associations with adherence, the NPZ appears to be the most effective representation of executive function because the NPZ is associated with medication in both bivariate and multivariate analyses. The relationship between executive function and adherence while controlling for demographic factors is unique. Previous attempts to find a multivariate relationship between executive function through composite executive function domain scores and individual tasks have failed (Ammassari et al., 2004; Applebaum, et al., 2009; Contardo, et al., 2009; Hinkin, et al., 2002; Hinkin, et al., 2004; Wagner, et al., 2002; Waldrop-Valverde, et al., 2006). One study found a multivariate relationship of an executive function factor score with a questionnaire regarding medication management, which is not a direct assessment of ART adherence (Waldrop-Valverde, et al., 2010). Still other studies have found neurocognitive effects controlling for demographics, but these studies used a composite score that contained tests from multiple cognitive domains (Ettenhofer, et al., 2009; Hinkin, et al.,

2004; Waldrop-Valverde, et al., 2008). This difference in the present finding may be attributable to the increased number of tests included in the executive domain NPZ, as previous domain scores generally used two or three executive function tests (Barclay, et al., 2007; Becker, et al., 2011; Ettenhofer, et al., 2010; Ettenhofer, et al., 2009; Hinkin, et al., 2002; Hinkin, et al., 2004; Levine, et al., 2005; Meade, et al., 2010; Waldrop-Valverde, et al., 2008; Waldrop-Valverde, et al., 2006), which may have under sampled the diversity of executive functions. The inclusion of six executive function tests in an examination of ART adherence is unprecedented and may have produced a more powerful domain score.

There are only a few individual executive function variables that have an association with adherence. The IGT raw score is associated with adherence in bivariate analyses, but this effect does not hold up when controlling for demographics and HIV disease progression variables. The time to complete the switching trail is associated with percent dose adherence as measured by the TLFB in bivariate and multivariate analyses. This effect is dubious, because it is only significant when controlling for the relationship between trails switching and percent dose adherence on the VAS, which, though not significant, is in the opposite direction. When examining the factor level scores, only Decision Making/Reinforcement Processing and Motor Impulsivity are associated with adherence in bivariate analyses. In multivariate analyses, Decision Making/Reinforcement Processing is not related to adherence, while Motor Impulsivity and Slowness of Processing reach a trend level of association.

As with the relationship between executive function and methamphetamine use, the lack of consistent findings for adherence leads one to question the differences between the present analyses and those already performed. The first noteworthy difference is that the majority of the tests themselves had not been used previously in examinations of ART adherence. The Counting

Span, Go-Nogo, IGT and IGT Variant have not been used in previous analyses of executive function and ART adherence. Second, the version of trails used here is a departure from the often-used Trails AB, although the D-KEFS trails used are very similar in instruction and are thought to measure the same constructs. The WCST is the only test that has been examined as a predictor of adherence. Because executive function can encompass many different aspects of function, perhaps these new tests are testing previously unmeasured aspects of executive function which are less sensitive to adherence differences.

Perhaps more telling than the choice of neurocognitive tests themselves, are the types of analyses run that are usually in adherence studies. The vast majority of studies that have described executive function effects on adherence by separating participants into two groups split on the level of adherence and using ANOVAs or t-tests (Avants, et al., 2001; Barclay, et al., 2007; Hinkin, et al., 2002; Hinkin, et al., 2004; Meade, et al., 2010; Solomon & Halkitis, 2008; Wagner, et al., 2002; Waldrop-Valverde, et al., 2010). To examine multivariate differences, logistic regression techniques have been employed. Researchers assessing the association between executive function and ART adherence while controlling for demographic factors have found no association (Ammassari, et al., 2004; Applebaum, et al., 2009; Avants, et al., 2001; Contardo, et al., 2009; Hinkin, et al., 2002; Wagner, et al., 2002; Waldrop-Valverde, et al., 2006) in all but one analysis that did not directly assess ART adherence (Waldrop-Valverde, et al., 2010). Similar to the differences seen between previous examinations of methamphetamine use and executive function, the present analysis sets a high bar by examining the association of the extent of cognitive deficit with the extent of nonadherence behavior while controlling for demographic factors. These differences between past and the present analyses not only explain

the **lack** of effects seen for the individual variables and factor scores, but also shed light on the **power** of the present NPZ score in detecting ART nonadherence behavior.

Chapter 7

Specific Aim 5. Compare each of three representations of executive function tests on their ability to predict adherence controlling for methamphetamine use characteristics.

Results

Bivariate ANOVA analyses were conducted examining methamphetamine use characteristics and executive function in participants who reported 80% or greater to those who reported less than 80% adherence. These splits were done for both methods of assessing adherence TLFB and VAS, and based on the level of adherence necessary to maintain viral suppression in most current ART medications (Maggiolo, et al., 2007; M. Martin, et al., 2008; Parienti, et al., 2010; Shuter, et al., 2007). Bivariate associations are displayed in Table 23.

The only difference for these two groups based on TLFB measured adherence is that those with greater adherence had fewer missed opportunities on the Go-Nogo. However, examining these two groups based on VAS measured adherence revealed a plethora of differences. Participants with 80% adherence or greater had lower methamphetamine dependence scores. These participants also had better scores on the executive domain NPZ score, the WCST Performance factor, the Executive Inhibition factor, the Decision Making/ Reinforcement Processing factor. Participants with 80% or greater VAS adherence had higher IGT scores, completed the switching trail quicker and had fewer missed opportunities on the Go-Nogo.

Logistic regression models were created with membership in the 80% or higher adherence group (based on VAS measurement) as the dependent variable. Methamphetamine use days and methamphetamine dependence scores were entered at step one, then each of the neurocognitive representations was entered in step two. Variables were entered at step two if they were significantly associated in bivariate analyses. Three models were created; model one entered the

executive domain NPZ at step two, model two entered executive function factor scores at step two, and model three entered individual neurocognitive variables at step two. All models are displayed in Table 24.

In step one the number of methamphetamine use days and dependence to methamphetamine score significantly predicted adherence group and accounted for 6.5% of the variance. Dependence score was a significant predictor in all models. In model one, entering the executive domain NPZ accounted for an additional 3.3% of the variance and was a significant predictor of 80% or better adherence. In model two, entering WCST Performance, Executive Inhibition, and Decision Making/Reinforcement Processing accounted for an additional 9.0% of the variance and Decision Making/ Reinforcement Processing was a significant predictor of 80% or better adherence. In model three, entering IGT score, WCST categories completed, switching trail time, and missed opportunities on the Go-Nogo accounted for an additional 13.4% of the variance. Participants with zero or one missed opportunities were significantly more likely to be in the 80% or better adherence group than those with 8 or more missed opportunities.

Discussion

Dichotomizing adherence to examine differences is a common method used in similar research (Barclay, et al., 2007; Hinkin, et al., 2004; Solomon & Halkitis, 2008; Waldrop-Valverde, et al., 2008; Waldrop-Valverde, et al., 2006). In both bivariate and multivariate analyses, better executive function and lower methamphetamine dependence scores were related to membership within the higher adherence group (as measured by the VAS). There was no relationship with executive function or methamphetamine use when examining adherence using the TLFB. Although both the TLFB and VAS assess adherence through self-report, they have several differences. The VAS measures adherence by asking participants to estimate the

percentage of a particular medication they have taken during the last 30 days. The participant places a line across a line with tic marks at each 10% increment representing his adherence. The differences in adherence scores between the two measures may stem from differences in the time frames being assessed, or the differences between remembering specific occurrences of behavior versus estimating how often that behavior occurs.

The fact that executive function was more associated with the estimate of long term adherence rather than the memory of short term events is interesting. Interpretations of this finding could be problematic for the data. It may be that those with higher or lower cognitive ability systematically over or underestimate (respectively) their success rate with regards to adherence. If true, the neurocognitive impact is less on adherence and more on *confidence* in adherence.

Multivariate models were constructed to examine the association between adherence groups and methamphetamine use behaviors. Interestingly, it was the methamphetamine dependence score and not number of methamphetamine use days that was a significant predictor of adherence. This finding is not entirely surprising because amount of use is not completely synonymous with problematic use. The methamphetamine dependence score measures the impact, or the disruption that the use of methamphetamine causes in a participant's life. What this finding suggests is that it is the extent of problems associated with methamphetamine, and not simple use amounts, which are important for how methamphetamine impacts health behaviors.

Differences among executive function representations in their predictive validity for adherence controlling for substances use. All three representations of executive function had bivariate relationships with adherence groups as measured by the VAS. When the factor scores

were examined, each factor score thought to measure some aspect of executive function—WCST Performance, Executive Inhibition and Decision Making/ Reinforcement Processing— was associated with adherence, while none of the non-executive factors reached significance. These findings support the idea that executive function is particularly important for ART adherence, at least in methamphetamine users.

When examining the individual scores on executive function tests, the majority of differences are seen in variables that can be confidently described as measuring executive function: IGT score, WCST categories completed, and switching trail time. The one exception to the pattern is missed opportunities on the Go-Nogo, which were associated with adherence groups. Interestingly this effect, which was the only one seen for TLFB adherence, transcended the measurement of adherence. This effect suggests that processes relating to attention are also important for adherence, as well as stressing the importance of measuring different aspects of neurocognition aside from executive function when examining ART adherence behavior.

The executive domain NPZ predicted adherence group above and beyond methamphetamine dependence score. When the factor scores were entered into a multivariate model, Decision Making/ Reinforcement Processing was the only significant neurocognitive parameter. This result demonstrates the benefit of using factor scores, as it allows for a more specific examination of aspects of executive function that are important for adherence. The ways in which ART behavior is reinforced are more important than, for example, cognitive flexibility or executive inhibition, giving researchers a clearer target for intervention. Intervening on the decision making process would afford the best chance of impacting adherence through executive function.

The multivariate results with the NPZ and factor scores can be contrasted with the result for the individual neurocognitive variables. While the whole model and step were significant, the only parameter that predicted adherence group was missed opportunities on the Go-Nogo. This finding is interesting when contrasted with the factor scores, as this variable is not a measure of executive function but is instead a measure of sustained attention. If the analyses were conducted using just the individual variables, although executive function would have been deemed important through bivariate results, sustained attention would be considered the most important measure for predicting adherence.

These findings regarding the associations between executive function and adherence groups controlling for methamphetamine use are unique because they find executive function deficits specifically as important. Previous research examining the relationships between neurocognitive factors and adherence controlling for substance use variables has found associations with nonspecific neurocognitive deficits and literacy controlling for cocaine use (Waldrop-Valverde, et al., 2008), as well as prospective memory controlling for cocaine use (Contardo, et al., 2009). Another study found that controlling for addiction severity verbal learning scores predicted self-report adherence in a study of injection drug users (Applebaum, et al., 2009). All three studies analyzed executive function in similar logistic regression models but did not find effects controlling for substance use. For this reason the present study is unique in finding specifically that executive function predicts adherence while controlling for methamphetamine use. This finding aligns with results indicating that neurocognitive function partially mediates the association of cocaine with nonadherence (Meade et al., 2010).

Chapter 8

Discussion

Due to the many analyses conducted across the course of this study, this discussion will begin with a summary of the results for each specific representation of executive function. Following will be a discussion of the results across the representations focusing on the strengths and weaknesses for each of the three methods. The implications of the results for HIV medication adherence and HIV+ substance users will be discussed. Next, this discussion will present some of the limitations of this work as well as considerations for future work. Lastly, there will be concluding statements on the nature of the problems with methods for operationalizing executive function both generally and specifically for HIV+ substance using populations.

Summary of Results for Individual Test Scores

Demographics. Because there are 16 individual variables stemming from six unique tasks, there are numerous associations between individual test scores and demographic factors. It is unsurprising, given the history of neurocognitive testing, that different individual variables are associated with age, education, income and race. The pattern of findings is generally consistent with existing literature. Age is associated with all variables that have a speed of processing component, and is also associated with a few executive function variables that do not rely on processing speed, including working memory and perseverative errors on the WCST. Tasks that measure complex working memory such as the Counting Span are thought to show age related decline (Braver & West, 2008), while the number of perseverative errors from the WCST is generally thought to be stable in age for those in their twenties through their fifties (Heaton & Psychological Assessment Resources Inc., 2003). The degree to which lower-level function may

explain these declines in working memory and WCST performance is debated (Braver & West, 2008; Hartman, et al., 2001; Salthouse, 1996).

Education, race and income comprise issues of privilege that are often associated with neurocognitive function tests. While many tests have norms that cover age and education, few have norms that tackle race or income. It was expected that raw measures, both executive function and lower-level function, would be elevated in educated, White or relatively wealthy participants. Few patterns of function emerged with demographic factors, as variables thought to represent higher and lower-level functions had significant associations for all three. However, it did appear that racial differences were driven by executive function rather than lower-level functions, with the exception of an effect seen in the measure of sustained attention. Black and Latino participants had more missed opportunities on the Go-Nogo than White participants.

Mental Health. While few relationships with depression and anxiety were seen for bivariate analyses, controlling for other demographic factors revealed associations between mental health and executive function variables. However, the direction of those relationships was not consistent. As in other studies, depression was associated with better scores on the IGT, presumably through decreasing sensitivity to reward (Smoski, et al., 2008). Response inhibition increased with depressive symptomatology as measured by the number of false alarms on the Go-Nogo. The opposite finding occurred with the switching trail, such that depression increased the time taken to complete the trail. This effect is unlikely to be due simply to processing or motor speed because the lower level trails (i.e., numbers and letters, and motor speed) were not affected.

