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UNIVERSITY OF CALIFORNIA, SAN DIEGO
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Theory of Mind and Risk Behavior in Individuals
with HIV and Methamphetamine Dependence

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Clinical Psychology

by

Jordan E. Cattie

Committee in charge:

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2015

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University of California, San Diego

San Diego State University

2015

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ABSTRACT OF THE DISSERTATION

Theory of Mind and Risk Behavior in Individuals
with HIV and Methamphetamine Dependence

by

Jordan E. Cattie

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2015

San Diego State University, 2015

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Methamphetamine (MA) dependence and HIV are associated with preferential injury to fronto-striatal-thalamo-cortical circuits and additive deleterious neurocognitive effects. However, their effects on social cognitive processes dependent upon these circuits (e.g., Theory of Mind; ToM) remain unknown. ToM describes the ability to mentalize beliefs and emotions of others in order to respond adaptively. As many HIV transmission risk scenarios are interpersonal, poorer ToM may bias individuals toward increased engagement in risk behaviors. This dissertation project aimed to: 1) examine separate and combined effects of HIV and

MA on ToM; 2) evaluate relationships between ToM and risk behaviors; and 3) examine these relationships in the context of decision-making and other executive functions.

Thirty-three HIV+/MA+, 32 HIV+/MA-, 31 HIV-/MA+, and 30 HIV-/MA- individuals completed ToM measures (Mind in the Eyes Task, Combined Stories Task, Questionnaire of Cognitive and Affective Empathy; QCAE), a psychiatric interview, self-report risk behavior questionnaires, and a full neuropsychological battery. Jonckheere-Terpstra tests evaluated whether results were consistent with an additive effect on ToM. Regression models were used to test for a moderating effect of decision-making on the relationship between ToM and HIV transmission risk behaviors in HIV+ individuals (independent of other clinical factors and executive functioning performance).

Jonckheere-Terpstra tests were significant for Mind in the Eyes performance (healthy individuals outperformed each single-risk group, and dual-risk groups performed most poorly) and approached significance on Combined Stories Task items. Self-reported ToM (QCAE) did not significantly differ. HIV+MA+ individuals engaged in significantly elevated rates of sexual and substance-related risk behaviors. In HIV+ individuals, MA group status was the only significant independent predictor of risk behavior; ToM performance (Eyes RT, Eyes # correct) approached significance. A moderating role of decision-making was not supported by the data. These results held in the context of executive functioning performance.

These analyses indicate that HIV infection and methamphetamine dependence are associated with poorer cognitive and affective ToM. Dual-risk groups performed more poorly than single-risk groups on ToM measures, demonstrated poorer decision-making, and engaged in elevated rates of risk behaviors. In HIV+

individuals, MA status robustly predicted risk behavior engagement, although aspects of ToM appear to play a role.

INTRODUCTION

Prevalence of HIV Infection and Methamphetamine Dependence in the General Population

According to estimates from the 2009 UNAIDS report on the global AIDS epidemic, there were approximately 33.3 million people living with HIV worldwide at the end of 2008 (Joint United Nations Programme on HIV/AIDS, UNAIDS; 2008), with over 1 million people living with HIV/AIDS in the United States (Hall et al., 2008). In the U.S., HIV is most commonly transmitted via specific sexual behaviors (anal or vaginal sex) or by sharing needles with an infected person. Less frequently, the virus is transmitted via oral sex, during childbirth, via breastfeeding, or exposure to infected blood or blood products. Due to rigorous mandated testing, it is unlikely that individuals in the U.S. will contract the virus through blood transfusions or organ transplant (CDC, 2012). Certain individuals are at increased risk for contracting the virus as a result of their engagement in multiple transmission risk behaviors, including injection drug users, who account for 30% of HIV infections outside of Africa (UNAIDS, 2006). Approximately 15-20% of injection drug users in the United States and Canada are infected with HIV, and are at increased risk for transmitting the virus via elevated rates of risky injecting practices (e.g., re-use of equipment, hurried injecting, and injecting when on "binges;" Mathers et al., 2008). One substance of abuse that is particularly risky in this regard is methamphetamine, which has been implicated as a predictor of HIV seroconversion (Chesney, Barrett, & Stall, 1998) and is also more broadly associated with increased rates of high risk sexual behavior that can heighten the risk of acquiring or transmitting sexually transmitted infections (STIs) and HIV disease (Kral et al., 2001).

Amphetamines are the second most commonly used illicit drug worldwide (United Nations Office on Drugs and Crime, 2009). Though multiple types exist, methamphetamine and amphetamine are reportedly the most off-used stimulants (United Nations Office on Drugs and Crime, 2009), most commonly via injection and smoking to provide greater bioavailability, faster onset, and higher peak effects relative to other modalities. In a 2005 survey, approximately 10 million people (or 4.5% of the U.S. population) reported using MA at least once in their lives as of 2005, and 1.4 million persons reported using MA in the past year (Substance Abuse and Mental Health Services Administration, 2006). Since this time, MA use appears to have plateaued somewhat through 2008 (decreasing from 731,000 past-month users in 2006 to 314,000 in 2008) before increasing again in 2009 (to 502,000 past-month users; Substance Abuse and Mental Health Services Administration, 2009). The number of first-time users also increased during this period, from 95,000 in 2008 to 154,000 in 2009 (SAMHSA, 2009). While MA use was more of a national phenomenon in the early to mid 2000s, the latest data suggest more regional specificity and a return to its more traditional rates of concentrated use in the Midwest (.5% of the population), South (.7%), and West (1.6%; SAMHSA, 2006). MA-related emergency room visits have continued to increase, and MA treatment admissions per 100,000 individuals were 68 nationally, 218 in California as of 2005 (SAMHSA, 2007). The economic cost associated with the burden of addiction, premature death, and drug treatment for MA is currently estimated at 23.4 billion dollars (Nicosia, Pacula, Kilmer, Lundberg, & Chiesa, 2009). Dependence typically develops following a period of sustained regular use, and increases the likelihood that users will transition to injecting, thereby increasing their HIV transmission risk (Darke, Cohen, Ross, Hando,

& Hall, 1994) and likelihood of contracting Hepatitis C (Shoptaw et al., 2008). The potential for dependence may be higher in the crystalline form of MA due to higher potency, purity, and likelihood of smoking and injection use (Degenhardt et al., 2010). It is clear that both conditions remain leading worldwide causes of disability, morbidity, and mortality (UNAIDS, 2009).

Co-Occurrence of HIV and Abuse of MA

MA abusers have significantly elevated infection rates for a number of infectious diseases, including HIV and hepatitis C, as a result of both injection drug use (i.e., needle sharing) and risky sexual behavior (e.g., unprotected sex). As such, MA users are at higher risk for HIV, and MA abuse is more prevalent in HIV+ individuals than in the general population. MA is one of the most common drugs of abuse among HIV+ individuals, as well as the most common drugs of abuse in those at highest risk for contracting HIV disease (Woody et al., 1999). While nationally approximately .6% of the population reports having used methamphetamine in the last year, prevalence of MA use disorders are much higher in HIV+ individuals. A recent multicenter, prospective, observational study by the CHARTER group (2010) observed a prevalence of approximately 17% lifetime and approximately 1-2% current MA use disorders among 15555 HIV+ individuals (Heaton et al., 2010). MA may increase the likelihood of HIV transmission through facilitating prolonged intercourse with more likelihood of vaginal or rectal trauma; additionally, MA may dry mucosa, leading to abrasions that can provide entry for HIV during sexual activity (CDC, 2009).

Though intravenous use confers direct risk of HIV disease transmission, MA has been implicated as a predictor of HIV seroconversion in certain groups whether used intravenously or via other administration methods such as smoking (Chesney et

al., 1998) potentially due to common subjective effects of MA (e.g., increased sexual arousal with reduced inhibition). Use of MA during recent sexual encounters has been associated with other HIV risk behaviors as well (e.g., injection drug use; Ghanem et al., 2011). In addition, MA users may exchange sex for money or drugs while intoxicated, leading to other MA-related risk factors for acquiring and transmitting HIV (Molitor, Truax, Ruiz, & Sun, 1998).

Risk factors for unprotected sexual activity and other HIV transmission behaviors are known to differ by gender, sexual identity, geographic and cultural borders (e.g., Courtenay-Quirk et al., 2008). As such, rates of HIV acquisition differ across subpopulations within the U.S., and the impact of MA abuse may disproportionately impact certain groups. For example, 61% of new HIV infections in the United States are among men who have sex with men (MSM; CDC, 2009). Unprotected anal sex is a primary risk factor for HIV transmission in this group, and is closely associated with methamphetamine use (CDC, 2007). In MSM who use MA, the incidence of HIV is more than double that of MSM who do not, and increased intensity of MA use has been associated with increased HIV risk (Rajasingham et al., 2012; Shoptaw & Reback, 2006). MSM who use MA may increase their risk factors (e.g., use condoms less often, have more sex partners, and engage in unprotected receptive anal intercourse) and HIV-related drug use risk factors (e.g., injecting vs. smoking or snorting; Buchacz et al., 2005). It is important to note that heterosexual individuals who are under the influence or chronically use MA are also at increased risk for engagement in practices that put them at risk for HIV and other STIs (Molitor et al., 1998), but the baseline prevalence of HIV and risk behaviors tends to be higher in MSMs, resulting in greater risk for transmission (CDC, 2009).

Despite the substantial public health risk conferred by HIV+ individuals who use MA, most harm reduction efforts are focused upon reducing injection risk or increasing condom use versus multiple patterns of risky use. Early intervention and preventive efforts are uncommon (Degenhardt et al., 2010). While social networks and norms have been linked to HIV risk behavior (Latkin, Kuramoto, Davey-Rothwell, & Tobin, 2010), little is known about the prevalence and extent of social cognitive deficits and their implications for HIV transmission risk behaviors.

Neurovirology of HIV Infection

HIV is a lentivirus that exerts pathogenic effects in both the immune and central nervous systems. The virus causes an acquired immune deficiency, primarily due to a depletion of CD4 lymphocytes. The virus infiltrates the central nervous system (CNS) early in the course of the disease (Grant, Wiley, & Wilkenstein, 1987), most likely via trafficking of infected cells (e.g., monocytes) across the blood-brain barrier. This results in neurodegeneration of specific cellular populations and pathways that regulate cognitive and motor functioning (Everall, Hansen, & Masliah, 2005). Although HIV does not productively infect neurons, HIV-related changes can be observed widely throughout the neocortex, white matter, and deep grey matter (e.g., Ellis, Calero, & Stockin, 2009). In addition to white matter damage, loss of interneurons and damage to microvasculature leads to compromised blood-brain barrier integrity (Everall et al., 2005). The virus also triggers a cascade of neurotoxic molecular events, such as the upregulation of chemokines (Gonzalez-Scarano & Martin-Garcia, 2005). As many as 50% of HIV-infected individuals exhibit HIV-related neuropathologies (Budka et al., 2005), often taking the form of neuronal apoptosis and/or synaptodendritic injury (Ellis, Langford, & Masliah, 2007; Moore et al., 2006).

Brain Systems Affected in HIV

Although HIV-associated neuropathologies are evident in a broad array of brain regions (e.g., hippocampus, parietal cortex) and HIV RNA may be present throughout the central nervous system, the fronto-striatal-thalamo-cortical circuits are among the most commonly affected regions and appear to be specifically vulnerable to the effects of HIV infection (e.g., Aylward et al., 1993). Following infection, the highest concentrations of HIV in the brain are found in the basal ganglia and frontal cortices (e.g., Aylward et al., 1993; Langford, Hurford, Hashimoto, Digicaylioglu, & Masliah, 2005; Wiley et al., 1999). Dendritic damage has been found particularly in the frontal cortex and basal ganglia, which has shown to be a strong correlate of the severity of HIV-associated neurocognitive impairment (Cherner et al., 2002; Ellis et al., 2007; Masliah et al., 1997; Moore et al., 2006). Consequently, HIV is most commonly associated with a profile of neurocognitive deficits similar to other 'subcortical' disorders suggestive of functional disruption of subcortical-frontal brain systems (e.g., Huntington's Disease or Parkinson's Disease; Cohen, 2009).

Neuroimaging studies have found cerebral volume loss (Di Sclafani et al., 1997; Patel et al., 2002; Stout et al., 1998), ventricular enlargement (Chiang et al., 2007), and reductions in caudate volume (Chiang et al., 2007; Di Sclafani et al., 1997), and corpus callosum (Thompson et al., 2006) in the brains of individuals infected with HIV. In addition, thinning of primary sensory, motor, and premotor cortices have been observed (Thompson et al., 2005). Studies using magnetic resonance spectroscopic (MRS) have found metabolic changes indicating inflammation and neuronal damage in frontal white matter (Chang et al., 2002; Paul et al., 2007; Sacktor et al., 2005), frontal gray matter (Lentz et al., 2009), and basal ganglia (Chang et al., 2002; Paul et al., 2007). Imaging studies have also detected correlations between brain abnormalities and poor neuropsychological (NP)

functioning in HIV infection. For example, Paul et al (2008) used magnetic resonance imaging (MRI) to show reductions in caudate and putamen volume that were significantly correlated with measures of executive functions, verbal learning, processing speed and fine motor skills. The authors of the study also used MRS to show that metabolic changes in these two structures correlated with measures of fine motor skills. A functional MRI study showed a significant increase in parietal and frontal lobe activation during an attention task in HIV-infected individuals as compared to HIV-uninfected individuals (Chang et al., 2001). A subsequent study by this group used MRS to show that metabolic changes in frontal white matter was correlated with poor performance on measures of executive function (Chang et al., 2002). More recently, reductions in white matter in the primary and sensory association areas were associated with cognitive deficits among individuals with AIDS (Lepore et al., 2008). Diffusion tensor imaging (DTI) studies have revealed significant correlations between microstructural abnormalities (i.e., increased mean diffusivity and reduced fractional anisotropy), and global cognitive impairment in the corpus callosum (Wu et al., 2006) and internal and external capsules (Gongvatana et al., 2009; Pfefferbaum, Rosenbloom, Adalsteinsson, & Sullivan, 2007).

Taken together, these neuropathology and neuroimaging findings indicate the location and extent of deleterious effects of HIV-infection in the brain. HIV appears to affect frontal cortices and the basal ganglia, and specifically, the white matter tracts connecting these systems. Importantly, the disruption of this fronto-striatal system appears to be associated with the cognitive deficits (e.g., executive dysfunction, slow processing speed) seen in a substantial proportion of HIV-infected individuals.

Neuropsychological Functioning in HIV Infection

While the prevalence of severe forms of HIV-associated neurocognitive disorders (HAND) has decreased since the use of combination antiretroviral therapies (cART) became widespread in the late 1990s, the prevalence and incidence of less severe forms of HAND remains a significant public health concern (Ances & Clifford, 2008). Today, approximately 30% of medically asymptomatic individuals and as many as 50% of symptomatic individuals exhibit neurocognitive impairment (Baldewicz et al., 2004; Heaton et al., 2010). Impairments tend to worsen with disease severity, such that the largest impairments are typically observed in individuals with later stage HIV or AIDS (Grant et al., 1995; Heaton et al., 2011). At the group level, HIV is associated with generally mild-to-moderate deficits in speeded information processing (e.g., Heaton et al., 1995), fine-motor coordination (e.g., Carey et al., 2004), attention/working memory (e.g., Martin et al., 2001), executive functions (e.g., Martin et al., 2004), and memory (Delis et al., 1995). In contrast, deficits in cognitive abilities typically associated with the posterior neocortex, such as constructional praxis, receptive language, and basic visuoperception, are less common in HIV-infected individuals (e.g., Heaton et al., 1995).

Moreover, the functional impact of cognitive decrements in persons infected with HIV is well documented, with nearly half of individuals with HIV-associated neurocognitive impairment experiencing significant functional problems in their everyday lives (Blackstone et al., 2012; Heaton et al., 2004). Specifically, neurocognitively impaired individuals have significant vocational difficulties (e.g., van Gorp, Baerwald, Ferrando, McElhiney, & Rabkin, 1999), increased dependence their instrumental activities of daily living (IADLs; Heaton et al., 2004), poorer adherence to cART (Waldrop-Valverde, Ownby, Wilkie, Mack, Kumar, & Metsch, 2006), greater risk of automobile driving accidents (Marcotte et al., 2004), and lower health-related

quality of life (Rosenbloom et al., 2007). There is preliminary evidence of associations between specific cognitive impairments and engagement in HIV risk behavior (e.g., Gonzalez et al., 2005), though these relationships have been more difficult to establish.

One domain that is especially important for functional outcomes is executive functions. Executive dysfunction remains highly prevalent in HAND (Heaton et al., 2011; Reger, Welsh, Razani, Martin, & Boone, 2002). In fact, among individuals with well-managed HIV disease, rates of impairment in executive functions may have actually increased relative to other cognitive domains, such as information processing speed, in the cART era (Heaton et al., 2011). All told, impaired executive functions are detected in approximately 50% of HIV+ individuals with neurocognitive impairment (Heaton et al., 2011). Executive dysfunction can emerge early in the course of infection (Moore et al., 2011), and the severity of impairment tends to increase with advancing HIV disease (Reger et al., 2002). Although there is no single prototypical pattern of neurocognitive impairment in HIV, it has been argued that executive dysfunction may be a cardinal feature of HAND in the cART era (Dawes et al., 2008). Executive functions rely heavily on the integrity of frontostriatal circuits (Mega & Cummings, 1994), which are commonly affected by HIV-associated neuropathologies (Everall et al., 2005). In HIV-infected populations, deficits have been observed on a variety of different executive functions, including measures of abstraction (Heaton et al., 1995), response inhibition (Tozzi et al., 1999), cognitive flexibility (Carter et al., 2003), planning (Cattie et al., 2012), and decision-making (Martin et al., 2004). These deficits are clinically meaningful in that executive dysfunction is among the strongest predictors of a wide range of everyday functioning

complications, including laboratory functional skills (e.g., medication management; Heaton et al., 2004), medication non-adherence (e.g., Hinkin et al., 2004), automobile driving (Marcotte et al., 2004), and vocational status (e.g., van Gorp et al., 1999; Rabkin et al., 2004).

