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Human immunodeficiency virus infection in the CNS and decreased dopamine availability: relationship with neuropsychological performance

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Abstract Human immunodeficiency virus (HIV-1) infection in the central nervous system (CNS) is associated with a wide range of neurological, cognitive, and behavioral problems. HIV-1 enters the brain soon after the initial infection and is distributed in varying concentrations in different regions with specific affinity to the subcortical regions, particularly the basal ganglia, causing neurodegeneration of dopaminergic regions and resulting in the decreased availability of dopamine (DA) in the CNS. Although there are numerous reports on HIV-1-associated neuropsychological (NP) impairment, there is a paucity of studies showing a direct relationship between the decreased availability of dopamine in different regions of postmortem brains of HIV-1-infected individuals and the level of performance in different NP functions during life. Dopamine is the key neurotransmitter in the brain and plays a regulatory role for motor and limbic functions. The purpose of the present study was to investigate the relationship between the decreased availability of dopamine found in the postmortem brain regions (fronto-cortical regions, basal ganglia, caudate, putamen, globus pallidus, and substantia nigra) of individuals with HIV/AIDS and the antemortem level of performance (assessed as *T* scores) in different NP functions. The relationship between HIV-1 RNA levels in different brain regions and the level of performance in different NP domains was also investigated. We found that although DA concentrations were 2–53% lower in the brain regions of HIV-1-infected, HAART-treated individuals, compared with HIV-negative controls, a 45% decrease in DA levels in the substantia nigra (SN) of HIV-1-infected individuals was significantly correlated with the low level of performance (*T* scores) in the speed of information processing, learning, memory, verbal fluency, and average *T* scores across domains. In case of homovanillic acid (HVA), the variable changes in different regions, including the substantia nigra, basal ganglia, caudate, and putamen (compared to that in the HIV-negative individuals), were significantly correlated with the level of performance (*T* scores) in motor functions, speed of information processing, and attention/working memory. HIVRNA levels in the frontal cortex, caudate, and GP were significantly inversely correlated with abstract/executive function, motor, learning, verbal fluency, and attention/working memory. No significant correlations were found between HIVRNA in other brain regions and NP performance. These findings suggest that the decreased availability of dopamine in the SN (the main site of DA synthesis in the CNS), and changes in the levels of HVA in different brain regions are, in part, related with the lower level of performance in some of the NP functions in individuals with HIV/AIDS.

Keywords HIV-1 infection · CNS · Dopamine · Neuropsychological deficits

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Introduction

Human immunodeficiency virus type 1 (HIV-1) infection and acquired immunodeficiency syndrome (AIDS) are

associated with a wide range of neurological, cognitive, and behavioral complications. The HIV-1 virus enters the central nervous system (CNS) within days of systemic infection, and the brain becomes an important target of damage in patients with HIV/AIDS (Ho et al. 1985). Various studies suggest that the virus enters the brain by utilizing one or more modes for its transport across the blood brain barrier, including infected monocytes or lymphocytes, or via the HIV-1-infected vascular endothelium; and it may also infiltrate directly as cell-free viral particles (Resnick et al. 1988; Banks et al. 2004; Bobardt et al. 2004). However, infiltration of infected monocytes as HIV-1 carriers has been suggested to play particularly an important role for viral entry into the CNS (Nottet et al. 1996; Gartner 2000). Once in the brain, HIV-1 lodges in varying concentrations in different regions, with high propensity for targeting the fronto-striatal circuitries, specifically the basal ganglia, as well as the other subcortical regions, leading to progressive neurodegenerative changes in these regions (Masliah et al. 1992). Although neurons themselves do not contain HIV-1 (Masliah et al. 1992), since the virus does not directly enter the neurons (Bagasra et al. 1996) due to the absence of receptors on the neuronal cell membranes (Broder and Dimitrov 1996), neurobiological changes, neuronal degeneration, and death are associated with the presence of virus in the CNS (Kolson et al. 1998; Nath and Geiger 1998; Kramer-Hammerle et al. 2005). Findings from several studies suggest that in the absence of opportunistic infections, HIV-1-associated neuronal loss found in different brain regions is a consequence of neuronal damage caused by the virus-related neurotoxins (Nath 2002), as well as the neurotoxic products generated by the infected extra-neuronal cells, including microglia and macrophages, and to some extent by astrocytes (Heyes et al. 1991; Brabers and Nottet 2006; Anderson et al. 2002; Brack-Werner 1999; Kaul and Lipton 2006). Recent studies by our group reported varying levels of HIV-1 RNA in different regions of postmortem brains with high concentration found in different nuclei of the basal ganglia, including the caudate nucleus, putamen, globus pallidus, and substantia nigra as well as in the fronto-cortical areas (Kumar et al. 2007). Since these subcortical regions are also rich in dopaminergic activity and neurotoxicity of the dopaminergic system has been associated with AIDS dementia (Nath et al. 2000), we propose that high levels of HIV-1 RNA found in these brain regions may be responsible for inducing the higher production of neurotoxins that result in the loss of dopaminergic neurons and a decrease in the availability of dopamine, leading to impairment in neuromotor and neurocognitive functions in individuals with HIV-1 infection.