Methamphetamine. There were few associations between individual neurocognitive variables and methamphetamine use characteristics. Controlling for demographic factors, the

only executive variables associated with methamphetamine use were the learning score on the variant, and the number of errors on the switching trail. Paradoxically, participants who used more methamphetamine were less likely to make errors on the switching trail. As noted in Chapter 5, it is difficult to be certain of the reasons for these paradoxical effects, but they may be due to different rates of use of other substances of abuse.

HIV disease progression and adherence. In linear regression models controlling for demographic factors, missed opportunities and Go-Nogo reaction time were associated with biological indicators of HIV suggesting that sustained attention and processing speed may be related to HIV disease progression. The only measure associated with adherence in multivariate analyses was the time to complete the switching trail, suggesting that executive function plays a role in adherence behaviors.

Dichotomized ART adherence. Those with 80% or better adherence, as measured by the VAS, scored higher on a number of neurocognitive variables. The executive function variables that were associated with better adherence were distributed across the different tests, and included: IGT score, number of categories completed on the WCST, and the time to complete the switching trail. In addition, fewer missed opportunities on the Go-Nogo were also associated with better adherence for both TLFB and VAS measures. At its core, adherence can be described as persistence in responding to the same stimuli over time. Thus, it is not surprising that missed opportunities would be associated with adherence, as it measures persistence in responding to the same stimuli over time. In multivariate logistic regression analyses controlling for methamphetamine dependence scores, it is this measure of attention, and not executive function measures, that is significantly associated with adherence.

Summary of Results for Executive Domain NPZ Score

Demographics. Increases in the executive domain NPZ score were associated with younger age, more years of education and White versus Latino ethnicity. As mentioned above, it is not surprising to find that raw measures of executive functioning are associated with age-related decline, education and race. Neurocognitive task performance is notoriously associated with these demographic factors.

Mental health. Increases in depressive symptoms were associated with increases in the executive domain NPZ score. Most studies of depression and executive function find *declines* associated with depression symptomatology (Kaiser, et al., 2003; Marazziti, et al., 2010; McLennan & Mathias, 2010) and this effect holds true in HIV+ populations (Fazeli, et al., 2011; Shimizu et al., 2011). Effects in this study appear to be driven by two of the six variables that make up the NPZ score. Better performance on both the IGT and the Go-Nogo were associated with increased depressive symptoms. While the effect seen in the Go-Nogo runs counter to the literature (Kaiser, et al., 2003), the effect seen in the IGT is not without precedent (Smoski, et al., 2008). Regardless, a researcher relying on the executive domain NPZ score could conclude falsely that depression is associated with increases in executive function for this population, highlighting the need to examine the functions at a more discrete level to avoid misinterpreting associations with the composite score.

Methamphetamine. Controlling for demographic factors, increases in the years since initiation of methamphetamine use was associated with increases in the NPZ score. This is likely a spurious finding, as there is nothing within the data or in the literature to suggest that years since initial use should be related to increases in function.

HIV disease progression and adherence. The executive domain NPZ was not associated with disease progression factors. However, even when controlling for demographic factors,

increases in the NPZ were associated with better adherence. Multivariate examinations of the association of neurocognitive function and adherence, controlling for demographics, have been unsuccessful in finding domain specific effects for executive function (Contardo, et al., 2009; Hinkin, et al., 2002; Hinkin, et al., 2004; Wagner, et al., 2002; Waldrop-Valverde, et al., 2006). Researchers have relied upon impairment scores or composite scores created across multiple domains to detect effects (Hinkin, et al., 2004; Waldrop-Valverde, et al., 2006) and thus, this is the first finding of an executive function effect on adherence controlling for demographic factors.

Dichotomized ART adherence. As mentioned in the previous section, the multivariate association between the executive domain NPZ and adherence controlling for demographic associations is unique within the adherence literature. The executive domain NPZ was associated with adherence in logistic regression analyses predicting higher adherence after controlling for methamphetamine dependence scores. This was not surprising, given that the NPZ was powerful enough to detect differences within a more stringent analysis.

Summary of Results for Factor Analytic Scores

Creation. The factor analysis yielded six factors: WCST Performance, Motor Impulsivity, Slowness of Processing, Executive Inhibition, Sustained Attention, and Decision Making/ Reinforcement Processing. Three of these factors clearly represent components of the larger construct of executive function: WCST Performance, Executive Inhibition, and Decision Making/ Reinforcement Processing. The other three factors were either clearly not executive in nature, Slowness of Processing, or questionably executive in nature, Sustained Attention and Motor Impulsivity.

Demographics. The factor scores associated with age in multivariate models controlling for other demographic factors were the nonexecutive factors, Slowness of Processing and

Sustained Attention. This is unsurprising as processing speed and motor speed are often the first deficits seen in HIV+ participants (McArthur, 2004; Nath, et al., 2008). Effects for education cut across executive and nonexecutive factors, as Executive Inhibition, Decision Making/ Reinforcement Processing and Slowness of Processing were all sensitive to differences in years of education. Racial and income affects were similarly distributed across executive and nonexecutive factors.

Mental health. Both factor scores relating to inhibition were associated with depression symptoms at the multivariate level. Interestingly, they were associated in the opposite direction. In chapter 2, it was hypothesized that false alarms and the switching trail would load together on a single inhibition factor. In the analysis, these two tests loaded on separate factors suggesting that the neurocognitive processes by which simple motor inhibition occurs in the Go-Nogo is different than the neurocognitive processes by which one cognitive set is inhibited in order to use a second set in the switching trail. The fact that these two factors are associated with depressive symptoms in opposite directions provides further evidence of the dissociation of these two processes.

Methamphetamine. As with the other representations of executive function, associations of the factor scores with methamphetamine use characteristics were problematic. The only association was an increase in Executive Inhibition in response to greater methamphetamine use. An increase in executive inhibition is one of the benefits of amphetamine treatments for Attention Deficit Disorder (Kempton et al., 1999; Langleben et al., 2006). However, it is unlikely that this finding was related to residual amounts of methamphetamine as performance on all tasks was unrelated to urine toxicology results. This association was more likely driven by probable associations with participant's history with other substances of abuse.

HIV disease progression and adherence. The only factor associated with biological measures of HIV severity was Sustained Attention. In bivariate analyses, Slowness of Processing and Decision Making/Reinforcement Processing were associated with adherence. However, at the multivariate level, no factor score was significantly associated with adherence controlling for demographic variables.

Dichotomized ART adherence. In bivariate analyses, performance on all three executive factors -- WCST Performance, Executive Inhibition and Decision Making/Reinforcement Processing – was significantly better among those who reported at least 80% adherence. When these three factors were entered into a logistic regression model predicting 80% adherence or better controlling for the effect of methamphetamine dependence score and methamphetamine use days, Decision Making/ Reinforcement Processing was the only significant neurocognitive parameter. This finding suggests that Decision Making/Reinforcement Processing is particularly important for adherence. Interventions for adherence in substance users may wish to target this aspect of function.

Comparison of the Strengths and Weaknesses of Executive Function Representations

Power. Because it is important to avoid type I errors in all research, having powerful methods for detecting differences is necessary. Composite neurocognitive NPZ scores have been proven a powerful method for detecting neurocognitive deficits related to ART adherence in HIV+ persons (Barclay, et al., 2007; Becker, et al., 2011; Ettenhofer, et al., 2010; Meade, et al., 2010). The present study uses this method, combining six tasks into a single executive domain NPZ score that was similarly effective in detecting differences in adherence. Using multiple executive function tests, this study was unique in showing an executive function relationship with adherence in multivariate methods controlling for demographic and mental health variables,

where previous studies using similar domain specific composite scores have failed (Contardo, et al., 2009; Hinkin, et al., 2002; Waldrop-Valverde, et al., 2006).

The individual variables did not have the power to detect adherence effects controlling for demographic effects; however, many bivariate relationships were significant. Nevertheless, it is important to understand that with 16 different variables, corrections for multiple observations would often be carried out. Using the conservative Bonferroni procedure for 16 observations, the criterion p value would be .0003, eliminating any effect that was seen in the present analysis. The Factor analytic method provides an intermediate option with regards to power. With only six factors, the adjustment for multiple comparisons is less drastic. The combination of the variables weighted by loading allows the measures to be aggregated, increasing the power for the measure.

Specificity. In addition to issues of power, problems with the operationalization of executive function can make it difficult to interpret results. As noted in Chapter 1, executive function involves the coordination of lower-level function; therefore, impairment on any given measure may be attributable to executive impairment as well as impairment on any one of the lower systems the executive coordinates to perform a task. Partially due to this issue of task impurity, the literature in inconsistent in defining what exactly is measured by a single task variable, much less which functions constitute the executive functions. Examining executive function with a domain NPZ score does not allow for the examination of the extent to which lower level cognitive difficulties are contributing to measurement error in the assessment of executive function. The finding that the executive domain NPZ score is associated with adherence controlling for demographic factors is relatively meaningless for future research, as the extent to which that NPZ score even measures executive function is debatable. Even putting aside the diversity of executive function, the finding might not even implicate the broader

category of executive function. This lack of specificity creates an obstacle to intervention, because an intervention designed to target attention deficits would look very different than one designed to target decision making.

In addition to the problems for intervention development, the use of such a composite score can be misleading, as evidenced by positive association of the executive domain NPZ with depression symptoms. It is unheard of to suggest that a broad aspect of neurocognitive function, such as executive function, is improved by symptoms of a debilitating disease. The specificity of the individual variables and factor scores make interpretations of relationships clearer.

Examining executive function using the individual variables created from a task helps clarify the functions related to various outcomes. The issue of task impurity, however, becomes a more difficult one. In examining significant effects seen for the switching trail, one cannot determine if the effect is one of motor speed, processing speed, or executive function. Examinations across tests may help answer some of these questions; for example, if the numbers and letters trails as well as the motor speed trail are not significant it may be assumed that the effect is executive in nature. When all three trails have significant associations, one can logically assume that the most basic function, motor speed, is related, but there is no simple way to ascertain if the executive component of the switching trail is contributing to the effect. The factor analysis allows for more careful consideration of these different aspects of function that are important within the wider array of variables. Taking this same example, it is clear when using the Executive Inhibition factor that effects are executive in nature, because the factor groups the switching trail time and switching trail errors without strong loadings from the other more basic trails variables. Meanwhile, a second variable, Slowness of Processing, was created with strong loadings from all of the timed trails variables, but not the number of switching errors. The pattern

of loadings in a factor analysis provides clues to understanding the functions represented by the factors it creates.

Another benefit of using factor analytic methods is the ability to examine questions in the literature about what specific function a particular test measures. The WCST and switching trail have been described as measuring cognitive flexibility, mental set shifting, inhibition, categorization and problem solving (Miyake, et al., 2000; Sanchez-Cubillo, et al., 2009). Factor analysis can help determine which tests and which variables have shared variance, and that overlapping variance may help to ascertain the essence of a particular function. For example, in the present analysis there were two tasks that have been described as tasks of set shifting: the WCST and the switching trail. However, these two variables had no overlap in the factor solution, which suggests that they are not measuring the same ability. Similarly the switching trail has been theorized as measuring inhibition, as have false alarms on the Go-Nogo. In the Factor analyses these two tests were also grouped differently, suggesting that to some extent these two types of inhibition require different skills.

When examining the association between executive function and health outcomes, such as ART adherence and substance use, being able to identify discrete functions is important for understanding the nature of the association. Using a factor analytic strategy increases the confidence in functional definitions made within research, making the knowledge gained in such explorations more valuable.

Implications of the Findings for HIV+ Methamphetamine Users

Executive functioning. This study clearly supports the notion that executive functioning is important for ART adherence among methamphetamine users. Of particular interest is the finding that the Decision Making/ Response Inhibition factor was important for adherence.

Decision making has not been extensively examined with regard to ART adherence. It may seem counterintuitive, considering the importance of adherence that physicians impart to their patients, to suggest that perhaps the reasons why people don't take their medications is they consciously **decide** not to take their medication. Within the literature examining participants' reasons for nonadherence, after the most common response of forgetting (Schonnesson, Ross, & Williams, 2004; Walsh, Horne, Dalton, Burgess, & Gazzard, 2001), there is a wide range of responses including unwanted side effects (Walsh, et al., 2001; Wroe & Thomas, 2003), not wanting to be reminded of their infection (Wroe & Thomas, 2003), or being concerned to take them with drugs or alcohol (Walsh, et al., 2001). Common to each of these secondary reasons is the deliberate choice to not take medication. The IGT and IGT variant provide a means for examining how reward and punishment impact choices. For example, studies have shown that impairment on the variant indicating hypersensitivity to punishment is associated with less sexual risk behavior (Kowalczyk, Walker, Pawson, Parsons, & Golub, 2010), and with a decrease in the association between methamphetamine use and missed medication (Kowalczyk, Surace, Tomassilli, Parsons, & Golub, 2011). Impairment on the basic task, indicating hypersensitivity to reward has been associated with more missed medication (Kowalczyk, et al., 2011) and an increase in sexual risk behavior (Kowalczyk, et al., 2010). A more careful examination of these two tests might reveal a pattern of responding that could be used to examine interventions to change the reward/punishment calculus for adherence behavior.