Decision-making, a cognitive construct under the umbrella of executive functions, is less typically assessed in HIV, but may aid in understanding the adverse functional and health-related consequences of HIV disease (Iudicello et al., in revision). Decision-making connotes the affective and cognitive processes involved in selecting an advantageous response from an array of possible behavioral choices (Bechara, Damasio, & Damasio, 2000). Deficits in decision-making have been observed in HIV+ individuals within (Martin et al., 2004) and outside the context of substance use disorders (Hardy, Hinkin, Levine, Castellon, & Lam, 2006). Moderate deficits have been observed in the context of HAND, particularly under specified and not ambiguous risk conditions (Iudicello et al., in revision). It has been hypothesized that these deficits may be attributable to increased difficulty inhibiting risky choices due to poorer inhibition in the context of potential rewards, or problems remembering the penalties associated with risky selections (Hardy et al., 2006). However, some groups have not observed associations between decision-making performance and attention, working memory, or other aspects of executive functions in HIV (Gonzalez et al., 2005; Hardy et al., 2006; Martin et al., 2004; Wardle, Gonzalez, Bechara, & Martin-Thormeyer, 2010), so it is possible that the cognitive processes involved in decision-making may be distinct from those measured by more traditional neuropsychological measures. Relationships between impaired decision-making and functional outcomes have been less straightforward than other aspects of executive

functions, but some data suggests that decision-making and functional outcomes may be related when affective decision-making is intact.

Importantly, HIV travels with a number of cofactors and comorbidities that can impact and exacerbate the cognitive dysfunction and functional implications of HIV. Among others, these factors include increasing age, HCV, and substance use disorders. As noted above, chronic MA abuse is particularly problematic in HIV+ individuals due to acute as well as long-term potential for increased rates of risk behaviors and, consequently, HIV disease transmission.

Methamphetamine Use and Dependence

MA dependence is a major risk factor for HIV infection, and as such, these two conditions commonly co-occur. MA is one of the most common drugs of abuse among HIV-infected individuals, as well as those at highest risk for HIV infection (NIDA, 2002; Woody et al., 1999). Methamphetamine (MA) is a potent, highly addictive and neurotoxic psychostimulant that is the second most commonly used substance of abuse worldwide, after cannabis (United Nations Office for Drugs and Crime, 2009). Users experience a number of positive sensations due to increased levels of dopamine, including euphoria, increased productivity, hypersexuality, decreased anxiety, and increased energy (Cretzmeyer, Sarrazin, Huber, Block, & Hall; 2003). However, MA dependence is associated with a variety of mental health, physical, occupational, relational, financial and legal problems (Degenhart et al., 2010). Chronic exposure to MA is associated with adverse neural, metabolic, and neuropsychological effects, as well as risk of associated functional declines and risk behaviors that may be compounded in the context of HIV.

Brain Systems Affected in MA Dependence

Methamphetamine is a derivative of the stimulant amphetamine, with structural differences from its parent drug that enable high lipid solubility and more rapid transport across the blood-brain barrier (Barr et al., 2006), resulting in profound central nervous system effects relative to other substances of abuse. MA administration results in the enhanced release of dopamine, norepinephrine and serotonin (Kokoshka et al, 1998) via redistribution from synaptic vesicle sites into the cytoplasm and altered reverse transport of dopamine across the plasma membrane to further increase dopamine concentration in the synapse (Sulzer, Sonders, Poulsen, & Galli, 2005). MA is typically smoked, injected, ingested, or snorted, resulting in an almost immediate "high" that may last for 8-12 hours due to the long half-life of MA. MA intoxication produces excessive excitation of the sympathetic nervous system, resulting in tachycardia, hypertension, and other peripheral effects in addition to MA-associated neurotoxicity to both the dopamine and serotonergic transmitter systems. Specifically, neurotoxic effects are most notable in the nigrostriatal dopaminergic pathways, causing striatal dopamine depletion and destruction of dopamine terminals (vs. cell loss) that impacts functioning in the fronto-striato-thalamo-cortical loops. When administered repeatedly and in large doses, MA has been hypothesized to produce oxidative stress and nitrosative (i.e., increase concentrations of reactive oxygen and nitrogen species) which can impair functioning of mitochondria, and alter functions of proteins critical to cellular homeostasis (Cadet & Krasnova, 2009). MA can also increase the permeability of the blood brain barrier (Kiyatkin et al., 2007) damaging myelin and white matter tracts (Berman et al., 2008), and altering gray matter density (Schwartz et al., 2010) and thereby promote cell injury. Neuroimmune factors, such as cytokines, chemokines, and cellular adhesion molecules may play a critical role in perpetuating neuronal injury and neuropsychiatric impairments

secondary to MA (Narita et al., 2008; Tocharus et al., 2010; Loftis et al., 2009).

Research in rodents and nonhuman primates suggest that these effects are at least partially reversible with time, depending on the amount and dosing of MA exposure (Friedman et al., 1998). Recovery may occur via compensatory increases in enzymatic activity in residual DA nerve terminals, DA axonal regeneration, and collateral DA sprouting (Harvey et al., 2000).

However, imaging evidence suggests that MA also produces lasting depressions in regional cerebral blood flow (e.g., Poleskaya et al., 2011), pathological cerebrovascular changes (e.g., focal areas or arterial narrowing and microhemorrhages; Meredith et al., 2005). In the brains of individuals who have chronically abused MA, MA-related abnormalities are readily observable on imaging, particularly those circuits that are important for executive functions. MA-related abnormalities are noted in gray matter structure of cingulate, limbic and paralimbic regions (e.g., Thompson et al., 2004; Berman et al., 2008; Salo et al., 2009).

Functional abnormalities in regional cerebral glucose metabolism are apparent in the anterior cingulate cortex (ACC), lateral prefrontal cortex, and parietal cortex (Volkow et al., 2001; London et al., 2004; Wang et al., 2004; Berman et al., 2008). It has been suggested that the transition to MA dependence may be facilitated by neural mechanisms; the switch from voluntary to compulsive drug abuse has been postulated to reflect a switch from healthy executive function mediated by the prefrontal cortex to striatal control over drug-taking behaviors (Everitt et al., 2008). A recent study supported this hypothesis, demonstrating hypoactivation in cortical areas important for executive functions (e.g., frontal gyrus, ACC) associated with this loss of cognitive control in MA dependence (Nestor, Ghahremani, Monterosso, & London, 2011).

Neuropsychological Functioning in MA Dependence

Growing evidence suggests that chronic MA use is frequently associated with mild-to-moderate neuropsychological impairments. It appears that approximately 40% of MA dependent individuals demonstrate global neuropsychological impairments (Rippeth et al., 2004). However, it has been more difficult to establish more specific neuropsychological profiles associated with chronic use of MA due to differences in study methodologies (e.g., demographic and substance use characteristics of included individuals), time points relative to MA administration (acute intoxication vs. long-term effects), and inclusion of different tests within NP batteries. A recent meta-analysis (Scott et al., 2007) indicated an overall medium effect size, larger than those that have been associated with cocaine and marijuana use (Jovanovski et al., 2005; Wolfson & Grant, 2003). Significant deficits were observed in a number of cognitive processes that are heavily reliant upon frontostriatal and limbic circuits, including episodic memory, psychomotor functions, complex information processing speed, and executive functions. In addition to neurocognitive difficulties, chronic MA users demonstrate significant psychosocial impairments across various aspects of everyday functioning. For example, Sadek et al. (2007) found that MA dependent adults were more likely to report dependence on instrumental activities of daily living (IADLs), and Henry et al. (2010) reported that MA-dependent individuals performed significantly more poorly on many functional domains as measured by the UCSD Performance-Based Skills Assessment (UPSA), including comprehension, finance, transportation, communication, and medication management, associated with impaired executive performance. Weber et al. (2012) observed that neurocognitive deficits play a particular role in the higher unemployment rates of MA-dependent individuals.

Within the domain of executive functions, MA has been associated with

impulsivity, disinhibition, reduced ability to suppress irrelevant information, difficulty in the strategic components involved in the retrieval of future intentions, risky decision-making, and increased distractibility (Salo et al., 2002; Monterroso, Aron, Cordova, Xu, & London, 2005; Hoffman, Moore, Templin, McFarland, Hitzemann, & Mitchell, 2006; Iudicello et al., 2011). Significant effects of lesser magnitudes were observed for attention/working memory, language, and visuoconstruction (Scott et al., 2007). On the whole, this profile of deficits is consistent with the observed neurotoxic effects of MA, but a number of studies suggest more specific relationships between MA-induced neural abnormalities, aspects of impaired cognitive performance, and maladaptive behaviors. Among them is the observed hypoactivation in areas that are important for executive functions (e.g., right inferior frontal gyrus, supplementary motor cortex/anterior cingulate gyrus) during cognitive control tasks (Nestor et al., 2011). In addition, individuals with histories of MA dependence have been observed to exhibit impaired inhibition, such that they have difficulty withholding/controlling an action or thought, which are thought to impact drug-seeking behavior, aggression, and risky sexual activities associated with MA use (Jentsch & Taylor, 1999; Semple et al., 2010; Watanabe-Galloway et al., 2009). Chronic MA users also demonstrate increased interaction with novel stimuli (Henry et al., 2011). These neurocognitive impairments, particularly those within the domain of executive functions, are widely hypothesized to increase the risk of everyday functioning problems and engagement in high-risk behaviors, both of which are common among MA users.

Importantly, chronic MA users also demonstrate persistent deficits in decision-making (e.g., Paulus et al., 2002; Paulus et al., 2003), which are hypothesized to contribute to continued drug use, risk behaviors, and interfere with engagement in

and completion of treatments for stimulant dependence (Nestor et al., 2008). Recent evidence suggests a direct association between MA-related executive impairments and neurotoxicity in the PFC, which plays a crucial role in decision-making (Sakagami et al., 2006). It has been hypothesized that decision-making dysfunction is due to differences in task-related activation in the dorsolateral and orbitofrontal prefrontal cortex. Consistent with this hypothesis, methamphetamine-dependent individuals demonstrate reduced activation in the dorsolateral prefrontal cortex and failure to activate in the ventromedial cortex (Paulus et al., 2002), as well as reduced activation in the anterior cingulate cortex (ACC), and parietal cortex. Altered fronto-parietal activity is evident during more difficult decisions, which may indicate inefficient processing (Paulus et al., 2007). Relative to abusers of other substances (e.g., alcohol), individuals who identify MA as their drug of choice may exhibit greater deleterious effects on several decision-making measures, though all substance abusers may adapt and maintain successful strategies to a lesser extent than healthy comparison participants (Gonzalez, Bechara, & Martin, 2007). Individuals addicted to MA may choose actions that result in immediate rewards, despite incurring future negative consequences, and these decision-making deficits may be more severe than in other executive areas (e.g., cognitive flexibility, working memory; van der Plas et al., 2009). Interestingly, reduced competent decision-making in MA has also been associated with increased tendency to postpone decisions, potentially due to the lack of competent strategies with which to resolve decisional conflicts (Gorodetzky et al., 2011).

Despite a significant body of evidence indicating cognitive decrements and adverse functional outcomes in chronic MA users, a recent critical review remarked

upon the number of existing studies in which MA dependent individuals, despite demonstrating lower group means on cognitive measures, remained within normal ranges when compared with normative data, thus calling into question whether each impairment represents a clinically significant deficit (Hart, Marvin, Silver, & Smith, 2012). However, the preponderance of disrupted functional outcomes in chronic MA use (e.g., work, communication, recreation, lack of health insurance, public assistance status, representation in burn and trauma units, domestic conflict, legal complications; Meredith et al., 2005) suggest that whether these are more highly associated with traditional cognitive functions or more specific cognitive functions, chronic exposure to MA results in a host of difficulties maintaining adaptive functioning.

Additive Neuropsychological Deficits in HIV/MA

HIV and MA independently confer neurotoxic effects that result in a variety of structural and functional brain changes, particularly in the frontal lobes and basal ganglia. Due to this convergent neuropathophysiology, MA and HIV may exert combined injury in an accelerated manner (e.g., Nath et al., 2001) or in a magnitude exceeding the neurotoxicity of either MA or HIV alone. This neurotoxicity may be potentiated via several mechanisms, including adverse effects on immune function, cytokine regulation, and cerebrovasculature. In turn, inflammation and oxidative stress may result in neurotoxicity in dopaminergic systems (Gonzalez & Cherner, 2008). In animal models, administration of MA has been observed to affect cytokine production, suppress immune function, and increase replication of HIV (Gavrilin, Mathes & Podell, 2002; In, Son, Rhee, & Pyo, 2005; Yu et al., 2002). In vitro, MA has also been shown to enhance HIV infection of macrophages (Liang et al., 2008). As a result, HIV+ individuals may be more vulnerable to opportunistic infections and

increased viral replication due to compromised host defenses as well as upregulated inflammatory responses (Gonzalez & Cherner, 2008). In addition, MA is toxic to dopaminergic neurons, and may potentiate the neurotoxic effects of HIV Tat and gp120 proteins (e.g., Cass et al., 2003), damaging neurons through oxidative stress, mitochondrial dysfunction, and inflammation. Both MA and gp120 have been observed to dysregulate the activity of endothelial tight junctions, allowing more HIV-infected cells to traffic into the CNS (Mahajan, et al., 2008). Indeed, HIV+ MA users demonstrate compounded loss of interneurons, most notably in the frontal cortex (Chana et al., 2006) as well as higher frequency of ischemic events, more pronounced loss of immunoreactivity, and a more severe microglial reaction post-mortem (Langford et al., 2003).

A number of studies (e.g., Chang et al., 2005) have suggested additive effects of MA and HIV on both glial and neuronal injury, especially in the striatal and frontal brain regions known to have the highest density of dopaminergic nerve terminals. Reduced N-acetyl aspartate (NAA), a putative marker of neuronal integrity, has been reported in brains of those with combined MA/HIV (Taylor et al., 2000; see also Chang et al., 2005). Additionally, increased concentrations of reactive inflammatory glial markers have been noted in the frontal white matter, potentially due to chronic exposure to excessive levels of dopamine that may stimulate HIV replication (Scheller et al., 2000). In the basal ganglia, there is evidence for a relative lack of inflammatory or repair responses (Chang et al., 2005). MA and HIV are also known to alter volumes of cortical, limbic, and striatal structures, though these relationships are not yet as well understood. Though the regional patterns of these changes overlap, effects on cortical volume may be in opposition (increased volume of basal ganglia in MA and cortical volume loss in HIV), though both are associated with neurocognitive

impairment (Jernigan et al., 2005). Opposing functional effects on neural circuits have been observed during tasks of motor programming as well, as HIV and MA produced less aberrant patterns of activation than either condition despite similar levels of impairment (Archibald et al., 2012). Lasting additive effects of HIV and MA dependence have been observed on measures of regional cerebral blood flow (Ances et al., 2011) and metabolite disturbances (via proton resonance spectroscopy; Taylor et al., 2000).

While each condition is separately associated with poorer neurocognitive status and well-documented impairments, MA and HIV also appear to confer additive neurocognitive effects in dually affected individuals (Rippeth et al., 2004). While a relatively greater number of studies have investigated the effects of polydrug use in HIV, the unique effects of methamphetamine and the convergence of these mechanisms with HIV warrant particular concern for striatal and striatal-cortical circuitries that appear selectively vulnerable to HIV and MA. For example, surging MA-related levels of dopamine are associated with dopaminergic neuronal degeneration and oxidative stress, which in may exacerbate the severity of and/or accelerate the progression of HIV-associated neurocognitive impairment (Purohit, Rapaka, & Shurtleff, 2011). Methamphetamine may exacerbate HIV-associated neurocognitive impairment even acutely after infection (Weber et al., 2012), and additive deleterious effects are also evident with immunosuppression, such that MA+ individuals demonstrate the highest rate of neurocognitive impairment (Carey et al., 2006). Rates of global neurocognitive impairment in one landmark study were 58% in HIV+/MA+ individuals, as compared with 40% in HIV-MA+, 38% in HIV+MA-, and 18% in HIV-/MA- individuals. Interestingly, global cognitive performance may not differ based on quantity or frequency of MA use, or by administration method

(intravenous vs. non-intravenous use; Rippeth et al., 2004). Additive impairments of HIV and MA are, in turn, associated with increased risk of adverse everyday functioning outcomes including unemployment (van Gorp et al., 1999), dependence in activities of daily living (Heaton et al., 2004) and poorer medication adherence (Moore et al., 2012). Current methamphetamine users taking ART medications also remain at greater risk for higher HIV RNA viral loads and lower CD4 counts even after cessation of active use, making them more likely to transmit the virus (Moore et al., 2012). In addition to impacting cognitive outcomes and everyday functioning, stimulant use directly and adversely impacts disease progression even in the context of adequate antiretroviral adherence (Carrico, 2011), and may reduce the effectiveness of antiretroviral therapies in individuals with HIV (Ellis et al., 2003).

Although risk for global impairment is increased in HIV+ individuals with chronic exposure to MA, elevated risk of certain specific deficits (e.g., executive dysfunction) may be conferred due to additive deleterious effects on neurocognitive functions mediated by frontal-subcortical systems. Possessing HIV and substance-related risk factors may result in additional difficulty with inhibition (Martin et al., 2004a), working memory (Farinpour et al., 2000), and executive control of memory (Martin et al., 2007), among other abilities. These deficits are of particular concern due to the magnitude of associations between executive deficits and everyday functioning problems (Heaton et al., 2004) as well as concerns that the nature of these impairments may relate to increased HIV transmission risk (e.g., Wardle et al., 2010). Relative to other substances, individuals who report MA as their "drug of choice" also demonstrate significantly larger impairments in the domain of executive functions (Gonzalez, Bechara, & Martin, 2007).

Relatedly, HIV+ substance dependent individuals and particularly HIV+

methamphetamine dependent individuals demonstrate notable deficits on tests of decision-making (e.g., Martin et al., 2004). As observed in the context of other executive functions, deleterious effects of MA on decision-making abilities may be larger than those observed in the context of other substances of abuse (e.g., alcohol; Gonzalez, Bechara, & Martin, 2007), and MA-using individuals may make similar levels of disadvantageous decisions across task blocks, in contrast to healthy control groups that tend to shift and maintain response selection from advantageous decks. Neither working memory nor procedural learning deficits appear to explain these differences in decision-making performance (Martin et al., 2004; Gonzalez et al., 2010). Interestingly, a recent study by Wardle and colleagues (2010) indicated that performance on a task of decision-making, and not measures of other executive functions, interacted with affective distress in HIV+ individuals with substance dependence disorders to predict risky sexual behavior (Wardle et al., 2010), suggesting that the uniquely affective element involved in this type of decision-making task may explain the correspondence between emotional distress and risk behavior outcomes. As HIV+ substance dependent individuals have higher rates of emotional distress, decision-making deficits in particular may interact with other factors to perpetuate maladaptive behaviors in this vulnerable group.