Dopaminergic dysfunctions in patients with HIV-1 infection were initially reported as clinical manifestation of psychomotor slowing, bradykinesia, tremor, apathy, and altered posture and gait (Navia et al. 1986; Arendt et al. 1990), symptoms similar to those associated with dopamine deficiency in Parkinson's disease (PD), and were observed even in the early stage of HIV-1 infection (Berger et al. 1994; Berger and Arendt 2000). Deficits in dopamine (DA) became further evident when the PD-like symptoms in some of the patients were found to exacerbate when treated with dopamine-blocking drugs, such as prochlorperazine, perphenazine, and trifluoperazine, and even with low-dose haloperidol (Hollander et al. 1985; Hriso et al. 1991; Mirsattari et al. 1998). These observations suggested that HIV-1 in the brain may be causing damage to dopaminergic activity in these patients. Other studies using magnetic resonance imaging (MRI) have found a reduction in the volume of basal ganglia, posterior cortex, and deep gray and white matter (Aylward et al. 1993, 1995), and functional MRI studies reported significant cerebral hemodynamic changes with increased cerebral blood volume in the deep and cortical gray matter, decreased *N*-acetyl aspartate/creatinine ratio, and elevated levels of choline in white matter in HIV-1-infected patients with cognitive impairment (Tracey et al. 1996, 1998).

Furthermore, changes in dopaminergic activity in the cerebrospinal fluid (CSF) of HIV-1-infected patients have been found to relate with neurological complications at different stages of disease progression, particularly with a significant decrease in the concentration of dopamine and homovanillic acid (HVA) in the CSF (Berger et al. 1994; Larsson et al. 1991; Di Rocco et al. 2000; Obermann et al. 2009) and a decrease of dopamine in the caudate of patients with HIV/AIDS (Sardar et al. 1996). In our recent studies, we found that the decrease in dopamine concentration in the CNS of HIV-1-infected individuals is not limited to a few regions in the brain but is significantly decreased in a number of cortical and subcortical regions including fronto-cortical areas, basal ganglia (BG), caudate, putamen, globus pallidus (GP), and substantia nigra (SN) (Kumar et al. 2009). However, it is not clearly understood whether the decrease in dopamine concentration in different brain regions is directly related with specific neuropsychological disorders found in patients with HIV/AIDS.

Neurocognitive disorders are the most prominent feature of HIV-1-associated complications of the CNS, and according to the earlier terminology of the American Academy of Neurology (AAN 1991), the disorders can range from minor cognitive motor disorders (MCMD) to HIV-associated dementia (HAD) (Heaton et al. 1995; Ances and Ellis 2007). However, the earlier criteria have been recently updated, and are now defined by three conditions for diagnosis of HIV-associated neurocognitive disorders (HAND) and encompass asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND),

