HHS Public Access

Author manuscript

J Neuroimmune Pharmacol. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

J Neuroimmune Pharmacol. 2016 September ; 11(3): 495–510. doi:10.1007/s11481-016-9699-0.

Effects of HIV and Methamphetamine on Brain and Behavior: Evidence from Human Studies and Animal Models

Virawudh Soontornniyomkij[1], **James P. Kesby**[1,2], **Erin E. Morgan**[1], **Amanda Bischoff-Grethe**[1], **Arpi Minassian**[1], **Gregory G. Brown**[1], **Igor Grant**[1], and **Translational Methamphetamine AIDS Research Center (TMARC) Group**

[1]Department of Psychiatry, School of Medicine, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0603, USA

Abstract

Methamphetamine (Meth) use is frequent among HIV-infected persons. Combined HIV and Meth insults may exacerbate neural injury in vulnerable neuroanatomic structures or circuitries in the brain, leading to increased behavioral disturbance and cognitive impairment. While acute and chronic effects of Meth in humans and animal models have been studied for decades, the neurobehavioral effects of Meth in the context of HIV infection are much less explored. In-depth understanding of the scope of neurobehavioral phenotypes and mechanisms in HIV/Meth intersection is needed. The present report summarizes published research findings, as well as unpublished data, in humans and animal models with regard to neurobehavioral disturbance, neuroimaging, and neuropathology, and *in vitro* experimental systems, with an emphasis on findings emerging from the National Institute on Drug Abuse (NIDA) funded Translational Methamphetamine AIDS Research Center (TMARC). Results from human studies and animal (primarily HIV-1 gp120 transgenic mouse) models thus far suggest that combined HIV and Meth insults increase the likelihood of neural injury in the brain. The neurobehavioral effects include cognitive impairment and increased tendencies toward impaired behavioral inhibition and social cognition. These impairments are relevant to behaviors that affect personal and social risks, e.g. worse medication adherence, riskier behaviors, and greater likelihood of HIV transmission. The underlying mechanisms may include electrochemical changes in neuronal circuitries, injury to white matter microstructures, synaptodendritic damage, and selective neuronal loss. Utilization of research methodologies that are valid across species is instrumental in generating new knowledge with clinical translational value.

Keywords

Cognition; gp120; Inhibition; Neuroimaging; Neuropathology; Tat

Corresponding author: Virawudh Soontornniyomkij, vsoontor@ucsd.edu, Telephone: +1 858 822-4546, Fax: +1 858 534-4484.
[2]Queensland Brain Institute, The University of Queensland, St. Lucia, Qld, Australia (current affiliation)

Part of this work was previously presented at the 2015 Global Health Conference in Hangzhou, People's Republic of China.

Disclosure: The authors declare that they have no conflict of interest.

Introduction

Widespread implementation of combination antiretroviral therapy (cART) in HIV-infected populations has markedly decreased the incidence of HIV-associated dementia (HAD), the severest form of HIV-associated neurocognitive disorders (HAND) (Bhaskaran et al. 2008; Garvey et al. 2011). Nonetheless, the overall prevalence of HAND (categorized according to the Frascati research terminology and criteria (Antinori et al. 2007) into three disorders of increasing severity of neurocognitive impairment: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HAD) has not declined (Valcour et al. 2004; Nath et al. 2008; Cysique and Brew 2009; Simioni et al. 2010; Heaton et al. 2011; Bonnet et al. 2013; Sacktor et al. 2016). For example, Heaton et al. (2010) reported a cross-sectional study during 2003-2007 from six university HIV clinics across the United States (*CNS HIV Antiretroviral Therapy Effects Research* [CHARTER]). Among 1,316 HIV-infected participants who did not have major comorbid risks for central nervous system (CNS) dysfunction, 32.7% had ANI, 11.7% MND, and 2.4% HAD. The pattern of neurocognitive impairment in the cART era was found to more commonly involve memory, learning, and executive functioning domains, in contrast to that in the pre-cART era showing impairment predominant in motor skills, cognitive speed, and verbal fluency (Heaton et al. 2011; Sacktor and Robertson 2014). HAND is a multifactorial syndrome attributed to the extent of HIV infection in the CNS and shaped by an array of cofactors, such as HIV-1 genetic variants, host genetic polymorphisms, chronic cART-related neurotoxicity, hepatitis C virus (HCV) co-infection, systemic chronic inflammation and metabolic disturbance, brain aging, and substance abuse (Nightingale et al. 2014).

A variety of substances of abuse, including methamphetamine (Meth), opiates, cocaine, and alcohol, are known to induce immune suppression and enhance HIV replication (Martin-Thormeyer and Paul 2009; Salamanca et al. 2014). Accumulating evidence from neuropsychological, neuroimaging, and neuropathological studies suggests that substance abuse heightens the adverse effects of HIV infection on the CNS (Anthony et al. 2008; Rosenbloom et al. 2010; Fama et al. 2011; Pfefferbaum et al. 2012; Zahr et al. 2014). Of particular public health importance, Meth is a highly potent and addictive psychostimulant that is abused by more than 25 million people in the world, which exceeds the number of people who use heroin and cocaine (Cadet and Krasnova 2009; Passaro et al. 2015). Meth abuse is prevalent in the United States, with an estimated 569,000 persons aged 12 or older reporting Meth use in the past month in a 2014 survey (Center for Behavioral Health Statistics and Quality 2015). Meth use is associated with significant adverse public health outcomes, such as increased risk behavior (e.g. unprotected sex with multiple partners and needle sharing) with resultant infectious disease transmission risk, increased risk of morbidity and mortality, and employment, legal, social, and economic problems (Semple et al. 2004; Gonzales et al. 2010).

Meth use is disproportionately frequent among men who have sex with men (MSM) (Colfax and Shoptaw 2005). In the San Diego area (California, USA), Hoenigl et al. (2016) found that 8.5% of 8,905 MSM reported Meth use in the past 12 months, and such use was associated with higher sexual risk behavior (i.e. condomless receptive anal intercourse with an HIV-infected male, increased number of male partners, and self-reported bacterial

sexually transmitted infection). The association between Meth use and HIV seroconversion for MSM was examined using longitudinal data from the Multicenter AIDS Cohort Study at four centers located in Baltimore–Washington D.C., Chicago, Pittsburgh, and Los Angeles (USA). The relative hazard of HIV seroconversion associated significantly with Meth use was 1.46. There was a significant joint relative hazard for Meth use and number of unprotected receptive anal sexual partners of 2.71 for MSM with one partner, which increased in a dose-dependent manner for more than one partners (Plankey et al. 2007).

Meth use is also prevalent among individuals who are already infected with HIV. A clinic-based survey of HIV-infected persons in San Francisco (California, USA) showed that 20% of MSM, 16% of heterosexual men, and 15% of women reported Meth use in the past month (Mitchell et al. 2006). In annual intercept surveys of MSM in New York City (USA) from 2002 to 2007 (Pantalone et al. 2010), HIV-infected MSM were more likely than HIV-seronegative MSM to report crystal Meth use when the data were collapsed across years (15.4% and 6.5%, respectively). In a nationwide online survey in Australia (Lyons et al. 2013), 13% of 1,135 MSM (age 40 years or older) reported Meth use in the past 12 months, and such use was more frequent among HIV-infected (24%) than HIV-seronegative (11%) MSM.

Further, a proportion of HIV-infected persons may initiate Meth use after receiving HIV diagnosis. In a survey of 100 MSM who used Meth in the past six months in the New York metropolitan area (Halkitis et al. 2016), 65% of 58 HIV-infected MSM initiated Meth use after HIV seroconversion, 26% had used Meth prior to seroconversion, and the remaining 9% initiated Meth use and seroconverted in the same year. In a study of 117 individuals with HIV and lifetime history of Meth dependence (along with diagnosis of Meth dependence or abuse within the past 18 months), Montoya et al. (2016) found that approximately 80% used Meth before and continued to use after receiving HIV diagnosis, and the remaining initiated Meth use after HIV seroconversion.

In sum, Meth use is a frequent cofactor in HIV disease. Importantly, HIV-infected Meth users may have higher plasma viral loads (Ellis et al. 2003; Moore et al. 2012; Feldman et al. 2015), possibly resulting from poor medication adherence (Reback et al. 2003; Moore et al. 2012) and/or the adverse impact of Meth on antiretroviral effectiveness (Ellis et al. 2003). It is likely that HIV-infected Meth users will transmit the virus to others while engaging in risky sexual activities (Colfax and Shoptaw 2005; Passaro et al. 2015). However, select HIV-infected Meth users on cART are virally suppressed (Massanella et al. 2015).

In the human brain, the pharmacokinetics of Meth is characterized by relatively fast uptake, widespread distribution, and slow clearance, based on positron emission tomography (PET) studies with [^{11}C]-d-Meth (Fowler et al. 2008; Volkow et al. 2010). Thus, the CNS of Meth users undergoes prolonged exposure to the sympathomimetic and toxic effects of Meth. The widespread distribution of Meth was also observed in the postmortem brains of chronic Meth users with Meth present in their blood (Kalasinsky et al. 2001). Accordingly, chronic Meth use may induce long-lasting injury involving broad CNS regions and not limited to neuroanatomic structures containing presynaptic monoaminergic nerve terminals (Cadet and Krasnova 2007; Kuhn et al. 2011). In support of this notion, a PET study with [^{11}C](*R*)-

PK11195 (a radiotracer targeting the 18-kDa translocator protein enriched in activated microglia) showed higher activated microglial density in multiple brain regions of abstinent Meth users when compared to age-matched control participants (Sekine et al. 2008). Such Meth-induced immune activation in the CNS may combine with HIV-related immune activation to increase hazard of neural injury in those persons with both risk factors.

Research Overview at Translational Methamphetamine AIDS Research Center (TMARC)

The United States National Institute on Drug Abuse (NIDA) supported TMARC was founded in 2009 at University of California San Diego. TMARC works to elucidate the neurobiological mechanisms and everyday impact of HIV- and Meth-induced CNS injury. To enhance a multidisciplinary translational approach, the work of TMARC is facilitated by several Cores that support standardized protocols of human and animal assessment, as well as laboratory, neuroimaging, and neuropathological methods. As such, TMARC is structured to promote bi-directional crosstalk between clinical and animal-model investigators and methods in order to expand our understanding of the HIV and Meth effects on neurobehavioral disturbance and underlying neuropathology. The human projects reflect an effort to identify who is at risk of acquiring and spreading HIV due to a variety of behavioral and cognitive deficits. The animal models allow us to mirror these efforts with experimental control over the mechanisms of HIV- and Meth-associated CNS injury.

The human research projects examine the effects of HIV, Meth, and aging on: risk taking, decision-making, and behavioral inhibition deficits; functional and structural connectivity in risk taking; and social cognition and HIV transmission risk. Extending and complementing the human studies are animal projects using transgenic mice expressing HIV-1 proteins, which examine the effects of Meth and aging on behavior and cognition, as well as gene expression in the context of behavioral and neuropathological changes.

Animal Models of HIV and Meth Neurotoxicity

Among a range of available animal models of human NeuroAIDS, simian immunodeficiency virus (SIV) infection of Asian macaques and (natural) feline immunodeficiency virus (FIV) infection of cats may be more closely reflective of HIV infection of the human CNS compared with transgenic rodent models (Crews et al. 2008; Marcondes et al. 2010; Fox and Gendelman 2012). Nonetheless, rodent models have relative advantages in terms of ease in handling, cost-effectiveness, a variety of standardized neurobehavioral tests, and a potential for host genetic manipulation (Gorantla et al. 2012). Rodent models commonly used in NeuroAIDS research include mice transgenic for the HIV-1 envelope glycoprotein gp120 (Toggas et al. 1994), regulatory transactivator of transcription protein (Tat) (Kim et al. 2003), or viral protein R (Vpr) (Jones et al. 2007), and rats transgenic for the *gag-pol*-deleted HIV-1 genome (i.e. expressing 7 of the nine HIV-1 genes) (Reid et al. 2001). In addition, there are chimeric virus constructs (e.g. EcoHIV and EcoNDK) enabling systemic infection and neuroinvasion in mice (Potash et al. 2005), and HIV-1 infection of humanized mice (models that include a functional human immune system) (Gorantla et al. 2010).

