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Neurobehavioral Alterations in HIV-1 Transgenic Rats: Evidence for Dopaminergic Dysfunction

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Abstract

Clinical studies have provided evidence that the progression of HIV-1-associated neurocognitive disorders (HAND) involves alterations in dopamine (DA) systems. Drugs of abuse that act on the brain DA system, such as cocaine (Coc), may exacerbate HIV-1 infection and consequent behavioral and neurological manifestations. In the present study, we used the HIV-1 transgenic (Tg) rat, which constitutively expresses 7 of the 9 HIV-1 genes, to assess potential DA system alterations in three behavioral assays: prepulse inhibition (PPI) of the auditory startle response (ASR), novelty and habituation/retention, and sensitization to Coc across repeated administration. Adult female Sprague-Dawley rats were tested in each experiment. The HIV-1 Tg animals were hyperreactive to auditory startle stimuli and displayed a leftward shift in the temporal window for maximal PPI, suggesting an alteration in sensorimotor gating. All animals displayed an initial robust locomotor response to a novel environment which dissipated with repeated testing; however, the HIV-1 Tg rats, relative to controls, consistently showed a weaker novelty response across monthly-spaced assessments. The HIV-1 Tg animals also showed decreased intrasession habituation of motor activity across 3-day periods that emerged across monthly-spaced locomotor activity sessions; a pattern consistent with impaired long-term episodic memory. Furthermore, the HIV-1 Tg group displayed differential cocaine-induced sensitization, observed both in initiation across the 10-day cocaine treatment, and in expression following a cocaine rechallenge after a 7-day abstinence. Collectively, the present data implicate that the non-infectious HIV-1 Tg rat, which resembles the complete suppression of infection in HIV-1 positive individuals under CART, displays sustained, if not permanent, alterations in the brain DA system.

Keywords

AIDS; dopamine; HAND; HIV-1 transgenic rat; cocaine sensitization; prepulse inhibition; sensorimotor gating; novelty; habituation; retention

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Introduction

The worldwide prevalence of HIV was estimated to be 34 million at the end of 2010 (UNAIDS Global Report 2011). Before the introduction of combination antiretroviral therapy (CART), HIV-1 related neuropsychological impairment occurred in approximately 30% of individuals with asymptomatic HIV infection and in 50% of those with acquired immunodeficiency virus (AIDS) (Heaton *et al.*, 1995). During the CART era, which brought about controlled HIV viremia and improved immune function, the incidence of the most severe form of neuropsychological impairment, dementia, was reduced from approximately 16% to 2% (Heaton *et al.*, 2010; McArthur *et al.*, 1993; Sacktor *et al.*, 2001). More importantly, however, there was a concomitant increase in the milder forms of HAND; thus, the total incidence of HAND, ranging from mild impairments to dementia, has remained the same. Approximately 50% of patients on CART are afflicted by these impairments, which disrupt their functioning in daily activities, as well as pose a greater risk for early mortality (Ances and Ellis, 2007).

The brain dopamine (DA) system has been implicated as a major target of HIV-1 infection. Reports of HIV-1 positive individuals with lower cerebrospinal fluid DA (Berger *et al.*, 1994), Parkinsonian symptoms, sensitivity to DA receptor antagonists, or abnormalities in basal ganglia structure and function (Berger & Nath, 1997; Koutsilieri *et al.*, 2002) provided some of the earliest lines of evidence that HIV-1 infection disrupts the DA system. Motor control, which relies on intact basal ganglia function, is thus commonly reported to be deficient in HIV positive individuals (Becker *et al.*, 2011; Robertson *et al.*, 2006; Sullivan *et al.*, 2011; Valcour *et al.*, 2008). Symptoms of HAND have also been associated with DA system dysfunction. Significant reductions in DA levels in the substantia nigra are correlated with poor performance on learning and memory tasks in HIV-1-positive individuals (Kumar *et al.*, 2011). Executive dysfunction, one of the most prominent features of HAND (Cysique *et al.*, 2004; Garvey *et al.*, 2009; Heaton *et al.*, 2011), is associated with decreases in homovanillic acid in people with HIV-1 (di Rocco *et al.*, 2000).

Reduced DA transporter (DAT) levels in the putamen and ventral striatum are also found in individuals with HAND (Chang *et al.*, 2008; Wang *et al.*, 2004). It is well established that DAT is critical for cognitive function, with roles in DA homeostasis, maintenance of stable synaptic DA concentrations, and regulation of disease and brain processes (Chudasama & Robbins, 2006; Nieoullon, 2002). As documented in our own work, the DAT is targeted by HIV-1 proteins Tat and gp120, resulting in transporter impairment (Aksenov *et al.*, 2008; Ferris *et al.*, 2009; Zhu *et al.*, 2009; Zhu *et al.*, 2011) and these effects are due to direct protein-protein interactions (Zhu *et al.*, 2009) involving an allosteric modulation of DAT by the Tat protein (Zhu *et al.*, 2011). In addition, DA-dependent signaling has been identified as a mechanism of HIV-1 protein neurotoxicity (Aksenova *et al.*, 2006; Silvers *et al.*, 2007; Wallace *et al.*, 2006). Clearly, although other neural systems may be involved, central DA system dysfunction often results from HIV-1 infection and is associated with subsequent cognitive deficits.