and HAD (Antinori et al. 2007). While ANI is referred to mild impairment in two or more cognitive areas without a clear effect on daily functioning, MND refers to the presence of mild to moderate deficits in two or more cognitive areas with mild interference in daily functioning; and HAD refers to moderate to severe deficits in two or more cognitive areas with significant impairment in daily functioning and making the person incapable of employment and unable to live independently. However, some of the studies cited in this report were carried out using the earlier AAN criteria (1991) and have used the terms such as MCMD and HAD for diagnosis of neurocognitive deficits. Accordingly, although the incidence of HAD, the most severe form of HAND, has declined since the introduction of HAART in 1996 and the survival rates have improved dramatically, the prevalence of milder forms of HAND remains an important unresolved problem (Sacktor 2002; McArthur 2004). Reports from recent longitudinal and cross-sectional studies have shown that despite antiretroviral therapy, abnormalities continue to occur in neuropsychological (NP) functions in the early and late stages of HIV-1 infection, and the symptoms of mild cognitive and motor functions remain prevalent in 20% of HIV-1-infected patients, and incidence of dementia in 50% of patients with AIDS (Heaton et al. 1995; Sacktor et al. 2002). These findings concur with the earlier reports that CNS may be an important reservoir for HIV to cause persistent neuropathogenesis in different areas of the brain (Bagasra et al. 1996; Schrager and D'Souza 1998). In fact, earlier studies by Becker et al. (1997) found that in HIV-1-infected individuals, the most affected cognitive deficits were psychomotor slowing and speed of information processing that can also be predictive of other cognitive deficits, including attention, working memory, recall memory, visuo-spatial functions, and learning and motor skill, similar to the deficits found in other studies (Heaton et al. 1995; Wilkie et al. 2000). For example, deficits in memory reported in early HIV-1 infection were predictive of subcortical disease model with specific defects found in learning efficiency, verbal memory, and information retrieval (Grant and Martin 1994; Peavy et al. 1994; Becker et al. 1997). Other studies found impairment to increase at each successive stage of infection and was related with cellular immune activation, CNS neurological abnormalities, and central brain atrophy detected with MRI (Heaton et al. 1995). Moreover, high levels of HIV RNA in the CSF of the infected patients were found to predict progression of NP impairment (McArthur et al. 1997; Ellis et al. 2002), suggesting that CSF viral load may trigger the neurodegenerative processes that may be associated with neurocognitive disorders, specifically in the areas of learning, attention, working memory, and motor function, consistent with the earlier findings (Heaton et al. 1995; Ellis et al. 1997).

Thus, the evidence to date from various studies suggests that despite HAART intervention, HIV-1 continues to be present in different brain regions in variable concentrations (Schrager and D'Souza 1998; Kumar et al. 2007) and is associated with varying degrees of neurodegenerative changes in the subcortical regions, particularly in the basal ganglia (Masliah et al. 1997; Everall et al. 1999), the region known to contain the highest concentration (>80%) of dopamine (Hornykiewicz 1973). Furthermore, studies showing that HIV-1 in the CNS causes damage to the neuronal cell bodies in the pars compacta of SN (Reyes et al. 1991; Itoh et al. 2000), the main site for dopamine synthesis, are also supported by the recent findings by us and others that dopaminergic activity is decreased in the CNS of HIV-1-infected individuals (Wang et al. 2004; Kumar et al. 2009). Although a large body of evidence exists, which shows impairment in NP performance in HIV-1-infected patients (Heaton et al. 1995; Sacktor 2002; Ellis et al. 2002; Woods et al. 2009), there is paucity of investigations on the relationship between the decreased availability of CNS dopamine and NP impairment, mainly due to the unavailability of postmortem tissues from different brain regions of HIV-1+ individuals for measurement of dopamine and their corresponding antemortem data on measures of NP performance for different domains. The establishment of tissue banks by the NIH/National NeuroAIDS Tissue Consortium (NNTC) has greatly facilitated investigations on HIV/AIDS-associated disease and neurodegenerative processes in the CNS. Since dopamine in the CNS has been associated with regulation of different cognitive functions (Previc 1999; Nieoullon 2002), we hypothesize that depletion in the availability of dopamine in different regions of postmortem brains of HIV-1-infected individuals (DA and HVA concentrations, relative to that in the same brain regions of HIV-negative cases), as well as high levels of HIV-1 RNA in the same brain regions, will be related with poor level of performance in different NP functions assessed prior to death.