Both HIV-1 gp120 and inducible Tat transgenic mouse models are useful for studying chronic neurotoxic effects of individual HIV proteins expressed in the CNS (Crews et al. 2008). Overall, both models have shown several neuropathological features observed in human AIDS brains (e.g. synaptodendritic loss, astrogliosis, and microgliosis) and neurobehavioral disturbances (Carey et al. 2012; Gorantla et al. 2012; Fitting et al. 2013; Marks et al. 2016). The effects of cofactors in HIV infection such as Meth exposure can be investigated in these animal models.

One of the aims of TMARC is to explore how animal studies can inform mechanisms of HIV and Meth interaction effects on the brain and behavior. To this end, studies are being conducted using both gp120 and inducible Tat transgenic mouse models. In addition to HIV protein types, the key difference between the two murine models is that gp120 protein is constitutively over-expressed in gp120 mice from conception, while the induction of Tat over-expression in Tat mice requires doxycycline treatment. Hence, with inducible Tat mice the temporal expression of Tat can be controlled to occur at various points in the life cycle (e.g. adolescence, young adulthood, and older age). The temporal control of Tat expression offers greater experimental control in relation to Meth exposure (e.g. before/during/after Meth at any age). Furthermore, both murine models are tested in the same battery of neurobehavioral paradigms, and their suitability as models of HIV neurotoxicity can be directly compared.

Behavioral and cognitive tasks in mouse models have been selected to approximate behavioral and cognitive changes noted in humans. Neuroimaging studies in animals have been attempted to parallel those in humans, both in methodology (e.g. magnetic resonance (MR) diffusion tensor imaging) and in terms of brain regions and circuitry foci. Given that a range of Meth use patterns exist in humans (Cho and Melega 2002), TMARC studies have included Meth exposure protocols for animals to elucidate the differential effects of acute, chronic, and binge Meth use.

Neurobehavioral Disturbance

In human studies, the individual and combined effects of HIV infection and Meth use on neurocognitive functioning, behavior, and daily life functioning were evaluated in adult participants classified into four risk groups (i.e. HIV–/Meth–, HIV–/Meth+, HIV+/Meth–, and HIV+/Meth+). With regard to neurocognitive functioning, seven domains were assessed: information processing speed, attention/working memory, learning, delayed recall, verbal fluency, abstraction/executive functioning, and motor/psychomotor speed, with statistical correction for demographic variables (i.e. age, sex, ethnicity, and education). Both the number and severity of deficits across the neuropsychological battery were considered to generate *global (neurocognitive) deficit scores* (i.e. the higher the score, the poorer the neurocognitive performance) (Woods et al. 2004).

Meth dependence was found to increase the rates of neurocognitive impairment in HIV-infected persons (Rippeth et al. 2004) particularly those who had advanced immune suppression (Carey et al. 2006). Even in the acute and early stages of HIV infection, Meth use was associated with neurocognitive impairment and an increased risk of clinically

significant challenges in real-world daily functioning (Doyle et al. 2013; Weber et al. 2013). In HIV-infected adults with past history of Meth dependence, Iudicello et al. (2014) showed that the impact of Meth on memory impairment might be more obvious in older age (> 50 years) compared to younger age (< 40 years).

In animal studies, the individual and combined effects of gp120 expression in the brain and Meth exposure on learning, memory, executive function, and behavioral inhibition were assessed in gp120 transgenic and littermate wild-type mice (i.e. four genotype/substance groups: gp120–/Meth–, gp120–/Meth+, gp120+/Meth–, and gp120+/Meth+). In those studies that used a *chronic Meth regimen*, the mice received either a chronic escalating-dose multiple-binge Meth regimen or saline vehicle subcutaneously for 25 days. That is, the Meth + mice were treated three times per day (10:00, 13:15, and 17:30 h) for 14 days with escalating doses of Meth, starting with 0.1 mg/kg body weight and increasing to 4.0 mg/kg, with a stepwise increase of 0.1 mg/kg per injection. After this 14-day period, the animals received four daily injections of 6.0 mg/kg Meth at 2-h intervals (10:00, 12:00, 14:00, and 16:00 h) during an 11-day *binge* period. This chronic Meth regimen was developed to mimic one of the pharmacokinetic profiles of Meth use in humans and avoid the development of Meth-induced hyperthermia (Kuczenski et al. 2007; Henry et al. 2013). Following varying periods of Meth abstinence, the mice underwent a battery of behavioral tests (Henry et al. 2013; Henry et al. 2014; Kesby et al. 2015b;Kesby et al. 2015a).

Cognitive Function

Translational studies comparing the effects of HIV infection and Meth dependence in humans with those of gp120 expression and Meth exposure in mouse models are scarce. However, these studies represent a powerful approach to the understanding of the contribution of HIV proteins to neurocognitive impairment. Kesby et al. (2015b) found strikingly similar profiles of learning impairment in humans and mouse models. For example, HIV infection in adult men, regardless of Meth dependence, was associated with impairment in the learning domain (Fig. 1a). Similarly, gp120 expression in male mice (7–8 months old), regardless of Meth exposure, was associated with impairment in discrimination learning in the attentional-set-shifting task administered two months after the completion of chronic Meth exposure (Fig. 1b). A key feature of this work was the use of similar analysis paradigms. The human testing featured a battery of tasks analyzed using adjusted *T*-scores that included all tests (relevant to the learning domain) and were accounted for age and demographics. For the mouse data, stages of discrimination learning within the attentional-set-shifting task were analyzed in an identical fashion. This analysis approach represents a novel way of comparing different tests and species when the same cognitive construct is being assessed.

In addition, this translational work by Kesby et al. (2015b) highlighted the additive effects of Meth dependence or exposure on learning impairment. In humans, the HIV+/Meth+ group had the highest proportion of learning impaired participants (66%). Similarly, the proportion of mice that failed to reach criteria throughout the attentional-set-shifting task was greatest in the gp120+/Meth+ group (54%). Accordingly, the susceptibility to, but not the severity of, learning impairment may be enhanced by Meth in HIV-infected individuals.

Kesby et al. (2015a) tested male gp120 mice (5–6 months old) in a battery of behavioral tests beginning one week after the termination of chronic Meth exposure. The gp120 expression disrupted associative memory performance in the object-in-place test, indicating contextual recognition memory impairment. Performance in the object-in-place test is heavily dependent on the functional integrity of medial prefrontal cortex, perirhinal cortex, and hippocampus circuitry (Barker et al. 2007; Barker and Warburton 2011). The gp120 expression was also associated with alterations in reversal learning in the Barnes maze test, a finding similar to that observed after Tat expression in inducible Tat mice (Kesby et al. 2016b), suggesting impairments in executive function. Meth exposure impaired spatial strategy during acquisition trials in the Barnes maze (indicating spatial learning deficit), with the gp120+/Meth+ group having the severest cognitive deficit in the final acquisition trials. Collectively, the findings suggest that HIV proteins and Meth may impair cognitive function both independently and in combination.

Behavioral Inhibition

Inhibition deficits are characterized by a reduced ability to control responses to stimuli. While some domains of inhibition such as exaggerated novelty seeking and perseveration are assessable in rodent models by quantifying activities of animals in open-field tasks, similar paradigms have not been utilized in human participants. A cross-species translational human open-field paradigm, the *human Behavior Pattern Monitor* (hBPM), was developed to be analogous to the mouse version (Young et al. 2007; Perry et al. 2009). Briefly, the hBPM is an unfamiliar room containing novel and engaging objects, where a participant is placed without instruction for a 15-minute period. Multiple domains of inhibition such as motor activity, novelty seeking, and behavioral self-regulation are collected via video recording and ambulatory monitoring of motor behavior.

Henry et al. (2011) assessed the effect of Meth dependence on inhibition deficits using the hBPM paradigm in 16 abstinent Meth-dependent adults and 18 control individuals. Meth-dependent participants exhibited increased total interactions with novel objects, greater time spent with objects, and greater repeated (perseverative) object interactions. Greater object interaction was associated with more frequent Meth use in the past year. The findings suggest that Meth dependence is associated with impaired inhibition, specifically increased novelty seeking. The advantage of using the hBPM is its ability to quantify and distinguish among multiple domains of inhibition, which may help us illuminate nuanced neurocognitive features in populations at risk of HIV transmission and substance abuse. For example, while the Henry et al. (2011) study illustrated that chronic Meth dependence increased novelty seeking, a one-time dose of amphetamine in healthy human volunteers increased motor activity without marked effects on novelty seeking in the hBPM (Minassian et al. 2016). The neurobiological differences that distinguish substance use disorders can be further elucidated in rodent models with analogous behavioral paradigms.

Inhibition deficits in Meth dependence appear to be related to risky decision-making, which is an important relationship to understand given that risky behaviors may increase HIV transmission. In the risky gains task (Paulus et al. 2003a), participants make serial decisions about whether to accept or reject a monetary amount displayed on a screen. Participants can

either choose to collect the smallest amount (i.e. the safe choice) or wait for the next trial, in which the amount doubles in value but also there is a risk of monetary loss rather than gain (i.e. the risky choice). With this task, one can assess the relative frequency of safe and risky choices. In preliminary studies of HIV-infected Meth-dependent participants (Minassian and Bischoff-Grethe, TMARC Projects 1 and 2, unpublished data), higher motor activity in the hBPM (quantified by increased movement counts) was found to correlate with a riskier decision-making strategy (i.e. higher frequency of risky choices in a behavioral choice paradigm) (Pearson $r = 0.66$, $p = 0.005$, $n = 16$). Furthermore, riskier decision-making was associated with poorer neurocognitive performance among HIV-infected Meth-dependent participants, as illustrated by an inverse correlation between global (neurocognitive) deficit scores and performance scores in the Iowa Gambling Task (Pearson $r = -0.48$, $p = 0.003$, $n = 38$). Elucidating specific *profiles* of inhibition deficits in HIV and Meth populations may aid the development of targeted cognitive and behavioral treatment interventions.

Based on self-report measures (rather than informant report, observation, or performance-based methods), Marquine et al. (2014) found that Meth dependence was independently associated with greater impulsivity/disinhibition, sensation seeking, and apathy (collectively called *frontal systems behavior*), whereas HIV infection was independently associated only with greater apathy. No significant combined effects of HIV and Meth were observed on these behavioral domains. Global neurocognitive impairment was relatively independent of frontal systems behavior.

In animal studies, Henry et al. (2013) assessed behavioral inhibition deficits in male and female mice, manifesting as increased motor activity, inappropriate perseverative behavior, and elevated exploratory response to novel stimuli. Chronic Meth exposure alone increased novel object interaction, indicating behavioral disinhibition. Female gp120+/Meth+ mice showed the highest level of exploration (hole-poking) compared to the other female mouse groups. The gp120 mice exhibited less rearing and slightly less locomotion, relative to the wild-type mice. The findings suggest both gp120 expression and chronic Meth exposure modify behavioral inhibition, but such effects may be sex-dependent. Although robust gender differences have not been reported in human studies using the analogous behavioral paradigm (i.e. the hBPM), it is important to examine gender differences in HIV and Meth interaction effects given potential gender or estrogen-related differences in CNS HIV infection (Wilson et al. 2006) and Meth neurotoxicity (Dluzen et al. 2003).

Prepulse Inhibition (PPI, a measure of sensorimotor gating) is regulated by a network of neural structures including the dopaminergic circuitry implicated in inhibitory function. PPI can be assessed across species. Impaired sensorimotor inhibition, measured by PPI of the eyeblink startle response, was observed in HIV-infected persons with neurocognitive impairment (in the domain of working memory in particular) compared to cognitively intact HIV-infected persons (Minassian et al. 2013), suggesting that early inhibition deficits accompany or may even precede downstream cognitive impairment in HIV-infected individuals.

In animal studies, Henry et al. (2014) studied PPI of the acoustic startle response in male and female mice. Before the beginning of chronic Meth exposure, female gp120 mice

exhibited decreased PPI compared with female wild-type mice, whereas male gp120 mice showed increased acoustic startle response compared with the other three groups. After seven days of Meth withdrawal, no consistent gp120 effect was observed, but (male and female) Meth-exposed mice exhibited increased PPI compared with vehicle-exposed mice. Sensorimotor gating has also been studied in other rodent models of HIV neurotoxicity and Meth exposure. For example, alterations in sensorimotor gating were reported in adolescent male HIV-1 transgenic F344 rats with acute Meth exposure (Moran et al. 2012). As the dose of Meth increased, PPI of the acoustic startle response decreased in both HIV-1 transgenic and wild-type rat groups. The HIV-1 rats displayed a greater dose-dependency to the Meth-induced disruption of PPI compared to the wild-type animals. There were also alterations in the dopaminergic system, as evidenced by lower tyrosine hydroxylase (TH) protein levels and higher monoamine oxidase A (MAOA) protein levels (based on Western blot analysis of midbrain extracts) in HIV-1 rats compared to wild-type animals in the context of acute Meth exposure (Moran et al. 2012). In another study, sensorimotor gating alterations were described in adult ovariectomized female HIV-1 transgenic Sprague–Dawley rats compared with wild-type animals (Moran et al. 2013). These two studies did not specifically explore potential sex differences in HIV-1 transgenic rat models.