One of the earliest neurological alterations found in the progression of HIV-1 infection, before more obvious cognitive symptoms are manifest, are disruptions in brainstem auditory evoked potentials (BAEP), a classic electrophysiological measure of sensory gating (Castello *et al.*, 1998; Fein *et al.*, 1995; Gil *et al.*, 1992; Goodwin *et al.*, 1996; Ollo *et al.*, 1991; Pagano *et al.*, 1992; Schroeder *et al.*, 1996; Vigliano *et al.*, 2000). Sensory gating is a centrally-mediated phenomenon which allows one to selectively process sensory information and allocate attention to the most relevant or salient stimuli. BAEP are typically suppressed to a test stimulus when another stimulus immediately precedes it. The brainstem and pedunculopontine pathways involved in this process also underlie the auditory startle

response (ASR) and prepulse inhibition (PPI) of the ASR measured in animal studies (Fendt *et al.*, 2001; Koch & Schnitzler, 1997). PPI is an operational measure of sensorimotor gating, a preattentive process in which the startle reflex is reduced when the startle stimulus is preceded 30-500 ms by a weak prepulse (Hoffman & Ison, 1980). Pharmacological studies have shown reductions in PPI after administration of direct and indirect dopamine (DA) agonists, such as apomorphine and amphetamine (Geyer *et al.*, 2001). Apomorphine-induced PPI deficits have been used as a preclinical model of schizophrenia, capturing both the dysfunction of the DA system and the preattentive deficits as measured with event-evoked potentials in individuals with schizophrenia. The use of behavioral measures such as the ASR and PPI that can detect early neurological alterations, especially those of the DA system, may be instrumental in predicting the development of HAND and thus determining an appropriate course of treatment.

Episodic memory is impaired in nearly half of HIV-1 positive individuals on CART, similar to pre-CART estimates (Heaton *et al.*, 2011). Deficits in episodic memory can be especially problematic for these individuals, who have daily routines centered on medication intake and medical appointments. The hippocampus, an integral structure in memory consolidation (Scoville and Milner, 1957; O'Keefe and Nadel, 1978), can accumulate high levels of HIV-1 (Wiley *et al.*, 1998), suggesting that hippocampal-mediated cognitive abilities may be particularly vulnerable. Clinical and preclinical studies have both provided evidence of the importance of the DA system in long-term memory. Difficulty in episodic memory retrieval is observed in Parkinson's disease patients (Dujardin and Laurent, 2003), and differences in episodic memory recall are associated with variations of the catechol O-methyltransferase gene (de Frias *et al.*, 2004), which influences the metabolic degradation of DA. When DA antagonists are infused into the rat hippocampus prior to encoding, long-term memory of paired associates is impaired (Bethus *et al.*, 2010). Thus, alterations in DA system activity may also contribute to memory deficits in HAND. Memory is commonly assessed in animal studies with measures of novelty detection and habituation (Barbosa *et al.*, 2012; Barker *et al.*, 2007; Dere *et al.*, 2005; DeVito & Eichenbaum, 2010; Eacott *et al.*, 2005; Ennaceur & Aggleton, 1997; Hannesson *et al.*, 2004; Hotte *et al.*, 2005). The detection of a novel experience and the long-term retention of it may be mediated, in part, by release of DA in the hippocampus (Lisman and Grace, 2005). Thus, the detection of novelty and habituation/retention may be relevant to study in animal models of HIV-1.

The effects of HIV-1 infection on brain DA systems may be further exacerbated by the abuse of drugs that also alter these systems (Purohit *et al.*, 2011). Evidence from clinical studies suggests that HIV-1 infection and drugs of abuse such as cocaine and methamphetamine may exert additive or synergistic effects on cognitive function (Carey *et al.*, 2006; Chang *et al.*, 2005; Ferris *et al.*, 2008; Nath *et al.*, 2001; Rippeth *et al.*, 2004). The combined effects are also observed *in vitro*; HIV-1 protein-induced neurotoxicity is potentiated by treatment with cocaine (Nath *et al.*, 2000; Turchan *et al.*, 2001; Yao *et al.*, 2009), and treatment with a D₁ DA antagonist was shown to block this potentiated effect (Aksenov *et al.*, 2006). Thus, the enhancement of HIV-1 protein-induced neurotoxicity by cocaine may occur through alterations in DA receptor function. Behavioral studies using animal models of HIV-1 infection have provided further evidence of the concerted effects of cocaine and HIV-1 proteins. Rats given bilateral, intra-accumbal microinjections of Tat1-72 had significantly increased locomotor activity following an acute i.v. cocaine injection, as well as reduced cocaine sensitization after repeated cocaine injections, relative to controls (Harrod *et al.*, 2008). Hyperdopaminergic tone in rats, as measured via microdialysis, is associated with attenuated cocaine sensitization following Tat injection; a finding not present after Tat or cocaine treatment alone (Ferris *et al.*, 2010). Cocaine sensitization is thus a useful metric of DA system function in animal models of HIV-1, given the above-mentioned findings and documented alterations in normal DA systems as a function of

cocaine sensitization (Kalivas and Duffy, 1993; Pierce and Kalivas, 1997; Wallace *et al.*, 1996).