Material and methods

Human postmortem brain tissues

The postmortem brain tissues from HIV-1-seropositive and HIV-negative control individuals used for this study were procured from the four centers of the NIH/NNTC, which includes the National Neurological Brain Bank (Los Angeles, CA), the Texas Repository for AIDS Neuropathogenesis Research (Galveston, Tex), the Manhattan Brain Bank (New York, NY), and the HIV Neurobehavioral Research Center brain bank (California NeuroAIDS Tissue Network, CNTN) at the University of California at San Diego.

The centers obtained informed consent of the family and approval of the respective institutional review board for human ethics for enrollment, evaluation, and every-6-months follow-up of these patients during life and for collecting data on various aspects of their health including physical, physiological, mental, cognitive, and neuropsychological (NP) functions, as well as for autopsy and donation of organ and body fluids (Anatomical Gift Act 1990). All procedures, including postmortem interval (PMI, within 24 h), as well as excision of tissues, labeling, and preservation, are carried out according to the guidelines instituted in the NNTC protocol (Morgello et al. 2001). Briefly, tissues after careful excision are immediately transferred to separate containers labeled for specific tissues and snap-frozen in liquid nitrogen and transferred to −80°C freezers until used. Postmortem CSF is collected from the lateral ventricles or basilar cistern and also stored frozen at −80°C. The PMI was 2–24 h for individuals included in this study. HIV-1+ individuals were 31–58 years of age, with duration of infection ranging between 1 and 21 years, and were free of any opportunistic infection of the CNS before death (between 1998 and 2005). The majority of HIV-1+ cases had used HAART regimen (n=33/38) prescribed as standard of care for each individual and included combinations of protease inhibitors, single or multiple nucleoside reverse transcriptase inhibitors plus one non-nucleoside reverse transcriptase inhibitor. Five HIV-1+ individuals did not receive HAART intervention. The tissues from different brain regions of HIV-negative individuals (six males and five females, age 35–66 years) were from those who died during the same span of time as HIV-1+ individuals (1998–2005) but due to different causes.

The neurocognitive status of HIV-1+ individuals was assessed at the NNTC centers. The criteria defined by the Memorial Sloan–Kettering (MSK) rating scale was used for assessment of neurocognitive functions. The test revealed the presence of probable or possible HAD, probable or possible MCMD, and impairment to a degree that they could carry out the activities of daily living. Among the 38 HIV-1+ cases, 12 individuals (32%) had diagnosis of probable HAD (score=2–4), eight (21%) had possible HAD (score=2–3), five cases (13.2%) had probable minor cognitive motor disorders (MCMD, score=2), two of them (5.3%) had possible MCMD (score=1–2), two (5.3%) had MCMD (score=1), four (10.5%) were impaired (score=1), one (2.6%) had no impairment (NPI, score=0), three (7.9%) were cognitively normal (score=0), and 1 (2.6%) was not evaluated.

NP functions were evaluated using assessment battery for seven specific domains, including abstract/executive functions, information processing speed, attention/working memory, learning, memory, verbal fluency, and motor skills (Butters et al. 1990). Abstract/executive function and mental flexibility were assessed with the Wisconsin Card Sorting Test (computerized 64-item version; Heaton et al. 1993), the Trail Making Test Part B (Heaton et al. 1991), and the Wechsler Adult Intelligent Scale III Letter–Number Sequencing test (WAIS-III; Wechsler 1997). The tests used for assessment of information processing speed included the WAIS-III Digit Symbol and WAIS-III Symbol Search (Wechsler 1997) subtests, and the Trail Making Test Part A. These tests also measure attention, sequencing, visual search, and motor functions (Heaton et al. 1991). Attention–working memory was tested with Paced Auditory Serial Attention Test (2.4-s interval only; Gronwall 1977), while learning and memory domains were tested by Hopkins Verbal Learning Test-Revised (Benedict 1997) and Brief Visual Memory Test-Revised (Benedict 1997). Verbal fluency was tested by Controlled Oral Word Association Test (FAS/PMR, Benton et al. 1994), and the psychomotor speed was tested by Grooved Pegboard Test (Mathews and Klove 1964). For this report, the data for NP assessment of participants conducted in the closest proximity to the individual's death were provided by the NNTC centers. The elapsed time for NP evaluation and death of majority of HIV-1-infected individuals was between 1 and 8 months (mean, 5.40±5.42). (However, one individual who was infected with HIV-1 for 17 years and was taking HAART had an elapsed time of 19 months between NP evaluation and death. But the longer elapsed time in this individual was not specifically found to influence the overall outcome of the relationship between NP evaluation scores and DA and DVA levels in the postmortem brain regions). The assessment of different NP domains was scored relative to published normative data. The Raw Scores on the individuals NP test were demographically corrected for age, gender, and education (standard scores, T scores) using the procedures described by Heaton et al. (1991, 1995).