The present study did not obtain consistent findings for a relationship between executive function and methamphetamine use. The lack of findings has been discussed extensively in previous sections, but it should be noted here that considering the flaws inherent in the design for detection, this lack of findings does not repudiate the large body of work indicating executive

function deficits in methamphetamine users (Scott, et al., 2007). However, the work that has been done examining methamphetamine-related cognitive difficulties is not without flaws itself, and issues exist similar to those found in the present study (i.e., lack of the use of norms to control for demographic differences, a lack of control for other drug use), calling into question the validity of the data that supports this commonly held view (Hart, et al., 2012).

Aside from the effects, or lack of effects, seen for executive function, several other findings from the present study are worth mentioning as they relate to the cognitive functioning of the present population.

Sustained attention. The analyses using factor analysis and individual variables suggest that there is a role for sustained attention beyond executive function in adherence. In multivariate analyses using individual variable predictors, missed opportunities on the Go-Nogo was the only significant neurocognitive predictor of percent dose adherence in logistic regression. This is an interesting finding given the sensitivity of dopaminergic systems to damage from HIV and methamphetamine (Chang, Cloak, et al., 2005; Maragos et al., 2002; Thrash, et al., 2009; Volkow, Chang, Wang, Fowler, Ding, et al., 2001) and the importance of those systems for attention in general (Nieoullon, 2002) and specifically for sustained attention (Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005). In a previous study examining sustained attention in HIV+ substance using participants, positive urine for stimulants (cocaine or methamphetamine) was associated with increases in missed opportunities on the continuous performance task (one similar to the Go-Nogo used presently) and that difference worsened over time with successive blocks (Levine et al., 2006). Although adherence was not specifically measured, those who tested positive for stimulants had worse viral load and CD4 counts than substance users who were negative for substances, however, these effects were not significant ($p = .13$, and $p = .08$

respectively). In the present study there were no differences in missed opportunities in relation to urine drug toxicology, but missed opportunities was associated with differences in adherence and in CD4 counts.

Neuroanatomical considerations. Due to the wide variety of tasks examined in the present study, and the three different operationalizations of executive function, the ability for the present analysis to inform the neuroanatomical literature is limited. As a whole, the tests rely upon a wide array of brain structures and functional modules. Although activity tends to be focused in the frontal lobes for all of these tasks, other lobes and subcortical regions of the brain are activated by them as well. The claim could be made that participants with poor NPZ scores are likely to have some frontal dysfunction, but that may not be the only site of dysfunction. In addition, the frontal lobes are varied in function and cytoarchitecture, so having the knowledge that there is some dysfunction somewhere in the frontal lobes is analogous to saying there is some dysfunction in executive function. Little can be done with such information.

Despite the difficulties mentioned above, the present study does suggest that some specific regions of the brain may warrant more attention for research in the fields of methamphetamine use and HIV. In aim 5, the factor analysis and the individual variables implicated different specific functions being important for adherence when controlling for methamphetamine dependence. For the individual variables, sustained attention, as measured by the number of missed opportunities on the Go-Nogo was the most important neurocognitive predictor of adherence. Decision Making/ Reinforcement Processing was the most important factor in predicting adherence with the factor scores. These two functions seem wildly different, but there is some neuroanatomical overlap. Those with right ventromedial prefrontal cortex damage consistently perform poorly on the IGT, while damage to the dorsolateral prefrontal

cortex yields more equivocal results (Buelow & Suhr, 2009). Likewise, those with damage to the right prefrontal cortex also have difficulties with sustained attention tasks (Sarter, Givens, & Bruno, 2001). This overlap gives provides reason to investigate the right prefrontal cortex for damage in those who have issues with adherence, but there is reason to be cautious with conclusions. For example, there is evidence that the same region of the brain, the ventromedial prefrontal cortex, is activated by the good decks for those who perform well, and the bad decks for those who perform poorly (Linnet, et al., 2011; Power, Goodyear, & Crockford, 2011) What this suggests is that poor performance on the IGT is not necessarily associated with damage to the brain, but to a difference in the way the valence of reinforcement is processed.

Implications for Intervention Development

The main problem with the usage of domain NPZ scores and general global neuropsychological function scores is that findings using such variables have limited application to real world intervention development. The results examining adherence controlling for methamphetamine use provide a good example of how different representations of executive function could lead to different conclusions with regards to developing interventions to impact adherence. A poor executive domain NPZ score was related to adherence controlling for methamphetamine use. However, in this analysis, and **any** analysis done with such a variable, all that one could target is the entirety of executive function. The likelihood of success with such an intervention is poor. Using both the individual variables and the factor scores allow for specific targets for adherence intervention, however these two methods provided very different answers for what to target.

The individual scores implicated poor IGT performance, a low number of categories completed on the WCST, and a slow time to complete the switching trail as predictive of poor

adherence. But it was missed opportunities on the Go-Nogo that was a significant predictor controlling for methamphetamine use characteristics and the other neurocognitive variables in the model. Missed opportunities, described here as measuring sustained attention, are usually thought of as a measure of attention and not executive functions, thought this can be debated. But it is interesting that in a study of executive function, attention is one of the functions that emerge in importance. What this finding suggests is that in order to have the greatest impact on adherence rates in those with neurocognitive difficulties, one would wish to target unintentional nonadherence. Because sustained attention is implicated in the individual variable analysis, it would be advantageous to develop interventions to work around a lack of sustained attention by increasing a participant's awareness of their need to take medication. These are simple interventions such as placing reminders with post it notes on bathroom mirrors, setting alarm clocks, or having a signal on a pill box that alerts the patient to whether or not their medication has been taken. Given the rise of popularity of mobile devices and smart phones, especially within the MSM community make SMS text messaging, or other preprogrammed reminders sent to mobile devices as particularly promising interventions (Haberer, 2010; Rotheram-Borus, 2010). In order to directly impact attention, pharmacological treatments that have been shown to be effective treating attention deficit disorder in adults may be useful here, such as modafinil (Meszaros et al., 2009; Turner, Clark, Dowson, Robbins, & Sahakian, 2004) and lisdexamfetamine dimesylate (Adler et al., 2008). It may seem odd to give another medication to a group of people who have problems taking medications, and even odder to give medications for attention deficit disorder, which are usually stimulant based, to a group of stimulant users. However, if the patient's problems stems from a lack of attention, the new medication might insure that more of all of the patient's medications are taken. In addition, drugs such as modafinil

and lisdexamfetamine dimesylate have been shown to have low abuse liability, even in participants with stimulant use disorders (Jasinski & Krishnan, 2009; Vosburg, Hart, Haney, Rubin, & Foltin, 2010)

The factor scores implicate intentional rather than nonintentional adherence as the best target for increasing adherence. The factor score for Decision Making/Reinforcement Processing significantly predicted adherence controling for the effect of methamphetamine use characteristics and other executive function variables. This finding bodes well for the parent project ACE, which uses cognitive behavioral skills training (CBST) as a component of it's intervention. Using such a treatment can impact the decisions a participant makes to not take their medication. These intentional missed doses can happen for a variety of reasons, many of which could be discussed with a CBST therapist in order to maximize the likelihood that the most healthy decision will be made. Some decisions to not take medication are simple and precipitated by a lack of information. For example, participnats have reported to their counselors within ACE that they do not know what to do when they miss a medication and remember later, so they err on the side of not taking their medication. A counselor can explain that the proper rule to follow when medications are missed, and reinforce that rule in session, hopefully increasing the percentage of medications taken. Other decisions aremore dificult to impact and involve weighing rewards against punishments. For example, if a participant is not taking their medication because of the negative side effects, a therapist may be able to discuss with the participant weighing the short term impact of a negative side effect (which should decrease over time due to tolerance) against the long term impact of disease progression. In addition, the therapist and participant could develop strategies to work around the problem maximizing positive reinforcement, perhaps building a contract where the participant agrees to continue

taking the unwanted medication, but also will discuss with their doctor as soon as possible changing to a different regimen. The impact of having a therapist who can work through the rewards and punishment associated with adherence, HIV, and substance use could have a positive impact on all three outcomes.

Limitations of the Current Study

Other substance use. The present study was enabled but also limited by having participants who were recruited from a behavioral randomized control trial in which they were concurrently participating. Because of the concurrent study, the present study could not control for other substance use. One of the secondary targets for the therapeutic intervention was polysubstance use. In order to determine intervention effectiveness, participants had to be free to use other drugs. Therefore, the present study could not require clean urines on the day of the neurocognitive assessment. While this was not a requirement, urine toxicology results were not associated with any differences in neurocognitive function. In addition to not requiring a clean urine screen, the selection criteria for the parent trial did not specify that methamphetamine was the participant's drug of choice; some participants in the sample reported having more problems with substances other than methamphetamine. This complicated interpretation of the findings with regard to methamphetamine-associated executive function deficits.

Task selection. The neurocognitive battery within this study was not designed to answer the present questions. Ideally, the tasks selected would have national norms, preferably for race as well as age and education. In most studies examining a global composite score, norms have been used to help control for these demographic factors, as well as allowing for a better understanding of what the scores mean in terms of "normal" function (Barclay, et al., 2007; Becker, et al., 2011; Ettenhofer, et al., 2010; Hinkin, et al., 2002; Hinkin, et al., 2004; Levine, et

al., 2005). This lack of norms makes it even more surprising that the present analysis found a multivariate effect on adherence for the executive domain NPZ controlling for demographic associations.

Another aspect of task selection that affected the interpretability of the results is the lack of a series of more basic functioning tests. A wider battery of measures would have enabled examination of other issues of task impurity, allowing for a cleaner interpretation of the factor analysis. More executive function tests would have allowed for a more complete characterization of executive function. The current results found three executive function factors, but this clearly does not represent the complete range of functions that comprise executive function. While more tests would have been preferable, studies of neurocognitive function are tiring for participants. There is a need to weigh the quality of data gathered from fatigued participants against the fullness of the battery. Additionally, no matter how full the neurocognitive battery, such a factor analysis could not guarantee complete representation of all executive functions.

Participant selection. Generalizability is always a concern for research. As was highlighted in chapter 1, the factor analysis of executive function tasks may be different given a different population. It is important to note that if these same tests were given to a sample of undergraduates, the elderly, or persons with traumatic brain injuries, the results of the factor analysis could be extremely different. Nevertheless, the present study is still significant for literature attempting to better define executive function.

Adherence measurement. The present study used two forms of self-reported adherence. While it would have been preferable to have objective measures of adherence, disease severity can stand in as an objective measure of adherence. In addition, the concept of medication persistence was not been studied. Research has begun to indicate that prolonged periods of

consistent missed medication are more closely associated with viral load increases than percent adherence levels (Altice & Bae, 2011; Bae, et al., 2011). The lack of an objective measure of adherence and no measure of persistence are methodological flaws. Nevertheless, studies have shown that self-reported adherence is a valid measure of adherence (K. M. Berg & Arnsten, 2006) and therefore, despite measurement that is not optimal, the associations found with neuropsychological function are important to consider.

Considerations for Future Research

Latent class analyses. In addition to examining executive functioning using factor analysis, there are other ways of representing executive function. One such method is latent class analyses. In latent class analyses, the data are examined for latent subgroups of participants with similar patterns of results. Instead of examining the pattern of variance across all participants to make a latent factor, as in factor analysis, latent class analysis examines the similarity of patterns of function that occur most frequently *within*-participants and places participants into groups based on that pattern. This approach not only allows one to examine how tests are related, but also how they are expressed by participants in the real world. This furthers the ability to extend research into development of theories and intervention, because examinations can focus on the associations between tests that are commonly seen in actual participants, as opposed to being developed through between-subjects analyses. Given certain patterns of function associated in the different HIV-Associated Neurocognitive Disorders (Woods, Moore, Weber, & Grant, 2009), it is likely that latent class analyses could be used to examine the course of the illnesses, as well as those behavioral disruptions one might expect considering a particular pattern of function. Examining executive function using new methods of representation could help solidify theories surrounding the nature of executive functions.

Day level associations. The present analysis has examined adherence and methamphetamine using aggregate scores. Considering the prominence of decision making within the context of adherence, it may be beneficial to examine day-level relationships using the TLFB data. Because data are collected in a time sensitive manner using the TLFB, it is possible to not only use that information to create aggregate data, but also to examine the associations between different behaviors within a given day. Because substance use is known to alter cognition, it is possible that the neurocognitive factors associated with adherence may differ between days where drugs are taken versus days where the participant is sober. In addition, using day-level analyses one can also examine, how neurocognitive factors change the strength of association between drug use and missed medication.

Different health behaviors can be examined using day-level models. There is a strong association between substance use in general, and methamphetamine use specifically, with risky sexual behaviors (Colfax & Guzman, 2006; Nakamura, Mausbach, Ulibarri, Semple, & Patterson, 2011; Parsons, 2006; Shoptaw, 2006). Examinations of the day-level associations of substance use and health risk behaviors provide a wealth of material for studying executive function generally, and decision making in particular. Given recent findings that undetectable viral loads are associated with an extremely reduced risk for transmission (Attia, Egger, Muller, Zwahlen, & Low, 2009; HPTN-052, 2011; Montaner, 2011; Montaner, et al., 2010), research into the associations between adherence and sexual risk may be increasingly important.