The findings in rodents, along with the results in humans indicating PPI deficits in HIV-infected persons with neurocognitive impairment (Minassian et al. 2013), suggest that inhibition deficits, which likely reflect HIV- and Meth-related alterations in dopaminergic signaling, may not occur as a global phenomenon but may emerge in association with higher-order cognitive deficits or biological variations, e.g. those affected by sex. The potential moderating effects of sex or estrogen warrant further investigation.

Social Cognition and Everyday Functioning

Social cognition in general refers to the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intention, disposition, and behavior of others. Although there is a growing body of literature showing that HIV infection and Meth use impact social cognition independently, very few studies have examined these effects in combination. TMARC has preliminary data on social cognition that suggest HIV infection in combination with Meth use may alter complex social behavior. An active study (TMARC Project 3) is collecting prospective data to examine these effects and potential relationship of social cognition deficits to behaviors in the real world. A critical aspect of social interactions that is affected by HIV and Meth is that individual is reading the emotions of others, which is typically measured as *facial affect recognition*. Preliminary data from TMARC Project 3 showed a large effect size for a comparison that revealed poorer facial affect recognition performance among HIV+/Meth+ individuals relative to HIV–/Meth– participants, with smaller effects observed for each single-risk group in comparison to the HIV–/Meth– group (Morgan, unpublished data).

Another domain of social cognition is *theory of mind*, which involves the ability to infer the intention, disposition, and beliefs of others (Green et al. 2008) across both emotional and cognitive information. Based on TMARC Project 3 pilot data (Morgan and Cattie, unpublished data), the HIV+/Meth+ group (compared to the HIV–/Meth– group) exhibited

impairment in the domain of *emotional* theory of mind, as measured by the Reading the Mind in the Eyes task (Baron-Cohen et al. 2001). This task is a typical measure that requires the participant to select the emotional perspective of another person based on presentation of eyes alone, without the benefit of other facial expression cues such as smiling, frowning, raising eyebrows, etc. Impairment in the domain of *cognitive* theory of mind [as measured by the Faux Pas Recognition task (Stone et al. 1998)] was shown in each of the three risk groups compared to the HIV–/Meth– group, with the HIV+/Meth+ group being most severely affected. One prior study to date demonstrated a combined effect of HIV and Meth on emotional, but not cognitive, theory of mind (Homer et al. 2013).

Taken together, these preliminary findings suggest that HIV infection and Meth use impair social cognition. This reduced emotional and cognitive resonance with others may manifest as real world difficulties in a variety of ways. Preliminary data have shown that among HIV-infected individuals, deficient emotional theory of mind was associated with poor everyday functioning in domains that specifically involved interacting with others, such as communication ability and employment status, but no relationship was observed for tasks that did not rely upon such interactions (Grabyan, Morgan et al., unpublished data). A currently unexplored yet critical real world domain that may also be impacted by social cognition deficits is HIV-related risk behavior. For example, failure to accurately read the emotional and cognitive perspective of others may lead persons to engage in risky behaviors with individuals whom they might not trust if their emotional theory of mind was intact, especially in people with impaired decision-making. Although hypothetical at this time, this relationship can be conceptualized in the context of the somatic marker hypothesis of affective decision-making (Bechara and Damasio 2005). This hypothesis states that negative experiences are *tagged* with somatic markers so that the next time when a similar situation is encountered, the somatic marker serves as a warning about the potential danger of the current situation. People with deficient theory of mind may not optimally develop these somatic markers for social situations involving risk, in part because they are not skilled at reading the emotions and intentions of others, which typically serve as an important basis for judging the relative riskiness of activities such as sexual intercourse (particularly unprotected anal sex, which carries a high risk of HIV transmission).

Importantly, the relationship of impaired social cognition to HIV transmission risk may also operate in the opposite direction, as some consider *empathy* to be a dimension of social cognition. HIV-infected individuals with decreased empathy, which has been observed among Meth users, may be more likely to disregard the risk to others of engaging in unprotected sex (namely, transmission of HIV and/or other sexually transmitted diseases). Additionally, a recent review of impaired social functioning among Meth users noted that a major reason that people abuse Meth is to facilitate social interactions, such as decreasing social or sexual inhibitions and extending the duration of these interactions [see (Homer et al. 2008)]. As such, Meth use may be a method of *self-medicating* social cognition deficits, with the unintended consequence of elevating the riskiness of the interaction. Project 3 of TMARC aims to directly examine the relationship between various domains of social cognition ability and HIV transmission risk behavior, which may shed light on this proposed relationship.

In a large cohort of 798 participants, Blackstone et al. (2013) assessed functional dependence including neurocognitive symptoms in daily life, instrumental and basic activities of daily living, and employment status. Both individual and combined effects of HIV infection and Meth use were observed across all measures of functional dependence. The frequency of global functional dependence was increased in the expected stepwise manner across the cohort, with the lowest in the HIV–/Meth– group (29%) and the highest in the HIV+/Meth+ group (69%). Within the HIV+/Meth+ group, functional dependence was associated with neurocognitive impairment, lower cognitive reserve, polysubstance use, and major depressive disorder. Collectively, the findings suggest that everyday functional dependence observed particularly in HIV-infected Meth users may be related to impaired social cognition; nonetheless, further human studies are needed to test this notion.

Sensitivity to Meth Reward

Using gp120 transgenic mice (3–4 months old), Kesby et al. (2014) investigated the effects of gp120 expression on associative learning, preference for Meth, and sensitivity to the conditioned rewarding properties of Meth. The gp120 mice exhibited no deficits in basic associative learning or motivation for natural reinforcer such as food pellets. In the two-bottle choice procedure with restricted access to Meth, the gp120 mice showed greater preference for Meth than the wild-type mice, indicating that gp120 expression enhanced the primary reinforcing properties of Meth. In the conditioned place preference test assessing drug seeking or incentive motivation associated with Meth reward, the gp120 mice showed Meth-induced conditioned place preference at lower Meth doses compared with the wild-type mice, indicating increased sensitivity to conditioned rewarding effects of Meth. Taken together, these findings suggest that gp120 expression alters brain reward function in response to Meth. A recent study in Tat transgenic mice has also demonstrated persistent increases in the sensitivity to Meth-induced reward enhancement (Kesby et al. 2016a), suggesting multiple HIV proteins may contribute to altered reward function. It is possible that the reward system is altered in HIV-infected individuals such that the susceptibility to Meth use is increased in this population.

Meth-Induced Stereotypic Behavior

The effects of repeated Meth administration were assessed on stereotypic behavior, such as head movement and rearing posture, as well as Meth-induced locomotor sensitization in adult male HIV-1 transgenic rats (3 months old) compared to wild-type animals (Liu et al. 2009). The head movement and rearing were determined daily for six days within three hours following intraperitoneal injection of 2.5 mg/kg body weight per day Meth or saline vehicle. Repeated Meth exposure induced progressive increases in stereotypic head movement and the number and duration of rearing in both HIV-1 rats and wild-type animals, but the effect of Meth was greater in the HIV-1 rats. In addition, the HIV-1 rats showed increased Meth-induced locomotor sensitization compared to wild-type animals, suggesting abnormalities in sensitivity to motivational effects of Meth.

Further, the effects of repeated Meth exposure on various domains of stereotypic behavior and locomotion were investigated in gp120 transgenic mice (9–13 months old) compared to littermate wild-type animals (Roberts et al. 2010). Mice received either intraperitoneal

injections of Meth at four increasing doses (1, 5, 10, and 30 mg/kg body weight) or saline vehicle across a period of two months. The gp120 effect was observed on certain stereotypic behavior such as head-up sniffing and total vertical activity, in which the gp120 mice exhibited higher response to Meth exposure compared to the wild-type animals. Collectively, the findings in both rat and mouse models suggest that Meth effects on stereotypic behavior may be enhanced in the presence of HIV protein expression.

Neuroimaging

In a structural MR imaging study in human participants (Jernigan et al. 2005), HIV infection was associated with decreased volumes of cortical, limbic, and striatal structures, while Meth dependence was associated with increased volumes of the parietal cortex and basal ganglia. Neurocognitive impairment correlated with decreased cortical volumes in HIV-infected participants but increased cortical volumes in Meth-dependent participants.

The combined effects of HIV infection and chronic Meth use (dependence or abuse) were observed on cerebral metabolite abnormalities denoting neuronal injury (lower *N*-acetylaspartate levels in the frontal cortex, frontal white matter, and basal ganglia) and glial activation (higher *myo*-inositol and choline levels in the frontal white matter), measured with proton MR spectroscopy (Chang et al. 2005). In another similar study (Taylor et al. 2007), the effects of Meth on cerebral metabolite alterations were not evident, but Meth appeared to modify the effects of HIV such that plasma HIV-1 RNA levels were found to correlate inversely with *N*-acetylaspartate levels and directly with *myo*-inositol levels in the frontal white matter only in the HIV+/Meth+ group.

In preliminary human studies, Brown et al. (TMARC Neuroimaging Core, unpublished data) used MR diffusion tensor imaging (DTI) to examine fractional anisotropy (FA, a DTI marker thought to represent CNS white matter integrity) in HIV-infected persons ($n = 18$), Meth-dependent participants ($n = 19$), and age- and education-matched control individuals ($n = 20$). Whole brain DTI images were acquired axially on a 1.5T General Electric magnet using a 2D spin echo, echo-planar imaging protocol (number of shots = 1; number of echoes = 1; TR = 9.7 s; TE = minimum; field of view (FOV) = 24 cm; matrix = 96 × 96; inplane resolution 2.5 × 2.5 mm; 46 interleaved slices, no spaces; slice thickness = 2.5 mm; $b = 0$, 1000 s/mm^2; 51 gradient directions, field maps to correct image distortions). Eddy current distortions were corrected using FSL's eddy current routine; FSL's DTI fit was used to fit the tensor model to diffusion data from each voxel. FA and related DTI parameters were calculated from the model fitted eigenvalues. The diffusion off image was co-registered to the subject's T1-weighted image using an affine transformation. The T1-weighted image was warped into the Talairach space and the joint co-registration and Talairach transformations were applied to the FA and related DTI maps to move each subject's DTI images into a standard space.

Results from the above studies (Brown et al., TMARC Neuroimaging Core, unpublished data) showed that HIV infection was associated generally with reduced FA in the cerebral white matter compared with the control (Fig. 2a). This finding was in keeping with other published data (Ragin et al. 2004; Stebbins et al. 2007; Hoare et al. 2011; Leite et al. 2013).

However, in Meth dependence the FA varied (either increased or slightly reduced in comparison to that in the control) from one region to another (Fig. 2a) (Kim et al. 2009; Zhuang et al. 2016). Furthermore, the correlation between the cerebral white mater FA and the global (neurocognitive) deficit scores (GDS) was examined in each of the risk groups. In the majority of cerebral white matter regions, FA measures correlated inversely with GDS in HIV infection, but directly with GDS in Meth dependence (Fig. 2b). In other words, neurocognitive impairment was associated with reduced FA in HIV-infected persons [in agreement with other published studies (Hoare et al. 2012; Stubbe-Drger et al. 2012)] but with increased FA in Meth-dependent participants.

Functional neuroimaging has demonstrated altered frontostriatal circuitry. In a *resting-state* functional MR study (Ipser et al. 2015), the HIV+ group ($n = 15$), compared to the HIV– group ($n = 15$), showed reduced dorsal caudate connectivity to frontal and parietal brain regions. Furthermore, reduced connectivity in the HIV+ group was observed between the dorsal caudate and dorsolateral prefrontal cortex, particularly in younger participants. These reductions were associated with cognitive impairment, as measured by global (neurocognitive) deficit scores. Results from *task-based* functional MR imaging also support HIV- associated alterations in frontostriatal tracts. Participants (21 HIV+ and 19 HIV–) performed the risky gains task during functional MR imaging (Connolly et al. 2014). While the two groups did not differ in terms of their behavior (i.e. exhibiting similar rates of risky decision-making), the HIV+ group (compared to the HIV– group) showed greater activation for risky choices within the caudate, anterior cingulate, and dorsolateral prefrontal cortex, but lower activation for safe choices within the anterior cingulate and dorsolateral prefrontal cortex. In addition, HIV-infected individuals with higher nadir CD4 T-cell counts demonstrated lower differential responses to safe versus risky choices in these regions (i.e. activation patterns more similar to those observed in HIV-seronegative individuals). This suggests that the severity of historical immunosuppression may exert a legacy effect on processing of risky choices in the HIV-infected brain.