The study reported here was approved by the Institutional Review Board (IRB) of the University of Miami, Miller School of Medicine. The postmortem tissues were obtained in dry ice from NNTC, according to the guidelines for overnight shipping and handling (US Federal Regulations 49 CFR 172 subpart H). Brain tissues were excluded from those with neuropsychiatric illness such as schizophrenia, long-term use of antipsychotic medication, history of stimulant drug dependency, CNS cancer, and opportunistic infection of the CNS and from those with CNS complications due to severe head injury with loss of consciousness for more than 30 min.

Concentrations of DA and HVA in tissues from different regions (frontal cortex, frontal cortex-area 4, frontal cortex-area 6, basal ganglia, caudate, putamen, globus pallidus, substantia nigra, as well as CSF) of postmortem human

brain of HIV-1+ (n=38) and HIV-negative (n=11) individuals were quantified using CoulArray high-performance liquid chromatography equipped with electrochemical detector system, and the results were expressed as DA $\log_{10}$ picogram per gram tissue and that of HVA as $\log_{10}$ nanogram per gram tissues. The values obtained on dopaminergic activity in different brain regions of HIV-negative individuals were used to compare and evaluate the percent changes found in the corresponding brain regions of HIV-1+ individuals. The same brain regions of HIV-1+ cases were also used to determine the levels of HIV-1 RNA ($\log_{10}$ RNA copies per gram tissue) using real-time RT-PCR. The details of the procedures for determination of dopamine as well as HIV-1RNA levels have been described earlier (Kumar et al. 2007, 2009).

Statistical analysis

Statistical analyses were carried out using the Statistical Package for the Social Sciences (version 17). Spearman's rho correlations (r_s) were determined between the available concentrations of DA ($\log_{10}$ picogram per gram tissue) and HVA ($\log_{10}$ nanogram per gram tissue) in different brain regions, as well as the levels of HIV-1 RNA ($\log_{10}$ copies per gram tissue) in the same brain regions and T score of subtest as well as the overall neuropsychological composite score for seven neuropsychological domains, including abstract executive function, speed of information processing, attention working memory, learning, memory, verbal fluency, and motor functions in HIV-1+ individuals. Because of the small sample size, the nonparametric Spearman rank order correlations were calculated using all available data on individuals' NP performance for each domain and DA, HVA, and HIVRNA levels in different brain regions. Correlations that were significant and those that approached conventional levels of significance are reported here.

Results

The demographic and clinical characteristics of HIV-1+ cases (n=38) are presented in Table 1. Percent decrease in DA and HVA concentration in each brain region of HIV-1+ cases (Table 2) was derived from the data in our earlier report (Kumar et al. 2009) and represents decreases relative to concentrations obtained in the same brain regions of HIV-negative individuals. The decrease in DA concentration was very variable and significant in the HIV-1+ brain regions (2% to 53%), including in GP, BG, caudate, SN, and putamen (24 –53%, p=0.005 to p=0.000).The highest decrease (53%) of DA was in the putamen, and low to moderate decrease (2–13 %, p=NS) was found in the fronto-cortical regions (including FC6, FC4, and FC). On the other hand, concentration of HVA in the same brain regions showed a different pattern of variation, with a decrease of 24% and 43% in FC and FC4, respectively, and 22.5% in the basal ganglia, and in contrast, an increase of 0.4% to 48% was found in the other brain regions (SN, putamen, caudate, globus, and FC4) (Table 2). However, concentrations of dopamine as well as HVA among different brain regions were strongly correlated (Table 3).