In addition to global cognitive, executive, and decision-making deficits, recent evidence suggests that neurodegenerative pathologies impacting fronto-striatal-thalamo-cortical functioning and dopaminergic systems also exert preferential structural and functional injury to circuits facilitating social cognitive processes guiding automatic as well as purposive behavior and enable selection and maintenance of adaptive behaviors. Indeed, the limited data available indicates that aspects of social cognition associated with poorer psychosocial functioning are impaired in both HIV

(Lysaker et al., 2012) and MA dependence (Kim et al., 2011). As HIV and MA confer additive risks to other aspects of neuropsychological functioning, it is possible that individuals who are part of both risk groups may be at elevated risk for deficits in social cognitive processes, and may demonstrate synergistic social cognitive impairments as well as associated disruptions in adaptive functioning.

Social Cognition and Theory of Mind

According to the American Psychological Association (2002), understanding the neural underpinnings and mechanisms driving social cognition may be one of the most important issues of the 21st century. Broadly, the term 'Social cognition' encompasses many diverse psychological constructs. This booming research area has historically focused on identifying the neural circuits supporting social functions in higher primates, thereby elucidating the "social brain hypothesis," as well as tracing the development of social cognitive abilities in typically developing individuals as well as those with pervasive impairments in social and interpersonal functioning.

The social brain hypothesis was originally proposed in the late 1980s as an explanation for why primates have unusually large brains relative to body size, compared to other vertebrates (Byrne & Whiten, 1988). It was concluded that primates live in more complex societies, and therefore need increased processing capacities in order to navigate these sophisticated environments. Indeed, mounting evidence suggests that social complexity (e.g., social group size, use of deception, and use of coalitions) correlates across species with neocortex volume (Schultz & Dunbar, 2010). For example, social network size and complexity correlates with volume of the amygdala (credited with involvement in emotional coding of social signals) as well as cortical thickness in regions of the frontal and temporal lobes; Bickart et al., 2010). Remarkably, these relationships between brain volume, social

environment, and social skill appear quite plastic. For example, superior temporal sulcus and prefrontal cortex volume is correlated with the size of the social groups in which rhesus macaques were housed. Within said social groups, volumes of these same regions have been observed to correlate with the dominance ranks of individual monkeys (Sallet et al., 2011). Therefore, the social brain hypothesis appears to apply generally to primates, and rapid phenotypic adaptability is evident (Dunbar, 2012) to a degree that has only been previously demonstrated in the hippocampi of London taxi drivers, whose volumes are significantly larger than controls and correlate with duration of time spent as a taxi driver (Maguire et al, 2000). It stands to reason that when these structures are injured, impairments may be observed in social cognitive functions, and changes in environment may also facilitate alterations in structures mediating social cognitive processing.

Research on social cognition has accelerated in recent years, spurred largely by advances in neuroimaging that has enabled the dissociation of these complex functions and the identification of *acquired* social cognitive deficits in a variety of clinical populations impacting frontostriatal systems. It is increasingly recognized that while some social deficits are broad and severe, conferring substantial impairments across many aspects of social functioning (e.g., autism and schizophrenia), other disease states (e.g., Parkinson's Disease; Huntington's Disease) are associated with specific and dissociable deficits in cognitive and affective functioning. These impairments may appear more subtle than those observed in autism or schizophrenia, but deficits in various aspects of social cognition are nonetheless associated with profound disruptions in psychosocial functioning and a wide range of adverse functional outcomes (e.g., health-related quality of life; Bodden et al., 2010). Thus, the experimental literature has rapidly generated a wide variety of measures

and paradigms with which to assess a broad array of social cognitive abilities, even as the field as a whole has continued to refine definitions of these constructs. Social cognitive abilities of particular interest to the National Institutes of Mental Health (as per a position statement in 2008) have included social perception (processing verbal or nonverbal cues to make inferences about complex situations), social knowledge (operation of goals, rules, and roles that guide interpersonal interactions), attributional bias (internal vs. external, situational vs. personal), emotional processing (identifying, understanding, and managing emotions), and theory of mind (also called mental state attribution; Green et al., 2008).

Theory of Mind is a core *cognitive* aspect of social cognition, and describes the ability to mentally represent another person's internal state in order to take their perspective and infer the intentions, dispositions, experiences, and beliefs of others (e.g., Premack & Woodruff, 1978). ToM qualifies as a "theory" because the ability involves making inferences about states that cannot be directly observed in order to guide behavior (Freedman & Stuss, 2011). This ability allows individuals to predict what others will think, feel, and do in a given situation in order to respond appropriately (Mengelberg & Siegert, 2003; Frith & Frith, 1999). Theory of Mind is employed both frequently and unconsciously. For example, how another person's behavior is perceived is influenced by beliefs about their intentions, and whether a source is deemed to be credible depends on the perception of the communicator in addition to the content of the message. In turn, individuals' actions are influenced by how they believe that other people will feel and react (Pynadath, Si, & Marsella, 2011). Although ToM is a profoundly interpersonal skill, this ability is also highly associated with recognition and self-regulation of one's own internal states due to a network of common neural mechanisms centered around the medial prefrontal cortex

(mPFC; Ochsner et al., 2004). It has been postulated that this common activity provides the basis for simulation, which facilitates vicarious experience or the understanding of other's actions and emotions through the lens of the self (Ochsner et al., 2008; Mitchell, Banaji, & MacRae, 2005). The neural network facilitating ToM extends beyond the mPFC to include the superior temporal sulcus, the temporal pole, and the amygdala (Kalbe et al., 2010). Deficits in ToM have been associated with a variety of adverse outcomes, including elevated personal distress, difficulty regulating emotional states and guiding adaptive decision-making, and disturbances in communication and social functioning.

Broadly, ToM is involved whenever one individual is required to represent the mental states of another. However, ToM can also be further separated into several component processes based on whether this decoding and reasoning pertains to states that are cognitive (e.g., knowledge or beliefs that can be rationally inferred) or affective (e.g., emotional states that require empathic perspective-taking; Kalbe et al., 2007). Whereas cognitive ToM may involve frontostriatal-dorsal circuitry primarily, affective ToM may invoke frontostriatal-limbic systems. Thus, these abilities can be selectively disrupted, as noted in lesion studies (Shamay-Tsoory & Aharon-Peretz, 2007) in some clinical populations (e.g., advanced Parkinson's Disease; 2009). Transcranial magnetic stimulation studies also support the relative functional independence of cognitive from affective ToM (e.g., Kalbe et al., 2010) as does evidence that cognitive and affective ToM are differentially associated with psychophysiological measures including skin conductance responses (SCRs; Kalbe et al., 2007). It is important to note that although different tests of ToM pertain to the same general construct, they may also differentially measure the various processes underlying aspects of ToM by including greater or lesser reliance on visual aspects of

ToM (e.g., Gregory et al., 2002), or higher order functions due to increased task complexity (e.g., first vs. second order inference; Perner et al., 1985). Due to the complexity of these considerations, multimodal measurement of ToM has been recommended whenever possible in order to explore both subcomponents and their relationship to other cognitive functions and clinical parameters.

Originally noted in social-developmental disorders, aspects of ToM are now recognized to be impaired in a number of neurodegenerative pathologies impacting fronto-striatal-thalamo-cortical functioning and dopaminergic systems, including Parkinson's Disease (Mengelberg & Siegert, 2003), Huntington's Disease (Allain et al., 2011), and frontotemporal dementia (Eslinger et al., 2006). Together with poor executive and regulation mechanisms, social cognitive deficits may impact disorganized behavior and provide a basis to explain the breakdown of interpersonal relationships associated with these diseases (Shany-Ur & Rankin, 2011; Allain et al., 2011). More recent evidence suggests that ToM impairments may also be commonly observed in individuals with HIV (e.g., Lysaker et al., 2012) and those with chronic exposure to methamphetamine (Kim et al., 2010). However, no studies to date have investigated whether individuals with both risk factors demonstrate additive or synergistic risk of ToM impairments, or whether accompanying functional risks may be magnified as well.

Theory of Mind in HIV Infection

As frontostriatal regions appear to be specifically vulnerable to HIV disease, HIV+ individuals may be subject to a variety of impairments associated with disrupted functioning in these systems. These may include the aforementioned cognitive deficits, which are well documented, as well as more recently identified psychological (e.g., apathy; Paul et al., 2005) and social cognitive (e.g., ToM) impairments that can

be linked to aspects of the neuropathological process in HIV. Both psychological and interpersonal functioning relies on a number of abilities under the umbrella of social cognition: specifically, ToM (perceiving, recognizing, and mentally representing others' internal states). For example, neural structures involved in facial emotion recognition processes center around the frontal-subcortical regions, interacting within a larger cortico-limbic system (Adolphs, 2002). Previously, disrupted emotion recognition had been observed in other patient populations with acquired neuroanatomical dysfunction in fronto-subcortical systems (e.g., PD and HD; Clark, Nearing, & Cronin-Golomb, 2008; Johnson et al., 2007), but deficits in emotion recognition and associated functional difficulties have more recently been identified in an HIV as well.

The first suggestion of ToM deficits in HIV were identified by Clark and colleagues (2010), who examined facial emotion recognition (an aspect of affective ToM) in 50 HIV-infected participants and compared their performance to that of 50 healthy comparison individuals. Results indicate that individuals with HIV demonstrate a general impairment in emotion recognition abilities, which is driven predominantly by a specific impairment in the ability to recognize fearful expressions. This deficit may render HIV+ individuals less likely to recognize potentially dangerous interpersonal scenarios. Furthermore, they observed an association between anger recognition abilities and current CD4 count, indicating that HIV disease severity may contribute to this acquired impairment in emotion processing and confer greater deficits in social cognitive processes with advancing disease. Disrupted frontostriatal structures and their connections with cortico-limbic networks, then, may contribute to emotion recognition abilities and associated difficulties with interpersonal functioning. Of note, post-hoc comparisons indicated that HIV+ individuals reported higher rates

of interpersonal distress (1.1 standard deviations above the general normative population's mean score), specifically on scales measuring management of anger/irritability in interpersonal relationships, self-sacrificing behaviors, and desire to connect with others. Taken together, these results suggest that HIV-associated neuropathological changes could contribute to poorer facial recognition abilities. The specificity of these effects to fear- and anger-recognition may place these individuals in harm's way (e.g., in HIV risk transmission scenarios), or reduce the likelihood that latent risks are detected. Whatever the mechanism, these emotion recognition deficits are in turn associated with disruptions in important aspects of interpersonal and psychological functioning. More recently, facial affect recognition abilities in HIV were found to be comparable to those in schizophrenia patients on a test using videotaped stimuli (Lysaker et al., 2012). In addition, performance on another ToM task (the Hinting Task, which involves inferring intentions from indirect verbal vignettes) was between .5 and 1.5 standard deviations below scores observed in normative populations. Though ToM has not been extensively studied in HIV, the available evidence suggests that individuals with HIV are impaired in multiple aspects of ToM that are associated with clinically significant psychosocial outcomes and may place them at higher risk in HIV transmission scenarios.

Theory of Mind in MA Dependence

In recent years, increased attention has also been garnered by social cognitive processes and disrupted social and interpersonal functioning in chronic MA users. Pre-dating all experimental studies to this effect, Homer (2008) published a critical review that proposed using a biopsychosocial approach in order to link the neurotoxic effects of prolonged MA exposure to disrupted behaviors and, likely, social cognition. Given the scope of neurological damage associated with MA abuse, these

investigators hypothesized that specific brain-behavior relationships related to ToM would elucidate the observed behavioral dysfunction in this population. This had been previously suggested by a number of animal studies indicating that even for weeks after MA exposure, rats and monkeys demonstrate significant social withdrawal (e.g., Clemens et al., 2004), potentially suggesting that MA-associated changes in social behavior have a physiological basis and may be explained in part by impairments in social cognitive processing. Further studies appeared warranted, as many behavioral changes in MA abuse (e.g., Clemens et al., 2004; Semple et al., 2005) and negative side effects (e.g., paranoia, increased aggressiveness, depression, and the need to hide increased usage) eventually lead to social isolation in users (Gorman et al., 2004; Kurtz, 2005).

As anticipated, subsequent experimental efforts have, indeed, identified ToM impairments in both active MA dependent and currently abstinent samples of former users. Henry et al. (2009) demonstrated that prior MA users with recent abstinence (6 months) had increased difficulty detecting subtle differences in mental states on the Eyes Task, as well as increased difficulty differentiating between more basic facial expressions relative to healthy individuals. In other words, these individuals demonstrated significant deficits in basic aspects of social perception, which may impair their abilities to successfully complete higher order processing (reliant upon these inputs) that enables the selection of adaptive behaviors. Importantly, the magnitude of these deficits (effect sizes 1.75 and 2.32) were comparable or greater than those observed on tests of memory and aspects of executive control, suggesting that the degree of MA-related social-cognitive impairment is as high or greater than the cognitive decrements observed in other domains. As these impairments in other aspects of cognitive performance have been linked to adverse everyday functioning

outcomes, impaired ToM may impact important functional outcomes as well. Bolstered by these findings, Henry and colleagues (2009) cited the investigation of more complex aspects of ToM (e.g., coordination of multiple perspectives, integration of mental states and behaviors) as important future directions for this area of research. Kim and colleagues (2011) have since accepted this challenge, assessing more sophisticated aspects of ToM as well as recognition of facial expressions in recently abstinent MA users. They found that, as in cocaine users and other conditions implicating amygdala function (e.g., Hariri et al., 2000), MA users exhibited specific deficits in identifying fearful expressions, as well as poorer performance on the Eyes test (requiring the discrimination of subtle mental states from pictures) and the Hinting task (a verbal task requiring participants to take others' perspectives in order to infer the real intentions behind indirect speech utterances). Yet again, MA users demonstrated reduced ability to identify or infer nonverbal cues as to the internal states of others, potentially reducing their ability to recognize interpersonal dangers. Further, emotion recognition abilities were associated with performance on the Eyes test but not the Hinting task, suggesting that ToM performance in these individuals may be multiply determined, depending on which specific abilities (e.g., verbal inference, visual perspective taking) are being assessed.

Theory of Mind in HIV and MA Dependence

Despite small preliminary studies indicating that ToM may be adversely affected by HIV infection (Lysaker et al., 2012) as well as MA dependence (Kim et al., 2011) alone, no studies to date have comprehensively assessed cognitive as well as affective ToM in these groups, nor examined the separate and possibly synergistic impacts on ToM in individuals with HIV and MA dependence. Indeed, the particular impairments noted in HIV and MA dependence may be compounded in individuals

with both risk factors due to shared mechanisms of pathophysiology, which could severely reduce interpersonal perception of harm in these individuals. Further, despite the suggestion that impaired ToM is associated with impaired interpersonal communication and poor adaptive-decision-making in other clinical groups, no attempt has been made to investigate whether adverse impacts of ToM impairments may be exacerbated in conditions which disproportionately affect critical regions for adaptive decision-making (e.g., vcPFC in MA dependence, HIV disease). As maladaptive or risky behaviors in these individuals may result in increased disease transmission and public health burden, it will be important for future research to ascertain the prevalence and severity of such deficits, as well as determine their relationship to impaired interpersonal functioning and risky behaviors for disease transmission.

HIV Transmission Risk Behaviors in HIV and MA Dependence

Efforts to contain the HIV epidemic have historically focused on either preventing uninfected persons from being infected, or diagnosing and treating as many HIV-infected persons as possible. However, as people with HIV continue to live longer and healthier lives, increasing attention has focused on positive prevention, or increasing safe practices among infected persons in order to mitigate transmission risk (Kalichman, 2000). As sexual transmission was an acquisition risk factor in approximately 88% of new HIV infections (CDC, 2006) and intravenous drug users are at significantly elevated risk for transmissions, efforts have focused on understanding the determinants of risky behaviors (e.g., unprotected sexual contact; sharing needles or illicit substance paraphernalia) and using these factors to inform public health interventions aimed at preventing and reducing risk behaviors. While successful public health efforts (e.g., condom accessibility, education programs) have

been successful in reducing rates of HIV transmission in most groups, high rates of risk behaviors are still observed in certain groups, including substance- (and particularly MA-) using populations (United Nations, 2006). In the context of HIV and MA, many factors may contribute to risk behavior phenotypes and contribute to the variance in risk behaviors observed from one individual to another. To date, a great deal of work on risk behavior phenotypes have focused on proximal factors such as psychosocial and substance use behaviors (Diclemente et al., 2008; Leigh & Stall, 1993). For instance, researchers have proposed an influence of both positive (Gonzalez, et al., 2005) and negative affect (McKirnan, Ostrow, & Hope, 1996) on increased risk taking behaviors in HIV, and substance-dependent HIV+ individuals are more likely to continue risky behavior after becoming aware of their diagnosis (Kalichman, 2008). However, recent studies have shown promise in identifying more distal factors such as specific neurocognitive impairments and biological or genetic factors that may be helpful in identifying vulnerable individuals and informing prevention efforts targeting risk behavior (Bousman et al., 2010). For example, it has been increasingly recognized that the vast majority of HIV transmission scenarios (e.g., deciding whether or not to engage in sexual contact; sharing of illicit substance paraphernalia) are inherently interpersonal (Logan, Cole, & Leukefeld, 2002), recruiting social cognitive processes and requiring ongoing assessment of risk (Kohler, Behrman & Watkins, 2007). As such, novel cognitive mechanisms (e.g., ToM) may provide additional explanatory power in predicting HIV transmission risk, over and above other less context-relevant cognitive factors.

Typically, learning of an HIV diagnosis tends to decrease risky sexual behavior. However, a subset of HIV-infected individuals (roughly one in three) continue to engage in high levels of risk behaviors after diagnosis, thereby placing

their partners at risk for HIV and themselves at risk for other sexually transmitted infection (e.g., Marks, Crepaz, Senterfitt, & Janssen, 2005; Hankins, Gendron, Tran, & Lamping, 1997). As many as one third of HIV-positive persons contract new sexually transmitted infections (STIs) after diagnosis (Kalichman, 2000). Some have hypothesized that common HIV-associated neurocognitive impairments (e.g., executive functions, learning and memory, and speed of information processing; Reger et al., 2002) may also contribute to disease transmission risk by biasing behavior or evaluation of risk in specific ways. For example, executive dysfunction may inhibit rational and safe decision-making by biasing choices toward immediate rewards rather than future outcomes, and further impairing impulse control (e.g., to practice safe sex). HIV-related deficits in aspects of episodic memory (e.g., prospective memory) may impair the ability to plan and carry out future intentions (Woods et al., 2009). Finally, slowed information processing may contribute to risky choices as well by preventing the timely consideration of risk variables during decision-making (Anand, Springer, Copenhaver, & Altice, 2010). Those with comorbid MA dependence may be at yet more elevated risk, as chronic MA abuse can impair many of the same abilities as HIV (Verdejo-Garcia, Lopez-Torecillas, Gimenez, & Perez-Garcia, 2004). Possessing HIV and substance-related risk factors may result in additional difficulty with inhibition (Martin et al., 2004a), working memory (Farinpour et al., 2000), and decision-making (Martin et al., 2004b), leading researchers to believe that these added executive burdens may result in risky behaviors due to increased difficulty inhibiting behaviors and biases toward choosing immediate rewards despite future consequences (Wardle, Gonzalez, Bechara, & Martin-Thormeyer, 2010). However, despite relationships between executive dysfunction and risky choices during laboratory tasks, the impact of executive dysfunction on real-world risk

behaviors in these groups remains largely unclear (Gonzalez et al., 2005). In one promising study, however, overactivity of dopamine in the prefrontal cortex due to a common polymorphism was associated with executive dysfunction, and interacted to predict a variety of sexual risk behaviors in HIV+ MA+ individuals (Bousman et al., 2010). The significance of this particular finding may stem from the specificity of these systems to interpersonal risk, in that dopamine plays a crucial in sexual arousal, motivation, and rewarding effects of sexual behavior. Due to the inherently social nature of HIV risk, researchers have increasingly turned to investigating how individuals estimate their personal HIV risk by evaluating (or failing to evaluate) characteristics of their partners.