In the current study, the HIV-1 transgenic (HIV-1 Tg) rat, which constitutively expresses 7 of the 9 HIV-1 genes, was used to determine the effects of the chronic expression of HIV-1 viral proteins on three putative DA-sensitive tasks: PPI of the ASR, novelty and habituation/retention, and cocaine sensitization. It was hypothesized that the HIV-1 Tg rats would show disruptions in these behavioral measures compared to non-transgenic control rats as a function of DA system alterations exerted by HIV-1. The assessments were planned to be conducted from 5 to 11 months of age, antecedent to the documented neurological symptoms or clinical signs of wasting (Peng *et al.*, 2010; but see observations of Reid *et al.*, 2001).

Methods

Subjects

Adult female ovariectomized Sprague-Dawley rats (HIV-1 Tg, n=9; control, n=11) were obtained from Harlan Sprague Dawley, Inc. (Indianapolis, IN) at 160 days of age and were group-housed throughout the study. Rodent food (Pro-Lab Rat, Mouse Hamster Chow #3000, NIH diet #31) and water were available *ad libitum*. The animals were maintained according to the National Institute of Health (NIH) guidelines in AAALAC-accredited facilities. The animal facility was maintained at $21^{\circ} \pm 2^{\circ}\text{C}$, $50\% \pm 10\%$ relative humidity and had a 12-h light:12-h dark cycle with lights on at 0700 h (EST). Rats were handled prior to any procedures to minimize stress during behavioral testing. The Institutional Animal Care and Use Committee (IACUC) of the University of South Carolina approved the research protocol.

Sensorimotor Gating Task

Apparatus—The startle platform (SR-Lab Startle Reflex System, San Diego Instruments, Inc., San Diego, CA) was enclosed in a 10 cm-thick double-walled, 81×81×116-cm isolation cabinet (external dimensions) (Industrial Acoustic Company, INC., Bronx, NY), rather than the 1.9 cm thick ABS plastic or laminate cabinets offered with this system. This double-walled isolation chamber provides over 30dB(A) of sound attenuation relative to the external environment. The ambient sound level in the chamber without any stimuli presented is 22dB(A). The high-frequency loudspeaker of the SR-Lab system (Radio Shack model#40-1278B) that was used to deliver all auditory stimuli (frequency range of 5k-16k Hz) was mounted inside the chamber 30 cm above the Plexiglas animal test cylinder. The animal's response to the auditory stimulus produced deflection of the test cylinder, which was converted into analog signals by a piezoelectric accelerometer integral to the bottom of the cylinder. The response signals were digitized (12 bit A to D) and saved to a hard disk. Response sensitivities were calibrated using a SR-LAB Startle Calibration System. Sound levels were measured and calibrated with a sound level meter (Kjaer Bruel 2203) with the microphone placed inside the Plexiglas cylinder.

Procedure—At 5 months of age, the auditory startle response (ASR) of the animals was assessed. Briefly, all animals were exposed to a 36-trial session on two consecutive days to habituate them to the startle stimulus and test procedures. Each session began with a 5-min acclimation period of 70dB(A) background white noise, followed by 36 trials of a 100dB(A) white noise stimulus with a 20 msec duration and a 10 sec intertrial interval (ITI). All test sessions were conducted in the dark.

One day after ASR habituation, prepulse inhibition (PPI) of the ASR was assessed for approximately 20 minutes. All animals were given a 5-min acclimation period in the dark with 70dB(A) background white noise, followed by 6 pulse-only ASR trials with a 10 sec ITI. There were 36 prepulse inhibition (PPI) trials with 0, 8, 40, 80, 120, and 4000 msec interstimulus intervals (ISIs) between prepulse (85dB(A), 20 msec duration) and the pulse stimulus, presented in a Latin-square design. The 0 and 4000 msec ISI trials were control trials used to calculate percent inhibition on PPI trials. The pulse stimulus intensity was 100dB(A) measured inside the test cylinder. A variable 20 sec ITI was used for PPI trials (range=15-25 sec). Animals were tested again with these same procedures at 6 and 7 months of age.

Novelty and Habituation/Retention Task

Apparatus—Locomotor activity chambers (Hamilton–Kinder Inc., Poway, CA) were square (40 × 40 cm) and detected free movement of animals by infrared photocell interruptions. This equipment used an infrared photocell grid (32 emitter/detector pairs) to measure locomotor activity. The chambers were converted into round (~40 cm diameter) compartments by adding clear Plexiglas inserts; photocell emitter/detector pairs were tuned by the manufacturer to handle the extra perspex width. All activity monitors were located in an isolated room.

Procedure—Animals were tested for novelty and habituation/retention to the locomotor activity chambers for three consecutive 60-min sessions, one/day, at three ages (6, 7, and 11 months old). In addition to the round activity chambers, prominent contextual features of the testing environment included dim diffuse lighting (~10 lux) and broad-band noise (65 dB(A)).

Cocaine Sensitization Task

Apparatus: As specified in the “Novelty and Habituation/Retention” section above

Procedure: Twenty-four hours after the last novelty/habituation session at age 11 months, all rats were injected with saline (i.p.) and placed into the activity chambers to measure baseline activity for 60 minutes. Animals were injected with Coc (10 mg/kg, i.p.) daily for 10 days, starting 24 hours after the saline testing session. They were placed into the activity chambers immediately after each injection, and locomotor activity was assessed for 60 minutes. After 7 days of abstinence, animals were administered Coc again and locomotor activity was measured for 60 minutes in the activity chamber.