An important question is whether risky behavior is driven by altered reactivity to positively or negatively valenced stimuli. Meth users are well known for dysfunctional decision-making, particularly influenced by the immediately preceding choice (Paulus et al. 2003b), and less able to adjust their decision-making based upon short-term versus long-term gains (Gonzalez et al. 2007). However, the neural functioning of expectancy and receipt of gains and losses remains unclear. A functional MR study was conducted to examine responses within the striatum to a probabilistic feedback expectancy task (Bischoff-Grethe, TMARC Project 2, unpublished data). Participants (17 Meth+ and 23 Meth–) were given visual cues that were probabilistically associated with monetary gain, loss, or neutral outcomes. The Meth+ group had lower functional activation to loss anticipation than the Meth– group in the ventral striatum and posterior caudate. The Meth+ group also demonstrated greater activation to loss outcomes than to gain outcomes in the anterior and posterior caudate. This decreased response to loss anticipation, along with the greater response to loss outcomes, suggests an altered ability to evaluate future risks and benefits based upon prior experience, thereby increasing the likelihood of poorer decision-making and increased risky behavior.

In animal studies, McKenna et al. (2016) characterized the long-lasting effects of chronic Meth exposure on the brain microstructure in male wild-type mice. The mice received either a chronic escalating-dose multiple-binge Meth regimen or saline vehicle subcutaneously for 25 days. After 3–4 months of Meth abstinence, the mice (9–10 months old) underwent *in vivo* MR DTI. There were four patterns of differential fractional anisotropy and mean diffusivity response in different neuroanatomic structures when comparing Meth-exposed mice with vehicle-exposed animals. Of note in the Meth-exposed mouse group, mean diffusivity correlated inversely with calbindin-1 (a member of the high-affinity cytosolic EF-hand family of intracellular calcium-binding proteins) immunoreactivity density in the dorsal hippocampus and directly with dopamine transporter immunoreactivity density in the caudate-putamen. The findings obtained from DTI in animal models are readily translatable across species. Importantly, region-specific signal alterations detected on DTI of the human brain may be utilized as the surrogate for brain neurochemical changes that are impractical to confirm directly in living humans.

Neuropathology

The effects of chronic Meth use on neuropathological changes have been investigated in postmortem HIV-infected brains (Langford et al. 2003; Everall et al. 2005; Chana et al. 2006). Langford et al. (2003) reported that among HIV encephalitis brains, those of chronic Meth users showed higher degrees of CD45-immunoreactive microgliosis and synaptophysin (SYP, a presynaptic terminal marker) immunoreactivity loss in the frontal cortex. In addition, selective loss of calbindin-1-immunoreactive interneurons in the frontal cortex was described particularly in the brains of HIV-infected Meth users with evidence of HIV encephalitis (Langford et al. 2003), which correlated with memory impairment (Chana et al. 2006). Everall et al. (2005) reported that transcript expression of select interferon-inducible genes in the frontal cortex was up-regulated in HIV encephalitis brains of Meth users compared with HIV encephalitis brains and HIV-infected brains (without significant pathology) of individuals with no history of Meth use. In all these studies, an association of Meth use with greater neuropathological changes was described in brains with HIV encephalitis. While the findings might not be applicable directly to virally suppressed individuals, they may be still useful in the current era of cART since the majority of people living with HIV are not virally suppressed (Skarbinski et al. 2015).

Recent studies using postmortem HIV-infected brains have addressed nuclear DNA methylation, mitochondrial DNA injury, and cerebral gliosis (Desplats et al. 2014; Soontornniyomkij et al. 2016; Var et al. 2016). Epigenetic changes were investigated in the frontal cortex of HIV-infected individuals with or without Meth dependence (Desplats et al. 2014). Meth was associated with increased expression levels of *DNMT1* gene (DNA (cytosine-5)-methyltransferase-1 enzyme involved in the maintenance of DNA methylation) and increased levels of global DNA methylation that correlated directly with HIV-1 RNA levels. Genome-wide profiling of DNA methylation in a subset of cases revealed differential methylation in select host genes involved in cellular pathways such as dopamine metabolism and transport. These findings suggest that HIV and Meth may act together in the brain to alter expression of select genes by regulating their DNA methylation.

In a clinico-pathological study of 78 HIV-infected individuals, Soontornniyomkij et al. (2016) showed that lifetime Meth dependence (based on the evaluation at the final follow-up visit closest to death, 18 persons with past diagnosis of Meth dependence and two persons with current diagnosis of Meth dependence) was associated with cerebral microgliosis (immunoreactivity for ionized calcium-binding adapter molecule-1 [Iba1]) in the temporo-parietal region. This association remained significant even after statistically adjusting for biologically-relevant covariates including HIV encephalitis, white matter lesions, opportunistic diseases, HCV seropositivity, and lifetime dependence on alcohol, opiates, and cannabis. However, there was no significant association of lifetime Meth dependence with microgliosis in the frontal or putamen-internal capsule region. No significant association was found between lifetime Meth dependence and other neuropathological changes including cerebral astrogliosis (glial fibrillary acidic protein [GFAP]), synaptodendritic (SYP and microtubule-associated protein-2 [MAP2, a somatodendritic marker]) loss in the frontal cortex, cerebral β-amyloid plaque deposition, and arteriolosclerosis in the forebrain white matter. These findings suggest that some of the pathological changes in certain brain regions might be reversible and have gradually diminished following extended abstinence from Meth (Volkow et al. 2001; Wang et al. 2004; Nordahl et al. 2005; Sekine et al. 2008; Salo et al. 2011; Yang et al. 2015). It is also possible that some of the brain pathological changes examined in this study (Soontornniyomkij et al. 2016) might not have been induced by Meth in the first place (Kitamura et al. 2010; Tong et al. 2014). It is possible that susceptibility to Meth neurotoxicity might vary from region to region in the CNS (Wang et al. 2004; Kuhn et al. 2011).

While a large number of animal studies have reported the effects of acute or chronic Meth exposure on various neuroanatomic structures (Kuczenski et al. 2007; Krasnova and Cadet 2009; Clark et al. 2013; Loftis and Janowsky 2014; Frank et al. 2016), to date only a few studies focused on the combined effects of HIV and Meth in animal models such as SIV-infected macaques (Bortell et al. 2015), FIV-infected cats (Huitron-Resendiz et al. 2010), and HIV-1 gp120 transgenic mice (Hoefer et al. 2015).

Hoefer et al. (2015) exposed gp120 mice of both sexes (3–4 months old) to a chronic escalating-dose multiple-binge Meth regimen via subcutaneous injection route for 25 days. Long-lasting effects of Meth were assessed after 6–7 months of Meth abstinence. The Barnes maze test revealed both gp120 expression and Meth exposure impaired spatial learning and memory, and the combination resulted in the most compromised performance. Neither gp120 expression nor Meth exposure affected locomotion. Electrophysiological studies in hippocampal slices showed that both gp120 expression and Meth exposure were associated with reduced long-term potentiation of synaptic transmission. Only gp120+/Meth + mice displayed reduced post-tetanic potentiation. Using fluorescence immunohistochemistry for SYP (a presynaptic terminal marker) and MAP2 (a somatodendritic marker), both gp120 expression and Meth exposure were associated with synaptodendritic loss in the hippocampus and cerebral cortex. The pattern of gene expression in the brain that was affected by gp120 expression and Meth exposure suggested a disturbance in the composition of both gamma-aminobutyric acid (GABA) and glutamate neurotransmitter systems. The findings suggest that chronic toxic effects of Meth on the CNS are long-lasting.

In Vitro Experimental Studies

Interactions between substances of abuse and HIV-1 gp120 and Tat proteins facilitate disruption of the blood-brain barrier, release of tissue necrosis factor-alpha (TNF) and other cytokines, up-regulation of C-C motif chemokine receptor-5 (CCR5) expression, and induction of oxidative stress (Martin-Thormeyer and Paul 2009). The toxic effects of either Meth or Tat or both on the blood-brain barrier, neurons, and glial cells have been investigated extensively in *in vitro* cell systems (Cisneros and Ghorpade 2012; Borgmann and Ghorpade 2015; Mediouni et al. 2015). Both Meth and Tat inhibited astroglial Wnt/β-catenin signaling (Sharma et al. 2011; Henderson et al. 2012). In astroglia, negative regulators of Wnt/β-catenin signaling were found to increase the degree of permissiveness to HIV replication, up-regulate the expression of transcription factors involved in the production of pro-inflammatory cytokines and chemokines, and down-regulate glutamine synthetase (an enzyme catalyzing the conversion of the excitatory neurotransmitter glutamate and ammonia into glutamine) (Al-Harthi 2012).

Addictive psychostimulants increase extracellular dopamine in select dopaminergic neuroanatomic structures in the CNS (Di Chiara and Bassareo 2007; Gaskill et al. 2013). The circulating CD14+/CD16+ monocyte subpopulation plays a critical role in HIV neuropathogenesis (Ellery et al. 2007; Fischer-Smith et al. 2008; Buckner et al. 2011). In an *in vitro* study by Coley et al. (2015), dopamine, as well as the D1-like dopamine receptor agonist SKF38393, increased migration and adhesion of CD14+/CD16+ monocytes (expressing all five dopamine receptors). In prior reports, dopamine increased the number of HIV-infected cells in primary cultures of human monocyte-derived macrophages (Gaskill et al. 2009) and the production of monocyte chemoattractant protein-1 (MCP1, also known as C-C motif chemokine ligand-2 [CCL2]) by macrophages (Gaskill et al. 2012). Collectively, these findings suggest that once CD14+/CD16+ monocytes transmigrate across the blood-brain barrier into the CNS parenchyma in response to chemokines, elevated extracellular dopamine in the brain (inherent to the context of Meth use) can promote the accumulation of CD14+/CD16+ monocytes in dopaminergic brain regions, thereby facilitating HIV persistence in the CNS, as well as local neuroinflammation.

Summary

Through a multidisciplinary and translational approach, the TMARC group is elucidating the complex patterns of adverse effects on brain structure and function due to HIV infection, Meth use, and their combination. Employing human and mouse studies in parallel allows for a unique opportunity to compare across these studies and to capitalize on the strengths of one approach to inform the other. For example, human studies provide the most direct and generalizable window into the target population. Nonetheless, the inherently quasi-experimental or associative nature of the human studies with significant variability of key features (e.g. host genetic profile, HIV-1 genetic variant, and degree of Meth use) limits the investigation of mechanisms of CNS injury. To complement this work, the mouse models adopted by TMARC allow for experimental control that facilitates targeted examination of the factors involved in neural injury and neurobehavioral disturbance. The use of two transgenic mouse models (i.e. HIV-1 gp120 and inducible Tat), with differences in the type

and temporal characteristics of HIV protein expression in the CNS, can further pinpoint the role of these proteins in CNS damage and their possible additive or synergistic effects with Meth.

Most findings from TMARC animal studies described in the present report are derived from gp120 transgenic mice in the first funding cycle. Studies using inducible Tat transgenic mice are being conducted in the second cycle, and the results are about to emerge (Kesby et al. 2016a; Kesby et al. 2016b). Findings from both humans and animal models thus far support the notion that combined HIV infection and Meth use increase the likelihood of neural injury in the CNS. The neurobehavioral effects include cognitive impairment and increased tendencies toward impaired behavioral inhibition and social cognition. These neurobehavioral impairments are relevant to important behaviors that affect personal and social risks, e.g. worse medication adherence, riskier behaviors, and greater likelihood of HIV transmission. The mechanistic underpinnings of neurobehavioral disturbance may include electrochemical alterations in neuronal circuitries, injury to white matter microstructures, and damage to synapses and dendrites, and ultimately selective neuronal loss. Mechanisms of combined HIV- and Meth-induced CNS injury may include increased trafficking of macrophages into the brain mediated by dopamine, favoring neuroinflammation, and possibly development of a viral reservoir in the brain.