While evidence has supported cognitive models of risk behavior engagement that include intentions and appraisals, partner and situational characteristics have also emerged as important predictors of HIV risk behavior (Norris et al., 2009). Although interventions for risk behavior reduction often target biased risk appraisal in these groups (DiClemente et al., 2009), evidence suggests that many individuals continue to engage in risky behaviors even when these processes remain intact (Purdie et al., 2011) and despite knowledge about behaviors that pose elevated risk for contracting HIV (Schmalzle, Shupp, Barth, & Renner, 2011). In contrast to classical theories of risk, which emphasize the role of cognitive estimates of risk probability and severity (e.g., Renner & Schupp, 2011), others posit that implicit processes may play a larger role in day-to-day thinking, especially in relation to the highly contextualized social and sexual domain (e.g., Norton et al., 2005; Ariely & Loewenstein, 2006; Ditto et al., 2006; Stacy et al., 2006; Loewenstein et al., 2001). Field studies have suggested that individuals often rationalize risky behaviors by reporting impressions of safety, which may arise from rapid and mostly automatic

stimulus processing. Described as a dual-process view, this theory posits that unless individuals are alerted by an intuitive alarm that a potential partner could be risky, individuals may not effortfully reflect upon or evaluate HIV transmission risk, and default to follow their habits (e.g., using or not using condoms or shared substance-related paraphernalia; Schmalzle et al., 2011). Below, this hypothesis is reviewed in the context of potential impacts of ToM on transmission risk behaviors.

Decision-Making as a Moderator of HIV Transmission Risk Behaviors

As reviewed above, specific neurocognitive impairments (particularly within the executive domain) have long been hypothesized to play a role in engagement in HIV transmission risk behaviors among HIV+ and MA+ individuals. Though it is clear that these relationships are complex and multiply determined, decision-making deficits have shown particular promise in the prediction of real-world risk outcomes in HIV and MA. Although these relationships have historically been difficult to establish (e.g., Gonzalez et al., 2005; Wardle et al., 2010), accumulating multidisciplinary evidence suggests that decision-making abilities may moderate the relationship between other cognitive abilities (namely, ToM) and engagement in HIV risk behaviors.

While many assume that HIV risk is assessed by deliberative, effortful reasoning, evidence using event-related potentials (ERPs) suggests that HIV risk may be rapidly inferred via implicit processes (Schmalzle et al., 2011). Individuals later deemed 'risky' elicited two ERP components that of significantly larger amplitudes than those observed for 'safe' individuals. When participants first viewed pictures of faces without any instructions, photos of 'risky' individuals elicited waveforms of similar morphology than those exhibited later when explicitly asked to evaluate the person's risk of having HIV. This type of implicit risk perception appears

to take into account elements such as perceived responsibility and trustworthiness, as well as cues such as clothing, attire, and social context (Renner, Schmalzle, & Schupp, 2012). Conclusions from these implicit processes are, in turn, related to approach or avoidance. However, this type of intuitive risk assignment may be more likely to fail in individuals with impaired ToM (e.g., HIV or MA dependent individuals) due to the anger- and fear-specific deficits observed in facial emotion recognition, potentially predisposing erroneous beliefs about risk from initial encounters.

Following initial components indicative of implicit processing, late positive components of higher amplitudes occur when "risky" persons are observed. This suggests that while identification of risk may occur implicitly, larger amplitude potentials occur as greater processing resources are drawn to the stimulus after significant risk cues are perceived. This larger amplitude may be associated with the conscious recognition, attention allocation, and recruitment of executive processes (Sergent et al., 2005; Del Cul et al., 2007) after a certain level of threat/emotional significance is determined by circuits including the amygdala, cingulate gyrus, temporal pole, and medial prefrontal cortex. In turn, these areas are interconnected with limbic regions such as the mPFC and autonomic control centers, which mediate the visceral consequences of affectively salient information. However, unless alerted by an intuitive visceral alarm, this effortful processing of risk may not take place. Per the Somatic Marker Hypothesis, dysregulation of these types of somatic bodily signals is related to poorer decision-making on laboratory-based tasks (e.g., Bechara et al., 1994). Such somatic markers, generated by affective information, purportedly constrains decision-making by giving various alternatives preferential availability over other alternatives, thereby leading to adaptive human functions. Individuals who have weaker physiological cues (e.g., those with vmPFC lesions) lack anticipatory skin

conductance responses that accompany poorer choices, and as a result, may perform in a riskier manner without such autonomic guidance. The pattern of responses observed in these individuals, including orientation to immediate prospects and insensitivity to future consequences, has been termed "myopia for the future" (Bechara, Tranel, & Damasio, 2000).

Given the prominent role of affective signals in this type of decision-making (vs. other "cooler" executive tasks) and the salience of these processes to the evaluation of sexual risk behavior (Gutnick et al., 2006), decision-making (as measured by the Iowa Gambling Task) is proposed as a moderator of the relationship between ToM and HIV transmission risk behaviors in this investigation. Specifically, impaired ToM, or the reduced ability to perceive relevant cues, predict behavior, and respond appropriately, may lead individuals to fail to perceive affect or misattribute intentions of others that may be indicative of elevated risk for HIV transmission. Without these inputs signaling potential threat and providing cues for adaptive decision-making, individuals with impaired ToM may not benefit from the influence of somatic cues, whether overt or covert, and thus may exhibit a bias toward elevated rates of engagement in HIV transmission risk behaviors. In addition to this potential bias in initial processing, these individuals may also fail to successfully navigate the more effortful, cognitively demanding second stage of decision-making.

Due to the specific impacts of both HIV infection and chronic exposure to MA (e.g., significant disruption to frontostriatal and prefrontal cortical functions), individuals with impaired ToM may fail to evaluate or appropriately act upon risk assessments even when they are called to conscious attention. For example, even upon deliberation, these individuals may be able to successfully infer the contingencies of the Iowa Gambling Task, or incorporate and maintain reversal

learning as certain decks become less advantageous (Toplak et al., 2010). While some processes implicating ToM (e.g., inferring other mental states to evaluate implicit risk) may occur relatively rapidly and implicitly (as in the Eyes task), other ToM processes are more demanding and complex, relying on intact prefrontostriatal processing. For example, more sophisticated ToM abilities may be required to complete real-world false-belief and deception tasks in order to evaluate whether, for example, a needle that has been offered may have been used previously, thereby putting the individual at risk for infectious diseases. Solving this quandary requires the individual to represent several mental states: 1) to determine who, of those present currently, could possibly know this information (cognitive ToM), 2) to identify the motivations of each individual to answer in their best interest (cognitive and affective ToM), and 3) to detect affect indicative of deception or unreliability in these responses (affective ToM). To complete the first part of the task, individuals must determine who was in the relevant location when others were using (based on arrival time, etc.) and could therefore speak to whether new equipment was sterile and old equipment was disposed of. Escalating the social-cognitive demands of the situation, this information must be queried appropriately and effectively. To complete the second, the individual must complete a multi-step reasoning process: are these sources intoxicated? Reliable? Long-time friends, acquaintances, or strangers? Trying to sell the paraphernalia and substances in question? Information from all sources must be integrated and arranged hierarchically to determine an appropriate source. To solve the third, individuals must integrate verbal and nonverbal information to evaluate the credibility of said source. The social-cognitive processes at work here require substantial complexity, flexibility, and speed of information processing in naturalistic settings, so it stands to reason that prefrontostriatal dysfunction (accompanied by

deficits in higher order operations such as prospective memory) in HIV+ SDIs would be associated with increased rates of HIV risk behaviors (as was demonstrated by Martin and colleagues; 2007). The particular applicability of ToM and other social cognitive abilities to HIV transmission risk scenarios raises the probability that these abilities, which are relatively independent from other aspects of executive functions (Pickup et al., 2008), may interact with affective decision making to predict engagement in HIV risk behaviors.

Summary

Theory of mind, or the ability to mentally represent others' internal states in order to predict what they will think, feel, and do, has received much recent attention as a potentially important determinant of interpersonal functioning (Mengelberg & Siegert, 2003). Behavioral consequences of impaired ToM may be of particular public health relevance in HIV and methamphetamine (MA) dependence, especially when these two conditions co-occur, due to potential impacts on disease transmission. Both conditions disproportionately affect the vmPFC and associated structures, potentially resulting in ToM impairments that manifest as a reduced capacity to perceive relevant cues, identify affect and intentions, predict others' behavior, and respond adaptively. In addition to breakdowns in interpersonal functioning (e.g., Phillips et al., 2011), impaired ToM has been singularly associated with poorer emotional decision-making abilities (Mimura et al., 2006), which are separable from cognitive abilities including other aspects of executive functions (Toplak et al., 2010). In transmission risk scenarios, then, poorer ToM may diminish adaptive decision-making capacity, such that individuals with impaired ToM may retain preferences for riskier choices despite long-term negative consequences, thereby increasing engagement in HIV transmission risk behaviors (e.g., risky sex and substance use). Historically, the

relationship between impaired decision-making and increased risk behavior engagement has been surprisingly difficult to establish, but ToM may provide explanatory power as a mechanism by which alterations in decision-making and, subsequently, risk behaviors can occur, given its robust associations with both decision-making and everyday outcomes.

Despite compelling associations between impaired ToM and risky decision-making in other populations, no studies to date have comprehensively assessed ToM in HIV, MA dependence, or dual risk groups. This theory-driven investigation of ToM may hold promise for elucidating the presence, severity, and nature of social cognitive (e.g., ToM) impairments in these high-risk groups, as well as the possible relationships between impairments in aspects of ToM and engagement in transmission risk behaviors. Results of this study may inform future prevention and rehabilitation efforts as in other populations, aspects of ToM have been successfully improved using cognitive skills training (Horan et al., 2009).

Aims and Hypotheses

Specific Aim 1: Determine the separate and joint effects of HIV and methamphetamine dependence on cognitive and affective aspects of Theory of Mind (ToM).

Hypothesis 1: It is hypothesized that HIV seropositive individuals and methamphetamine dependent individuals will demonstrate poorer ToM relative to demographically matched comparison participants, as measured by performance-based laboratory tasks and self-report instruments. It is hypothesized that comorbid HIV disease and MA dependence will exert synergistic effects on ToM.

Specific Aim 2: Evaluate the relationship between ToM and engagement in HIV transmission risk behaviors.

Hypothesis 2: Poorer ToM abilities will be significantly associated with higher rates of HIV transmission risk behaviors, independent of other clinical factors (e.g., affective distress).

Specific Aim 3: Evaluate the potential moderating role of affective decision-making in a model predicting HIV transmission risk behaviors.

Hypothesis 3: The relationship between ToM performance and level of engagement in HIV transmission risk behaviors will be moderated by affective decision-making (as measured by the Iowa Gambling Task).

Specific Aim 4: Evaluate the potential moderating role of affective decision-making in a model predicting HIV transmission risk behaviors, in the context of traditional measures of executive functions.

Hypothesis 4: Affective decision-making will emerge as a significant moderator, and executive functions will not significantly affect the relationship between ToM and transmission risk behaviors.

METHOD

Participants

We utilized a cross-sectional group comparison design that aimed to recruit at least 30 HIV+/MA+, 30 HIV+/MA-, 30 HIV-/MA+ and 30 HIV-/MA- individuals in order to ensure adequate sample size to test the proposed hypotheses. All told, 163 individuals were screened for participation, 139 individuals were enrolled in the study, and 126 were deemed eligible after having completed the study. Of the 139 individuals who were enrolled, 13 were excluded due to positive urine toxicology tests on the day of testing or inconsistency (upon structured diagnostic interview on the day of testing) with cell-specific diagnostic criteria. The final sample included 30 HIV-/MA-, 31 HIV-/MA+, 32 HIV+/MA-, and 33 HIV+/MA+ participants. Participants were either recruited from a current ongoing research program housed at the UCSD HIV Neurobehavioral Research Program (TMARC, HNRC, CNTN studies) or recruited from the community for enrollment in TMARC parent study. Consistent with TMARC criteria inclusion, one HIV- group ($n = 31$) had a past diagnosis of MA dependence with MA abuse or dependence within 18 months (HIV-MA+), one HIV- group ($n = 30$) had no history of MA dependence or abuse (HIV-MA-), one HIV+ group ($n = 33$) had a past diagnosis of MA dependence with MA abuse or dependence within 18 months (HIV+MA+), and one HIV+ group ($n = 32$) had no history of methamphetamine dependence or abuse (HIV+MA-). To the extent possible, study cells were balanced on demographic characteristics, psychiatric comorbidity (e.g., depression), and disease severity (for HIV groups).

For those individuals recruited through ongoing HNRP protocols, demographic, neuromedical, neuropsychiatric, and standard neuropsychological data were collected during standard parent study protocols before interested and eligible

participants were approached for participation in this dissertation study. Interested individuals then scheduled a follow-up social cognition visit. For those individuals recruited from the community, a screening phone interview was completed in order to assess HIV status and lifetime and recent substance-related diagnoses (in order to assess eligibility for MA+ cells). If upon phone screening individuals appeared likely to qualify for the study, an official TMARC screening visit was conducted, and interested individuals who met parent study criteria at this point were eligible to schedule a follow-up social cognition visit if desired. On the day of the social cognition adjunct study visit, all participants provided written informed consent before completing an approximately 2-hour battery of social cognition tasks and self-report measures. We utilized data from the standard neuropsychological test battery and psychiatric evaluations collected as part of other HNRP studies (e.g., HNRC, TMARC, CNTN). For individuals who completed their parent study visit 14 days or more before the social cognition visit, the psychiatric evaluation and substance use interview were repeated on the day of testing in order to assess recent symptoms and substance use. The study protocol was executed in accordance with the standards approved by the University of California, San Diego Human Research Protections Program.

Inclusion criteria:

- Ability to provide informed consent
- Age 18-60 years at the time of enrollment
- No current substance abuse or dependence
- See above for description of group-specific MA use parameters

Exclusion criteria: Exclusion criteria include any conditions that may confound interpretation of findings, including:

- **Neurologic:** head injury with loss of consciousness for greater than 30

minutes (or resulting in neurologic complications), penetrating skull wounds, brain surgery, active seizure disorder, or other CNS disorders that might affect neuropsychological functioning (e.g., meningitis, stroke, heavy metal poisoning, Parkinson's disease).

- **Psychiatric:** meeting DSM-IV criteria for current psychiatric disorders with the exception of mood disorders (i.e., schizophrenia or schizoaffective disorder, current non-MA substance dependence) as determined by a structured clinical interview (Composite International Diagnostic Interview [CIDI]; World Health Organization, 1998).
- **Severe learning disabilities** (e.g., word reading standard score < 70)
- **Current substance intoxication:** current intoxication as determined by on-site urine toxicology for illicit or prescribed substances, breathalyzer test, and clinical assessment.

Measures

Self-report:

- **Sexual Risks Scale** (DeHart & Birkimer, 1997). The Sexual Risk Scale consists of 31 items to assess the frequency of sexual risk behaviors (e.g., number of partners, number of partners with HIV, frequency of engagement in various behaviors) during the participant's most sexually active year and the current year. The Sexual Risk Scale was used to assess frequency of recent and maximal levels of engagement in sexual HIV risk transmission behaviors. Greater scores indicate higher risk behavior engagement. The scale contains subscales measuring attitudes about safer sex, normative beliefs,

intention to try to practice safer sex, expectations about the feasibility of safer sexual activity, perceived susceptibility to HIV/AIDS, and substance use.

- **Risk Assessment Battery - Revised (RAB;** (Navaline, et al., 1994). This questionnaire includes two subscales evaluating sex- and drug-related risk behaviors for the 6 months prior to the assessment. Higher scores indicate greater overall risk of HIV transmission. Total RAB scores range from 0 to 40. The RAB (total and sex and drug subscale scores) was used to assess sexual and substance-related risk behaviors for the 6 months prior to the assessment as well as 'ever'.
- **Questionnaire of Cognitive and Affective Empathy (QCAE;** Reniers, Corcoran, Drake, Shryane, & Vollm, 2010). This 31-item self-report questionnaire utilizes items derived from several well-validated measures of cognitive and affective empathy (e.g., Baron-Cohen et al., 2003). Five internally valid subscales comprise cognitive (perspective taking, online simulation) and affective empathy (emotion contagion, proximal responsivity, and peripheral responsivity), and were confirmed via confirmatory factor analysis in a separate sample. Each item is rated on a 4-point scale with response options *strongly agree*, *slightly agree*, *slightly disagree*, *strongly disagree*. This measure was used to evaluate the relationship between self-reported and experimental measures of aspects of Theory of Mind.

Clinical Interviews:

- **Composite International Diagnostic Interview (CIDI Version 2.1,** World Health Organization, 1997). The CIDI is a computer-assisted

structured clinical interview designed to assess psychiatric and substance-related symptoms and assign current and lifetime diagnoses according to DSM-IV diagnostic criteria.