Attention. This study suggests that sustained attention is important for medication adherence in methamphetamine-using participants. These findings make sense considering that adherence is a behavior that must be sustained over a long period of time. Beyond these findings, the cognitive domain of attention is one that may be fertile for similar explorations. Attention,

like executive function, has multiple components and problems with its operationalization (Foldi, Lobosco, & Schaefer, 2002; Levine et al., 2008). Unlike executive function, there is a clearer understanding of expected results regarding factor analyses of neuropsychological tasks of attention. Mirsky and colleagues (1991) noted in multiple samples four components of attention from neuropsychological tests: Focus-Execute, Shift, Encode and Sustain. In the HIV literature, attention has received too little attention, with the majority of work taking place prior to the regular use of the next generation of ART medications (for review see: Levine, et al., 2008). Concerns for dopaminergic structures relating to HIV and stimulant use and new work showing specific age-related differences in attention for HIV+ older adults (Van Dyk et al., 2011a, 2011b), present a strong case for a comprehensive study of attention as it relates to adherence in HIV+ individuals.

The Representation of Executive Functions: How Unity and Diversity Play a Role

Perhaps the most important aspect of the present analysis is not related to HIV or substance use, but the factor analysis itself. In previous attempts to analyze the factor structure of executive function, two methods have generally been used. One is to examine a variety of tests from across neurocognitive function, including a few measures of executive function. These examinations tend to lead to single factors of executive function (Ardila, et al., 1998; Ardila & Pineda, 2000; Dawes, et al., 2008; Fals-Stewart & Bates, 2003; Waldrop-Valverde, et al., 2010), because in comparisons between executive function tests and other tests of neurocognitive function, the unity of executive function is highlighted. Executive function tests share more similarities with each other than with attention tasks, or motor tasks, or memory tasks; therefore, when examining the factor structure of such a battery, the similarities in the variance of executive function tests are highlighted. The present study falls into the second set of studies, in

which numerous executive function tasks are given together and the factor structure of executive function alone is examined. Many of these studies are designed to examine executive function from the perspective of Baddeley's model of the central executive (1986). For example, in the seminal work by Miyake and colleagues (2000) small discrete tasks were used to create a confirmatory factor analysis that could be thought of as three functions of the central executive; updating, shifting, and inhibition. These three factors have been repeated in several studies using more complex tasks (Latzman & Markon, 2010), with studies adding new factors of access (Fisk & Sharp, 2004; Verdejo-Garcia & Perez-Garcia, 2007), and decision making (Verdejo-Garcia & Perez-Garcia, 2007) to this conceptualization of executive function. The present study did not use the previous work to name factors, though these studies were considered. The differences between the present study and the previous studies mentioned highlight the difficulties inherent in characterizing executive function with factor analysis. While the majority of work that examined executive function factors in the context of the Baddeley's model was completed with non-clinical populations (Fisk & Sharp, 2004; Latzman & Markon, 2010; Miyake, et al., 2000), the present study relied on a clinical population. Numerous studies have shown that examining clinical populations can lead to differences in the factor structure of executive function (Goldman, et al., 1996; Greve, et al., 1998). In addition, the tests used in the present study were to a large extent complex (i.e., IGT, IGT variant, WCST, Trails, Counting Span), and it is unclear what these tests actually measure (i.e., IGT, IGT variant, WCST, Trails). Furthermore, this grouping of tests Trails), has not been examined previously in a factor analysis of executive function (i.e., IGT variant, Go-Nogo, Counting Span). Studies that have added unique tests have found unique answers. The addition of the IGT led to findings of a decision making factor in one study (Verdejo-Garcia & Perez-Garcia, 2007), and the addition of the Tower of London test led

to the finding of a planning factor in another study (Weintraub et al., 2005). The differences among populations studied and tests used help explain the differences seen in the present factor analysis.

The present analysis raises questions about how studies of executive function might have varied given subtle differences in the variables entered or the analysis plan. For example, in studies using the WCST, perseverative errors are often used alone (Ettenhofer, et al., 2006), or in conjunction with number of trials (Fisk & Sharp, 2004), or categories completed (Bamdad, et al., 2003), both of which have a high correlation to perseverative errors. In each of these studies, there is an assumption that when these variables load on a factor, that factor represents some form of set shifting. However, in the present study non-perseverative errors also loaded with perseverative errors on a factor. Without convergent evidence from the switching trail, it was not appropriate to limit the factor to simply shifting. This calls into question the assumption that each perseverative error represents a participant who cannot break from the previous set. These findings suggest that this assumption may not be true, and perhaps the participant is generating new hypotheses that are unrelated to the three categorical rules within the WCST.

Another point of difference that may help inform the literature is the separation of different forms of inhibition found in the present study. While Miyake and colleagues (2000) used a variety of inhibitory tasks and found a single inhibition factor, the present study using two tests of inhibition found two factors representing inhibition. This result calls into question the unitary construct of inhibition. In fact, the weakest loading for Miyake and colleagues' confirmatory factor analysis was the Stop-Signal task (very similar to the Go-Nogo) on their inhibition factor. Perhaps if more complex tasks were used, this form of motor inhibition may have been distinguishable in analyses from executive inhibition as in the present analysis.

In conclusion, work surrounding the representation of executive function, and neurocognitive function in general, is important for both basic and applied research. The present study illustrates that without careful examinations of what neuropsychological tests are actually measuring within the population being studies, the associations that are drawn from function to behavior are just associations between abstract tasks and behavior. The information that is gleaned from combining tests with simple methods, such as the domain NPZ, limits the intervention development and further consideration of what specific functions are necessary for real world behaviors. This is particularly important when addressing the behavior of HIV+ persons as it relates to neurocognitive function. For the HIV+ person, the issue of health behavior is paramount, as mistakes in health behavior are magnified. Accurate definition of these functions is increasingly important because, despite viral suppression, HIV-Associated Neurocognitive Disorders are still extremely prevalent (Heaton et al., 2011; Simioni et al., 2010). The patterns of dysfunction that are found in these illnesses could be impacted upon to increase the longevity and quality of life for HIV+ persons.

While the applications to the study of behaviors associated with HIV is of importance, the present analysis also helps to further characterize the nature of executive function. The methods detailed here should be repeated in other samples, and with different neuropsychological tests. Each step towards characterizing executive function at this basic level will help bring the scientific community closer to throwing out the notion of the executive function "garbage can." Then research on meaningful ways of impacting and increasing specific aspects of function would be easier to develop as there would be clear categories of persons that can be tested with interventions designed to impact cognition directly. Being able to impact

specific functional deficits directly would be useful, not just for health behaviors, but for a myriad of other aspects of life as well.

Table 1.

Descriptive statistics of continuous participant characteristics, N = 156

Variable Type	Variable	Mean	SD	Range
Demographics	Age	41.1	8.7	24 - 63
	Education (years)	14.4	2.5	5 - 20
Mental Health	CES-D Depression Score	24.9	11.1	0 - 50
	STAI- Trait Anxiety	19.9	6.1	10 - 38
Meth-amphetamine Use	Years Since First Meth Use[q]	9.9	7.8	<1 - 41
	CIDI-SAM Meth Dependence Score[m]	3.7	2.1	0 - 7
	Severity of Dependence Score	5.2	3.1	0 - 15
	Days of meth use (last 30 days TLFB)	5.5	5.3	1 - 30
Disease Progression	Years Since Diagnosis[m]	11.8	7.2	<1 - 26
	Years on HAART	7.8	5.8	<1 - 22
	Number of Different Regimens	3.2	2.8	1 - 25
	Viral Load	34,258	112,733	<20 - 1,027,658
	Log Viral Load	2.55	1.3	<1.29 - 6.01
	CD4 Count	458.7	254.5	23 - 1,144
Adherence	% Dose Adherence (last 14 days TLFB)	71.1	29.7	0 - 100%
	% Dose Adherence (last 30 days VAS)	67.3	24.5	0 - 99%

Missing data for scales is indicated by [m] (n = 154), and [q] (n = 155).

Table 2.

Descriptive statistics of discrete participant characteristics, N = 156

Variable Type	Variable	Category	N	%
Demographic	Race/Ethnicity	Black/African American	52	33.3
		Hispanic/Latino	44	28.2
		White/Caucasian	50	32.1
		Other	10	6.4
	Income	Less than $10,000 per year	57	36.5
		$10,000 - $19,999	50	32.1
		$20,000 or greater per year	48	30.8
		Refused to answer	1	0.6
	Relationship Status	Single	106	67.9
		Partnered	50	32.1
Disease Progression	Viral Load[†]	Undetectable <48	84	53.8
		Detectable ≥48	72	46.2
	CD4 count	≤200	29	18.6
		>200, <500	63	40.4
		≥500	64	41
Adherence	% Dose Adherence (last 14 days TLFB)	≥80%	86	55.1
		<80%	70	44.9
	% Dose Adherence (last 30 days VAS)	≥80%	68	43.6
		<80%	88	56.4

Missing data for scales is indicated by [m] (n = 154). [†] Viral loads under 48 are considered undetectable.

Table 3.

Neurocognitive continuous variable descriptive data, N = 156

Test	Variable	Mean	SD	Range
Counting Span	Span Score	31.2	20.3	0 - 92
Iowa Gambling Task	Total Raw	7.4	27.6	-48 - 76
	Learning Score	11.2	11	-24 - 40
	Total T-score	46.1	9.2	26 - 74
Iowa Gambling Task Variant	Total Raw τ^1	12.4	35.7	-95 - 88
	Learning Score	8.7	11.1	-12 - 36
Wisconsin Card Sort	Perseverative Errors Raw τ^2	23.8	14.4	4 - 71
	Non-perseverative Errors Raw τ^4	22.8	14.9	2 - 74
	Categories Completed	3.8	2.2	0 - 6
	Failure To Maintain Set τ^1	1.1	1.4	0 - 6
	Perseverative Errors T-Score	38.3	12.2	19 - 81
	Non-perseverative Errors T-Score	38	10.2	19 - 65
Go/No-go	False Alarms	20.3	14.7	0 - 68
	Missed Opportunities	8.2	11.9	0 - 72
	Reaction Time (msec) τ^2	473.5	62.9	332 - 665
D-KEFS Trails	Switching Raw (sec) τ^3	92.3	42.6	32 - 224
	Numbers and Letters Raw (sec) τ^2	34.3	12.1	13 - 78
	Motor Speed Raw (sec) τ^2	27.6	12	7 - 70
	Errors in Switching Raw	1.4	3.1	0 - 32
	Switching Standard Score	8.9	3.4	1 - 14
	Numbers and Letters Composite Standard Score	10.2	3.2	1 - 16
	Motor Speed Standard Score	10.8	2.2	1 - 15
	Errors in Switching Standard Score	10.1	2.6	1 - 12

Variables that were truncated at three standard deviations above and below the mean are indicated by τ, the number of participants truncated is indicated in the superscript.

Table 4.

Neurocognitive categorical variable descriptive data, N = 156

Test	Variable	Category	*n*	%
Go/No-go	Missed Opportunities	0 or 1	42	26.9
		2-7	61	39.1
		8 or more	53	34
D-KEFS Trails	Errors in the Switching Trial	0	74	47.4
		1	36	23.1
		2	22	14.1
		3-6	20	12.8
		9 or more	4	2.6

Table 5.

Neuropsychological test correlations Pearson r and Spearman rho, N = 156

	1	2	3	4	5	6	7	8	9	10[o]	11	12	13	14	15
1. Span Score	-														
2. IGT Total	.18*	-													
3. IGT Learn	.17*	.37**	-												
4. IGTV Total	.13	.16	.15	-											
5. IGTV Learn	.16*	.24**	.18*	.30**	-										
6. WCST PE[v]	.34**	.15	.17*	.13	.21**	-									
7. WCST NPE[v]	.35**	.03	.12	.08	.08	.40**	-								
8. WCST CatCo	.36**	.08	.16*	.13	.15	.74**	.76**	-							
9. WCST FtMS[v]	.13	.05	.13	-.05	.09	-.07	-.04	.14	-						
10. GNG FA[v]	.27**	.11	.02	-.03	-.03	-.02	.13	.06	.04	-					
11. GNG MO[ov]	.27**	.18*	-.03	.02	.17*	.14	.14	.16*	-.08	.25**	-				
12. GNG RT[v]	.17*	.03	-.04	.06	.14	.13	-.01	.01	-.07	-.42**	.41**	-			
13. Switch[v]	.38**	.16*	.19*	.06	.18*	.36**	.21**	.29**	-.03	.04	.37**	.20*	-		
14. NaL[v]	.37**	.14	.05	.08	.18*	.22**	.17*	.21**	.01	.09	.28**	.26**	.56**	-	
15. Motor[v]	.10	.12	.18*	.08	.08	.13	.11	.16*	.10	.01	.13	.17*	.29**	.41**	-
16. SE[ov]	.30**	-.02	.12	.10	.11	.17*	.12	.17*	-.07	.08	.15	.01	.55**	.08	.13

[v] = variables are reverse coded so that better performance is the higher value. [o] = *Variables are ordinal, Spearman rho is used.*
** = $p \leq .05$ ** = $p \leq .01$ IGT = Iowa Gambling Task, IGTV = Variant, PE = Perseverative Errors, NPE = Non-perseverative Errors, CatCo = Categories Completed, FtMS = Failure to Maintain Set, GNG = Go-Nogo, FA = False Alarms, MO = Missed Opportunities, RT = Reaction Time, Switch = Time to Complete Switching Trail, NaL = Mean Time to Complete Numbers and Letters Trails, Motor = Time to Complete Motor Speed Trail, SE = Number of Switching Errors.*

Table 6.