Continuation of TMARC work will allow us to determine the relative strengths and limitations of the rodent models with respect to reproducing HIV- and Meth-associated neurobehavioral deficits. In addition to clarifying the neurotoxic mechanisms, the animal models may be helpful in exploring neuroprotective measures. As the older HIV-infected population is growing (Centers for Disease Control and Prevention 2014), TMARC Projects are also examining the effect of aging as another cofactor. It is of interest to study the potential influence of suppressive cART on neurobehavioral outcomes in HIV-infected Meth users (Massanella et al. 2015). Utilization of research methodologies that are translatable across species is instrumental in generating new knowledge with clinical translational value.

Acknowledgments

This work was supported by the United States National Institutes of Health (NIH) grants P50 DA026306 (to I. Grant, G. G. Brown, A. Minassian, A. Bischoff-Grethe, E. E. Morgan, and V. Soontornniyomkij), P01 DA012065 (to I. Grant), T32 DA031098 (to I. Grant), P30 MH062512 (to I. Grant), R01 MH105319 (to V. Soontornniyomkij), R01 MH096648 (to V. Soontornniyomkij), and R01 AG043384 (to V. Soontornniyomkij).

The Translational Methamphetamine AIDS Research Center (TMARC) is supported by Center award P50 DA026306 from the National Institute on Drug Abuse (NIDA) and is affiliated with the University of California, San Diego (UCSD), the Sanford-Burnham Medical Research Institute (SBMRI), and the University of California, Irvine (UCI). The TMARC is composed of: Director – Igor Grant, M.D.; Co-Directors – Ronald J. Ellis, M.D., Ph.D., Scott L. Letendre, M.D., and Cristian L. Achim, M.D., Ph.D.; Center Manager – Mariana Cherner, Ph.D.; Associate Center Manager – Erin E. Morgan, Ph.D.; Assistant Center Manager – Aaron M. Carr, B.A.; Behavioral Assessment and Medical (BAM) Core–Neuromedical and Laboratory Unit (NLU): Scott L. Letendre, M.D. (Core Co-Director/NLU Chief), Ronald J. Ellis, M.D., Ph.D.; BAM Core–Neuropsychiatric Unit (NPU): Robert K. Heaton, Ph.D. (Core Co-Director/NPU Chief), J. Hampton Atkinson, M.D., Thomas D. Marcotte, Ph.D., Erin E. Morgan, Ph.D., Matthew Dawson (NPU Manager); Neuroimaging (NI) Core: Gregory G. Brown, Ph.D. (Core Director), Thomas T. Liu, Ph.D., Miriam Scadeng, Ph.D., Christine Fennema-Notestine, Ph.D., Sarah L. Archibald, M.A., John R. Hesselink, M.D., Mary Jane Meloy, Ph.D., Craig E.L. Stark, Ph.D.; Neuroscience and Animal Models (NAM) Core: Cristian L. Achim, M.D., Ph.D. (Core Director), Marcus Kaul, Ph.D., Virawudh Soontornniyomkij, M.D.; Pilot and Developmental (PAD) Core: Mariana Cherner, Ph.D. (Core Director), Stuart A. Lipton, M.D., Ph.D.; Pilot Study Leaders: Jennifer E. Iudicello, Ph.D., Assawin Gongvatana, Ph.D., Rachel D. Schrier, Ph.D., Virawudh Soontornniyomkij, M.D., Marta Massanella, Ph.D.; Administrative Coordinating Core

(ACC)–Data Management and Information Systems (DMIS) Unit: Anthony C. Gamst, Ph.D. (Unit Chief), Clint Cushman, B.A. (Unit Manager); ACC–Statistics Unit: Florin Vaida, Ph.D. (Unit Chief), Ian S. Abramson, Ph.D., Reena Deutsch, Ph.D., Anya Umlauf, M.S.; ACC–Participant Unit: J. Hampton Atkinson, M.D. (Unit Chief), Jennifer Marquie-Beck, M.P.H. (Unit Manager); Project 1: Arpi Minassian, Ph.D. (Project Director), William Perry, Ph.D., Mark A. Geyer, Ph.D., Jared W. Young, Ph.D.; Project 2: Amanda B. Grethe, Ph.D. (Project Director), Susan F. Tapert, Ph.D., Assawin Gongvatana, Ph.D.; Project 3: Erin E. Morgan, Ph.D. (Project Director), Igor Grant, M.D.; Project 4: Svetlana Semenova, Ph.D. (Project Director); Project 5: Marcus Kaul, Ph.D. (Project Director). The views expressed in this article are those of the authors and do not reflect the official policy or position of the United States Government.

References

Al-Harthi L. Interplay between Wnt/β-catenin signaling and HIV: virologic and biologic consequences in the CNS. J Neuroimmune Pharmacol. 2012; 7:731–739. [PubMed: 23065461]

Anthony IC, Arango JC, Stephens B, Simmonds P, Bell JE. The effects of illicit drugs on the HIV infected brain. Front Biosci. 2008; 13:1294–1307. [PubMed: 17981630]

Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007; 69:1789–1799. [PubMed: 17914061]

Barker GR, Warburton EC. When is the hippocampus involved in recognition memory? J Neurosci. 2011; 31:10721–10731. [PubMed: 21775615]

Barker GR, Bird F, Alexander V, Warburton EC. Recognition memory for objects, place, and temporal order: a disconnection analysis of the role of the medial prefrontal cortex and perirhinal cortex. J Neurosci. 2007; 27:2948–2957. [PubMed: 17360918]

Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The “Reading the Mind in the Eyes” Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J Child Psychol Psychiatry. 2001; 42:241–251. [PubMed: 11280420]

Bechara A, Damasio AR. The somatic marker hypothesis: A neural theory of economic decision. Game Econ Behav. 2005; 52:336–372.

Bhaskaran K, Mussini C, Antinori A, Walker AS, Dorrucci M, Sabin C, Phillips A, Porter K. Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy. Ann Neurol. 2008; 63:213–221. [PubMed: 17894380]

Blackstone K, Iudicello JE, Morgan EE, Weber E, Moore DJ, Franklin DR, Ellis RJ, Grant I, Woods SP. Human immunodeficiency virus infection heightens concurrent risk of functional dependence in persons with long-term methamphetamine use. J Addict Med. 2013; 7:255–263. [PubMed: 23648641]

Bonnet F, Amieva H, Marquant F, Bernard C, Bruyand M, Dauchy FA, Mercié P, Greib C, Richert L, Neau D, Catheline G, Dehail P, Dabis F, Morlat P, Dartigues JF, Chêne G. Cognitive disorders in HIV-infected patients: are they HIV-related? AIDS. 2013; 27:391–400. [PubMed: 23079813]

Borgmann K, Ghorpade A. HIV-1, methamphetamine and astrocytes at neuroinflammatory Crossroads. Front Microbiol. 2015; 6:1143. [PubMed: 26579077]

Bortell N, Morsey B, Basova L, Fox HS, Marcondes MC. Phenotypic changes in the brain of SIV-infected macaques exposed to methamphetamine parallel macrophage activation patterns induced by the common gamma-chain cytokine system. Front Microbiol. 2015; 6:900. [PubMed: 26441851]

Buckner CM, Calderon TM, Willams DW, Belbin TJ, Berman JW. Characterization of monocyte maturation/differentiation that facilitates their transmigration across the blood-brain barrier and infection by HIV: implications for NeuroAIDS. Cell Immunol. 2011; 267:109–123. [PubMed: 21292246]

Cadet JL, Krasnova IN. Interactions of HIV and methamphetamine: cellular and molecular mechanisms of toxicity potentiation. Neurotox Res. 2007; 12:181–204. [PubMed: 17967742]

Cadet JL, Krasnova IN. Molecular bases of methamphetamine-induced neurodegeneration. Int Rev Neurobiol. 2009; 88:101–119. [PubMed: 19897076]

Carey AN, Sypek EI, Singh HD, Kaufman MJ, McLaughlin JP. Expression of HIV-Tat protein is associated with learning and memory deficits in the mouse. Behav Brain Res. 2012; 229:48–56. [PubMed: 22197678]

Carey CL, Woods SP, Rippeth JD, Gonzalez R, Heaton RK, Grant I. Additive deleterious effects of methamphetamine dependence and immunosuppression on neuropsychological functioning in HIV infection. AIDS Behav. 2006; 10:185–190. [PubMed: 16477511]

Center for Behavioral Health Statistics and Quality. Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health. HHS Publication No SMA 15-4927, NSDUH Series H-50. 2015. Retrieved from http://www.samhsa.gov/data/

Centers for Disease Control and Prevention. HIV Surveillance Report. 2014. http://www.cdc.gov/hiv/library/reports/surveillance/, November 2015 Edition

Chana G, Everall IP, Crews L, Langford D, Adame A, Grant I, Cherner M, Lazzaretto D, Heaton R, Ellis R, Masliah E. Cognitive deficits and degeneration of interneurons in HIV+ methamphetamine users. Neurology. 2006; 67:1486–1489. [PubMed: 17060582]

Chang L, Ernst T, Speck O, Grob CS. Additive effects of HIV and chronic methamphetamine use on brain metabolite abnormalities. Am J Psychiatry. 2005; 162:361–369. [PubMed: 15677602]

Cho AK, Melega WP. Patterns of methamphetamine abuse and their consequences. J Addict Dis. 2002; 21:21–34. [PubMed: 11831497]

Cisneros IE, Ghorpade A. HIV-1, Methamphetamine and Astrocyte Glutamate Regulation: Combined Excitotoxic Implications for Neuro-AIDS. Curr HIV Res. 2012; 10:392–406. [PubMed: 22591363]

Clark KH, Wiley CA, Bradberry CW. Psychostimulant abuse and neuroinflammation: emerging evidence of their interconnection. Neurotox Res. 2013; 23:174–188. [PubMed: 22714667]

Coley JS, Calderon TM, Gaskill PJ, Eugenin EA, Berman JW. Dopamine increases CD14+CD16+ monocyte migration and adhesion in the context of substance abuse and HIV neuropathogenesis. PLoS One. 2015; 10:e0117450. [PubMed: 25647501]

Colfax G, Shoptaw S. The methamphetamine epidemic: implications for HIV prevention and treatment. Curr HIV/AIDS Rep. 2005; 2:194–199. [PubMed: 16343378]

Connolly CG, Bischoff-Grethe A, Jordan SJ, Woods SP, Ellis RJ, Paulus MP, Grant I. Translational Methamphetamine AIDS Research Center Group. Altered functional response to risky choice in HIV infection. PLoS One. 2014; 9:e111583. [PubMed: 25347679]

Crews L, Lentz MR, Gonzalez RG, Fox HS, Masliah E. Neuronal injury in simian immunodeficiency virus and other animal models of neuroAIDS. J Neurovirol. 2008; 14:327–339. [PubMed: 18780234]

Cysique LA, Brew BJ. Neuropsychological functioning and antiretroviral treatment in HIV/AIDS: a review. Neuropsychol Rev. 2009; 19:169–185. [PubMed: 19424802]

Desplats P, Dumaop W, Cronin P, Gianella S, Woods S, Letendre S, Smith D, Masliah E, Grant I. Epigenetic alterations in the brain associated with HIV-1 infection and methamphetamine dependence. PLoS One. 2014; 9:e102555. [PubMed: 25054922]

Di Chiara G, Bassareo V. Reward system and addiction: what dopamine does and doesn't do. Curr Opin Pharmacol. 2007; 7:69–76. [PubMed: 17174602]

Dluzen DE, Tweed C, Anderson LI, Laping NJ. Gender differences in methamphetamine-induced mRNA associated with neurodegeneration in the mouse nigrostriatal dopaminergic system. Neuroendocrinology. 2003; 77:232–238. [PubMed: 12766323]

Doyle KL, Morgan EE, Morris S, Smith DM, Little S, Iudicello JE, Blackstone K, Moore DJ, Grant I, Letendre SL, Woods SP. Real-world impact of neurocognitive deficits in acute and early HIV infection. J Neurovirol. 2013; 19:565–573. [PubMed: 24277439]

Ellery PJ, Tippett E, Chiu YL, Paukovics G, Cameron PU, Solomon A, Lewin SR, Gorry PR, Jaworowski A, Greene WC, Sonza S, Crowe SM. The CD16+ monocyte subset is more permissive to infection and preferentially harbors HIV-1 in vivo. J Immunol. 2007; 178:6581–6589. [PubMed: 17475889]