Neuropsychological Battery (see Table 1):

A comprehensive neuropsychological battery meeting the standard of practice for neuropsychological research in HIV (Butters, et al., 1990) was administered to all study participants during separate parent study visits. The approximately 3 hour battery includes measures divided into seven domains in the following manner:

- **Verbal Fluency:** Controlled Oral Word Association Test (COWAT-FAS; Gladsjo, et al., 1999).
- **Attention/Working Memory:** Wechsler Adult Intelligence Scale-III (WAIS-III; Heaton, Taylor & Manly, 2002; The Psychological Corporation, 1997) Letter Number Sequencing; Paced Auditory Serial Attention Test (Diehr et al., 2003).
- **Learning:** Hopkins Verbal Learning Test-Revised (HVLTR; Benedict, Schretlen, Groninger, & Brandt, 1998) Total Trial 1-3 Recall, Brief Visuospatial Memory Test-Revised (BVMTR; Benedict, 1997) Total Trial 1-3 Recall.
- **Memory:** HVLTR Delayed Recall (Benedict et al., 1998), BVMTR Delayed Recall (Benedict, 1997).
- **Speed of Information Processing:** Trail Making Test Part A (TMT-A, (Heaton, Grant, & Matthews, 1991), WAIS-III Digit Symbol and Symbol Search (Heaton et al., 2002; The Psychological Corporation, 1997).
- **Executive Functions:** Wisconsin Card Sorting Test-64 Card Version (WCST-64; Kongs, Thompson, Iverson, & Heaton, 2000) Perseverative responses; Trail Making Test Part B (TMT-B; Heaton et al., 1991).

- **Motor:** Grooved Pegboard, Dominant and Non-dominant hand (Heaton et al., 1991; Kløve, 1963).

Raw scores from the measures listed above were converted to demographically-corrected and practice-corrected scaled scores and deficit scores whenever possible, using the best available normative data. These corrections were utilized in order to minimize the effect of demographic characteristics, such as age, education, sex, and ethnicity, on neuropsychological test performance. Average scaled scores were calculated for each neurocognitive domain, and domain scores were subsequently averaged to create a global summary score for the neuropsychological battery.

Theory of Mind (ToM) Battery

Combined Stories Task

The combined stories task encompasses four vignette tasks (Hinting, False Belief, Faux-pas, and Strange Stories) that have been widely used in the ToM experimental psychology literature (see Figure 1 for sample prompt). To avoid ceiling effects in higher functioning individuals, items cover attribution of a full range of mental states, including beliefs/knowledge, intentions, and emotions. This multifaceted measure of cognitive and affective ToM (Achim et al., 2012) includes scores for attribution of mental states to others and control conditions including 1) general nonsocial reasoning, 2) linkage of mental states to behaviors, and 3) items taxing attention/memory. Each vignette was read aloud to the participant by the examiner using the procedures specified by Achim and colleagues (2012), though this study will also include the collection of reaction time data for each item (specifically, latency between the end of the vignette and participant's first response).

Revised Eyes Task

A computerized version of the Revised Eyes Task (Baron-Cohen, Wheelwright, Hill, Raste & Plumb, 2001), a revision of the original "Reading the Mind in the Eyes" Test (1997), will be utilized as a measure of affective ToM. Participants will be required to infer the mental states of a person from a photograph showing only the person's eye region, which requires them to take the perspective of another person and understand the semantics of a mental state lexicon in order to successfully identify the correct descriptor. This purportedly takes place at an unconscious, rapid, and automatic level. Thirty-six photographs will be presented to each participant, each of which must be matched to one-word printed descriptors (e.g., "surprised," "afraid"). Participants will receive one point for each correct item, with higher scores indicating higher accuracy. In addition, reaction time data (specifically, latency [in seconds] between picture administration and participant's first response) will be collected. This revised test has demonstrated sensitivity to subtle impairments in typically developing adult populations as well as clinical samples (Baron-Cohen et al., 2001).

Decision-Making Test

Iowa Gambling Task

Decision-making abilities were assessed using the Iowa Gambling Task (Bechara et al., 1994), which is a 100-item measure designed to assess the adaptiveness of real-world decision making in a laboratory setting. The task has been used as a probe of judgment and decision-making that is typically impaired in patients with lesions of the ventromedial prefrontal cortex (Bechara et al., 1994). In this task, participants are given a hypothetical loan and asked to choose cards one at a time from a computerized display of four decks, each of which is associated with a different monetary win-loss contingency. Based on the magnitude and frequency of

wins vs. losses, each deck can be classified as either 'risky' or 'safe.' Choices from 'risky' decks are disadvantageous in that they eventually result in lower net 'winnings' at the end of the task. Task performance was indexed by the number of cards selected from risky vs. safe decks in the trials of interest (trials 40-100, representing choices made after deck contingencies have typically been learned). As such, task performance will be operationalized as the number of risky choices (selections from decks A and B) subtracted from the number of safe choices (selections from decks C and D) for trials 40 through 100.

DATA ANALYSIS

Quality Assurance and Data Preparation

During study visits, ToM and risk behavior data were collected by either the PI or a psychometrist who had been trained on the protocol and observed by the PI for reliability. After collection, raw data was scored blindly in batches by the PI, and subsequently entered by the PI into a secure computer which was backed up electronically. All paper and electronic files were deidentified; study materials did not contain any personal identifiers. All study materials were housed in a locked file cabinet in a key-card access building. Access to study materials were restricted to the PI and psychometrist.

When all data had been entered, the distributions of the data were checked; specifically, outliers (defined as more than 4 standard deviations from the mean) were assessed for and removed. All outcome variables were examined for normality and homogeneity of variance (Shapiro–Wilk test, Levene’s Test). Transformations were made or a nonparametric procedures were utilized as needed to meet requirements for the proposed multiple regression models for Aims 2-4. Due to their non-normal

distributions, RAB Substance Use variables were dichotomized in order to facilitate the proposed analyses. In the case of substance use variables with high proportions of '0' responses, these variables were dichotomized to represent recent and remote risk behaviors (Yes/No). To correct for multiple statistical comparisons, statistical significance was defined as $p < 0.01$ (Bland and Altman, 1995) for Aims 2-4. Missing data was replaced with mean values for the participant on the construct of interest.

Statistical analysis

Aim 1 hypothesis analytical approach: HIV-MA-, HIV-MA+, HIV+MA-, and HIV+MA+ groups were compared on primary ToM measures (self-reported ToM abilities, Questionnaire of Cognitive and Affective Empathy Total; Accuracy and Reaction Time measures on the Mind in the Eyes Task; Mentalizing and Control items on the Combined Stories Task). Jonckheere–Terpstra tests were conducted in order to determine whether means for task performance significantly differed in the direction specified (i.e., Dual-risk group $<$ HIV+ and MA+ Single-risk groups $<$ non-HIV non-MA Comparison group). Statistically significant ordered effects were followed by planned post-hoc Wilcoxon rank sum tests and evaluation of effect sizes in order to identify group-level differences underlying these effects.

Dependent Variables (outcome measures):

ToM individual variables:

1. Questionnaire of Cognitive and Affective Empathy (Total Score; Cognitive Empathy; Affective Empathy)
2. Mind in the Eyes Task Mentalizing Items (Accuracy; RT)
3. Mind in the Eyes Task Control Items (Accuracy; RT)

4. Combined Stories Task Mentalizing Items (# correct)
5. Combined Stories Task Memory/Comprehension Items (# correct)
6. Combined Stories Task First-order inference items (# correct)
7. Combined Stories Task Non-social reasoning items (# correct)

Aim 2 hypothesis analytical approach: Multiple linear regression was used to determine the independent effect of ToM on measures of risk behavior engagement in the HIV+ group, with MA group (MA+ vs. MA-) included in this regression. Covariates were selected from among demographic characteristics that differed between groups and other leading predictors of HIV transmission risk, including affective distress [BDI score], sociodemographic variables relevant to base rate and risk engagement [sexual preference], and global cognitive status. To minimize the probability of committing a Type II error, we planned to include as covariates only those factors that significantly differ between HIV+ study groups; no variable examined met this criterion. To minimize the probability of committing a Type I error, we employed a critical alpha of .01. This multiple regression analysis was powered to detect medium effect sizes with group status (MA status) and other relevant clinical factors (e.g., depression) included (N=65).

Dependent Variables (outcome measures, Aims 2-4):

ToM individual variables:

1. Risk Assessment Battery (Total score)
2. Risk Assessment Battery Sexual Risk (Past 6 months)
3. Risk Assessment Battery Drug Risk (Past 6 months)
4. Risk Assessment Battery Sexual Risk (Ever)

5. Risk Assessment Battery Drug Risk (Ever)
6. Sexual Risks Scale Total (# correct)
7. Sexual Risks Scale (Subscales)

Aim 3 analytical approach: This multiple regression analysis predicting HIV transmission risk behaviors was repeated in the HIV+ group, this time in a hierarchical fashion, including decision-making in step 2, in order to assess the potential moderating role of decision-making on the relationship between ToM and indices of risk behavior engagement. The first step of this hierarchical analysis included variables representing ToM abilities and clinical factors differing between groups. The second level included the continuous decision-making variable.

Aim 4 analytical approach: This multiple regression analysis predicting HIV transmission risk behaviors was repeated in the HIV+ group in a hierarchical fashion, including decision-making and executive functions in Step 2 of the regression. This analysis evaluated the potential moderating role of affective decision-making in a model predicting HIV transmission risk behaviors, in the context of traditional measures of executive functions.

RESULTS

Demographics and disease characteristics

The demographic and clinical characteristics of the study participants are presented in Table 1. The study groups were comparable on age, ethnicity, and word reading score (p s > .08). The cohort was composed predominantly of individuals who self-identified their ethnicity and race as non-Hispanic Caucasian. Study groups were significantly different with regard to gender; the HIV-MA- group contained the greatest relative proportion of females (50%), while the other three groups were predominantly male. The groups also significantly differed on educational attainment at the omnibus level, driven by HIV-MA+ individuals reporting significantly fewer years of education (on average, 12.7) relative to HIV-MA- individuals (on average, 13.7). HIV+ groups did not significantly differ from one another in terms of gender or education. With regard to psychiatric characteristics, the four groups did not significantly differ on POMS Total Mood Disturbance score, proportion meeting criteria for current major depressive disorder, or proportion meeting criteria for current or lifetime bipolar disorder (p s > .10). However, rates of lifetime major depression were significantly lower in the healthy comparison group (p < .01); BDI-II scores fell in the 'minimal' range for the HIV-MA- group and 'mild' range for the HIV+MA-, HIV-MA+, and HIV+MA+ groups. Significant differences were found between the four groups for lifetime alcohol dependence (p < .01) and combined non-alcohol substance dependence (p < .05), whereas rates of lifetime cocaine, opioid, and methamphetamine lifetime dependence did not differ between study groups. Regarding MA use parameters, the two MA+ groups did not significantly differ in terms of days since last use, age of first use, total quantity, or total days spent using MA (p s > .10). With regard to HIV disease characteristics (plasma viral load, %

detectable, current CD4, nadir CD4, estimated duration of infection, % AIDS), no significant differences were found between the two HIV+ groups. Participants in these groups had, on average, current CD4 counts above 550 and low HIV viral load, which is indicative of well-controlled HIV disease. Complete demographic, psychiatric, medical, and neurocognitive characteristics are presented in Table 1.

Theory of Mind Differences by Risk Group

Jonckheere–Terpstra tests were conducted in order to determine whether ToM performance medians significantly differed in the direction specified by study hypotheses (Dual-risk < HIV < Healthy comparison; Dual-risk < MA < Healthy comparisons). Results of these tests are displayed in Table 2.

Questionnaire of Cognitive and Affective Empathy. On the QCAE (reflecting self-reported ToM abilities), the tests of ordered alternatives were not significant for self-reported Total Empathy, Cognitive Empathy, or Affective Empathy (all $p > .70$).

Mind in the Eyes Task. On Mind in the Eyes accuracy items, the test was significant for Accuracy (# Correct Mentalizing Items) for both HIV (z statistic = 2.76, $p = .003$) and MA comparisons (z statistic = 2.86, $p = .002$). Planned Wilcoxon tests indicated that the HIV-MA- group performed significantly more poorly than the HIV+MA+ group, and effect sizes were small ($g = .43$) between HIV-MA- and single-risk groups. Effect sizes were also small between HIV+MA+ individuals and HIV-MA+ ($g = .26$) as well as HIV+MA- groups ($g = .19$). Jonckheere–Terpstra tests for Control performance (# Correct Animals) and Reaction time (Correct mentalizing and control items) were not significant in HIV or MA (all $p > .14$). Mind in the Eyes task results by group are displayed in Figures 3 and 4.

Combined Stories Task. On Combined Stories Task Mentalizing items, the test of ordered alternatives approached significance for MA (z statistic = 1.51, $p < .07$)

and HIV (z statistic = 1.36, $p < .09$.) Planned follow-up Wilcoxon tests indicated that performance of healthy controls was significantly better than that of both single-risk groups ($ps < .01$), and dual-risk group performed most poorly ($ps < .01$). Effect sizes between HIV-MA- individuals and single-risk groups were large (gs and small between single-risk and dual-risk groups ($g = .17$ and $.36$ for HIV and MA, respectively). Combined Stories Task results by group are displayed in Figure 5.

Independent Effects of ToM on Risk Behavior Engagement in HIV+ Individuals

Separate multiple regressions were conducted in order to explore the effects of ToM variables on each index of risk behavior engagement (total and subscale scores from the Risk Assessment Battery and Sexual Risks Scale). As such, predictors included MA status as well as either 1) Combined Stories Task Mentalizing Score, 2) Eyes Task Mentalizing Score, or 3) Eyes Task Reaction Time for Correct Mentalizing Items. A critical alpha level of $.01$ was set for all analyses.

Combined Stories Task Mentalizing Score: In the models including methamphetamine status as well as Stories Task Mentalizing score, results revealed significant overall models predicting Risk Assessment Battery (RAB) Total Score [$F(2, 63) = 8.54; p = .0001$], RAB Sexual Risk (Past 6 months) [$F(2, 63) = 4.75; p = 0.0049$], RAB Drug Risk (Last 6 Months) Yes/No [$\chi^2 = 17.62; p = .0005$] and RAB Drug Risk (Ever) Yes/No [$\chi^2 = 27.80; p = .0001$]. The model predicting RAB Sexual Risk (Ever) approached significance [$F(2, 63) = 3.48; p = .0217$]. The only measured demographic, psychiatric, or HIV-related variable that significantly differed between HIV+ study groups (at $p < .05$) was lifetime alcohol dependence, so this additional covariate was included in these models. Methamphetamine group status was a significant predictor in each of these models (all $ps < .01$); however, mentalizing performance (as measured by the Combined Stories Task) was not a significant

predictor in any model (all $ps > .08$). Regression results are presented in Table 3. Models predicting Sexual Risks Scale were not significant (all model $ps > .10$).

Eyes Task Mentalizing Score: In the models including methamphetamine status as well as Eyes Task Mentalizing score, results revealed significant overall models predicting Risk Assessment Battery (RAB) Total Score [$F(2, 63) = 8.54; p = .0002$], RAB Drug Risk (Ever) Yes/No [$\chi^2 = 24.90; p < 0.0001$], RAB Sexual Risk (Past 6 months) [$F(2, 63) = 4.13; p = 0.0101$], and RAB Drug Risk (Past 6 Months) Yes/No [$\chi^2 = 23.20; p < .0001$]. The model predicting RAB Sexual Risk (Ever) [$F(2, 63) = 3.37; p = .0245$], approached significance (with critical alpha set at .01). The only measured demographic, psychiatric, or HIV-related variable that significantly differed between HIV+ study groups (at $p < .05$) was lifetime alcohol dependence, so this additional covariate was included in these models. Methamphetamine group status was a significant predictor in each of these models (all $ps < .01$). Mentalizing performance (as measured by Total Correct responses on the Mind in the Eyes Task) was not a significant predictor in any of these models ($ps > .01$), but approached significance in predicting RAB Drug Risk (Last 6 Months) Yes/No ($p < .02$). Regression results are presented in Table 4. Models predicting Sexual Risks Scale indices were not significant (all model $ps > .17$).

Eyes Task Reaction Time for Correct Mentalizing Items: In the models including methamphetamine status as well as Eyes Task Reaction Time for Correct Mentalizing items, results revealed significant overall models predicting Risk Assessment Battery (RAB) Total Score [$F(2, 63) = 9.07; p = .0002$], RAB Sexual Risk (Past 6 months) [$F(2, 63) = 4.22; p = 0.0090$], RAB Sexual Risk (Ever) [$F(2, 63) = 5.12; p = 0.0033$], RAB Drug Risk (Past 6 Months) Yes/No [$\chi^2 = 17.63, p = .0005$], and RAB Drug Risk (Ever) Yes/No [$\chi^2 = 27.79; p < 0.0001$]. The only measured

demographic, psychiatric, or HIV-related variable that significantly differed between HIV+ study groups (at $p < .05$) was lifetime alcohol dependence, so this additional covariate was included in these models. Methamphetamine group status was a significant predictor in each of these models (all p s $< .01$). Mentalizing RT (as measured during the Mind in the Eyes Task) was not a significant predictor in any of these models (using a critical alpha of .01), but approached significance in predicting RAB Sexual Risk (Ever); $p = .0393$. Regression results are presented in Table 4. Models predicting Sexual Risks Scale indices were not significant (all model p s $> .10$).

Effects of Decision-Making on Risk Behavior Engagement in HIV+ Individuals

On the Iowa Gambling task, decision-making performance was operationalized as the number of advantageous selections minus the total number of selections from the disadvantageous decks for trials 40-100 (widely regarded to represent risky decisions made after adequate opportunity to learn the task's contingencies vs. risky decisions made under uncertainty within the first two task blocks). Scores between the four groups significantly differed from one another ($p < .05$); pairwise differences indicated that this effect was driven by significantly poorer performance in the HIV+MA+ group relative to the HIV-MA- group. See Figure 7.

As proposed, the separate multiple regression analyses predicting HIV transmission risk behaviors (described in Aim 2) were repeated in the HIV+ group, this time in a hierarchical fashion, including decision-making in step 2, in order to assess the potential moderating role of decision-making on the relationship between ToM and indices of risk behavior engagement. As in Aim 2, regression models predicting RAB Total Score, RAB Sexual Risk (Last 6 Months), RAB Sexual Risk (Ever), and RAB drug-related risk (Ever; dichotomous) were significant at a critical

alpha of .01. However, the only significant predictor in each model was MA status (all $ps < .01$); in none of these models was decision-making or any ToM index significantly and independently predictive of any risk outcome (all $ps > .10$).

Given the robust group effects observed in Aim 2, the proposed moderating relationship between decision-making and ToM was also tested separately within each HIV+ study group (HIV+MA- and HIV+MA+) to determine whether effects of ToM may differ by MA group status. Separate multiple regression analyses were run for each index of HIV transmission risk behaviors (Sexual Risks Scale, Risk Assessment Battery). Independent variables included ToM index (either Combined Stories Task Mentalizing Score, Eyes Task Mentalizing Score, or Eyes Task Reaction Time for Correct Mentalizing Items), decision-making performance (number of advantageous selections minus the total number of selections from the disadvantageous decks for trials 40-100), and the interaction between ToM and decision-making. In HIV+MA+ individuals, no models were significant at a critical alpha of .01. In HIV+MA- individuals, the model predicting RAB Sexual Risk (Ever) was significant ($F=8.40$; $p = .0005$). In this model, there was a significant main effect of Eyes Task RT (standardized beta = 0.69), such that longer reaction time was associated with higher sexual risk behavior engagement.