Locomotor activity was more precisely measured as distance traveled in the center and periphery (cm) and time spent in center and periphery (secs), as the majority of locomotor activity in rats, with or without repeated cocaine administration, is directed toward the periphery of the test chamber. However, centrally-directed activity may also increase with cocaine sensitization (Wallace *et al.*, 1996). ‘Center’ dependent measures refer to a circular region located in the center most portion of the compartment. ‘Peripheral’ dependent measures refer to a circular region surrounding the center located in the outer-most portion of the compartment. In order to determine the activity in center versus periphery, Hamilton-Kinder, Inc. software was used to impose a circular region (~25% of total area) in the center of the compartment during the data reduction phase (i.e., following completion of the activity session) of the experiment, yielding the activity data in the center.

Statistical Analysis

All data were analyzed using analysis of variance (ANOVA) techniques (SPSS 17). A four-way mixed-factor ANOVA was performed on peak ASR amplitude and latency for the 0-4000 msec ISIs, with group (HIV-1 Tg vs. control) as the between-subjects factor, and age, ISI, and trial as the within-subjects factors. A three-way mixed-factor ANOVA was performed on percent PPI [difference between average peak amplitude at 0 and 4000 msec ISIs and at 100 msec ISI (averaged from the 80 and 120 msec ISIs) divided by average peak amplitude at 0 and 4000 msec ISIs, multiplied by 100] with group as the between-subjects factor and age and trial as the within-subjects factors. Locomotor activity data were also analyzed using ANOVA techniques, with distance traveled in the periphery, time spent in the periphery, distance traveled in the center, and time spent in the center as the dependent variables. For habituation data, a four-way mixed factor ANOVA was performed with group as the between-subjects factor and age, session, and trial block as the within-subjects factors. For the saline day and Coc rechallenge day data, a 2 (group) x 6 (trial block) ANOVA was conducted. For the 10-day Coc sensitization period data, a 2(group) x 10 (day) ANOVA was conducted. Linear and non-linear regression analysis was performed, as necessary, to further understand the more complex interaction terms that were detected. An α level of $p = 0.05$ was considered significant for all statistical tests. Given our focus on the detection of early and/or subtle behavioral alterations, estimates of statistical power are also reported; high power estimates are consistent with an adequate number of subjects, a reasonable effect size, and good experimental precision available to detect a “true” effect when it exists.

Results

Body Weight

The HIV-1 Tg group weighed significantly less than the control group across the 6-month period during which they were tested, $F(1, 18) = 27.6$, $p = 0.001$ (See Fig.1). Both groups increased significantly in body weight across this period [HIV-1 Tg: $F(48, 384) = 72.9$, $p = 0.001$; Control: $F(48, 480) = 69.8$, $p = 0.001$]. There was no significant interaction between group and age, suggesting that the groups did not differ in their rates of growth.

Sensorimotor Gating Task

Mean peak amplitude data from the ASR habituation trials are illustrated in Figure 2. Both groups decreased on this measure across trial blocks [$F(5, 95) = 5.07$, $p_{GG} = 0.01$, Power=0.85], but there was no interaction between group and trial block, suggesting that both groups habituated to the auditory startle stimulus at a similar rate across the 36-trial session. Linear regression analysis on the mean peak amplitude data revealed that the HIV-1 Tg and control groups had significantly different intercepts, $F(1, 8) = 6.5$, $p = 0.05$, but not different slopes, indicating an overall greater amplitude of response in the HIV-1 Tg group throughout the habituation session.

Mean peak amplitude during PPI trials is illustrated in Figure 3 (top panel). There was no significant overall difference in mean peak amplitude between the HIV-1 Tg and control groups; however, there was a significant group x ISI interaction, $F(5, 90) = 6.2$, $p = 0.001$ (Power=0.99), as well as a significant group x age x ISI interaction, $F(10, 180) = 2.4$, $p = 0.01$ (Power=0.99). There were also main effects of age, $F(2, 36) = 13.7$, $p = 0.001$ (Power=1.0), and ISI, $F(5, 90) = 104.3$, $p_{GG} = 0.001$ (Power=1.0). The most prominent two-way interaction of group x ISI, as observed in Fig.3, was attributable to three interesting findings: 1) the HIV-1 Tg group displayed significantly higher peak amplitude of response during the control trials (0 and 4000 msec ISIs), consistent with the previous ASR habituation data; 2) percent PPI was not significantly different between treatment groups (averaged across age: HIV-1 Tg: $M = 84.3\%$, $SEM = 2.6$; Control: $M = 86.6\%$, $SEM = 1.3$); and 3) a shift was

observed in the inflection point of the peak inhibition curve, indicated by a significant group x ISI interaction, $F(5,90)=6.2$, $p = 0.001$ (Power=0.99), with a quadratic component, $F(1,18)=5.7$, $p = 0.05$.

A significant group x ISI interaction was observed for mean peak latency, $F(5,90)=8.1$, $p = 0.001$ (Power=1.0), as well as a significant main effect of ISI (0-4000 msec), $F(5, 90) = 64.9$, $p = 0.001$ (Power=1.0) (data not shown). Most prominently, the HIV-1 Tg group displayed significantly longer latencies on the control trials, relative to the control group, $F(1,18)=15.0$, $p = 0.001$ (Power=0.95), as well as significantly shorter latencies on the PPI trials (excluding the 80 msec ISI), relative to the control group, $F(1,18)=4.9$, $p = 0.05$ (Power=0.55).