Ellis RJ, Childers ME, Cherner M, Lazzaretto D, Letendre S, Grant I. HIV Neurobehavioral Research Center Group. Increased human immunodeficiency virus loads in active methamphetamine users are explained by reduced effectiveness of antiretroviral therapy. J Infect Dis. 2003; 188:1820–1826. [PubMed: 14673760]

Everall I, Salaria S, Roberts E, Corbeil J, Sasik R, Fox H, Grant I, Masliah E. Methamphetamine stimulates interferon inducible genes in HIV infected brain. J Neuroimmunol. 2005; 170:158–171. [PubMed: 16249037]

Fama R, Rosenbloom MJ, Sassoon SA, Thompson MA, Pfefferbaum A, Sullivan EV. Remote semantic memory for public figures in HIV infection, alcoholism, and their comorbidity. Alcohol Clin Exp Res. 2011; 35:265–276. [PubMed: 21121935]

Feldman MB, Thomas JA, Alexy ER, Irvine MK. Crystal methamphetamine use and HIV medical outcomes among HIV-infected men who have sex with men accessing support services in New York. Drug Alcohol Depend. 2015; 147:266–271. [PubMed: 25482501]

Fischer-Smith T, Bell C, Croul S, Lewis M, Rappaport J. Monocyte/macrophage trafficking in acquired immunodeficiency syndrome encephalitis: lessons from human and nonhuman primate studies. J Neurovirol. 2008; 14:318–326. [PubMed: 18780233]

Fitting S, Ignatowska-Jankowska BM, Bull C, Skoff RP, Lichtman AH, Wise LE, Fox MA, Su J, Medina AE, Krahe TE, Knapp PE, Guido W, Hauser KF. Synaptic dysfunction in the hippocampus accompanies learning and memory deficits in human immunodeficiency virus type-1 Tat transgenic mice. Biol Psychiatry. 2013; 73:443–453. [PubMed: 23218253]

Fowler JS, Volkow ND, Logan J, Alexoff D, Telang F, Wang GJ, Wong C, Ma Y, Kriplani A, Pradhan K, Schlyer D, Jayne M, Hubbard B, Carter P, Warner D, King P, Shea C, Xu Y, Muench L, Apelskog K. Fast uptake and long-lasting binding of methamphetamine in the human brain: comparison with cocaine. Neuroimage. 2008; 43:756–763. [PubMed: 18708148]

Fox HS, Gendelman HE. Commentary: Animal models of neuroAIDS. J Neuroimmune Pharmacol. 2012; 7:301–305. [PubMed: 22549136]

Frank MG, Adhikary S, Sobesky JL, Weber MD, Watkins LR, Maier SF. The danger-associated molecular pattern HMGB1 mediates the neuroinflammatory effects of methamphetamine. Brain Behav Immun. 2016; 51:99–108. [PubMed: 26254235]

Garvey L, Winston A, Walsh J, Post F, Porter K, Gazzard B, Fisher M, Leen C, Pillay D, Hill T, Johnson M, Gilson R, Anderson J, Easterbrook P, Bansi L, Orkin C, Ainsworth J, Phillips AN, Sabin CA. HIV-associated central nervous system diseases in the recent combination antiretroviral therapy era. Eur J Neurol. 2011; 18:527–534. [PubMed: 21159073]

Gaskill PJ, Carvallo L, Eugenin EA, Berman JW. Characterization and function of the human macrophage dopaminergic system: implications for CNS disease and drug abuse. J Neuroinflammation. 2012; 9:203. [PubMed: 22901451]

Gaskill PJ, Calderon TM, Coley JS, Berman JW. Drug induced increases in CNS dopamine alter monocyte, macrophage and T cell functions: implications for HAND. J Neuroimmune Pharmacol. 2013; 8:621–642. [PubMed: 23456305]

Gaskill PJ, Calderon TM, Luers AJ, Eugenin EA, Javitch JA, Berman JW. Human immunodeficiency virus (HIV) infection of human macrophages is increased by dopamine: a bridge between HIV-associated neurologic disorders and drug abuse. Am J Pathol. 2009; 175:1148–1159. [PubMed: 19661443]

Gonzales R, Mooney L, Rawson RA. The methamphetamine problem in the United States. Annu Rev Public Health. 2010; 31:385–398. [PubMed: 20070191]

Gonzalez R, Bechara A, Martin EM. Executive functions among individuals with methamphetamine or alcohol as drugs of choice: preliminary observations. J Clin Exp Neuropsychol. 2007; 29:155–159. [PubMed: 17365250]

Gorantla S, Poluektova L, Gendelman HE. Rodent models for HIV-associated neurocognitive disorders. Trends Neurosci. 2012; 35:197–208. [PubMed: 22305769]

Gorantla S, Makarov E, Finke-Dwyer J, Castanedo A, Holguin A, Gebhart CL, Gendelman HE, Poluektova L. Links between progressive HIV-1 infection of humanized mice and viral neuropathogenesis. Am J Pathol. 2010; 177:2938–2949. [PubMed: 21088215]

Green MF, Penn DL, Bentall R, Carpenter WT, Gaebel W, Gur RC, Kring AM, Park S, Silverstein SM, Heinssen R. Social cognition in schizophrenia: an NIMH workshop on definitions, assessment, and research opportunities. Schizophr Bull. 2008; 34:1211–1220. [PubMed: 18184635]

Halkitis PN, Levy MD, Solomon TM. Temporal relations between methamphetamine use and HIV seroconversion in gay, bisexual, and other men who have sex with men. J Health Psychol. 2016; 21:93–99. [PubMed: 24578373]

Heaton RK, Clifford DB, Franklin DR, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 2010; 75:2087–2096. [PubMed: 21135382]

Heaton RK, Franklin DR, Ellis RJ, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol. 2011; 17:3–16. [PubMed: 21174240]

Henderson LJ, Sharma A, Monaco MC, Major EO, Al-Harthi L. Human immunodeficiency virus type 1 (HIV-1) transactivator of transcription through its intact core and cysteine-rich domains inhibits Wnt/β-catenin signaling in astrocytes: relevance to HIV neuropathogenesis. J Neurosci. 2012; 32:16306–16313. [PubMed: 23152614]

Henry BL, Minassian A, van Rhenen M, Young JW, Geyer MA, Perry W. Effect of methamphetamine dependence on inhibitory deficits in a novel human open-field paradigm. Psychopharmacology (Berl). 2011; 215:697–707. [PubMed: 21279333]

Henry BL, Geyer MA, Buell MR, Perry W, Young JW, Minassian A. Prepulse inhibition in HIV-1 gp120 transgenic mice after withdrawal from chronic methamphetamine. Behav Pharmacol. 2014; 25:12–22. [PubMed: 24281153]

Henry BL, Geyer MA, Buell M, Perry W, Young JW, Minassian A. Translational Methamphetamine AIDS Research Center Group. Behavioral effects of chronic methamphetamine treatment in HIV-1 gp120 transgenic mice. Behav Brain Res. 2013; 236:210–220. [PubMed: 22960458]

Hoare J, Fouche JP, Spottiswoode B, Sorsdahl K, Combrinck M, Stein DJ, Paul RH, Joska JA. White-Matter damage in Clade C HIV-positive subjects: a diffusion tensor imaging study. J Neuropsychiatry Clin Neurosci. 2011; 23:308–315. [PubMed: 21948892]

Hoare J, Westgarth-Taylor J, Fouche JP, Spottiswoode B, Paul R, Thomas K, Stein D, Joska J. A diffusion tensor imaging and neuropsychological study of prospective memory impairment in South African HIV positive individuals. Metab Brain Dis. 2012; 27:289–297. [PubMed: 22569999]

Hoefer MM, Sanchez AB, Maung R, de Rozieres CM, Catalan IC, Dowling CC, Thaney VE, Pina-Crespo J, Zhang D, Roberts AJ, Kaul M. Combination of methamphetamine and HIV-1 gp120 causes distinct long-term alterations of behavior, gene expression, and injury in the central nervous system. Exp Neurol. 2015; 263:221–234. [PubMed: 25246228]

Hoenigl M, Chaillon A, Moore DJ, Morris SR, Smith DM, Little SJ. Clear links between starting methamphetamine and increasing sexual risk behavior: a cohort study among men who have sex with men. J Acquir Immune Defic Syndr. 2016; 71:551–557. [PubMed: 26536321]

Homer BD, Halkitis PN, Moeller RW, Solomon TM. Methamphetamine use and HIV in relation to social cognition. J Health Psychol. 2013; 18:900–910. [PubMed: 22992584]

Homer BD, Solomon TM, Moeller RW, Mascia A, DeRaleau L, Halkitis PN. Methamphetamine abuse and impairment of social functioning: a review of the underlying neurophysiological causes and behavioral implications. Psychol Bull. 2008; 134:301–310. [PubMed: 18298273]

Huitron-Resendiz S, Henriksen SJ, Barr MC, Testa MP, Crawford E, Parsons LH, Sanchez-Alavez M, Phillips TR. Methamphetamine and lentivirus interactions: reciprocal enhancement of central nervous system disease. J Neurovirol. 2010; 16:268–278. [PubMed: 20608774]

Ipser JC, Brown GG, Bischoff-Grethe A, Connolly CG, Ellis RJ, Heaton RK, Grant I. Translational Methamphetamine AIDS Research Center Group. HIV infection is associated with attenuated frontostriatal intrinsic connectivity: a preliminary study. J Int Neuropsychol Soc. 2015; 21:203–213. [PubMed: 25824201]

Iudicello JE, Morgan EE, Gongvatana A, Letendre SL, Grant I, Woods SP. Detrimental impact of remote methamphetamine dependence on neurocognitive and everyday functioning in older but not younger HIV+ adults: evidence for a legacy effect? J Neurovirol. 2014; 20:85–98. [PubMed: 24470237]

Jernigan TL, Gamst AC, Archibald SL, Fennema-Notestine C, Mindt MR, Marcotte TD, Marcotte TL, Heaton RK, Ellis RJ, Grant I. Effects of methamphetamine dependence and HIV infection on cerebral morphology. Am J Psychiatry. 2005; 162:1461–1472. [PubMed: 16055767]

Jones GJ, Barsby NL, Cohen EA, Holden J, Harris K, Dickie P, Jhamandas J, Power C. HIV-1 Vpr causes neuronal apoptosis and in vivo neurodegeneration. J Neurosci. 2007; 27:3703–3711. [PubMed: 17409234]

Kalasinsky KS, Bosy TZ, Schmunk GA, Reiber G, Anthony RM, Furukawa Y, Guttman M, Kish SJ. Regional distribution of methamphetamine in autopsied brain of chronic human methamphetamine users. Forensic Sci Int. 2001; 116:163–169. [PubMed: 11182268]

Kesby JP, Markou A, Semenova S. Cognitive deficits associated with combined HIV gp120 expression and chronic methamphetamine exposure in mice. Eur Neuropsychopharmacol. 2015a; 25:141–150. [PubMed: 25476577]

Kesby JP, Markou A, Semenova S. The effects of HIV-1 regulatory TAT protein expression on brain reward function, response to psychostimulants and delay-dependent memory in mice. Neuropharmacology. 2016a; doi: 10.1016/j.neuropharm.2016.06.011

Kesby JP, Hubbard DT, Markou A, Semenova S. Expression of HIV gp120 protein increases sensitivity to the rewarding properties of methamphetamine in mice. Addict Biol. 2014; 19:593–605. [PubMed: 23252824]

Kesby JP, Markou A, Semenova S. Group T. Effects of HIV/TAT protein expression and chronic selegiline treatment on spatial memory, reversal learning and neurotransmitter levels in mice. Behav Brain Res. 2016b; 311:131–140. [PubMed: 27211061]

Kesby JP, Heaton RK, Young JW, Umlauf A, Woods SP, Letendre SL, Markou A, Grant I, Semenova S. Methamphetamine exposure combined with HIV-1 disease or gp120 expression: comparison of learning and executive functions in humans and mice. Neuropsychopharmacology. 2015b; 40:1899–1909. [PubMed: 25652249]

Kim BO, Liu Y, Ruan Y, Xu ZC, Schantz L, He JJ. Neuropathologies in transgenic mice expressing human immunodeficiency virus type 1 Tat protein under the regulation of the astrocyte-specific glial fibrillary acidic protein promoter and doxycycline. Am J Pathol. 2003; 162:1693–1707. [PubMed: 12707054]

Kim IS, Kim YT, Song HJ, Lee JJ, Kwon DH, Lee HJ, Kim MN, Yoo DS, Chang Y. Reduced corpus callosum white matter microstructural integrity revealed by diffusion tensor eigenvalues in abstinent methamphetamine addicts. Neurotoxicology. 2009; 30:209–213. [PubMed: 19135475]