Decision-Making, Executive Functions, and Risk Behaviors in HIV+ Individuals

As proposed, separate multiple regression analyses were conducted for each index of HIV transmission risk behaviors (Sexual Risks Scale, Risk Assessment Battery). Independent variables included ToM index (either Combined Stories Task Mentalizing Score, Eyes Task Mentalizing Score, or Eyes Task Reaction Time for Correct Mentalizing Items) as well as decision-making performance (number of advantageous selections minus the total number of selections from the

disadvantageous decks for trials 40-100) and average executive functioning performance (scaled score) in step 2 of the regression. Significant regression models predicted RAB Total Score, RAB Sex Risk (Ever) and RAB Drug Risk (Ever) Yes/No, and yielded no significant interactions and no significant main effects of IGT performance. However, main effects of MA group were once again observed in predicting RAB total, RAB sexual risk (ever), and RAB drug risk (ever), indicating that HIV+MA+ individuals engaged in higher levels of risk behaviors relative to HIV+MA- individuals.

As above (described in Aim 3), these analyses were repeated within each HIV+ study group to elucidate the effects underlying the robust main effect of MA group. In HIV+MA+ individuals, no models were significant at a critical alpha of .01. In HIV+MA- individuals, the model predicting RAB Sexual Risk (Ever) was significant ($F = 6.21$; $p = .0018$); the model tested in Aim 3 held in the context of executive domain performance. Complete model statistics are reported in Table 6. In this model, there was a significant main effect of Eyes Task RT (standardized beta = 0.71), such that longer reaction was associated with higher sexual risk behavior engagement.

DISCUSSION

The present study sought to examine the performance of a group of HIV-infected individuals with a history of methamphetamine dependence as compared with individuals with only HIV infection, only methamphetamine dependence, and healthy comparison individuals on several measures of social cognition (specifically, ToM). Consistent with the findings of preliminary studies, both HIV infection (e.g., Lysaker et al., 2012) and methamphetamine dependence (Kim et al., 2011) were associated with decrements in performance-based tasks of ToM. To our knowledge, this was the largest study to date to assess ToM in these populations (Homer et al., 2013), and the first to provide adequate sample size to investigate possible additive or synergistic effects of HIV and MA on cognitive and affective aspects of ToM. Indeed, both single-risk groups performed more poorly relative to controls on ToM accuracy measures (effect sizes ranged from small to large between tasks), and dual-risk groups performed more poorly on ToM accuracy measures relative to groups with HIV infection or MA dependence alone. In terms of accuracy scores, significant ordered effects were observed on the Mind in the Eyes task and approached significance on the Combined Stories task, whereas no significant ordered effects were observed on reaction time measures and self-reported ToM abilities. Effect sizes for differences in ToM accuracy between single-risk and dual-risk groups were small to moderate (Cohen, 1988), indicating that although dual-risk individuals exhibited reliably poorer performance relative to healthy comparison participants on all performance-based ToM assessments, synergistic effects of the two conditions on measures of ToM were not supported by results of this study. Rather, our results indicate the presence of additive effects of HIV and MA on affective, but not cognitive, aspects of ToM. In addition to the additive effects of HIV and MA on glial and

neuronal injury (Chang et al., 2005), traditional neuropsychological impairments (Rippeth et al., 2004; Carey et al., 2006), and the increased risk of adverse daily functioning outcomes (van Gorp et al., 1999; Heaton et al., 2004; Moore et al., 2012) associated with these additive effects, our data suggests that fundamental aspects of social cognition may be impacted in a similar fashion. These additive impairments in affective ToM may be associated with these and other difficulties in aspects of everyday living.

With regard to reaction time performance on a measure of affective ToM (Mind in the Eyes), a surprising finding emerged: reaction times for the HIV+MA- group were significantly slower than the HIV+MA+ group for correct mentalizing items, while accuracy scores and reaction times on control items were comparable. Several possibilities may explain these findings. First, although both HIV+ groups performed more poorly relative to comparison participants, our results may suggest a speed by accuracy tradeoff in the HIV+MA- group that was specific to mentalizing items. This may indicate reduced efficiency specific to the processing of social but not 'control' items, which HIV+MA- individuals may have attempted to compensate for by favoring accuracy over speed in order to maximize the likelihood of choosing the correct response. Although we may have expected to observe a similar effect in the HIV+MA+ group (particularly given evidence of impaired sustained attention in MA users; Levine et al., 2006), it is possible that the MA-specific effects on this particular task would bias reaction times in the opposite direction. Specifically, MA users may demonstrate impulsivity and impaired inhibition, such that they may have more difficulty withholding responses (Monterosso et al., 2005) in order to maximize accuracy on the task. Alternatively, methamphetamine use may be associated with benefits in certain specific aspects of neuropsychological functioning in HIV+

individuals. At the neural level, at least two studies indicate opposing effects of HIV and MA. Effects on cortical volume are opposite (increased volume of basal ganglia in MA, cortical volume loss in HIV), although both conditions are associated with cognitive impairment (Jernigan et al., 2005). On tasks of motor programming, HIV and MA produced less aberrant patterns of activation than either condition alone despite similar levels of impairment (Archibald et al., 2012). In addition, behavioral evidence indicates that stimulant use may partially mitigate some HIV-associated deficits. Before the widespread availability of cART, psychostimulants were proposed as an adjuvant treatment for HIV+ individuals in order to mitigate symptoms of cognitive dysfunction (Fernandez & Levy, 1990). Specifically with regard to reaction time performance, methylphenidate has been associated with improved reaction times on computerized measures in individuals demonstrating either HIV-associated cognitive slowing or depressive symptoms, while individuals without cognitive slowing at study entry did not show increased benefit from methylphenidate relative to a placebo (Hinkin et al., 2001). It is possible that some individuals in the HIV+MA+ group may demonstrate additional cognitive slowing if not for their MA use.

It is worth noting that there were no significant differences observed between study groups on the QCAE, a measure of self-reported cognitive (e.g., "I can usually appreciate the other person's viewpoint, even if I do not agree with it") and affective empathy (e.g., "I can tell if someone is masking their true emotion"). The groups were comparable on all subscales of the measure, which may be surprising given robust differences on performance-based measures, in particular, those requiring affective ToM. In fact, self-ratings of social competence have not commonly been associated with performance-based measures of social cognition or interpersonal functioning (e.g., Brackett et al., 2006). Results of other studies indicate that this discrepancy

between self-reported abilities and performance-based abilities may be driven more by personality factors underlying perceived competence than insight into real-world functioning difficulties. To explore other aspects of self-reported social and community functioning, we also examined measures of social support and social network size and complexity, which we hypothesized may be impacted in groups with lower performance-based ToM. Interestingly, the four groups did not significantly differ in terms of their perceived social support, based on their responses on a measure that assessed feelings of “having someone they could count on,” both emotionally and instrumentally. However, all three risk groups differed significantly from comparison participants on numeric indices of current social network size and complexity. Notably, scores on this measure have been significantly associated with immune functioning (which has clear implications for the HIV+ groups; Cohen et al., 1997) as well as other important outcomes including amygdala volume (Bickart et al., 2011) and amygdala-cortical functional connectivity (Bickart et al., 2012). Although individuals in our sample reported experiencing relatively comparable levels of support, these numeric estimates suggest that those in our risk groups may have more fragile social networks, and that the loss of significant persons would have a larger proportionate impact on their overall levels of emotional and instrumental support. HIV+ and MA+ individuals may therefore be at elevated risk of poorer outcomes associated with lower levels of social and interpersonal engagement. Across many populations spanning the lifespan, these risks are significant; for example, socially isolated people have two to four times increased risk of all-cause mortality compared with those with extended ties to friends, relatives, and the community (e.g., Bowling & Grundy, 1998). In samples of older adults, an active and socially integrated life has been found to be protective against cognitive declines, and

additionally improve prognosis after stroke and other acute events (Fratiglioni, Paillard-Borg, & Winblad, 2004), even when controlling for the impact chronic health conditions (Barnes et al., 2004). Social disengagement has been associated with increased risk for mortality as well as conversion to a higher level of cognitive dysfunction at 3-year, 6-year, and 12-year follow-up (Bassuk, Glass, & Berkman, 1999). In terms of mood, patients with poorer ToM during remission from acute episodes of major depressive disorder are at higher risk of relapsing within 1 year (Inoue, Yamada, & Kanba, 2006). In light of these and other findings, it appears that the social cognitive deficits exhibited by our study groups may be associated with meaningful adverse outcomes (specifically, smaller and less complex social networks), which may themselves be associated with increased risk in terms of mood/quality of life as well as cognition and health outcomes. Further study may continue to elucidate other functional correlates of impaired ToM that are more specific to the context of HIV disease and substance use.

After characterizing group differences across several measures of ToM, we examined the correspondence between ToM and one particularly important set of everyday functioning outcomes. Specifically, we examined the incidence of HIV transmission risk behaviors in HIV+ individuals, controlling for MA group status. Models including ToM indices and MA group status significantly predicted many indices of recent and lifetime risk behavior. However, contrary to expectations, these models were not driven by significant main effects of ToM; only Eyes Task accuracy and reaction time approached significance in these models. Although we may have expected to observe higher rates of risk behavior engagement in HIV+MA+ based on evidence of more sexual partners, decreased condom use, prostitution, and sex with known injection drug users in MA users (e.g., Molitor et al., 1998), we expected that

poorer ToM may also independently increase risk behavior engagement. After all, the vast majority of HIV transmission scenarios (e.g., deciding whether or not to engage in sexual contact; sharing of illicit substance paraphernalia) are inherently interpersonal (Logan, Cole, & Leukefeld, 2002), recruiting social cognitive processes and requiring ongoing assessment of risk (Kohler, Behrman & Watkins, 2007). Several possibilities may explain the lack of significant associations between ToM and risk behaviors in our HIV+ sample. First, the HIV+ groups did not significantly differ in their attitudes, intentions, or expectations to have safe sex, whereas significant differences were apparent in recent and remote risk behaviors. Conscious risk appraisal, therefore, may be a more distal factor relative to risk behavior engagement than we had initially anticipated. If this is the case, failures in ToM that result in poorer conscious risk appraisal may not necessarily influence real-world risk outcomes. However, other more implicit affective processes may show more promise in predicting risk behaviors, consistent with prior studies suggesting that HIV risk may be rapidly inferred via implicit processes, and that unless individuals are alerted by an intuitive alarm that a substance-related or sexual behavior may be risky, effortful risk-related processing may not take place (Schmalzle et al., 2011). This hypothesis is supported by the trend-level effects we observed of Mind in the Eyes performance (a perceptual, implicit task) on risk behavior engagement, while no significant associations were observed between risk behaviors and the more conscious, reasoning-focused Combined Stories Task, which is more reliant on cognitive ToM processes.

Alternatively, the role of social cognitive processes (specifically, ToM) in determining risk appraisal, attitudes about risk, or risk behavior engagement may vary substantially based on the substance use context. This hypothesis is supported by

the differential relationships between ToM and HIV transmission risk behavior engagement in the HIV+MA- and HIV+MA+ groups. In HIV+ individuals who were not chronic users of methamphetamine, aspects of affective ToM were significantly and independently associated with indices of sexual risk behavior. Specifically, the fact that efficiency of affective ToM and not accuracy of affective ToM is associated with elevated risk behavior engagement may lend credence to one of our proposed mechanisms: slowed information processing (specifically, inefficient processing of affective social information) may contribute to risk by preventing the timely consideration of risk variables (Anand, Springer, Copenhaver, & Altice, 2010). In contrast, no significant relationships between ToM and risk behaviors were observed in HIV+MA+ individuals, the group with the highest overall scores on both sexual and substance-related risk indices. It may be that in this group, the relationship between ToM and risk behavior is washed out by the influence of proximal heavy substance use, as well as the accompanying environmental risks associated with methamphetamine in particular. MA may be expected to have a particularly profound influence on sexual risk behavior, as it is frequently used as a catalyst to initiate, enhance, and prolong sexual encounters (Halkitis, 2009), self-medicate negative affective associated with HIV+ serostatus (Semple, Patterson, & Grant, 2002). In addition, researchers have noted increased incidence of sexual risk behaviors in the service of obtaining the drug; in one recent sample, 43% of the cohort reported trading sex for methamphetamine within the past 2 months (Semple, Strathdee, Zians, & Patterson, 2010). Interestingly, our data further suggests that recent MA use may have direct effects on attitudes and intentions regarding sexual behaviors. Whereas attitudes favoring safe sex, intentions to have safe sex, and expectations of having safe sex in the HIV+ sample were moderately negatively associated with

recent and remote sexual risk behaviors (rhos between -0.35 and -0.52), significant correlations were also observed between intentions and expectations for safe sex and MA use parameters in the HIV+MA+ group. For example, having more days since last MA use was associated ($\rho = .44, p < .02$) with higher expectations to use safe sexual practices, and having fewer days since last use was associated with riskier sexual behaviors over the preceding 6 months ($\rho = -0.52, p < .01$) and over the lifespan ($\rho = -0.36, p < .01$). These data suggest that risk appraisal in HIV+MA+ individuals may be directly influenced by recency and chronicity of MA use. Providing additional incentives and supports to assist individuals early in recovery from MA may be doubly beneficial; not only may they gain traction in their recovery and continue to abstain from use, but they may also reduce engagement in sexual risk behaviors as they progress in treatment.

Based on the accumulating literature relating decision-making and other executive processing to aspects of social cognition, we initially hypothesized that decision-making performance may moderate the relationship between ToM and engagement in HIV transmission risk behaviors. However, this moderating relationship was not supported by the data. As stated above, ToM indices were not robustly associated with risk behaviors, and no significant interactions with IGT performance were observed. As has been observed by other investigators (e.g., Gonzalez et al., 2005), despite the relationships between executive dysfunction and risky choices during laboratory tasks, we did not observe significant relationships between executive dysfunction and real-world risk behaviors. Despite the prominence of decision-making deficits in chronic MA users (Chang et al., 2002, 2005; Fishbein et al., 2005) and predictive relationships with relapse (Paulus et al., 2005) and acquisition of HIV infection (Semple et al., 2005; Shrem and Halkitis, 2008), results

regarding these associations are mixed. Some investigators have observed effects of executive mediation or moderation (e.g., Solomon, 2012), while Homer and colleagues (2013) recently utilized similar ToM tasks (Mind in the Eyes, Hinting Task) and also observed null effects of executive performance on risk behaviors in HIV and MA users. It is possible that other executive substrates (e.g., inhibition; Martin et al., 2004b) or laboratory measures may be more closely related to risky behaviors, in that they may lead to increased difficulty inhibiting behaviors and biases toward choosing immediate rewards despite future consequences (Wardle, Gonzalez, Bechara, & Martin-Thormeyer, 2010). It may also be possible that the temporal precedence of executive and ToM impairments do not necessarily coincide (e.g., Homer et al., 2013); if so, future investigation of the chronology of social cognition impairments relative to deficits in other executive processes may be helpful in order to better understanding these complex relationships.

From a measurement standpoint, the current study endeavored to test ToM in a multifaceted manner; specifically, we included three measures of this construct in order to assess a broad range of ToM abilities across the four study groups. One instrument was a self-report measure, geared toward providing an estimate of individuals' subjective or perceived ToM abilities, which we hoped to contrast with objective ability on two performance-based tasks. Of the behavioral tasks selected, the Mind in the Eyes task was composed of visual stimuli; task demands were more perceptual in nature, requiring participants to correctly characterize facial expressions based on subtle visual cues. Task stimuli include photographs restricted to the eye region (outcomes included accuracy [# correct items] as well as efficiency [reaction time.]) On the other hand, the Combined Stories Task required quite different abilities. These stimuli were presented verbally as participants read a brief vignette aloud, then

answered several follow-up questions (based on information that was directly stated or could be indirectly inferred from each vignette). Naturally, this task included higher demands for participants' verbal comprehension and reasoning abilities. Due to the exploratory nature of the study, we initially aimed to measure ToM broadly in order to detect possible effects of HIV, chronic MA use, and comorbid HIV and MA dependence that may have been differentially observable across various aspects of ToM or stimulus presentations. As a consequence of the broad measurement included within the study, we were able to conduct exploratory post-hoc investigations of the correspondence between the three measures. Surprisingly, the three primary ToM tasks were observed to be orthogonal in all three risk groups; the only significant associations between tasks were observed in the healthy comparison group. In HIV-MA- individuals, a significant positive correlation was noted between self-reported ToM (QCAE Total) and accuracy on the Mind in the Eyes task (Spearman's $\rho = .37$, $p < .05$). A moderate positive association between Mind in the Eyes reaction time and QCAE Affective Empathy subscale score (Spearman's $\rho = .39$, $p < .05$) was also observed. These findings align with one proposed neuroanatomical model (Keysers & Gazzola, 2007) which distinguishes between 1) pre-reflective, intuitive tasks that promote increased activation of the premotor and parietal areas, insula, and S-II (which are typically positively associated with empathy scores) and 2) tasks requiring conscious reflection, which are associated with increased activation in ventral aspects of the medial prefrontal cortex. By this logic, Mind in the Eyes performance and QCAE self-reported affective empathy should conceivably be positively associated, whereas the Stories task would not be expected to relate as closely to other measures. The lack of significant associations between these ToM indices in the other three study groups may be due to a variety of factors, including lack of insight

(which would explain lack of self-reported difficulties in ToM in risk groups evidencing poorer laboratory-based performance). However, the presence of poorer performance across several aspects of ToM in risk groups seems to suggest a somewhat consistent pattern of impaired performance in the context of HIV disease and/or chronic methamphetamine use, which may impact daily functioning and/or important activities of daily living. ToM may therefore become a target of interventions, or may feature within other behavioral work (for example, using a modular approach within risk-reduction interventions) in order to help guide individuals toward more adaptive social and community functioning. For example, if bottom-up perceptual processes are more closely associated with risk relative to top-down processing, perhaps script learning or hands-on practice identifying “risk cues” (whether visual, verbal, situational) would be useful in order to help individuals at risk for poorer ToM more effectively recognize cues that may influence behavior via somatic marker-like mechanisms.