Factor analysis structure matrix, N = 156

	Factors	1	2	3	4	5	6
	Eigenvalue	3.73	1.73	1.54	1.39	1.17	1.1
Test	Variable			Factor Loading			
Count Span	Span Score	.375*	-.318*	-.405*	.270	.290	.294
IGT	Total	.105	-.123	-.207	.020	.051	.614**
	Learning Score	.174	-.031	-.121	.105	-.071	.584**
IGTV	Total	.138	.021	-.121	-.009	.038	.308*
	Learning Score	.164	.003	-.234	.080	.146	.402*
Wisconsin Card Sorting Test	Perseverative Errors[v]	.741**	-.032	-.288	.269	.159	.338*
	Non-perseverative Errors[v]	.761**	-.159	-.205	.147	.051	.134
	Categories Completed	.998**	-.104	-.277	.179	.039	.281
	Failure To Maintain Set[v]	.139	-.038	-.033	-.098	-.112	.164
Go-Nogo	False Alarms[v]	.089	-.995**	-.074	.041	-.124	.028
	Missed Opportunities[ov]	.184	-.289	-.333*	.275	.601**	.110
	Reaction Time[v]	.017	.355*	-.292	.120	.865**	.066
D-KEFS Trails	Switching Time[v]	.291	-.110	-.597**	.839**	.311*	.266
	Errors in Switching[ov]	.200	-.081	-.129	.700**	.142	.055
	Number and Letter Time[v]	.217	-.139	-.990**	.220	.320*	.195
	Motor Speed Time[v]	.170	-.041	-.429*	.132	.164	.220

[v] = variables are reverse coded so that better performance is the higher value. [o] = Variables are ordinal, Spearman rho is used.
* Factor Loading > *.3* ***Factor Loading* > *.5*

Table 7.

Executive domain NPZ and factor score descriptive data, N = 156

Method	Variable	Mean	SD	Range
NPZ	Executive Domain (ED)	0	0.56	-1.35 - 1.62
Factor Analysis	Factor 1:WCST Performance (WCSTP)	0	1.00	-1.75 - 1.12
	Factor 2: Motor Impulsivity (MI)	0	1.00	-1.42 - 3.21
	Factor 3: Slowness of Processing (SP)	0	1.00	-1.77 - 3.62
	Factor 4: Trails Switching (TS)	0	0.92	-3.21 - 1.33
	Factor 5: Sustained Attention (SA)	0	0.92	-2.84 - 1.8
	Factor 6: Decision Making (DM)	0	0.80	-1.63 - 1.95

Table 8.

Executive domain NPZ and factor score Pearson correlations, N = 156

Variable		1	2	3	4	5	6	NPZ^p
NPZ	1. Executive Domain	-						
Factor Scores	2. WCSTP	.52**	-					.40**
	3. Motor Impulsivity	-.52**	-.13	-				-.69**
	4. Slow Processing	-.39**	-.29**	.13	-			-.05
	5. Executive Inhibition	.23**	.19*	-.10	-.27**	-		.03
	6. Sustained Attention	.16*	.06	.06	-.37**	.28**	-	.21*
	7. Decision Making	.71**	.38**	-.07	-.35**	.15	.09	.74**

** = $p \leq .05$ ** = $p \leq .01$ NPZ^p indicates partial correlation with the executive domain NPZ score controlling for all other factor scores.*

Table 9.

Pearson, Spearman and partial correlations of neuropsychological variables with demographic and mental health variables (N = 156)

Variable	IGT		IGTV		Count	Go-Nogo		
	Total	Learn	Total	Learn	Span	FA[v]	MO[vo]	RT[v]
Age	.002	-.017	-.051	-.017	-.225**	.131†	-.035	-.286**
Education (years)	.256**	.148†	-.008	.100†	.368**	.120†	.123†	-.069
CES-D Depression Score	.133†	.032	.020	.036	.020	.153†	.027	-.119†
STAI- Trait Anxiety	.081	.097†	.038	.074	-.036	.149†	-.049	-.106†

	WCST					Trails		
	PE[v]	NPE[v]	CatCo	FtMS[v]	Switch[v]	SE[vo]	NaL[v]	Motor[v]
Age	-.219**	-.118†	-.108†	.083	-.139†	.034	-.197*	-.137†
Education (years)	.171*	.163*	.209**	.138†	.368**	.261**	.203*	.147†
CES-D Depression Score	.078	-.093†	-.020	-.123†	-.204*	-.056	-.067	-.155†
STAI- Trait Anxiety	-.036	-.074	-.121†	-.106†	-.124†	.089	-.059	-.132†

[v] = variables are reverse coded so that better performance is the higher value. [o] = Variables are ordinal, Spearman rho is used. † = $p \leq .25$ * = $p \leq .05$ ** = $p \leq .01$

Table 10.

Bivariate ANOVA, and ordinal probit analysis of individual neuropsychological variable differences based on categorical demographic variables, (N = 156)

Variable			IGT Total			IGT Learning			IGTV Total			IGTV Learning		
		n	M	SD	*p*	M	SD	*p*	M	SD	*p*	M	SD	*p*
Race	Black	52	4.0	25.8	.257	9.1	10.9	.331	12.8	29.3	.528	7.0	9.4	.083†
	Latino	44	5.3	27.1		11.9	11.7		8.0	35.5		8.0	10	
	White	50	13.8	28.5		13.0	10.6		17.6	41.2		11.9	13.2	
	Other	10	2.2	32.2		10.0	10.5		4.4	38.8		5.0	10.2	
Income	< 10,000	54	1.2	29.3	.073†	9.8	8.9	.363	18.0[b]	32.3	.033*	7.6	9.1	.426
	$10,000 - $19,999	49	9.5	25.7		11.4	12.3		1.4[a]	38.1		8.7	13.0	
	≥ 20,000	47	13.1	26.3		12.8	11.9		16.5[b]	35.1		10.4	11.0	
			WCST PE[v]			WCST NPE[v]			WCST CatCo			WCST FtMS[v]		
		n	M	SD	*p*	M	SD	*p*	M	SD	*p*	M	SD	*p*
Race	Black	52	46.3	13.4	.463	48.4	16.4	.181†	3.3	2.2	.046*	4.6	1.4	.057†
	Latino	44	45.2	15.5		52.2	11.7		3.6	2.2		4.8	1.5	
	White	50	49.3	14.5		54.1	13.9		4.5	2.0		5.3	1.2	
	Other	10	50.4	13.8		46.6	21.6		3.3	2.6		4.5	1.6	
Income	< 10,000	54	43.4	15.9	.043*	50.3	15.5	.282	3.3[b]	2.1	.038*	4.5	1.5	.087†
	$10,000 - $19,999	49	48.8	13.4		49.6	15.6		3.6	2.3		5.1	1.3	
	≥ 20,000	47	50.0	13.0		54.0	13.4		4.4[a]	2.1		5.0	1.4	

[v] = variables are reverse coded so that better performance is the higher value. Superscript on mean indicates differences between groups based on Tukey's B post hoc analyses p ≤ .05. † = p ≤ .25 * = p ≤ .05 ** = p ≤ .01

Table 10

Bivariate ANOVA, and ordinal probit analysis of individual neuropsychological variable differences based on categorical demographic variables, (N = 156)

Variable			Counting Span			GNG FA[v]			GNG MO[vo]			Go Nogo RT[v]		
		n	M	SD	*p*	M	SD	*p*	β	*p*	Omni *p*	M	SD	*p*
Race	Black	52	29.5	20	.189†	48.8[a]	15.4	.076†	-.670[b]	.003	.006**	187.9	63.7	.631
	Latino	44	27.4	17.2		46.0	15.9		-.714[b]	.002		189.4	62.6	
	White	50	36.0	22.2		50.1[a]	11.9		0[a]	ref		192.2	64.2	
	Other	10	32.7	22.2		37.7[b]	15.9		-.495	.198		216.0	57	
Income	< 10,000	54	27.4[b]	16.3	.028*	49.0	15.2	.642	-.126	.561	.777	191.2	64.8	.825
	$10,000 - $19,999	49	29.7	22.9		46.4	15.3		126	.515		187.1	57.2	
	≥ 20,000	47	37.6[a]	20.6		48.4	12.2		0	ref		195.1	67.2	

			Trails Switch[v]			Trails SE[vo]			Trails NaL[v]			Trails Motor[v]		
		n	M	SD	*p*	β	*p*	Omni *p*	M	SD	*p*	M	SD	*p*
Race	Black	52	118.0[b]	48.2	.000**	-.709[b]	.002	.019*	42.1	12.3	.209†	40.2	12.0	.070†
	Latino	44	124.0	39.4		-.421	.074		42.0	12.1		40.8	12.2	
	White	50	151.8[a]	28.7		0[a]	ref		46.5	10.1		44.8	10.5	
	Other	10	136.7	50.9		-.369	.345		44.7	18.7		48.3	15.3	
Income	< 10,000	54	114.4[b]	47.7	.000**	0[b]	ref	.006**	43.2	10.1	.004**	41.9	11.7	.100†
	$10,000 - $19,999	49	133.5[a]	41.1		.407	.056		39.9[b]	15.3		40.0	12.6	
	≥ 20,000	47	150.2[a]	28.3		.707[a]	.002		48.0[a]	9.2		45.1	11.3	

[v] = variables are reverse coded so that better performance is the higher value. [O] = Ordinal variable thus ordinal probit analysis was completed using the generalized linear model. Superscript on mean indicates differences between groups based on Tukey's B post hoc analyses. p ≤ .05. † = p ≤ .25 * = p ≤ .05 ** = p ≤ .01

Table 11.

Linear regression and ordinal probit analyses using demographic and mental health variables to predict individual neurocognitive variables

	IGT Total (n = 155)				IGT Variant Learning (n = 156)				Counting Span (n = 155)			
Omnibus Tests:	r^2	Adj r^2	f	*p*	r^2	Adj r^2	f	p	r^2	Adj r^2	f	*p*
	.105	.081	4.412	.002**	.045	.020	1.787	.134	.168	.122	3.681	.001**
Parameter Estimates	B	SE	β	*p*	B	SE	β	p	B	SE	β	*p*
Constant	-36.54	15.454	--	.019*	8.336	5.902	--	.160	35.242	13.302	--	.009**
Age	–				–				-.630	.179	-.271	.001**
Education (years)	2.638	.916	.236	.005**	.233	.375	.052	.535	1.893	.686	.230	.006**
CES-D Depression	.394	.194	.159	.044*	–				.067	.140	.036	.634
STAI - Trait Anxiety	–				–				–			
Black	–				-4.768	2.162	-.202	.048*	-1.349	4.018	-.031	.738
Latino	–				-3.299	2.276	-.133	.110	-7.987	3.995	-.178	.047*
White	–				ref		1		ref		1	
Other	–				-6.370	3.778	-.145	.089	-2.291	6.703	-.028	.733
< 10,000	-8.148	5.520	-.143	.142	–				-6.104	4.048	-.145	.134
$10,000 - $19,999	-1.866	5.455	-.032	.733	–				-5.970	4.006	-.131	.159
≥ 20,000	ref		1		–				ref		1	

– = variable not entered in the equation because bivariate relationship p > .25. ‡ = variable was dropped from the equation due to issues of multicollinearity. * = p ≤ .05 ** = p ≤ .01.

Table 11 continued.

Linear regression and ordinal probit analyses using demographic and mental health variables to predict individual neurocognitive variables

Omnibus Tests:	WCS PE^{v} (n = 155)			WCS CatCo (n = 155)			WCS FtMS^{v} (n = 155)					
	r^2	Adj r^2	f	r^2	Adj r^2	f	r^2	Adj r^2	f	r^2	Adj r^2	f
	.105	.081	4.412	.105	.081	4.412	.105	.081	4.412	.105	.081	4.412
Parameter Estimates	B	SE	β	*p*	B	SE	β	*p*	B	SE	β	*p*
Constant	47.125	7.894	--	.000**	5.260	1.582	--	.001	5.092	.874	--	.000**
Age	-.396	.129	-.240	.002**	-.038	.020	-.150	.063	–			
Education (years)	.937	.484	.160	.054	.129	.077	.143	.097	.034	.050	.059	.490
CES-D Depression	–				–				‡			
STAI - Trait Anxiety	–				-.045	.029	-.124	.126	-.026	.019	-.109	.180
Black	–				-.914	.457	-.193	.048*	-.696	.297	-.230	.021*
Latino	–				-.802	.452	-.163	.078	-.509	.292	-.161	.084
White	–				ref		1		ref		1	
Other	–				-1.085	.757	-.120	.154	-.663	.491	-.114	.179
< 10,000	ref		1		-.474	.463	-.103	.308	ref		1	
$10,000 - $19,999	4.652	2.873	.151	.088	-.379	.455	-.080	.407	.456	.276	.150	.101
≥ 20,000	4.529	2.710	.145	.117	ref		1		.142	.300	.046	.637

– = variable not entered in the equation because bivariate relationship p > .25. ‡ = variable was dropped from the equation due to issues of multicollinearity. * = p ≤ .05 ** = p ≤ .01.