Kitamura O, Takeichi T, Wang EL, Tokunaga I, Ishigami A, Kubo S. Microglial and astrocytic changes in the striatum of methamphetamine abusers. Leg Med (Tokyo). 2010; 12:57–62. [PubMed: 20110187]

Krasnova IN, Cadet JL. Methamphetamine toxicity and messengers of death. Brain Res Rev. 2009; 60:379–407. [PubMed: 19328213]

Kuczenski R, Everall IP, Crews L, Adame A, Grant I, Masliah E. Escalating dose-multiple binge methamphetamine exposure results in degeneration of the neocortex and limbic system in the rat. Exp Neurol. 2007; 207:42–51. [PubMed: 17603040]

Kuhn DM, Angoa-Pérez M, Thomas DM. Nucleus accumbens invulnerability to methamphetamine neurotoxicity. ILAR J. 2011; 52:352–365. [PubMed: 23382149]

Langford D, Adame A, Grigorian A, Grant I, McCutchan JA, Ellis RJ, Marcotte TD, Masliah E. Patterns of selective neuronal damage in methamphetamine-user AIDS patients. J Acquir Immune Defic Syndr. 2003; 34:467–474. [PubMed: 14657756]

Leite SC, Correa DG, Doring TM, Kubo TT, Netto TM, Ferracini R, Ventura N, Bahia PR, Gasparetto EL. Diffusion tensor MRI evaluation of the corona radiata, cingulate gyri, and corpus callosum in HIV patients. J Magn Reson Imaging. 2013; 38:1488–1493. [PubMed: 23559497]

Liu X, Chang L, Vigorito M, Kass M, Li H, Chang SL. Methamphetamine-induced behavioral sensitization is enhanced in the HIV-1 transgenic rat. J Neuroimmune Pharmacol. 2009; 4:309–316. [PubMed: 19444617]

Loftis JM, Janowsky A. Neuroimmune basis of methamphetamine toxicity. Int Rev Neurobiol. 2014; 118:165–197. [PubMed: 25175865]

Lyons A, Pitts M, Grierson J. Methamphetamine use in a nationwide online sample of older Australian HIV-positive and HIV-negative gay men. Drug Alcohol Rev. 2013; 32:603–610. [PubMed: 24219659]

Marcondes MC, Flynn C, Watry DD, Zandonatti M, Fox HS. Methamphetamine increases brain viral load and activates natural killer cells in simian immunodeficiency virus-infected monkeys. Am J Pathol. 2010; 177:355–361. [PubMed: 20489154]

Marks WD, Paris JJ, Schier CJ, Denton MD, Fitting S, McQuiston AR, Knapp PE, Hauser KF. HIV-1 Tat causes cognitive deficits and selective loss of parvalbumin, somatostatin, and neuronal nitric oxide synthase expressing hippocampal CA1 interneuron subpopulations. J Neurovirol. 2016; doi: 10.1007/s13365-016-0447-2

Marquine MJ, Iudicello JE, Morgan EE, Brown GG, Letendre SL, Ellis RJ, Deutsch R, Woods SP, Grant I, Heaton RK. “Frontal systems” behaviors in comorbid human immunodeficiency virus infection and methamphetamine dependency. Psychiatry Res. 2014; 215:208–216. [PubMed: 24290100]

Martin-Thormeyer EM, Paul RH. Drug abuse and hepatitis C infection as comorbid features of HIV associated neurocognitive disorder: neurocognitive and neuroimaging features. Neuropsychol Rev. 2009; 19:215–231. [PubMed: 19468837]

Massanella M, Gianella S, Schrier R, Dan JM, Perez-Santiago J, Oliveira MF, Richman DD, Little SJ, Benson CA, Daar ES, Dube MP, Haubrich RH, Smith DM, Morris SR. Methamphetamine Use in HIV-infected Individuals Affects T-cell Function and Viral Outcome during Suppressive Antiretroviral Therapy. Sci Rep. 2015; 5:13179. [PubMed: 26299251]

McKenna BS, Brown GG, Archibald S, Scadeng M, Bussell R, Kesby JP, Markou A, Soontornniyomkij V, Achim C, Semenova S. Microstructural changes to the brain of mice after methamphetamine exposure as identified with diffusion tensor imaging. Psychiatry Res. 2016; 249:27–37. [PubMed: 27000304]

Mediouni S, Garibaldi Marcondes MC, Miller C, McLaughlin JP, Valente ST. The cross-talk of HIV-1 Tat and methamphetamine in HIV-associated neurocognitive disorders. Front Microbiol. 2015; 6:1164. [PubMed: 26557111]

Minassian A, Young JW, Cope ZA, Henry BL, Geyer MA, Perry W. Amphetamine increases activity but not exploration in humans and mice. Psychopharmacology (Berl). 2016; 233:225–233. [PubMed: 26449721]

Minassian A, Henry BL, Woods SP, Vaida F, Grant I, Geyer MA, Perry W. Translational Methamphetamine AIDS Research Center Group. Prepulse inhibition in HIV-associated neurocognitive disorders. J Int Neuropsychol Soc. 2013; 19:709–717. [PubMed: 23552464]

Mitchell SJ, Morris SR, Kent CK, Stansell J, Klausner JD. Methamphetamine use and sexual activity among HIV-infected patients in care--San Francisco, 2004. AIDS Patient Care STDS. 2006; 20:502–510. [PubMed: 16839249]

Montoya JL, Cattie J, Morgan E, Woods SP, Cherner M, Moore DJ, Atkinson JH, Grant I. The impact of age, HIV serostatus and seroconversion on methamphetamine use. Am J Drug Alcohol Abuse. 2016; 42:168–177. [PubMed: 26837461]

Moore DJ, Blackstone K, Woods SP, Ellis RJ, Atkinson JH, Heaton RK, Grant I. Methamphetamine use and neuropsychiatric factors are associated with antiretroviral non-adherence. AIDS Care. 2012; 24:1504–1513. [PubMed: 22530794]

Moran LM, Booze RM, Webb KM, Mactutus CF. Neurobehavioral alterations in HIV-1 transgenic rats: evidence for dopaminergic dysfunction. Exp Neurol. 2013; 239:139–147. [PubMed: 23063600]

Moran LM, Aksenov MY, Booze RM, Webb KM, Mactutus CF. Adolescent HIV-1 transgenic rats: evidence for dopaminergic alterations in behavior and neurochemistry revealed by methamphetamine challenge. Curr HIV Res. 2012; 10:415–424. [PubMed: 22591365]

Nath A, Schiess N, Venkatesan A, Rumbaugh J, Sacktor N, McArthur J. Evolution of HIV dementia with HIV infection. Int Rev Psychiatry. 2008; 20:25–31. [PubMed: 18240060]

Nightingale S, Winston A, Letendre S, Michael BD, McArthur JC, Khoo S, Solomon T. Controversies in HIV-associated neurocognitive disorders. Lancet Neurol. 2014; 13:1139–1151. [PubMed: 25316020]

Nordahl TE, Salo R, Natsuaki Y, Galloway GP, Waters C, Moore CD, Kile S, Buonocore MH. Methamphetamine users in sustained abstinence: a proton magnetic resonance spectroscopy study. Arch Gen Psychiatry. 2005; 62:444–452. [PubMed: 15809412]

Pantalone DW, Bimbi DS, Holder CA, Golub SA, Parsons JT. Consistency and change in club drug use by sexual minority men in New York City, 2002 to 2007. Am J Public Health. 2010; 100:1892–1895. [PubMed: 20724693]

Passaro RC, Pandhare J, Qian HZ, Dash C. The Complex Interaction Between Methamphetamine Abuse and HIV-1 Pathogenesis. J Neuroimmune Pharmacol. 2015; doi: 10.1007/s11481-015-9604-2

Paulus MP, Rogalsky C, Simmons A, Feinstein JS, Stein MB. Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. Neuroimage. 2003a; 19:1439–1448. [PubMed: 12948701]

Paulus MP, Hozack N, Frank L, Brown GG, Schuckit MA. Decision making by methamphetamine-dependent subjects is associated with error-rate-independent decrease in prefrontal and parietal activation. Biol Psychiatry. 2003b; 53:65–74. [PubMed: 12513946]

Perry W, Minassian A, Paulus MP, Young JW, Kincaid MJ, Ferguson EJ, Henry BL, Zhuang X, Masten VL, Sharp RF, Geyer MA. A reverse-translational study of dysfunctional exploration in psychiatric disorders: from mice to men. Arch Gen Psychiatry. 2009; 66:1072–1080. [PubMed: 19805697]

Pfefferbaum A, Rosenbloom MJ, Sassoon SA, Kemper CA, Deresinski S, Rohlfing T, Sullivan EV. Regional brain structural dysmorphology in human immunodeficiency virus infection: effects of acquired immune deficiency syndrome, alcoholism, and age. Biol Psychiatry. 2012; 72:361–370. [PubMed: 22458948]

Plankey MW, Ostrow DG, Stall R, Cox C, Li X, Peck JA, Jacobson LP. The relationship between methamphetamine and popper use and risk of HIV seroconversion in the multicenter AIDS cohort study. J Acquir Immune Defic Syndr. 2007; 45:85–92. [PubMed: 17325605]

Potash MJ, Chao W, Bentsman G, Paris N, Saini M, Nitkiewicz J, Belem P, Sharer L, Brooks AI, Volsky DJ. A mouse model for study of systemic HIV-1 infection, antiviral immune responses, and neuroinvasiveness. Proc Natl Acad Sci U S A. 2005; 102:3760–3765. [PubMed: 15728729]

Ragin AB, Storey P, Cohen BA, Epstein LG, Edelman RR. Whole brain diffusion tensor imaging in HIV-associated cognitive impairment. AJNR Am J Neuroradiol. 2004; 25:195–200. [PubMed: 14970017]

Reback CJ, Larkins S, Shoptaw S. Methamphetamine abuse as a barrier to HIV medication adherence among gay and bisexual men. AIDS Care. 2003; 15:775–785. [PubMed: 14617499]

Reid W, Sadowska M, Denaro F, et al. An HIV-1 transgenic rat that develops HIV-related pathology and immunologic dysfunction. Proc Natl Acad Sci U S A. 2001; 98:9271–9276. [PubMed: 11481487]

Rippeth JD, Heaton RK, Carey CL, Marcotte TD, Moore DJ, Gonzalez R, Wolfson T, Grant I. Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons. J Int Neuropsychol Soc. 2004; 10:1–14. [PubMed: 14751002]

Roberts AJ, Maung R, Sejbuk NE, Ake C, Kaul M. Alteration of Methamphetamine-induced stereotypic behaviour in transgenic mice expressing HIV-1 envelope protein gp120. J Neurosci Methods. 2010; 186:222–225. [PubMed: 19917310]

Rosenbloom MJ, Sullivan EV, Pfefferbaum A. Focus on the brain: HIV infection and alcoholism: comorbidity effects on brain structure and function. Alcohol Res Health. 2010; 33:247–257. [PubMed: 23584066]

Sacktor N, Robertson K. Evolving clinical phenotypes in HIV-associated neurocognitive disorders. Curr Opin HIV AIDS. 2014; 9:517–520. [PubMed: 25203640]

Sacktor N, Skolasky RL, Seaberg E, Munro C, Becker JT, Martin E, Ragin A, Levine A, Miller E. Prevalence of HIV-associated neurocognitive disorders in the Multicenter AIDS Cohort Study. Neurology. 2016; 86:334–340. [PubMed: 26718568]

Salamanca SA, Sorrentino EE, Nosanchuk JD, Martinez LR. Impact of methamphetamine on infection and immunity. Front Neurosci. 2014; 8:445. [PubMed: 25628526]

Salo R, Buonocore MH, Leamon M, Natsuaki Y, Waters C, Moore CD, Galloway GP, Nordahl TE. Extended findings of brain metabolite normalization in MA-dependent subjects across sustained abstinence: a proton MRS study. Drug Alcohol Depend. 2011; 113:133–138. [PubMed: 20739127]

Sekine Y, Ouchi Y, Sugihara G, Takei N, Yoshikawa E, Nakamura K, Iwata Y, Tsuchiya KJ, Suda S, Suzuki K, Kawai M, Takebayashi K, Yamamoto S, Matsuzaki H, Ueki T, Mori N, Gold MS, Cadet JL. Methamphetamine causes microglial activation in the brains of human abusers. J Neurosci. 2008; 28:5756–5761. [PubMed: 18509037]