Correlations were determined between the available concentrations of DA ($\log_{10}$ picogram per gram tissue) and HVA ($\log_{10}$ nanogram per gram tissue) as well as between the levels of HIVRNA ($\log_{10}$ copies per gram tissue) in different brain regions of HIV-1+ cases and the antemortem T scores as a measure of performance for different NP domains (Table 4). Our findings reveal (Table 4) that DA concentration in the SN correlated significantly with the level of performance in speed of information processing (r_s=0.528; p=0.030), learning domain (r_s=0.466, p=0.033), and verbal fluency (r_s=0.428, p=0.047), as well as in the memory (r_s=0.518; p=0.019) and average domains T scores (r_s=0.569; p=0.006). On the

Table 1 Clinical and demographic characteristics of HIV-1+ cases

Specific characteristics	HIV-1+
N	38
Year of HIV-1 diagnosis	1987–2001
Duration of HIV-1 disease	1–21 years
Year of death	1998–2005
Age at death	31–58 years
Postmortem interval (PMI)	2–24 h (mean±SD; 9.41±5.74)
Gender	32 men (84%), 6 women (16%)
Ethnicity	Caucasian=24 (63%); Hispanic whites=4 (10.5%); African-American=5(13.3%); Native American=4 (10.5%); Asian=1 (2.7%)
Opportunistic infection	No opportunistic infections at the time of death
Antiretroviral therapy	Majority on HAART (N=33); NO HAART (N=5)
Neurocognitive deficits	Probable HAD=12; possible HAD=8; probable MCMD=5; possible MCMD=2; MCMD=2; impaired=4; NPI=1; normal=3; no evaluation=1
AIDS dementia—MSK rating	0–4
NP evaluations, elapsed time (months) before death	5.40±5.42
T scores in different domains	*T* scores 6–99
Deficit scores (NNTC key; *T* scores 40+=0)	No deficits
T scores <40 to <20	1 to 5 (mild to severe deficits)

Table 2 Dopaminergic deficits (%) and HIV-1 RNA levels in different regions of postmortem brains of HIV-1+ individuals

Brain regions	Decrease in dopamine (%)	Decrease in HVA (%)	HIVRNA (log_{10} copies/g tissue)
Frontal cortex (FC)	−13 (24)	−24 (24)	2.68±1.32 (9), ND (16)
FC4	−5 (13)	−43 (13)	3.80±0.96 (5), ND (8)
FC6	−2 (13)	+48 (12)	3.55±1.89 (7), ND (6)
Basal ganglia	−28 (15)	−22.5 (5)	3.29±1.49 (10), ND (5)
Caudate	−47 (14)	+16 (14)	4.63±1.38 (6), ND (8)
Putamen	−53 (14)	+2 (14)	3.05±1.52 (9), ND (4)
Globus pallidus	−24 (13)	+17 (13)	3.42±1.10 (5), ND (7)
Substantia nigra	−45 (23)	+0.4 (23)	3.44±1.77 (10), ND (12)

The data presented here are partial representation of the data from the earlier report (Kumar et al. 2009). The percent changes in DA and HVA concentration in different brain regions were determined from the concentrations in the same brain regions of HIV-negative individuals. HIV-1 RNA levels (log_{10} copies per gram tissue) in different brain regions were variable (Kumar et al. 2007). Numbers in parenthesis = number of samples from HIV-1+ individuals. *ND* not detected

other hand, HVA concentrations in different brain regions (both decrease and increase) were found to correlate with the level of performance in different NP domains. In the BG, concentration of HVA was significantly correlated with performance in the motor domain (r_s=0.661, p=0.038). In the caudate nucleus, HVA concentration was significantly correlated with the level of performance in the motor domain and information processing speed (r_s=−0.594, p=0.042; and r_s=−0.738, p=0.037; respectively), whereas in the putamen, levels of HVA were significantly correlated with performance in attention/working memory (r_s=0.720, p=0.008), and correlations between the concentrations of HVA in the SN approached statistical significance with the level of performance in the motor domain (r_s=0.440, p=0.059, n=19), but in FC6, HVA levels were correlated with attention/working memory (r_s=−0.775, p=0.041).