Given the evidence of poorer ToM in HIV+ individuals, individuals with histories of chronic MA use, and their comorbidity, a number of possibilities for intervention may be helpful in these populations. If the primary goal is to improve ToM abilities in general, several pilot studies focused on training ToM through focused social discourse have demonstrated effectiveness in this regard (e.g., Ozonoff & Miller, 1995; Guajardo & Watson, 2001), although many of these have focused on individuals with developmentally acquired deficits in social cognition. Preliminary data on Social Cognition and Interaction Training (SCIT) groups in schizophrenia, focusing on emotion and social perception, theory of mind, attributional style (e.g., blame, hostility, and aggression), cognitive flexibility, and social relationships are also encouraging, and are associated with improved social relationships and reduced

aggressiveness (Combs et al., 2007). However, if deficits in ToM and other aspects of social cognition are contributors to the smaller and less complex social networks we observed in our clinical populations, fostering these networks themselves may be another fruitful intervention target. Broader goals of facilitating community and support associated with treatment and health behaviors within populations of HIV+ and substance-using individuals may also be important steps toward developing stronger social networks and increased quality of life in these vulnerable populations, as well as promoting better disease-specific outcomes and more beneficial health outcomes. For example, studies of women with HIV indicate that those with larger social support networks report better mental health and quality of life (Gielen, McDonnell, Wu, O'Campo, & Faden, 2001). In men and women, greater levels of social and community integration has also been associated with better medication adherence in HIV (Gonzalez et al., 2004), and HIV-specific social support has been associated with reduced HIV risk behaviors (Darbes & Lewis, 2005). In addition, resources facilitating connections among HIV+ individuals and individuals in treatment for MA use may secondarily serve to reduce stigma, which has been recognized as a substantial barrier to receiving treatment in these groups (Semple, Grant, & Patterson, 2005; Sayles et al., 2009).

Although ToM indices were not significant predictors of risk behaviors, the robust effects of MA group on risk outcomes observed in HIV+ individuals highlight the necessity of tailored risk interventions geared toward this group. Historically, critiques of risk-prevention programs for HIV+ populations have been numerous; many earlier programs did not involve behavioral scientists and/or are not based on well-tested theories of behavior change, often focusing solely on providing information about HIV (Fisher & Fisher, 2000), which has consistently been shown to

be unrelated to HIV risk behavior change. However, a recent meta-analysis of newer programs effects illustrates that prevention skill-building interventions administered in healthcare contexts can be effective in reducing unprotected sex and acquisition of sexually transmitted diseases in HIV+ individuals (Crepaz et al., 2006). Notably, however, there was no significant reduction in reported rates of needle-sharing, suggesting that targeted interventions for substance users may be required to reduce these risk behaviors. Indeed, results of this dissertation underscore the elevated rates of both sexual and substance-related HIV transmission risk behaviors in HIV+ methamphetamine users, even in a cohort with relatively high educational attainment and well-managed HIV disease. Evidence from interventions including substance-use treatment components are encouraging; in one example, 1 year post-intervention, associated rates of methamphetamine and sexual risk behaviors were reduced, and reductions were noted in number of anonymous sexual partners (Reback, Larkins, & Shoptaw, 2004). Participants also reported an increased sense of responsibility to disclose their HIV status. With more tailored treatment (for example, interventions targeted specifically to men who have sex with men) in this group, robust effects above standardized interventions have also been observed. For example, one randomized controlled trial demonstrated that contingency management and CBT+contingency management conditions performed better than standard CBT arms, and culturally tailored CBT for gay men significantly reduced unprotected anal intercourse in treatment. Reductions in outcomes were sustained for one year (Shoptaw et al., 2004). A follow-up study including modified (gay-specific) CBT and contingency management arms, the combined intervention arm resulted in maximal benefit maintenance (including drug use outcomes and sexual behavior changes) after 26 weeks (Reback & Shoptaw, 2011). Overall, the evidence appears to support

drug abuse treatment programs as a primary HIV prevention strategy as well as HIV transmission prevention strategy in this population. On a larger scale, these individual-level interventions may promote a larger culture of sobriety and safer sex; Bandura's (1998) social cognitive theory cites the necessity of both self-regulatory skills to manage health habits, as well as dependable social supports. By implementing social systems to combat the methamphetamine abuse epidemic instead of aiming to change individual behavior, the current risk level demonstrated by HIV+MA+ individuals may be mitigated to some degree.

Several limitations of the present study must be acknowledged. First, the sample size of the present study is relatively small and the four groups were not well matched in terms of certain factors, including affective distress, non-MA substance use history, and neuropsychological performance. Recruiting a prospective sample that was balanced on these factors (especially in terms of global cognitive functioning) would more clearly illustrate social cognitive effects of these conditions, and alleviate the possibility that performance on these measures may be partially attributable to differences in other domains underlying ToM tasks (e.g., verbal, speed of information processing, etc.). That said, our sample is, to our knowledge, the largest of its kind to comprehensively assess ToM in these difficult-to-recruit populations, and provides a starting point in terms of identifying factors that may be taken into consideration throughout design (e.g., more comprehensive executive battery to identify ToM correlates) and recruitment (e.g., full battery completed in advance to reduce missing data due to attrition/loss to follow-up in substance users) to reduce the possibility of potential confounds. In addition, while the selected tasks provided a broad assessment of ToM abilities, appropriate normative data was not available. To increase the utility of these existing experimental measures, it would be

helpful to establish clinical cutoffs or cut points that are meaningfully associated with important outcomes. In addition, this study is limited in terms of conclusions that can be drawn regarding the clinical significance of the poorer ToM abilities that were observed in our risk groups. While risk behaviors were carefully assessed, other data that may provide an estimate of broader social and community integration would have been useful for interpretation. Future efforts might endeavor to assess social cognition in these groups more broadly, in addition to capturing other aspects of everyday functioning that are likely to be impacted by poor social cognition (e.g., historical rates of social/community functioning to assess any change over time). Future efforts may also adopt longitudinal techniques, in order to better understand the progression of social cognitive deficits throughout the course of HIV disease and/or substance addiction and recovery. This study was unable to account for whether social cognitive deficits were preexisting in the individuals at high risk for HIV acquisition or addiction, or whether these deficits were truly acquired. Prospective efforts would be better situated to address these questions. In addition, imaging techniques would be useful in order to shed light on the substrates underlying the affective deficits we observed in HIV+ and MA+ populations. Yet another potentially fruitful area for future studies might be to develop more naturalistic novel performance-based laboratory measures. For example, tasks might potentially involve confederates in order to approximate more naturalistic interactions, as well as require them to complete various social reasoning and inference tasks in real-time). This type of data may more clearly illustrate the effects of poor social cognition outside the context of developmental conditions or severe mental illness, and may be more likely to correspond to important outcomes (e.g., risk behaviors).

Overall, our findings complement and expand upon the results of previous studies by highlighting the independent effects of HIV infection and methamphetamine dependence on tasks of cognitive and affective theory of mind, and by demonstrating that having both illnesses may result in additional difficulties processing social and interpersonal information. While few relationships with risk behaviors were significant at the critical alpha required to correct for multiple comparisons in this study), several trend-level effects of ToM in HIV+ individuals suggest that ToM ability may be one among many potential determinants of risk behaviors in HIV+ individuals. Importantly, our data also illustrate the powerful contribution of MA status to high-risk sexual and substance-related behaviors. Future studies may continue to elucidate the types and extent of social cognitive impairments which may be impacted by HIV and MA dependence, as well as those which may be associated with functional difficulties or increased risk for adverse outcomes in everyday life. This type of investigation may aid in the overall goal of illustrating the effects of poor social cognition outside the context of developmental conditions or severe mental illness, which are increasingly being recognized by researchers and providers, yet remain far from well-understood.

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FIGURES



Surprised

Sure about
something

Joking

Happy

Figure 1: A sample Item from the Mind in the Eyes Test – Revised.

-- Choose the correct response to each question --

Laurie and Beth are playing in the same room.
Laurie puts away her ball in the basket and leaves
the room. Beth takes Laurie's ball and places it
in a box.

When Laurie returns to the room, where will she
think the ball is put away?

The basket

The box

Figure 2: A sample item from the Combined Stories Task.

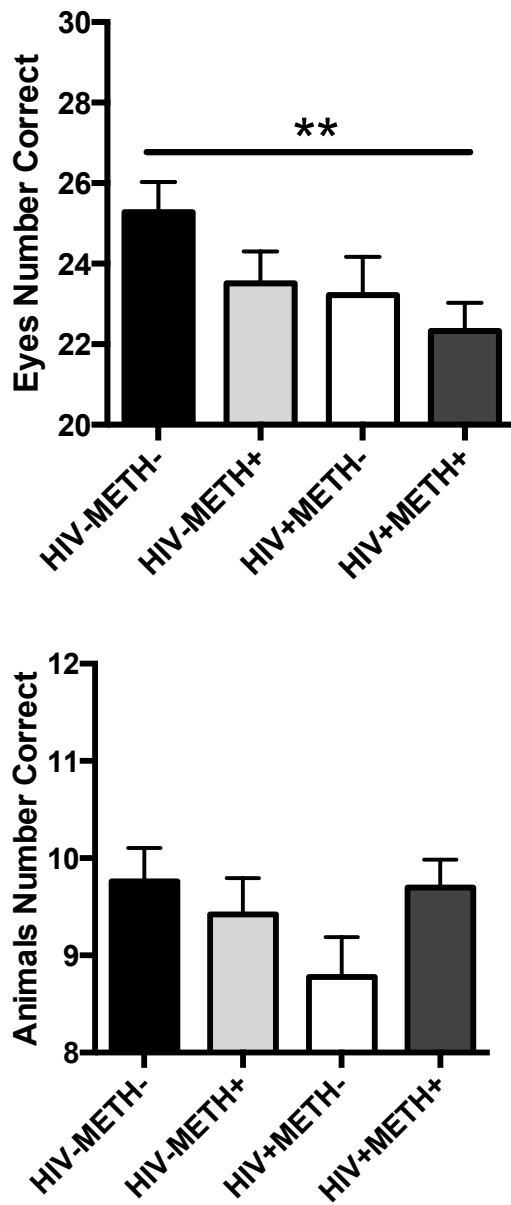


Figure 3: Accuracy by Study Group on Mind in the Eyes Test -- Revised.

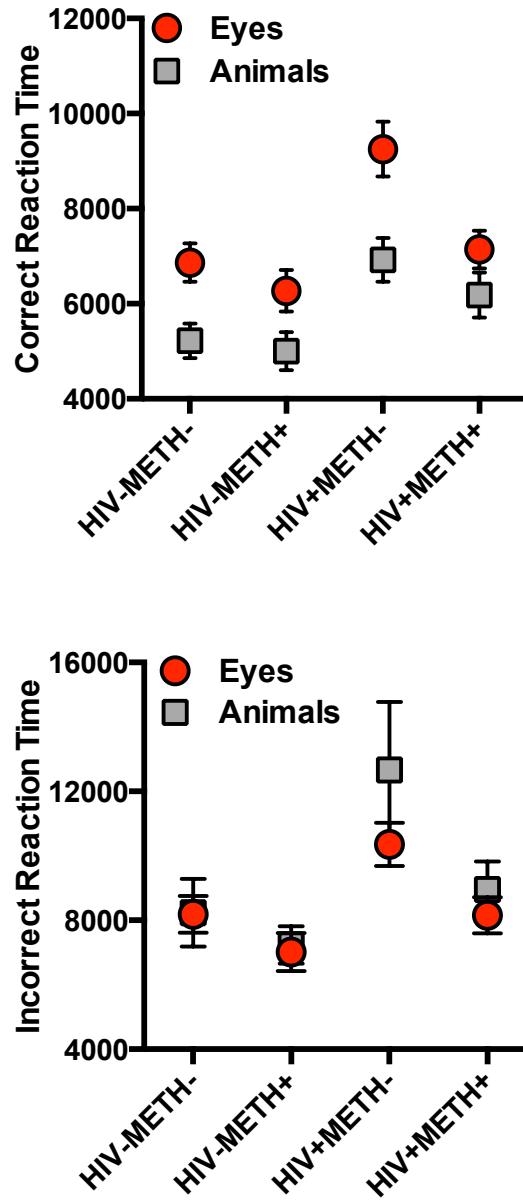


Figure 4: Reaction Time by Study Group on Mind in the Eyes Test -- Revised.

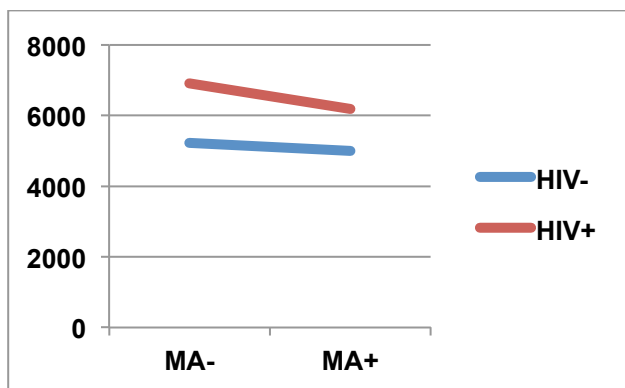
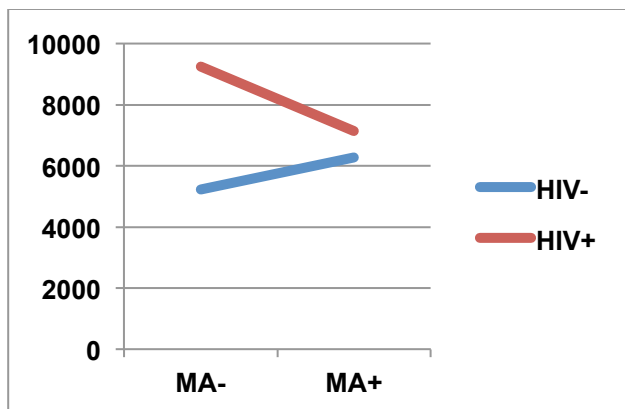


Figure 5. Correct Reaction Time by Study Group (Mind in the Eyes – Revised Mentalizing Items above; Mind in the Eyes -- Revised Control Items below).

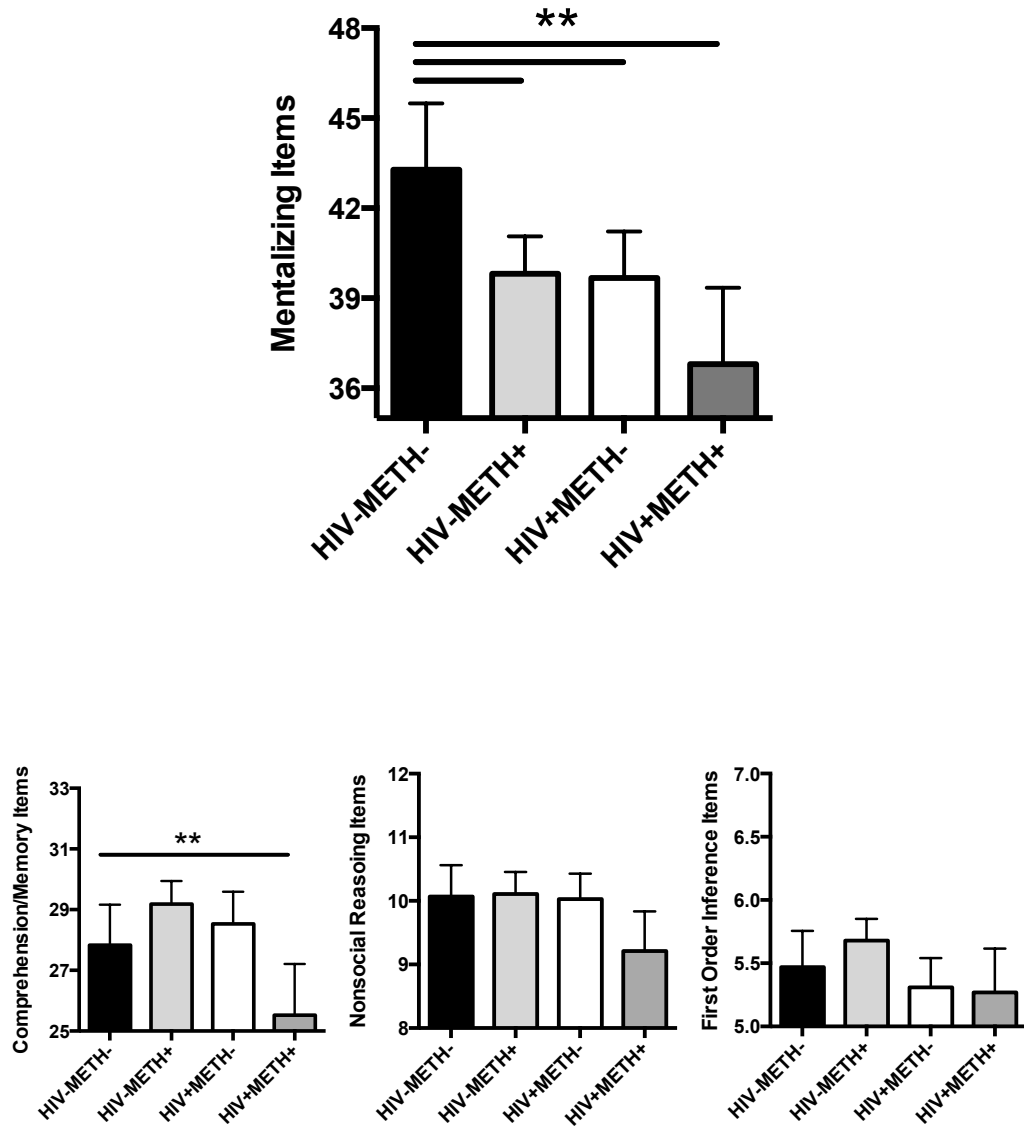
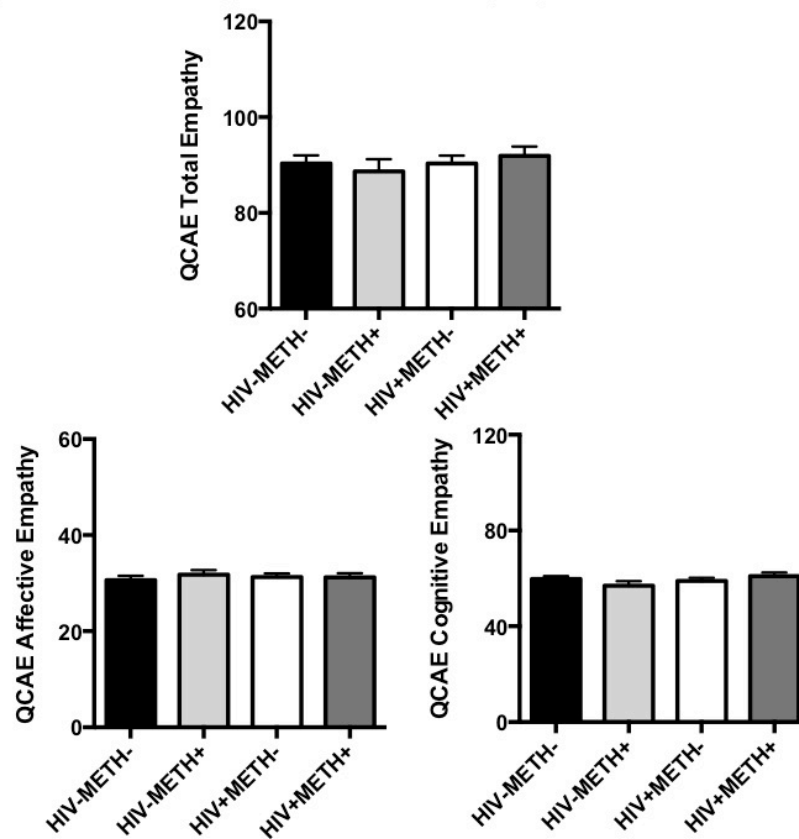


Figure 6: Combined Stories Task Performance.