Table 11 continued.

Linear regression and ordinal probit analyses using demographic and mental health variables to predict individual neurocognitive variables

Omnibus Tests:	Go/No-go FA^{v} (n = 156)				Go/No-go MO^{vo} (n = 156)				Go/No-go RT^{v} (n = 156)			
	r^2	Adj r^2	f	r^2	likelihood χ^2		*p*		f	r^2	Adj r^2	f
	.105	.081	4.412	.105	12.285		.015*		4.412	.105	.081	4.412
Parameter Estimates	B	SE	β	p	B	SE	Exp(B)	*p*	B	SE	β	p
Constant	26.573	9.609	--	.006**	N/A	--	--	--	296.79	26.17	--	.000**
Age	.175	.134	.104	.193	–				-2.106	.553	-.293	.000**
Education (years)	.697	.493	.116	.160	.004	.0381	1.004	.919	–			
CES-D Depression	.225	.104	.170	.032*	–				-.753	.434	-.133	.085
STAI - Trait Anxiety	‡				–				–			
Black	-.121	2.953	-.004	.967	-.580	.235	.515	.005**	–			
Latino	-3.338	2.988	-.117	.266	-.707	.234	.491	.002**	–			
White	ref		1		ref		1		–			
Other	-11.03	5.008	-.184	.029*	-.473	.384	.612	.204	–			
< 10,000	–				–				–			
$10,000 - $19,999	–				–				–			
≥ 20,000	–				–				–			

– = variable not entered in the equation because bivariate relationship p > .25. ‡ = variable was dropped from the equation due to issues of multicollinearity. * = p ≤ .05 ** = p ≤ .01.

Table 11 continued.

Linear regression and ordinal probit analyses using demographic and mental health variables to predict individual neurocognitive variables

Omnibus Tests:	Trails Switch^{v} (n = 155)				Trails SE^{vo} (n = 155)			
	r^2	Adj r^2	f	r^2	likelihood χ^2		*p*	
	.305	.267	8.022	.000**	22.049		.001**	
Parameter Estimates	B	SE	β	p	B	SE	Exp(B)	*p*
Constant	124.26	24.62	--	.000**	N/A	--	--	--
Age	-.950	.344	-.194	.007**	–			
Education (years)	4.674	1.319	.269	.001**	.094	.040	1.098	.019*
CES-D Depression	-.643	.270	-.167	.018**	–			
STAI - Trait Anxiety	‡				–			
Black	-21.67	7.730	-.239	.006**	-.473	.240	.623	.049*
Latino	-24.05	7.686	-.254	.002**	-.286	.241	.751	.236
White	ref		1		ref		1	
Other	-7.976	12.895	-.046	.537	-.147	.402	.863	.714
< 10,000	ref		1		ref		1	
$10,000 - $19,999	13.21	7.240	.145	.070	.320	.219	1.377	.143
≥ 20,000	18.42	7.787	.200	.019*	.418	.241	1.518	.083

Omnibus Tests:	Trails NaL^{v} (n = 155)				Trails Motor^{v} (n = 155)			
	r^2	Adj r^2	f	r^2	r^2	Adj r^2	f	r^2
	.160	.120	3.994	.000**	.115	.067	2.382	.019*
Parameter Estimates	B	B	SE	β	B	B	SE	β
Constant	48.216	7.594	--	.000**	52.020	8.528	--	.000**
Age	-.317	.107	-.228	.004**	-.229	.110	-.168	.038*
Education (years)	.938	.410	.190	.024*	.604	.417	.124	.149
CES-D Depression	–				‡			
STAI - Trait Anxiety	–				-2.83	.159	-.144	.076
Black	-2.005	2.407	-.078	.406	-4.006	2.466	-.158	.106
Latino	-4.398	2.394	-.164	.068	-4.353	2.436	-.164	.076
White	ref		1		ref		1	
Other	-2.390	4.016	-.048	.553	2.874	4.081	.059	.482
< 10,000	-2.237	2.406	-.089	.354	-.170	2.499	-.007	.946
$10,000 - $19,999	-6.664	2.388	-.257	.006**	-2.782	2.545	-.109	.259
≥ 20,000	ref		1		ref		1	

– = variable not entered in the equation because bivariate relationship p > .25. ‡ = variable was dropped from the equation due to issues of multicollinearity. * = p ≤ .05 ** = p ≤ .01.

Table 12.

Pearson and partial correlations of executive domain NPZ and neuropsychological factor scores with demographic, methamphetamine use, and mental health variables, (N = 156)

Variables	Executive		Factor Scores				
	NPZ	WCSTP	MI	SP	EI	SA	DM
Age	-.129†	-.110†	-.107†	.210**	-.069	-.262**	-.083
Education (years)	.275**	.213**	-.141†	-.231**	.327**	-.006	.276**
CES-D Depression	.145†	-.012	-.142†	.065	-.191*	-.081	.070
STAI - Trait Anxiety	.070	-.114†	-.139†	.062	-.079	-.073	.045

† = $p \leq .25$ * = $p \leq .05$ ** = $p \leq .01$

Table 13.

Bivariate ANOVA, and ordinal probit analysis of executive domain NPZ and factor neuropsychological scores differences based on categorical demographic variables, (n = 156)

Variables			Executive Domain NPZ			Factor Scores WCST Performance			Factor Scores Motor Impulse			Factor Scores Slow Process		
		n	M	SD	*p*	M	SD	*p*	M	SD	*p*	M	SD	*p*
Race	Black	52	-.037	.520	.031*	-.209	1.003	.039*	-.049[b]	1.038	.061†	.161	1.004	.100†
	Latino	44	-.129	.501		-.070	1.000		.134	1.067		.144	.958	
	White	50	.184	.590		.324	.898		-.199[b]	.825		-.278	.855	
	Other	10	-.159	.676		-.223	1.186		.663[a]	1.066		-.079	1.535	
Income	< 10,000	57	-.086[b]	.527	.036*	-.204[b]	.956	.037*	-.064	1.020	.637	.075[b]	.828	.002**
	$10,000 - $19,999	50	-.056	.617		-.056	1.063		.088	1.066		.293[b]	1.246	
	≥ 20,000	48	.176[a]	.499		.291[a]	.940		-.079	.809		-.386[a]	.768	

			Factor Scores Executive Inhibition			Factor Scores Sustained Attention			Factor Scores Decision Making		
		n	M	SD	*p*	M	SD	*p*	M	SD	*p*
Race	Black	52	-.280[b]	1.088	.002**	-.074	.888	.481	-.174	.744	.022*
	Latino	44	-.129	.884		-.108	.921		-.089	.791	
	White	50	.381[a]	.615		.124	.979		.283	.791	
	Other	10	.121	.835		.237	.817		-.120	.881	
Income	< 10,000	57	-.388[b]	1.120	.000**	-.017	.950	.673	-.209[b]	.772	.014*
	$10,000 - $19,999	50	.146[a]	.721		-.071	.904		.014	.814	
	≥ 20,000	48	.310[a]	.667		.093	.928		.244[a]	.765	

Superscript on mean indicates differences between groups based on Tukey's B post hoc analyses p ≤ .05. † = p ≤ .25 * = p ≤ .05 ** = p ≤ .01

Table 14.

Linear regression using demographic and mental health variables to predict executive domain NPZ and factor neuropsychological scores

	Executive Domain NPZ (*n* = 154)				Factor Scores WCSTP (n = 155)				Motor Impulsivity (*n* = 156)			
Omnibus Tests:	r^2	Adj r^2	f	p	r^2	Adj r^2	f	p	r^2	Adj r^2	f	p
	.201	.157	4.586	.000**	.124	.076	2.583	.011*	.092	.055	2.512	.024*
Parameter Estimates	B	SE	β	p	B	SE	β	p	B	SE	β	p
Constant	-.373	.358	--	.299	.650	.710	--	.361	1.570	.700	--	.026*
Age	-.012	.005	-.187	.014*	-.018	.009	-.153	.057	-.010	.009	-.088	.274
Education (years)	.062	.018	.276	.001**	.070	.033	.172	.085	-.054	.033	-.132	.111
CES-D Depression	.008	.004	.165	.029*	−				-.014	.007	-.159	.044*
STAI - Trait Anxiety	−				-.022	.013	-.137	.083	‡			
Black	-.058	.108	-.049	.595	-.410	.205	-.193	.047*	.057	.200	.027	.777
Latino	-.282	.108	-.229	.010**	-.398	.201	-.169	.067	.280	.203	.127	.168
White	ref		1		ref		1		ref		1	
Other	-.301	.180	-.133	.097	-.521	.336	-.126	.133	.769	.340	.189	.025*
< 10,000	-.148	.109	-.128	.177	-.212	.208	-.108	.309	−			
$10,000 - $19,999	-.194	.108	-.163	.074	-.179	.204	-.084	.383	−			
≥ 20,000	ref		1		ref		1		−			

− = variable not entered in the equation because bivariate relationship. ‡ = variable removed from equation due to collinearity. p > .25. * = p ≤ .05 ** = p ≤ .01.

Table 14 continued.

Linear regression using demographic and mental health variables to predict executive domain NPZ and factor neuropsychological scores

	Factor Scores											
	Slow Processing (n = 155)				Executive Inhibition (n = 153)				Decision Making (n = 152)			
Omnibus Tests:	r^2	Adj r^2	f	p	r^2	Adj r^2	f	p	r^2	Adj r^2	f	p
	.184	.145	4.039	.000**	.233	.196	6.372	.000**	.126	.091	3.557	.003**
Parameter Estimates	B	SE	β	p	B	SE	β	p	B	SE	β	p
Constant	-.389	.616	--	.528	-.795	.484	--	.102	-.591	.451	--	.193
Age	.028	.009	.244	.002**	–				–			
Education (years)	-.085	.033	-.209	.012*	.078	.029	.208	.009**	.064	.027	.197	.020*
CES-D Depression	–				-.013	.006	-.154	.036*	–			
STAI - Trait Anxiety	–				–				–			
Black	.218	.195	.103	.265	-.448	.175	-.229	.011*	-.276	.161	-.163	.088
Latino	.407	.194	.184	.038*	-.396	.173	-.194	.023*	-.294	.160	-.166	.068
White	ref		1		ref		1		ref		1	
Other	.230	.326	.057	.482	-.046	.291	-.012	.875	-.280	.268	-.086	.299
< 10,000	.227	.195	.110	.247	ref		1		-.258	.161	-.156	.111
$10,000 - $19,999	.543	.194	.255	.006**	.435	.163	.221	.009**	-.123	.160	-.072	.444
≥ 20,000	ref		1		.386	.175	.194	.029*	ref		1	

– = variable not entered in the equation because bivariate relationship. ‡ = variable removed from equation due to collinearity.
* = p ≤ .05, ** = p ≤ .01.

Table 15.

Pearson, Spearman and partial correlations of individual neuropsychological variables with methamphetamine use variables (N = 156)

Variable		Count	IGT		IGTV		Go/No-go		
	n	Span	Total	Learn	Total	Learn	FA^{v}	MO^{vo}	RT^{v}
Years of Meth Use$^{\&}$	155	.042	.106†	-.038	.149†	-.028	.080	-.063	-.113†
CIDI-SAM Meth Dependence	154	-.097†	.096†	.050	.082	.167*	-.091	.069	.181*
Severity of Dependence	156	.028	.118†	.033	.083	.132†	.011	.092	.066
Days of meth use	156	-.058	-.021	-.017	.065	-.148†	-.059	-.096†	-.006

		WCS					Trails		
	n	PE^{v}	NPE^{v}	CatCo	FtMS^{v}	Switch^{v}	SE^{vo}	NaL^{v}	Motor^{v}
Years of Meth Use$^{\&}$	155	.138†	-.031	.048	.080	.038	-.022	.065	.047
CIDI-SAM Meth Dependence	154	.041	-.085	-.053	-.140†	-.097†	.037	.021	-.059
Severity of Dependence	156	-.073	-.115†	-.113†	-.020	-.084	.022	-.062	-.090
Days of meth use	156	-.046	-.072	-.074	.069	.119†	.167*	-.112†	.113†

^{v} = Variables are reverse coded so that better performance is the higher value. ^{o} = Variables are ordinal, Spearman rho is used.
$^{\&}$ = Partial correlation controlling for age. † = $p \leq .25$ * = $p \leq .05$ ** = $p \leq .01$.

Table 16.