Semple SJ, Patterson TL, Grant I. The context of sexual risk behavior among heterosexual methamphetamine users. Addict Behav. 2004; 29:807–810. [PubMed: 15135564]

Sharma A, Hu XT, Napier TC, Al-Harthi L. Methamphetamine and HIV-1 Tat down regulate β-catenin signaling: implications for methampetamine abuse and HIV-1 co-morbidity. J Neuroimmune Pharmacol. 2011; 6:597–607. [PubMed: 21744004]

Simioni S, Cavassini M, Annoni JM, Rimbault Abraham A, Bourquin I, Schiffer V, Calmy A, Chave JP, Giacobini E, Hirschel B, Du Pasquier RA. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. AIDS. 2010; 24:1243–1250. [PubMed: 19996937]

Skarbinski J, Rosenberg E, Paz-Bailey G, Hall HI, Rose CE, Viall AH, Fagan JL, Lansky A, Mermin JH. Human immunodeficiency virus transmission at each step of the care continuum in the United States. JAMA Intern Med. 2015; 175:588–596. [PubMed: 25706928]

Soontornniyomkij V, Umlauf A, Soontornniyomkij B, Batki IB, Moore DJ, Masliah E, Achim CL. Lifetime methamphetamine dependence is associated with cerebral microgliosis in HIV-1-infected adults. J Neurovirol. 2016; doi: 10.1007/s13365-016-0441-8

Stebbins GT, Smith CA, Bartt RE, Kessler HA, Adeyemi OM, Martin E, Cox JL, Bammer R, Moseley ME. HIV-associated alterations in normal-appearing white matter: a voxel-wise diffusion tensor imaging study. J Acquir Immune Defic Syndr. 2007; 46:564–573. [PubMed: 18193498]

Stone VE, Baron-Cohen S, Knight RT. Frontal lobe contributions to theory of mind. J Cogn Neurosci. 1998; 10:640–656. [PubMed: 9802997]

Stubbe-Drger B, Deppe M, Mohammadi S, Keller SS, Kugel H, Gregor N, Evers S, Young P, Ringelstein EB, Arendt G, Knecht S, Husstedt IW. German Competence Network HA. Early microstructural white matter changes in patients with HIV: a diffusion tensor imaging study. BMC Neurol. 2012; 12:23. [PubMed: 22548835]

Taylor MJ, Schweinsburg BC, Alhassoon OM, Gongvatana A, Brown GG, Young-Casey C, Letendre SL, Grant I. Effects of human immunodeficiency virus and methamphetamine on cerebral metabolites measured with magnetic resonance spectroscopy. J Neurovirol. 2007; 13:150–159. [PubMed: 17505983]

Toggas SM, Masliah E, Rockenstein EM, Rall GF, Abraham CR, Mucke L. Central nervous system damage produced by expression of the HIV-1 coat protein gp120 in transgenic mice. Nature. 1994; 367:188–193. [PubMed: 8114918]

Tong J, Fitzmaurice P, Furukawa Y, Schmunk GA, Wickham DJ, Ang LC, Sherwin A, McCluskey T, Boileau I, Kish SJ. Is brain gliosis a characteristic of chronic methamphetamine use in the human? Neurobiol Dis. 2014; 67:107–118. [PubMed: 24704312]

Valcour VG, Shikuma CM, Watters MR, Sacktor NC. Cognitive impairment in older HIV-1-seropositive individuals: prevalence and potential mechanisms. AIDS. 2004; 18(1):S79–86. [PubMed: 15075502]

Var SR, Day TR, Vitomirov A, Smith DM, Soontornniyomkij V, Moore DJ, Achim CL, Mehta SR, Perez-Santiago J. Mitochondrial injury and cognitive function in HIV infection and methamphetamine use. AIDS. 2016; 30:839–848. [PubMed: 26807965]

Volkow ND, Fowler JS, Wang GJ, Shumay E, Telang F, Thanos PK, Alexoff D. Distribution and pharmacokinetics of methamphetamine in the human body: clinical implications. PLoS One. 2010; 5:e15269. [PubMed: 21151866]

Volkow ND, Chang L, Wang GJ, Fowler JS, Franceschi D, Sedler M, Gatley SJ, Miller E, Hitzemann R, Ding YS, Logan J. Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. J Neurosci. 2001; 21:9414–9418. [PubMed: 11717374]

Wang GJ, Volkow ND, Chang L, Miller E, Sedler M, Hitzemann R, Zhu W, Logan J, Ma Y, Fowler JS. Partial recovery of brain metabolism in methamphetamine abusers after protracted abstinence. Am J Psychiatry. 2004; 161:242–248. [PubMed: 14754772]

Weber E, Morgan EE, Iudicello JE, Blackstone K, Grant I, Ellis RJ, Letendre SL, Little S, Morris S, Smith DM, Moore DJ, Woods SP. Substance use is a risk factor for neurocognitive deficits and neuropsychiatric distress in acute and early HIV infection. J Neurovirol. 2013; 19:65–74. [PubMed: 23250704]

Wilson ME, Dimayuga FO, Reed JL, Curry TE, Anderson CF, Nath A, Bruce-Keller AJ. Immune modulation by estrogens: role in CNS HIV-1 infection. Endocrine. 2006; 29:289–297. [PubMed: 16785604]

Woods SP, Rippeth JD, Frol AB, Levy JK, Ryan E, Soukup VM, Hinkin CH, Lazzaretto D, Cherner M, Marcotte TD, Gelman BB, Morgello S, Singer EJ, Grant I, Heaton RK. Interrater reliability of clinical ratings and neurocognitive diagnoses in HIV. J Clin Exp Neuropsychol. 2004; 26:759–778. [PubMed: 15370374]

Yang S, Belcher AM, Chefer S, Vaupel DB, Schindler CW, Stein EA, Yang Y. Withdrawal from long-term methamphetamine self-administration ‘normalizes’ neurometabolites in rhesus monkeys: a (1) H MR spectroscopy study. Addict Biol. 2015; 20:69–79. [PubMed: 23910722]

Young JW, Minassian A, Paulus MP, Geyer MA, Perry W. A reverse-translational approach to bipolar disorder: rodent and human studies in the Behavioral Pattern Monitor. Neurosci Biobehav Rev. 2007; 31:882–896. [PubMed: 17706782]

Zahr NM, Mayer D, Rohlfing T, Sullivan EV, Pfefferbaum A. Imaging neuroinflammation? A perspective from MR spectroscopy. Brain Pathol. 2014; 24:654–664. [PubMed: 25345895]

Zhuang W, Tang Y, Zhong N, Jiang H, Du J, Wang J, Zhao M. Persistent Microstructural Deficits of Internal Capsule in One-Year Abstinent Male Methamphetamine Users: a Longitudinal Diffusion Tensor Imaging Study. J Neuroimmune Pharmacol. 2016; doi: 10.1007/s11481-016-9673-x

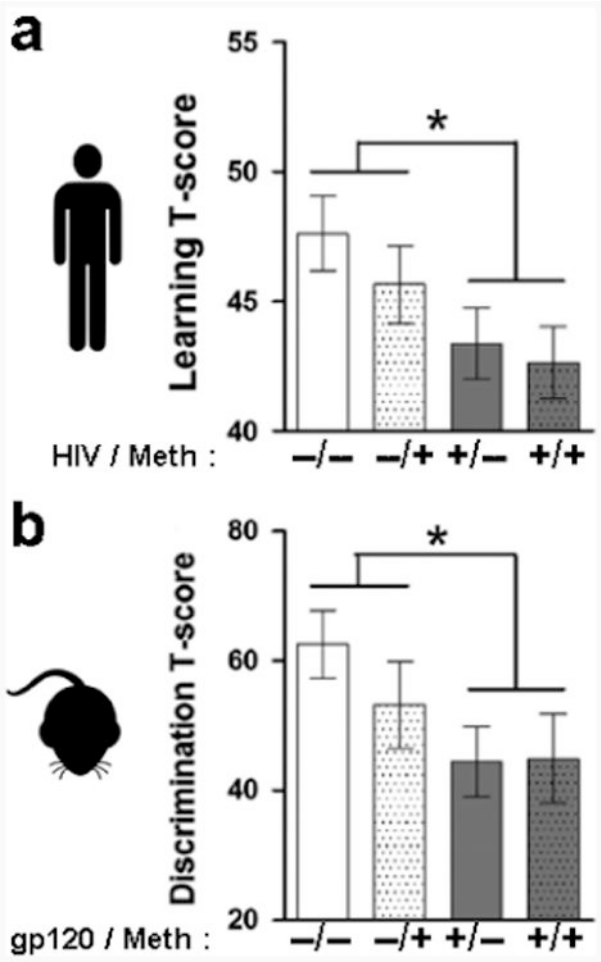

Fig. 1.

Translational evidence of neurobehavioral disturbance. Learning functions assessed in humans (adult men, $n = 29–36$ per group) and mice (adult male, $n = 6–10$ per group). (**a**) In humans, demographically adjusted *T*-scores for learning tasks were lower in HIV-infected persons compared to HIV-seronegative participants, regardless of lifetime methamphetamine (Meth) dependence. (**b**) In mice, dimension-adjusted *T*-scores for discrimination learning in the attentional-set-shifting task were lower in HIV-1 gp120 transgenic mice than in wild-type mice, regardless of Meth exposure. The data are expressed as mean ± standard error of the mean, * $p < 0.05$. Adapted with permission from (Kesby et al. 2015b).

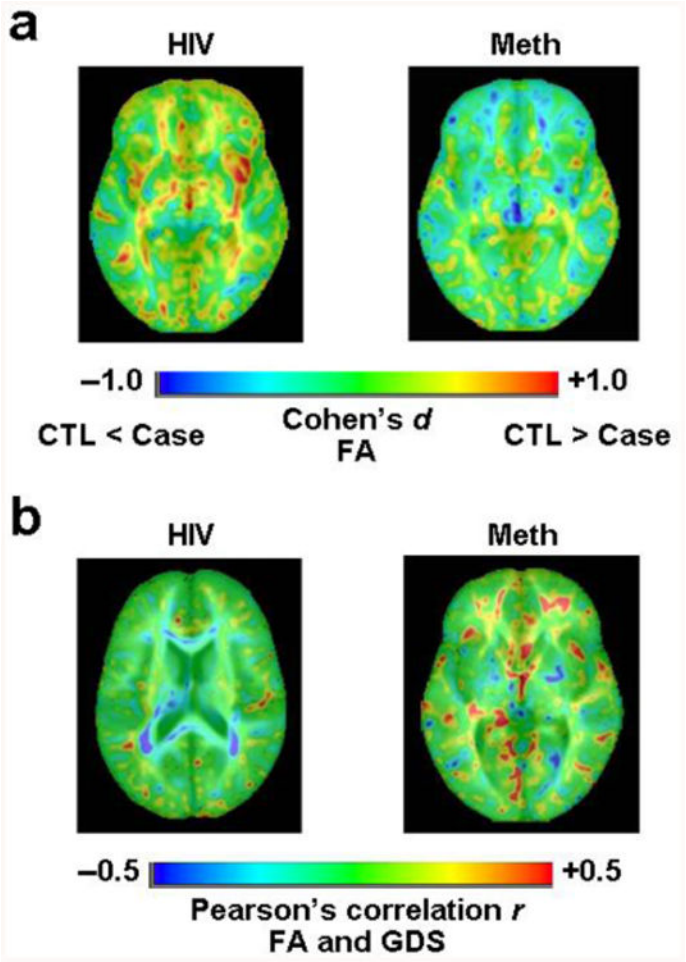

Fig. 2.

Preliminary studies using magnetic resonance diffusion tensor imaging in humans. (**a**) Each of the HIV-infected ($n = 18$) and methamphetamine (Meth)-dependent ($n = 19$) case groups is compared with the age- and education-matched control (CTL, $n = 20$) group. The fractional anisotropy (FA) in the cerebral white matter of the HIV group is generally lower than in the CTL group. In the Meth group, however, the FA varies (either increased or slightly reduced in comparison to that in the CTL group) from region to region. (**b**) The correlation between the cerebral white mater FA and the global (neurocognitive) deficit scores (GDS) is examined in each of the risk groups. In the majority of cerebral white matter regions, FA measures correlate inversely with GDS in the HIV group, but directly with GDS in the Meth group. Note that these observed correlations occur on different brain slices for the two separate groups.