(A) Questionnaire of cognitive and affective empathy

**Figure 7:** Questionnaire of Cognitive and Affective Empathy Scores.

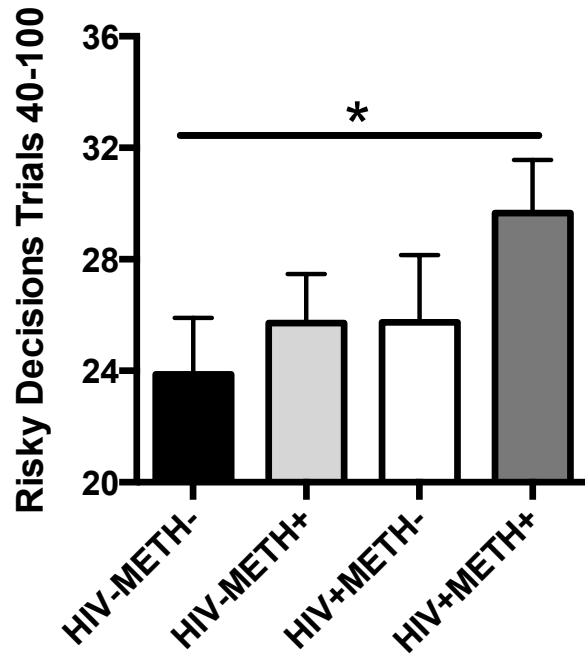


Figure 8: Iowa Gambling Task Performance.

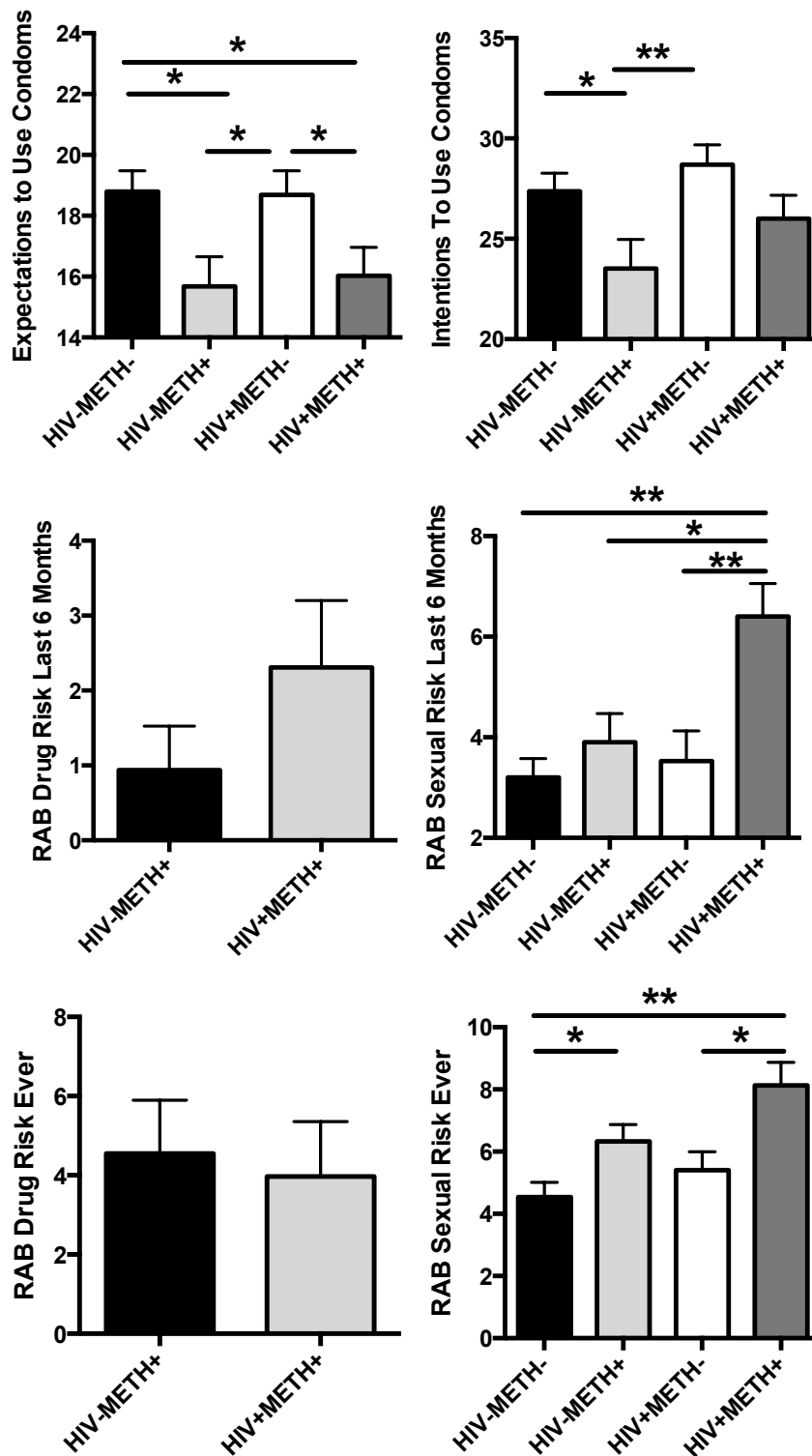


Figure 9: Transmission Risk Behaviors by Study Group.

TABLES

Table 1: Descriptive Characteristics of Participants (N= 125)

Variable	HIV-MA- (n=29)	HIV-MA+ (n=31)	HIV+MA- (n=31)	HIV+MA+ (n=33)	p
Demographic Characteristics					
Age (years)	44.7(13.0)	43.1(11.7)	45.8(12.3)	46.5(10.8)	.67
Education (years)	13.8(1.5)	12.7(1.9)	13.5(1.9)	13.3(1.8)	.02*
Word Reading (SS)	102.7(11.0)	96.1(9.7)	98.2(12.3)	96.0(10.7)	.05
Sex (% male)	51.7	74.2	83.9	90.9	.01*
Ethnicity (% Caucasian)	65.5	67.7	64.5	60.6	.79
Psychiatric Characteristics					
Total Mood Disturbance*	41.9(28.3)	59.6(40.1)	58.5(43.4)	54.6(38.2)	.27
MDD Current (%)	3.5	8.0	10.3	10.0	.75
MDD Lifetime	17.2	32.0	65.5	41.9	.01*
BDI-II	5.2(7.2)	14.6(9.3)	9.6(9.3)	13.3(10.7)	.01*
Bipolar I or II Current (%)	0%	7.7% (2)	0.0%	3.1% (1)	.23
Bipolar I or II Lifetime (% , #)	0.0%	11.5 (3)	13.8% (4)	15.2% (5)	.20
Substance Use Characteristics					
Lifetime Alcohol Dependence	10.3%	34.6%	12.9%	36.4%	.02*
<i>Lifetime Other Substance Dependence</i>					
Marijuana	3.4%	3.9%	3.2%	18.2%	.06
Cocaine	3.4%	19.2%	6.5%	18.2%	.14
Opioids	0.0%	15.4%	3.2%	15.2%	.06
Medical/HIV Disease Characteristics					
Duration of infection (months)	-	-	159.1 (107.8)	130.1 (99.8)	.30
Current CD4	-	-	567.8 (343.7)	596.4 (345.2)	.89
Nadir CD4	-	-	199.8 (166.4)	257.1 (204.0)	.25
AIDS (%)	-	-	66.7	48.3	.15
Plasma viral load (rnlog10)	-	-	1.97	2.27	.08
% Detectable	-	-	83.9%	66.7%	.13
Currently on cART	-	-	90.3%	82.1%	.36
MA Use Parameters					
Days since last use	-	108.7 (121.1)	-	102.0 (205.2)	.18
Age of first use	-	28.6 (12.5)	-	26.7 (10.1)	.69
Total Quantity	-	4444.7 (835.3)	-	3127.5 (62.9.8)	.11
Total Days	-	3078.6 (3463.3)	-	2497.1 (3079.3)	.17

Table 1: Descriptive Characteristics of Participants (N= 125), cont.

Variable	HIV-MA- (n=29)	HIV-MA+ (n=31)	HIV+MA- (n=31)	HIV+MA+ (n=33)	<i>p</i>
Neurocognitive status					
Global mean SS	10.4(1.5)	9.6(1.8)	8.8(2.6)	8.2(2.0)	>.01*
Executive SS	10.1(2.2)	9.4(2.3)	9.4(3.2)	8.5(2.3)	.11
Verbal SS	10.9(2.2)	10.6(2.5)	9.5(2.8)	9.2(2.0)	.02*
SIP SS	11.1(2.0)	10.4(2.1)	9.2(3.2)	8.8(2.2)	>.01*
Learning SS	9.3(2.0)	8.3(2.3)	7.1(2.8)	6.8(2.8)	>.01*
Recall SS	9.5(2.0)	8.7(2.4)	7.1(3.0)	6.6(3.0)	>.01*
Working Mem SS	11.0(2.0)	9.8(3.0)	9.8(3.0)	9.0(2.3)	.02*
Motor SS	10.6(3.1)	8.4(3.1)	8.7(3.5)	7.7(3.2)	.01*
Everyday Functioning					
BADL complaints	0.2 (0.4)	0.6 (1.1)	0.6 (1.0)	0.7 (0.9)	.11
IADL complaints	0.1 (0.4)	1.2 (1.8)	1.6 (2.5)	1.5 (2.1)	<.01*
IADL dependent (%)	3.5	34.6	29.0	31.3	.03*
Employed (%)	64.3	19.2	29.6	20.0	<.01*

Note. SS = Scaled score. Mem = Memory.

Table 2: Johnkheere-Terpstra Ordered Effect Test Results.

Measure		Hypothesis		Z statistic and p-value
1	Stories QM	a	Dual \leq HIV \leq Healthy	z = 1.36, p = 0.088
		b	Dual \leq METH \leq Healthy	z = 1.51, p = 0.066
2	Stories QR	a	Dual \leq HIV \leq Healthy	z = -0.32, p = 0.626
		b	Dual \leq METH \leq Healthy	z = -0.35, p = 0.636
3	Stories QC	a	Dual \leq HIV \leq Healthy	z = 1.18, p = 0.119
		b	Dual \leq METH \leq Healthy	z = 1.24, p = 0.108
4	Stories Q1	a	Dual \leq HIV \leq Healthy	z = -1.28, p = 0.899
		b	Dual \leq METH \leq Healthy	z = -1.08, p = 0.861
5	Eyes correct	a	Dual \leq HIV \leq Healthy	z = 2.76, p = 0.003
		b	Dual \leq METH \leq Healthy	z = 2.86, p = 0.002
6	Control correct	a	Dual \leq HIV \leq Healthy	z = 0.18, p = 0.430
		b	Dual \leq METH \leq Healthy	z = 0.24, p = 0.405
7	Eyes correct RT	a	Healthy \leq HIV \leq Dual	z = -0.20, p = 0.578
		b	Healthy \leq METH \leq Dual	z = 0.10, p = 0.462
8	Control correct RT	a	Healthy \leq HIV \leq Dual	z = 0.75, p = 0.228
		b	Healthy \leq METH \leq Dual	z = 1.07, p = 0.143
9	QCAE cognitive	a	Dual \leq HIV \leq Healthy	z = -0.60, p = 0.725
		b	Dual \leq METH \leq Healthy	z = -0.56, p = 0.711
10	QCAE affective	a	Dual \leq HIV \leq Healthy	z = -0.83, p = 0.797
		b	Dual \leq METH \leq Healthy	z = -0.875, p = 0.809
11	QCAE total	a	Dual \leq HIV \leq Healthy	z = -0.75, p = 0.774
		b	Dual \leq METH \leq Healthy	z = -0.59, p = 0.721

Table 3: Independent Effects of Stories Task Performance on Risk Behaviors in HIV+ Individuals ($n=64$).

Outcome	Model	Parameter (st β)	p- value
Risk Assessment Battery (RAB) Total			
Adjusted R ²	.27		
F	8.54		.0001*
MA status		-0.56	.0001*
Stories QM		-0.02	.89
LT Alcohol Dependence		0.02	.82
RAB Sexual Risk (Last 6 Months)			
Adjusted R ²	.15		
F	4.75		.0049*
MA status		-0.40	.0018*
Stories QM		0.16	.18
LT Alcohol Dependence		0.00	.96
RAB Drug Risk (Last 6 Months) Yes/No			
R ²	.31		
ChiSquare	17.62		.0005
MA status			.0001*
Stories QM			.98
LT Alcohol Dependence			.51
RAB Sexual Risk (Ever)			
Adjusted R ²	.11		
F	3.48		.0217*
MA status		-0.40	.0035*
Stories QM		0.07	.60
LT Alcohol Dependence		0.10	.45
RAB Drug Risk (Ever) Yes/No			
R ² (U)	.43		
ChiSquare	27.80		.0001*
MA status			.0001*
Stories QM			.08
LT Alcohol Dependence			.43

Note. St=standardized. Models predicting Sexual Risk Scale indices were not significant.

Table 4: Independent Effects of Eyes Task Performance on Risk Behaviors in HIV+ Individuals ($n=64$).

Outcome	Model	Parameter (st β)	p-value
Risk Assessment Battery (RAB) Total	.28		
Adjusted R ²			
F	9.07		.0002*
MA status		-0.60	<.0001*
Eyes Task RT		0.12	.29
LT Alcohol Dependence		0.02	.80
RAB Sexual Risk (Last 6 Months)			
Adjusted R ²	.13		
F	4.22		.0090*
MA status		-0.45	.0011*
Eyes Task RT		0.08	.48
LT Alcohol Dependence		0.03	.79
RAB Drug Risk (Last 6 Months) Yes/No			
R ²	.30		
ChiSquare (U)	17.63		.0005*
MA status			.0003*
Eyes Task RT			.92
LT Alcohol Dependence			.51
RAB Sexual Risk (Ever)			
Adjusted R ²	.17		
F	5.12		.0033*
MA status		-0.50	.0003*
Eyes Task RT		0.27	.0393
LT Alcohol Dependence		0.11	.36
RAB Drug Risk (Ever) Yes/No			
R ²	.40		
ChiSquare (U)	27.79		<.0001*
MA status			<.0001*
Eyes Task RT			.33
LT Alcohol Dependence			.24
Risk Assessment Battery (RAB) Total			
Adjusted R ²	.27		
F	8.54		.0002
MA status		-0.56	<.0001*
Eyes Task # Correct		0.02	.81
LT Alcohol Dependence		0.03	.88

Table 4: Effects of Eyes Task Performance on Risk Behaviors in HIV+ Individuals (n=64), cont.

Outcome	Model	Parameter (st β)	p-value
RAB Sexual Risk (Last 6 Months)	.13		
Adjusted R2	4.13		
F			.0101*
MA status		-0.43	.0011*
Eyes Task # Correct		-0.03	.83
LT Alcohol Dependence		0.06	.61
RAB Drug Risk (Last 6 Months) Yes/No			
R2	.40		
ChiSquare (U)	23.20		<.0001*
MA status			<.0001*
Eyes Task # Correct			.0181
LT Alcohol Dependence			.39
RAB Sexual Risk (Ever)			
Adjusted R2	.11		
F	3.37		.0245*
MA status		-0.41	.0025*
Eyes Task # Correct		0.00	.98
LT Alcohol Dependence		0.11	.38
RAB Drug Risk (Ever) Yes/No			
R2	.38		
ChiSquare (U)	24.90		<.0001*
MA status			<.0001*
Eyes Task # Correct			.81
LT Alcohol Dependence			.29

Note. St=standardized. Models including MA status predicting Sexual Risk Scale indices were not significant.

Table 5: Independent Effects of Decision-Making and ToM Performance on Risk Behaviors in HIV+MA- Individuals ($n=32$).

Outcome	Model	Parameter (st β)	p-value
RAB Sex Risk (Ever)			
Adjusted R2	.45		
F	8.40		.0005*
IGT (CD-AB, 40-100)		0.45	.0197
Eyes Task RT		0.69	.0001*
IGT x Eyes Task RT		0.04	.44

Table 6: Independent Effects of Decision-Making, ToM Performance, and Executive Functions on Risk Behaviors in HIV+MA- Individuals (N=32).

Outcome	Model	Parameter (st β)	p-value
RAB Sexual Risk (Ever)			
Adjusted R ²	.45		
F	6.21		.0018*
IGT (CD-AB, 40-100)		0.38	.06
Mind in Eyes Mentalizing RT		0.71	.0002*
IGT (CD-AB, 40-100) x Stories Mentalizing		-0.01	.93
Executive domain adj SS		0.14	.37

Table 7: Neuropsychological Test Battery

<i>Language</i>
Controlled Oral Word Association Test
<i>Attention/working memory</i>
Paced Auditory Serial Addition Test
WAIS-III Letter Number Sequencing
<i>Learning</i>
Hopkins Verbal Learning Test-Revised (Trials 1-3)
Brief Visuospatial Memory Test (Trials 1-3)
<i>Memory</i>
Hopkins Verbal Learning Test-Revised (Delayed recall)
Brief Visuospatial Memory Test (Delayed recall)
<i>Speed of Information Processing</i>
WAIS-III Digit Symbol & Symbol Search
Trails Part A
<i>Abstraction/Executive Functioning</i>
Wisconsin Card Sorting Test (64-item) Perseverative Responses
Trails Part B
<i>Motor</i>
Grooved Pegboard Test (Dominant & Non-Dominant Hands)

Note: WAIS-III=Wechsler Adult Intelligence Scale-III