Novelty and Habituation/Retention Task

Distance traveled in the periphery of the chambers during the locomotor activity test sessions is illustrated in Fig 4. (left panels). The ANOVA conducted on the distance traveled in the periphery revealed a group x age x day x block interaction [$F(20,360)=7.3$, $p = 0.001$, Power=1.0], which was further explored with nonlinear regression analysis. As is readily apparent, a prominent component of that interaction was the robust response to novelty seen in both groups of animals, as evident in their first 10 min of locomotor activity. One phase exponential decay regression analysis revealed that the HIV-1 Tg rats locomoted significantly less (i.e., a shorter distance) in the periphery during the first 10-min block of the first session at each age tested, compared to the control rats [6 months: $F(3,114)=6.6$, $p = 0.001$; 7 months: $F(3,114)=8.8$, $p = 0.001$; 11 months: $F(3,114)=8.8$, $p = 0.001$]. Further, at the initial 6-month test age, the HIV-1 Tg rats locomoted significantly less during the first 10-min block across the consecutive 3-day sessions.

With respect to intrasession habituation, the pattern revealed within that complex 4-way interaction suggested the HIV-1 Tg rats failed to display the progressive intrasession habituation noted across age in the control animals. By the second session at 7 and 11 months, there was no significant difference in distance traveled in the periphery across trial blocks between the HIV-1 Tg and control rats, but by the third session at each of these ages, the HIV-1 Tg rats failed to habituate across blocks to the same extent as the control rats [7 months: $F(1,114)=6.9$, $p = 0.01$; 11 months: $F(1,114)=5.3$, $p = 0.05$]. For distance traveled in the center (data not shown), both the HIV-1 Tg group and the control group decreased in distance traveled in the center across trial blocks [HIV-1 Tg: $F(5, 40) = 50.8$, $p = 0.001$; control group: $F(5, 50) = 106.7$, $p = 0.001$], but the HIV-1 Tg group traveled a significantly shorter distance in the center compared to the control group, $F(1, 18) = 30.9$, $p = 0.001$.

The temporal measures confirmed the overall pattern seen in the distance measures. HIV-1 Tg animals spent significantly more time in the periphery [$F(1, 18) = 16.1$, $p = 0.001$, Power=0.97] and less time in the center [$F(1, 18) = 16.1$, $p = 0.001$, Power=0.97] of the activity chamber compared to the control animals during the habituation trials across all ages tested. As evident in Fig 4 (right panels), both groups showed significant increases in time spent in the periphery across blocks [HIV-1 Tg: $F(5, 40) = 11.9$, $p_{GG} = 0.01$; Control: $F(5, 50) = 23.9$, $p = 0.001$], but a significant group x block interaction [$F(5, 90) = 8.6$, $p = 0.001$, Power=1.0] was consistent with the fact that the HIV-1 Tg group spent the majority of their locomotor activity in the periphery throughout the session, whereas the control group increased their peripheral activity across the session. A group x block interaction was also found for time spent in the center of the chamber [$F(5, 90) = 8.6$, $p = 0.001$, Power=1.0], indicating the inverse pattern of behavior relative to that seen with time spent in the periphery.

On average, both groups spent the majority of each hour-long session in the periphery of the test chamber (HIV-1 Tg: 3462.1 s, 96.2%; control: 3062.9 s, 85.1%); therefore, the focus of the subsequent cocaine locomotor sensitization task was on time spent and distance traveled in the periphery.

Cocaine Sensitization Task

On the saline injection day, no significant differences between the groups in distance traveled or time spent in the periphery were detected.

Across the 10-day cocaine injection days, evidence for differential sensitization to repeated daily cocaine was observed in the significant group $\times$ day interaction for distance traveled in the periphery, as illustrated in Figure 5 [$F(9, 162) = 2.16$, $p = 0.03$, Power=.87]. Furthermore, the HIV-1 Tg group, but not the control group, showed an significant linear trend for day, $F(1,8)=12.99$, $p = 0.01$. The main effect of group was also significant, $F(1,18) = 8.7$, $p = 0.01$ (Power=0.80); the HIV-1 Tg group traveled a significantly greater distance in the periphery than the control group did across the 10-day period.

For time spent in the periphery, there was no differential change in either group across the 10-day period; however, there was a significant main effect of group, $F(1,18)=5.79$, $p = 0.03$ (Power=0.62), with the HIV-1 Tg group spending significantly more time in the periphery.

After a 7-day abstinence, the administration of cocaine yielded additional evidence for group differences. The HIV-1 Tg group traveled a significantly greater distance in the periphery [$F(1, 18) = 8.3$, $p = 0.01$, Power=0.78] and spent significantly more time in the periphery [$F(1, 18) = 13.2$, $p = 0.01$, Power=0.93] compared to control animals on the rechallenge day. As one might anticipate, the inverse pattern was observed on the center measures; the HIV-1 Tg group traveled a significantly smaller distance in the center [$F(1, 18) = 5.8$, $p = 0.05$, Power=0.63] and spent less time in the center of the activity chamber compared to the control group [$F(1, 18) = 13.2$, $p = 0.01$, Power=0.93] on the rechallenge day.