Hierarchical models using methamphetamine use variables to predict individual neuropsychological variables controlling for demographic and mental health variables

	IGTV Learning (*n* = 154)				Go Nogo RT^{v} (*n* = 153)				Trails SE^{vo} (*n* = 153)			
Step one:	Δr^2 =	.044	p =	.151	Δr^2 =	.117	p =	.000**	χ^2 =	22.049	p =	.000**
Parameter Estimates	B	SE	β	p	B	SE	β	p	B	SE	Exp (B)	p
Age	–				-1.829	.582	-.263	.002**	–			
Education (years)	.472	.376	.104	.212	–				.084	.040	1.087	.038*
CES-D Depression	–				-1.281	.467	-.236	.007**	–			
STAI - Trait Anxiety	–				–				–			
Black	-4.250	2.231	-.180	.059	–				-.473	.240	.613	.043*
Latino	-4.113	2.260	-.166	.071	–				-.286	.241	.767	.275
White	ref		1		–				ref		1	
Other	-5.536	3.776	-.123	.145	–				-.147	.402	.779	.545
< 10,000	–				–				ref		1	
$10,000 - $19,999	–				–				.317	.220	1.373	.150
≥ 20,000	–				–				.414	.244	1.512	.090
Step two:	Δr^2 =	.116	p =	.009**	Δr^2 =	.046	p =	.018*	χ^2 =	29.417	p =	.000**
Years of Meth Use	–				-.350	.657	-.045	.595	–			
CIDI-SAM Meth	.924	.518	.171	.077	6.977	2.497	.239	.006**	–			
SDS Meth	.271	.345	.075	.433	–				–			
Meth Use Days	-.422	.168	-.202	.013*	–				.055	.023	1.057	.010**

– = variable not entered in the equation. * = p ≤ .05 ** = p ≤ .01.

Tables 17.

Pearson correlations of executive domain NPZ and factor neuropsychological scores with methamphetamine use variables (N = 156)

Variable		Executive		Factor Scores				
	n	NPZ	WCSTP	MI	SP	EI	SA	DM
Years of Meth Use[&]	155	.184*	.050	-.076	-.069	-.002	-.098†	.094†
CIDI-SAM Meth Dependence	154	.051	-.047	.085	-.032	-.096†	.156†	.095†
Severity of Dependence	156	.060	-.106†	-.012	.054	-.053	.080	.079
Days of meth use	156	-.042	-.079	.057	.109†	.199*	-.015	-.040

[&] = Partial correlation controlling for age. † = $p \leq .25$ * = $p \leq .05$ ** = $p \leq .01$.

Table 18.

Hierarchical models using methamphetamine use variables to predict executive domain NPZ and factor neuropsychological variables controlling for demographic and mental health variables

	Executive Domain				Factor Scores							
	NPZ (*n* = 154)				WCST Performance (*n* = 155)				Slow Processing (*n* = 155)			
Step one:	Δ r2 =	.200	p =	.000**	Δ r2 =	.124	p =	.011*	Δ r2 =	.184	p =	.000**
Parameter Estimates	B	SE	β	p	B	SE	β	p	B	SE	β	p
Age	-.016	.005	-.248	.003**	-.019	.009	-.162	.046*	.027	.009	.234	.002**
Education (years)	.057	.019	.252	.002**	.059	.035	.146	.090	-.090	.033	-.222	.007**
CES-D Depression	.007	.004	.133	.081	–				–			
STAI - Trait Anxiety	–				-.016	.014	-.099	.243	–			
Black	-.050	.108	-.043	.643	-.407	.206	-.192	.049*	.228	.194	.107	.241
Latino	-.289	.106	-.236	.007**	-.364	.203	-.165	.075	.434	.193	.196	.026*
White	ref		1		ref		1		ref		1	
Other	-.346	.178	-.154	.054	-.511	.340	-.126	.135	.163	.325	.040	.617
< 10,000	-.177	.178	-.154	.104	-.198	.209	-.096	.344	.232	.193	.112	.233
$10,000 - $19,999	-.220	.107	-.186	.041*	-.177	.205	-.083	.389	.544	.192	.255	.005**
≥ 20,000	ref		1		ref		1		ref		1	
Step two:	Δ r^2 =	.027	p =	.026*	Δ r^2 =	.004	p =	.442	Δ r2 =	.020	p =	.058
Years of Meth Use	.013	.006	.186	.026*	–				–			
CIDI-SAM Meth	–				–				–			
SDS Meth	–				-.021	.0274	-.065	.442	–			
Meth Use Days	–				–				.027	.014	.144	.058

– = variable not entered in the equation. * = p ≤ .05 ** = p ≤ .01.

Table 18 continued

Hierarchical models using methamphetamine use variables to predict executive domain NPZ and factor neuropsychological variables controlling for demographic and mental health variables

	Factor Scores											
	Executive Inhibition (*n* = 153)				Sustained Attention (n = 153)				Decision Making (*n* = 153)			
Step one:	Δ r2 =	.227	p =	.000**	Δ r2 =	.079	p =	.000**	Δ r2 =	.126	p =	.003**
Parameter Estimates	B	SE	β	p	B	SE	β	p	B	SE	β	p
Age	–				–				–			
Education (years)	.078	.030	.189	.019*	-.024	.009	-.229	.009**	.065	.028	.200	.021*
CES-D Depression	-.011	.007	-.130	.117	–				–			
STAI - Trait Anxiety	–				–				–			
Black	-.435	.176	-.221	.015*	–				-.261	.164	-.153	.114
Latino	-.364	.174	-.178	.038*	–				-.297	.162	-.163	.069
White	ref		1		–				ref		1	
Other	-.109	.292	-.029	.10	–				-.288	.270	-.089	.288
< 10,000	ref		1		–				-.290	.164	-.175	.078
$10,000 - $19,999	.434	.165	.220	.009**	–				-.131	.162	-.077	.420
≥ 20,000	.027	.013	.152	.030*	–				–			
Step two:	Δ r2 =	.021	p =	.142	Δ r2 =	.017	p =	.256	Δ r^2 =	.001	p =	.764
Years of Meth Use	–				-.009	.010	-.080	.352	.003	.008	.033	.675
CIDI-SAM Meth	-.014	.038	-.030	.719	.049	.034	.113	.157	.049	.030	.127	.106
SDS Meth	–				–				–			
Meth Use Days	.027	.013	.152	.049*	–				–			

– = variable not entered in the equation. * = p ≤ .05 ** = p ≤ .01.

Table 19.

Pearson, Spearman and partial correlations of individual neuropsychological variables with disease progression variables and medication adherence (N = 156)

Variables	Count	IGT		IGTV		Go-Nogo		
	Span	Total	Learn	Total	Learn	FA[v]	MO[vo]	RT[v]
Years Since Diagnosis[&]	-.092	-.072	-.033	.130†	-.019	-.069	-.075	.027
Years on ART[$]	.038	.074	-.019	-.003	-.030	.131†	.099†	-.001
# of Diff Regimens[$]	.021	-.049	-.029	.028	.034	-.118†	-.020	.009
Log Viral Load	-.005	-.153†	.004	.046	-.088	-.051	-.236**	-.167*
CD4 Count	.091	.102†	.034	.047	.161*	.138†	.326**	.160*
% adherence (TLFB)	.079	.115†	.036	.062	.104†	.123†	.169*	-.007
% adherence (VAS)	.107†	.171*	.052	.037	.136†	.133†	.242**	-.018

	WCST					Trails		
	PE[v]	NPE[v]	CatCo	FtMS[v]	Switch[v]	SE[vo]	NaL[v]	Motor[v]
Years Since Diagnosis[&]	.044	-.013	-.023	-.154†	-.027	-.044	-.092	-.002
Years on ART[$]	.062	.044	.081	.101†	-.016	.046	-.051	-.024
# of Diff Regimens[$]	.023	.041	.089	.107†	.078	.068	.053	-.028
Log Viral Load	-.067	-.025	-.031	.034	-.040	.088	-.148†	.037
CD4 Count	.010	-.065	-.048	.035	.071	.094†	.137†	.012
% adherence (TLFB)	.086	.027	.084	-.020	.161*	.041	.172*	-.072
% adherence (VAS)	.057	.072	.136†	.046	.140†	.001	.146†	-.038

[v] = variables are reverse coded so that better performance is the higher value. [o] = Variables are ordinal, Spearman rho is used. [&] = examinations with years since diagnosis is a partial correlations controlling for age. [$] = examinations with years on ART is a partial correlations controlling for the above variable. † = $p \leq .25$ * = $p \leq .05$ ** = $p \leq .01$

Table 20.

Hierarchical models using disease progression and adherence variables to predict individual neuropsychological variables controlling for demographic and mental health variables

	GNG MO^{vo} (n = 156)				Go Nogo RT^{v} (n = 156)				Trails Switch^{v} (n = 155)			
Step one:	χ^2 =	12.29	p =	.015*	Δ r2 =	.124	p =	.011*	Δ r2 =	.305	p =	.000**
Parameter Estimates	B	SE	Exp B	p	B	SE	β	p	B	SE	β	p
Age	–				-2.162	.545	-.300	.000**	-.992	.343	-.203	.004**
Education (years)	-.005	.039	.995	.906	–				4.407	1.316	.254	.001**
CES-D Depression	–				-.786	.428	-.139	.068	-.660	.271	-.171	.016*
STAI - Trait Anxiety	–				–				–			
Black	-.393	.252	.675	.118	–				-23.31	7.913	-.257	.004**
Latino	-.558	.243	.572	.022*	–				-25.86	7.793	-.274	.001**
White	ref		1		–				ref		1	
Other	-.558	.397	.572	.159	–				-7.254	12.88	-.042	.574
< 10,000	–				–				ref		1	
$10,000 - $19,999	–				–				14.75	7.227	.162	.043*
≥ 20,000	–				–				20.10	7.814	.218	.011*
Step two:	χ^2 =	27.42	p =	.001**	Δ r^2 =	.033	p =	.017*	Δ r2 =	.019	p =	.131
Years on ART	-.004	.019	.995	.906	–				–			
# of Diff Regimens	.013	.042	.996	.836	–				–			
Log Viral Load	‡				-8.550	3.530	-.183	.017*	–			
CD4 Count	.001	.0004	1.001	.001**	‡				–			
% adherence (TLFB)	‡				–				.329	.164	.229	.044*
% adherence (VAS)	.006	.004	1.006	.119	–				-.329	.203	-.189	.108

– = variable not entered in the equation. ‡ = variable removed from equation due to collinearity. * = p ≤ .05 ** = p ≤ .01.

Table 21.

Pearson correlations of executive domain NPZ and factor neuropsychological scores with disease progression variables and medication adherence (n = 156)

Variables	Executive	Factor Scores					
	NPZ	WCSTP	MI	SP	EI	SA	DM
Years Since Diagnosis[&]	-.026	-.025	.071	.092	-.004	-.001	-.045
Years on ART[$]	.103†	.146†	-.137†	.041	.002	.037	.035
# of Diff Regimens[$]	-.020	.075	.114†	-.056	.068	-.015	.001
Log Viral Load	-.082	-.039	.067	.154†	.015	-.212**	-.084
CD4 Count	.138†	-.036	-.156†	-.143†	.051	.241**	.102†
% adherence (TLFB)	.167*	.089	-.135†	-.179*	.111†	.054	.118†
% adherence(VAS)	.180*	.142†	-.145†	-.161*	.077	.048	.165*

[&] = examinations with years since diagnosis is a partial correlations controlling for age. [$] = examinations with years on ART are partial correlations controlling for the above variable. † = $p \leq .25$, * = $p \leq .05$, ** = $p \leq .01$.

Table 22.

Hierarchical models using disease progression and adherence variables to predict executive domain NPZ and factor neuropsychological variables controlling for demographic and mental health variables

	Executive Domain NPZ (n = 155)				Factor Scores: WCS Performance (n = 155)				Factor Scores: Motor Impulsivity (n = 156)			
Step one:	Δ r2 =	.201	p =	.000**	Δ r2 =	.124	p =	.011*	Δ r2 =	.092	p =	.024*
Parameter Estimates	B	SE	β	p	B	SE	β	p	B	SE	β	p
Age	-.017	.006	-.263	.003**	-.026	.011	-.231	.014*	-.004	.010	-.037	.691
Education (years)	.065	.018	.285	.001**	.066	.035	.162	.060	-.054	.033	-.133	.108
CES-D Depression	.009	.004	.186	.015*	–				‡			
STAI - Trait Anxiety	–				-.019	.013	-.113	.165	-.030	.013	-.185	.022*
Black	.024	.113	.020	.830	-.341	.212	-.161	.109	-.100	.208	-.047	.632
Latino	-.229	.109	-.186	.037*	-.337	.206	-.152	.103	.181	.205	.082	.379
White	ref		1		ref		1		ref		1	
Other	-.260	.109	-.115	.150	-.471	.341	-.116	.169	.665	.340	.164	.052
< 10,000	-.126	.109	-.109	.249	-.187	.208	-.090	.370	–			
$10,000 - $20,000	-.185	.108	-.156	.087	-.195	.205	-.091	.343	–			
> 20,000	ref		1		ref		1		–			
Step two:	Δ r^2 =	.037	p =	.082	Δ r^2 =	.018	p =	.230	Δ r2 =	.027	p =	.112
Years on ART	.013	.008	.137	.115	.025	.016	.146	.110	-.016	.015	-.091	.314
# of Diff Regimens	–								‡			
Log Viral Load	–								–			
CD4 Count	.000	.000	.042	.535					‡			
% adherence (TLFB)	‡				–				–			
% adherence (VAS)	.004	.002	.158	.047*	.003	.003	.062	.453	-.007	.003	-.160	.055

– = variable not entered in the equation. ‡ = variable removed from equation due to collinearity. * = p ≤ .05 ** = p ≤ .01.