Discussion

Differential variations in the DA system as a function of the HIV-1 transgene were implicated across all three behavioral and/or pharmacological assessments. The assessments, conducted from 5 to 11 months of age, were antecedent to any documented neurological symptoms or clinical signs of wasting (Peng *et al.*, 2010; but see observations of Reid *et al.*, 2001). The HIV-1 Tg animals were hyperreactive to auditory startle stimuli and displayed a leftward shift in the temporal window for maximal PPI, suggesting an alteration in sensorimotor gating. All animals displayed an initial robust locomotor response to a novel environment which dissipated with repeated testing; however, the HIV-1 Tg rats, relative to controls, consistently showed a weaker novelty response across monthly-spaced assessments. The HIV-1 Tg animals also showed decreased intrasession habituation of motor activity across 3-day periods that became evident across monthly-spaced locomotor activity sessions; a pattern consistent with impaired long-term episodic memory. Furthermore, the HIV-1 Tg group displayed differential cocaine-induced sensitization, observed both in initiation across the 10-day cocaine treatment, and in expression following a cocaine rechallenge after a 7-day abstinence. The non-infectious HIV-1 Tg rat, which resembles the complete suppression of infection in HIV-1 positive individuals under CART, displays behavioral changes implicating sustained, if not permanent, alterations in the brain DA system.

During both ASR habituation trials and PPI control trials, HIV-1 Tg animals exhibited a higher response amplitude compared to the control animals. Latency to peak amplitude

during PPI control trials was also significantly longer in the HIV-1 Tg group, and changes in amplitude and latency across ISI in the HIV-1 Tg group were significantly different from those observed in the control animals. Specifically, the HIV-1 Tg group displayed a leftward shift in the ISI function with peak inhibition of the startle response at the 40 msec ISI; the control group had peak inhibition at the 80 msec ISI. The leftward shift in the ISI function mirrors that seen in previous work from our laboratory, in rats that were acutely injected with the HIV-1 viral protein Tat (Fitting *et al.* 2006a) or gp120 (Fitting *et al.*, 2006b). In the latter study, administration of apomorphine, a DA agonist, appeared to restore the response amplitude of the gp120-treated animals to a profile resembling that of the saline- and vehicle-treated animals. Although we did not administer a drug challenge targeted to the DA system prior to ASR and PPI testing in the present study, the similarity of our findings to those in Fitting *et al.* (2006a) suggest that the HIV-1 Tg rat expresses DA system alterations as do rats that received neonatal intra-hippocampal injections of the HIV-1 protein gp120. We have also demonstrated ASR and PPI alterations in the HIV-1 Tg F344 rat at 35-45 days of age (Moran *et al.*, 2012). Furthermore, the current findings demonstrate the persistence of ASR and PPI alterations through 7 months of age in the HIV-1 Tg rat; the Tat-injected animals were tested at 30 and 60 days of age. The generality of the effects of chronic low level HIV-1 viral protein exposure supports the use of sensorimotor gating as an integral component of a cognitive model of HAND that can be assessed across rat strain, age, and method of HIV-1 viral protein exposure. The altered ASR and PPI observed in these animal studies parallel clinical observations of abnormal sensory gating in HIV-1 positive individuals as measured with the BAEP, one of their earliest detected neurological alterations (Castello *et al.*, 1998; Fein *et al.*, 1995; Gil *et al.*, 1992; Goodwin *et al.*, 1996; Ollo *et al.*, 1991; Pagano *et al.*, 1992; Schroeder, *et al.*, 1996; Vigliano *et al.*, 2000). Assessing sensorimotor gating alterations in animal models of HIV-1 may provide insight to the mechanisms underlying the progression of HAND, as well as offer an early biomarker of HAND and potential therapeutic targets.

In addition to sensorimotor gating alterations, the HIV-1 Tg animals also exhibited differences in their locomotor activity response to placement in a novel environment. Although no examination of which components of the novel environment (e.g., chamber shape, light and sound levels) was undertaken, such contextual features are well-appreciated to comprise attributes of a memory (Mactutus & Riccio, 1978; Spear & Riccio, 1994). In the first habituation session at each age tested, as well as during each of the three test sessions at the initial 6-month test age, the HIV-1 Tg rats traveled a shorter distance in the periphery than the control animals did during the first 10-minute block, suggesting an altered response to the novel context. Differences in locomotor responses to novel environments have been associated with variations in the DA system. Greater D₂ receptor density (Hooks *et al.*, 1994), lower basal levels of DA (Hooks *et al.*, 1992), and higher DA uptake in the nucleus accumbens (Chefer *et al.*, 2003) and the prefrontal cortex (Zhu *et al.*, 2007) have been reported in rats that have weaker responses to novelty. There is growing evidence that the HIV-1 Tg rat displays alterations in the DA system (Moran *et al.*, 2012; Webb *et al.*, 2010); altered DA function may underlie their lower response to novelty. If the DA alterations typically found in animals that are less responsive to novelty do in fact underlie the HIV-1 Tg group's behavior in the present experiment, then the validity of the HIV-1 Tg rat as a model of HIV-1 would be further strengthened, with parallels to the lowered DA levels and altered DAT function found in individuals with HIV-1 (Berger *et al.*, 1994; diRocco *et al.*, 2000; Kumar *et al.*, 2011; Wang *et al.*, 2004).