Table 22 continued.

Hierarchical models using disease progression and adherence variables to predict executive domain NPZ and factor neuropsychological variables controlling for demographic and mental health variables

	Factor Scores							
	Slow Processing (*n* = 155)				Executive Inhibition (*n* = 153)			
Step one	Δ r2 =	.184	p =	.000**	Δ r2 =	.227	p =	.000**
Parameter Estimates	B	SE	β	p	B	SE	β	p
Age	.029	.009	.253	.001**	–			
Education (years)	-.079	.033	-.195	.019*	.077	.030	.205	.011*
CES-D Depression	–				-.013	.006	-.151	.043*
STAI - Trait Anxiety	–				–			
Black	.150	.200	.071	.454	-.439	.176	-.224	.014*
Latino	.366	.196	.165	.064	-.391	.174	-.192	.026*
White	ref		1		ref		1	
Other	.182	.326	.045	.578	-.032	.293	-.009	.914
< 10,000	.227	.195	.110	.245	ref		1	
$10,000 - $20,000	.508	.193	.238	.010**	.385	.176	.224	.008**
> 20,000	ref		1		.440	.164	.194	.030
Step two	Δ r2 =	.021	p =	.152	Δ r2 =	.001	p =	.650
Years on ART	–				–			
# of Diff Regimens	–				–			
Log Viral Load	‡				–			
CD4 Count	.000	.000	-.046	.561	–			
% adherence (TLFB)	-.451	.258	-.135	.083	.105	.230	.034	.650
% adherence (VAS)	‡				–			

– = variable not entered in the equation. ‡ = variable removed from equation due to collinearity. * = $p \leq .05$ ** = $p \leq .01$.

Table 22 continued.

Hierarchical models using disease progression and adherence variables to predict executive domain NPZ and factor neuropsychological variables controlling for demographic and mental health variables

	Factor Scores							
	Sustained Attention (n = 153)				Decision Making (*n* = 153)			
Step one	Δ r2 =	.069	p =	.001**	Δ r2 =	.126	p =	.003**
Parameter Estimates	B	SE	β	p	B	SE	β	p
Age	–				–			
Education (years)	-.027	.008	-.251	.001**	.063	.027	.193	.023*
CES-D Depression	–				–			
STAI - Trait Anxiety	–				–			
Black	–				-.219	.169	-.129	.199
Latino	–				-.251	.164	-.142	.128
White	–				ref		1	
Other	–				-.262	.271	-.081	.336
< 10,000	–				-.249	.163	-.150	.129
$10,000 - $20,000	–				-.100	.161	-.059	.534
> 20,000	–				–			
Step two	Δ r2 =	.068	p =	.003**	Δ r^2 =	.008	p =	.510
Years on ART	–				–			
# of Diff Regimens	–				–			
Log Viral Load	‡				–			
CD4 Count	.001	.000	.230	.003**	.000	.000	.050	.540
% adherence (TLFB)	–				–			
% adherence (VAS)	–				.002	.003	.075	.362

– = variable not entered in the equation. ‡ = variable removed from equation due to collinearity. * = p ≤ .05 ** = p ≤ .01.

Table 23.

ANOVA and χ^2 analyses comparing participants with 80% adherence or greater to those with less than 80% adherence

Variable		Percent Dose Adherence (TLFB)					Percent Dose Adherence (VAS)				
		< 80% (n = 70)		≥ 80% (n = 86)			< 80% (n = 88)		≥ 80% (n = 68)		
		M	SD	M	SD	*p*	M	SD	M	SD	*p*
Adherence	% adherence (TLFB)	46.7	28.6	91.6	5.9	.00**	58.4	32.6	88.3	12.3	.00**
	% adherence (VAS)	51.1	24.8	80.6	14.1	.00**	51.8	21.8	87.5	5.8	.00**
Meth Use	Years of Meth Use	9.6	7.9	10.2	7.7	.67	10.3	8.5	9.4	6.7	.46
	CIDI-SAM Meth Dependence Score	3.9	2.2	3.5	2.0	.21	4.0	2.1	3.2	1.9	.02*
	Severity of Dependence	5.3	3.1	5.0	3.1	.61	5.5	3.2	4.7	2.9	.09
	Days of Meth Use (TLFB)	5.8	5.0	5.3	5.6	.55	6.1	5.5	4.7	5.0	.12
NPZ	Executive Domain	-.092	.598	.075	.518	.06	-.082	.589	.106	.504	.04*
Factor Analysis	WCS Performance	-.139	1.046	.114	.951	.12	-.140	1.062	.182	.887	.05*
	Motor Impulsivity	.142	1.100	-.116	.899	.11	.072	1.150	-.093	.759	.31
	Slowness of Processing	.128	1.147	-.104	.848	.15	.122	1.111	-.158	.808	.08
	Executive Inhibition	-.122	.963	.100	.875	.13	-.141	1.013	.182	.750	.03*
	Sustained Attention	-.109	.933	.089	.908	.18	-.071	.912	.092	.934	.28
	Decision Making	-.059	.805	.048	.795	.41	-.145	.808	.188	.752	.01**

* = p ≤ .05 ** = p ≤ .01

Table 23 continued.

ANOVA and χ^2 analyses comparing participants with 80% adherence or greater to those with less than 80% adherence

Variable		Percent Dose Adherence (TLFB)					Percent Dose Adherence (VAS)				
		< 80% (n = 70)		≥ 80% (n = 86)			< 80% (n = 88)		≥ 80% (n = 68)		
		M	SD	M	SD	*p*	M	SD	M	SD	*p*
Counting	Span Score	29.0	21.1	32.9	19.5	.24	29.2	19.8	33.8	20.8	.16
IGT	Total	5.7	26.6	8.7	28.4	.50	3.6	27.1	12.3	27.6	.05*
	Learning	10.8	9.8	11.5	12.0	.67	9.7	10.5	13.1	11.5	.06
	Variant Total	10.5	33.1	14.0	37.8	.55	10.8	30.1	14.6	42.0	.51
	Variant Learning	8.3	10.5	9.1	11.6	.66	7.7	11.0	10.0	11.3	.21
WCS	Perseverative Errors[v]	45.5	14.6	48.6	14.2	.19	46.2	15.4	48.5	13.0	.31
	Non-perseverative Errors[v]	49.3	16.1	52.8	13.8	.15	50.1	15.4	52.6	14.2	.32
	Categories Completed	3.5	2.3	4.0	2.1	.13	3.5	2.4	4.1	2.0	.05*
	Failure To Maintain Set[v]	4.9	1.4	4.9	1.5	.99	4.7	1.5	5.0	1.3	.19
Go-Nogo	False Alarms [v]	45.8	16.2	49.2	13.4	.16	46.9	16.9	48.8	11.4	.43
	Reaction Time[v]	188.6	64.7	193.9	61.7	.60	190.1	62.8	193.4	63.5	.75
D-KEFS Trails	Switching[v]	125.2	45.4	137.0	39.7	.08	123.5	47.3	142.3	33.2	.01**
	Numbers and Letters[v]	42.2	14.1	44.8	10.2	.18	42.4	13.6	45.2	9.7	.15
	Motor Speed[v]	44.1	10.2	41.0	13.1	.11	43.1	11.6	41.4	12.5	.36
					χ^2	p				χ^2	*p*
Trails	Errors in Switching[ov]				5.13	.16				3.15	.370
GNG	Missed Opportunities[ov]				6.61	.04*				11.18	.004**

* = p ≤ .05 ** = p ≤ .01

Table 24.

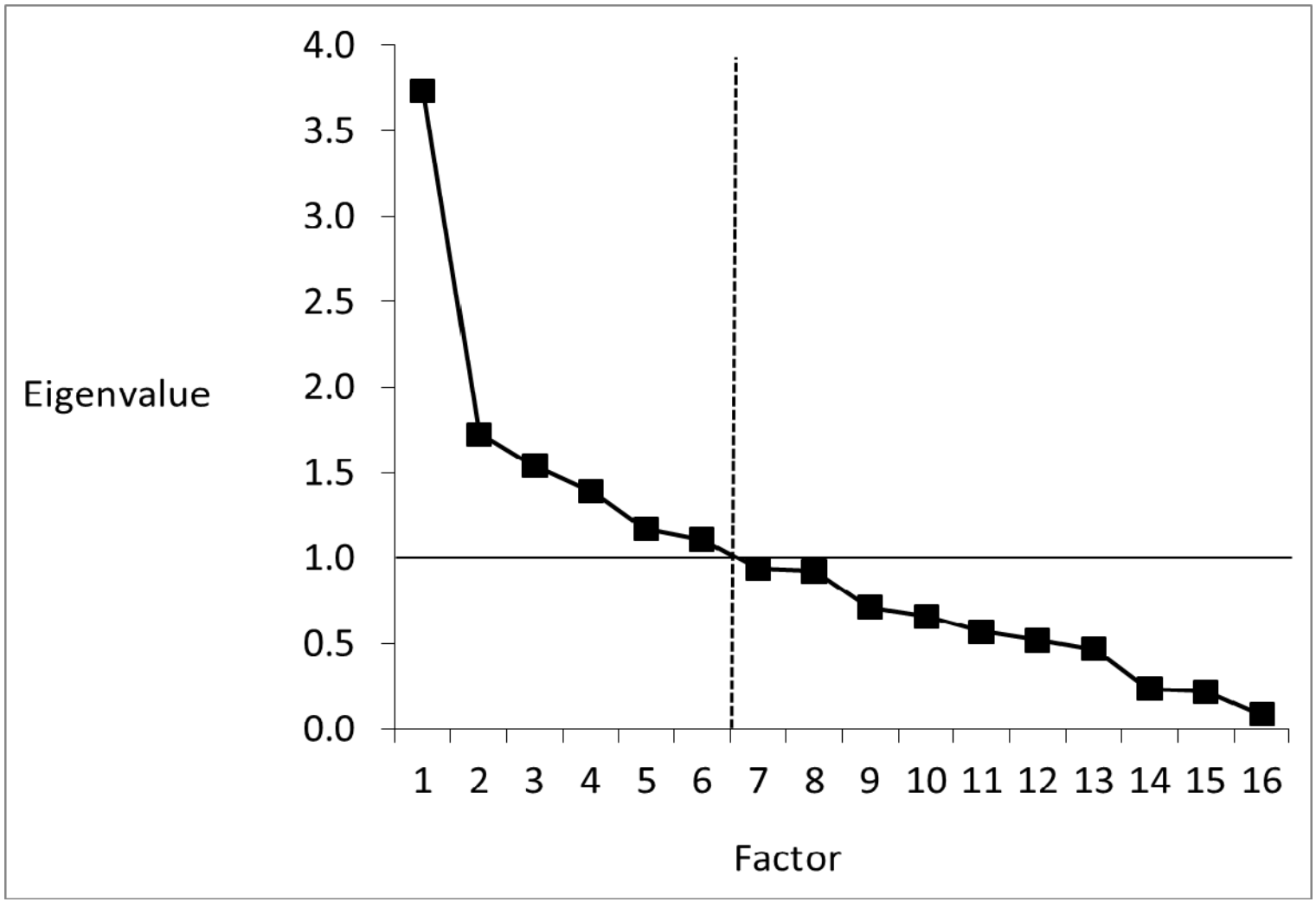
Logistic regression models using neuropsychological variables to predict participants with >80% adherence as measured by the VAS controlling for CD4 count, methamphetamine use and methamphetamine dependence (n = 153)

	Step one:	r^2 =	.065	p =	.022*	r^2 =	.065	p =	.022*	r^2 =	.065	p =	.022*
	Parameter Estimates	B	SE	Exp(B)	p	B	SE	Exp(B)	p	B	SE	Exp(B)	p
	CIDI-SAM Meth Dependence Score	-.195	.085	.823	.022*	-.193	.089	.824	.029*	-.219	.091	.803	.016*
	TLFB Meth Use	-.039	.034	.961	.245	-.050	.036	.951	.154	-.040	.035	.961	.261
	Step two:	Δr^2 =	.033	p =	.043*	Δr^2 =	.090	p =	.010**	Δr^2 =	.134	p =	.004**
	Parameter Estimates	B	SE	Exp(B)	p	B	SE	Exp(B)	p	B	SE	Exp(B)	p
Model 1:	Executive NPZ	.623	.313	1.864	.046*								
Model 2:	WCST Performance					.100	.190	1.106	.597				
	Trails Switching					.365	.211	1.440	.083				
	Decision Making					.496	.247	1.641	.039*				
Model 3:	IGT Total									.006	.005	1.006	.248
	WCST CatCo									.074	.085	1.010	.385
	Trails Switching[v]									.006	.005	1.006	.248
	GNG 0-1 MO									ref		1	
	GNG 2-7 MO									-.404	.442	.668	.362
	GNG ≥8 MO									-1.28	.506	.278	.020*

* = $p \leq .05$ ** = $p \leq .01$.

Figure 1.

Scree plot of factor solution



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