The HIV-1 Tg animals showed decreased intrasession habituation of motor activity across the 3-day assessment periods that emerged across the at least monthly-spaced locomotor activity sessions; a pattern consistent with impaired long-term episodic memory. Differential intrasession habituation was observed during many of the test sessions, most notably during

the third session at 7 and 11 months, in which the HIV-1 Tg group, relative to the control group, maintained a higher level of activity across the latter half of the session. However, the HIV-1 Tg rats exhibited intrasession habituation during the second session at 7 and 11 months that was comparable to that of the control group. Intrasession habituation may be dependent on DA system functioning as well. For example, DAT knockout mice (Giros *et al.*, 1996, Zhuang *et al.*, 2001) and rats administered apomorphine, a D₁/D₂ agonist, (Carlsson, 1972) display reduced intrasession habituation of locomotor activity. It is unclear, however, whether their relative lack of intrasession habituation may be attributable to hyperactivity induced by the heightened activity of the DA system.

In the present study, the reduced intrasession habituation exhibited by the HIV-1 Tg rats provides evidence of a deficit in episodic memory. It is noteworthy that this deficit was only apparent after retest (retention) intervals of 1 and 4 months. Encoding and later retrieving information from episodic memory may rely partly on DA release in the hippocampus (Lisman and Gross, 2005). A relationship between DA system function and memory processes has been suggested by reduced episodic memory retrieval in individuals with Parkinson's disease (Dujardin and Laurent, 2003), as well as the observed differences in episodic memory recall as a function of variations of the catechol O-methyltransferase gene (de Frias *et al.*, 2004), which influences the metabolic degradation of DA. Furthermore, when DA antagonists are infused into the rat hippocampus prior to encoding, long-term memory of paired associates is impaired (Bethus *et al.*, 2010). Nearly half of HIV-1 positive individuals on CART, similar to pre-CART estimates, show deficits in long-term episodic memory (Heaton *et al.*, 2011) which may be due to higher viral levels in the hippocampus (Wiley *et al.*, 1998) and subsequent dysfunction of memory-dependent DA systems.

Cocaine sensitization, operationalized as a progressive increase in locomotor activity, was differentially altered in the HIV-1 Tg animals. The HIV-1 Tg group traveled an increasingly greater distance in the periphery across the 10-day sensitization period, whereas the control group traveled approximately the same distance on each day and also traveled less in the periphery than the HIV-1 Tg group. In addition, the HIV-1 Tg group spent significantly more time in the periphery across the 10-day period compared to the control group. The differences between groups that were observed during the 10-day initiation of cocaine sensitization were also detected on the cocaine rechallenge day, after a 7-day abstinence. Distance traveled and time spent in the periphery were again greater in the HIV-1 Tg group. The observed differences between the HIV-1 Tg and control groups were only detected after repeated cocaine administration, as the two groups did not show significant differences in behavior on the saline treatment day prior to the 10-day cocaine treatment. The administration of a drug which acts on the DA system was necessary to expose the DA system alterations present in the HIV-1 Tg rat.

Several alterations in the DA system occur during the initiation of cocaine sensitization. Behavioral sensitization during repeated cocaine administration is accompanied by elevated levels of extracellular DA in the nucleus accumbens and striatum (Kalivas & Duffy, 1993). DA receptor changes also occur in concert with behavioral sensitization following repeated cocaine injections. Up-regulation of D₃ receptors in the striatum and down-regulation of D₃ receptors in the nucleus accumbens were observed following daily cocaine injections over a 14-day period (Wallace *et al.*, 1996). Both types of alterations in receptor density were significantly related to increases in centrally directed activity across the test period. Regarding centrally-directed activity, both the HIV-1 Tg group and the control group increased their activity across the 10-day Coc treatment period, but with no compelling difference between the groups. However, the significant increase in peripheral activity across the 10-day period in the HIV-1 Tg group and the lack of change in peripheral activity

in the control group suggest that the HIV-1 transgene produces robust DA-system-dependent alterations in Coc sensitization.

Expression of Coc sensitization, as the enduring neural changes that underlie the increased response following repeated Coc treatment, is evaluated after a period of withdrawal from Coc. In the present study, animals were administered Coc after a 7-day abstinence following the 10-day period of daily injections, and each group responded similarly to how they responded at the end of the 10-day Coc treatment. Previous studies have demonstrated that behavioral sensitization may be observed in response to a cocaine challenge after several weeks without cocaine treatment (Kalivas & Stewart, 1991). Extracellular DA levels in the striatum (Kalivas & Duffy, 1993) and nucleus accumbens (Kuczenski & Segal, 1990) have been found to decrease in response to a cocaine challenge administered after a 1-4 day period of abstinence, but increase when the period is extended to 11-15 days (Kalivas & Duffy, 1993). Reduction of DA transporter (DAT) density in the nucleus accumbens shell, prefrontal cortex, and dorsal striatum of rats after 10 days or more of withdrawal from repeated cocaine administration has been reported in several studies (for review, see Pierce & Kalivas, 1997). Despite the differences in DA levels over varying abstinence lengths in these cited studies, behavioral sensitization to a cocaine challenge was still observed at the various time points. The present data show that the differences between groups that were observed during the 10-day Coc treatment period were maintained after the 7-day abstinence, such that the HIV-1 Tg group continued to travel a significantly greater distance and spend significantly more time in the periphery than the control group. It is possible that the normal alterations in DA levels and DAT density found during expression of Coc sensitization were disrupted in the HIV-1 Tg group, thus producing the significant differences in behavior between the two groups.

Clinical studies have demonstrated DA system dysfunction in HIV-1 positive individuals (Berger *et al.*, 1994; Berger & Nath, 1997; Koutsilieri *et al.*, 2002) as well as correlations between HAND and DA markers (di Rocco *et al.*, 2000; Kumar *et al.*, 2011; Wang *et al.*, 2004). While HIV-1 infection alone can produce deficits in a range of cognitive functions that rely on intact DA function, it is particularly important to recognize that cocaine and other drugs that are well-known to act on the DA system may exacerbate these cognitive deficits through a cascade of events (see review of Purohit *et al.*, 2011). First, cocaine substantially increases DA concentrations in the synaptic cleft by binding to DAT. Second, the cocaine-induced increase DA concentrations can allow for activation of microglia via DA receptors. Next, HIV replication and production of inflammatory mediators, including chemokines and TNF-alpha, are increased due to microglial activation. Finally, TNF-alpha and HIV-1 viral proteins gp120 and Tat can induce apoptosis of DA neurons, which may underlie the cognitive deficits of HAND.

In summary, sensorimotor gating, novelty responsiveness, long-term episodic memory, and cocaine sensitization were differentially altered in adult HIV-1 Tg Sprague-Dawley rats vs. control rats. Early-detected alterations in the startle response and the preattentive process of sensorimotor gating, in the absence of observable clinical signs, may have significant predictive utility as biomarkers regarding the progression of DA alterations in HIV-1 infection. This may be especially true in the comorbid condition of HIV-1 and drug abuse that acts directly on the DA system, precipitating an exacerbation of the effects of HIV-1 proteins on neurological function. The observed behavioral differences between the two groups are consistent with the emerging alterations in the DA system reported in this animal model of HIV-1 and suggest functional consequences of chronic low level of exposure to the HIV-1 proteins which resemble the suppression of infection in HIV-1 positive individuals under CART.

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Abbreviations

ANOVA	Analysis of variance
ASR	Auditory startle response
BAEP	Brain auditory evoked potentials
CART	Combination antiretroviral therapy
DA	Dopamine
DAT	Dopamine transporter
HIV-1	Human immunodeficiency virus-1
HAND	HIV-1 associated neurologic disorders
PPI	Prepulse inhibition
Tg	Transgenic

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Highlights

- HIV-1 Tg rats show altered PPI, novelty response, habituation and Coc sensitization
- Deficits were prior to any noted neurological symptoms or clinical signs of wasting
- Alterations in the DA system are implicated in the non-infectious HIV-1 Tg rat

Figure 1.

Mean body weight of the HIV-1 Tg animals and control animals across age with the best fit nonlinear regression ($\pm 95\%$ CI). The HIV-1 Tg group weighed significantly less than the control group across the six-month period during which they were tested. Both groups increased significantly in body weight across this period but the groups did not differ in their rates of growth.

Figure 2.

Mean peak amplitude data from ASR habituation trials with the best fit linear regression ($\pm 95\%$ CI). Linear regression analysis on the mean peak amplitude data revealed that the HIV-1 Tg and control groups habituated to the startle stimulus at the same rate, but the HIV-1 Tg group had an overall greater amplitude of response throughout the habituation session.

Figure 3.

Mean peak amplitude during PPI trials (Top panel: control group; Bottom panel: HIV-1 Tg group). There was no significant overall difference in mean peak amplitude between the HIV-1 Tg and control groups; however, a leftward shift was observed in the inflection point of the peak inhibition curve of the HIV-1 Tg group, indicated by a significant group x ISI interaction.

Figure 4.

Distance traveled (left panels) and time spent (right panels) in the periphery of the activity chamber during locomotor activity habituation trials across six 10-min trial blocks in three daily consecutive test sessions at 6, 7, and 11 months of age. Nonlinear analysis was used to fit the best single phase exponential decay (distance traveled) and single phase exponential association (time spent) functions to the data (mean $\pm$ 95% CI). In the first habituation session at each age tested, as well as during each of the three test sessions at the initial 6-month test age, the HIV-1 Tg rats traveled a shorter distance in the periphery than the control animals did during the first 10-minute block, suggesting an altered response to the novel context. The HIV-1 Tg rats also exhibited decreased intrasession habituation of motor activity, most notably during the third session at 7 and 11 months, in which the HIV-1 Tg group, relative to the control group, maintained a higher level of activity across the latter half of the session. Both groups showed significant increases in time spent in the periphery across blocks, but the HIV-1 Tg group spent significantly more time in the periphery than the control group.

Figure 5.

Distance traveled (top panel) and time spent (bottom panel) in the periphery of the activity chamber on the saline injection day, across 10 days of Coc injection, and on the Coc rechallenge day (day 17). No significant differences between the HIV-1 Tg group and the control group were found on the saline injection day in either measure. Nonlinear analysis was used to fit the best single phase exponential decay (distance traveled) and single phase exponential association (time spent) functions to the data (mean $\pm$ 95% CI). The HIV-1 Tg group traveled progressively more in the periphery across the 10 days of cocaine injections. They also traveled a greater distance and spent more time in the periphery than the control group during the 10-day period as well as on the Coc rechallenge day.