The levels of HIVRNA in the same brain regions were also variable, ranging between one and six log_{10} copies per gram tissue (Table 2). A significant inverse correlation was found (Table 4) between the levels of HIVRNA in FC and performance in abstract/executive functions, motor, learning, and average domain *T* scores and between HIV-1 VL in FC6 and attention/working memory performance (r_s=−0.775, p=0.041) and overall cognitive functioning as measured via the average *T* scores across domains (r_s=−0.905, p=0.002). The levels of HIVRNA in the caudate correlated with attention/working memory (r_s=−0.894; p=0.041), whereas correlation approached statistical significance between the levels of HIV-1 RNA in GP and learning domains (r_s=−0.949, p=0.051).

Neuropsychological variables and the range of *T* scores as well as descriptive statistics of *T* scores for different NP domains in HIV-1+ individuals are presented in Table 5. A scatter plot of *T* scores of each individual (*Y*-axis) assessed in each NP domain (*X*-axis) is shown in Fig. 1. These data show that although many individuals had functioning at normal or near-normal levels, a number of them were

Table 3 Correlations (r_s) between the inter-regional dopamine (log_{10} picogram per gram tissue) and HVA (log_{10} nanogram per gram tissue) concentrations in postmortem brains of HIV-1+ cases

Dopamine and HVA in brain regions	Number	Correlations (r_s)
DA in FC4 vs DA in FC6	13	r_s=0.747[a] (p=0.003)
DA in FC vs DA in BG	13	r_s=0.907[a] (p=0.000)
DA in FC6 vs DA in caudate	11	r_s=0.609[b] (p=0.047)
DA in SN vs DA in FC	15	r_s=0.779[a] (p=0.001)
DA in SN vs DA in BG	9	r_s=0.767[b] (p=0.016)
DA in SN vs DA in caudate	7	r_s=0.750 (p=0.052)
DA in caudate vs DA in GP	12	r_s=0.636[b] (p=0.026)
DA in putamen vs DA in GP	11	r_s=0.755[a] (p=0.007)
DA in putamen vs DA in caudate	13	r_s=0.819[a] (p=0.001)
DA in FC4 vs HVA in GP	10	r_s=0.697[b] (p=0.025)
DA in FC4 vs HVA in putamen	10	r_s=0.867[a] (p=0.001)
HVA in FC4 vs HVA in FC6	12	r_s=0.846[a] (p=0.001)
HVA in SN vs HVA in BG	9	r_s=0.867[a] (p=0.002)

[a] Correlations are significant at the 0.01 level (two-tailed)

[b] Correlations are significant at the level of 0.05 (two-tailed)

Table 4 Correlations (Spearman rho) between concentration of DA and HVA and HIV-1 RNA in different brain regions and *T* scores of different NP domains evaluated in HIV-1+ cases

DA, HVA, and HIV-1 RNA levels and NP domains (*T* scores)	Number	Correlations (r_s)
DA in SN and speed of inform processing	17	r_s=0.528* (p=0.030)
DA in SN and learning domain	21	r_s=0.466* (p=0.033)
DA in SN and memory domain	20	r_s=0.518** (p=0.019)
DA in SN and verbal fluency	22	r_s=0.428 *(p=0.047)
DA in SN and average domain *T* score	21	r_s=0.569** (p=0.006)
HVA in BG vs motor domain	10	r_s=0.661* (p=0.038)
HVA in SN vs motor domain	19	r_s=0.440 (p=0.059)
HVA in caudate vs motor domain	12	r_s=−0.594* (p=0.042)
HVA in caudate vs speed of inform proc.	8	r_s=−0.738* (p=0.037)
HVA in putamen vs attention/work memory	12	r_s=0.720** (p=0.008)
HVA in FC6 vs attention/working memory	7	r_s=−0.775* (p=0.041)
HIV-1 VL in FC vs abstract/executive functions	7	r_s=−0.750 (p=0.052)
HIV-1 VL FC vs motor domain	17	r_s=−0.511* (p=0.036)
HIV-1 VL in FC vs learning domain	4	r_s=−0.420 (p=0.074)
HIV-1 VL in FC vs verbal fluency	8	r_s=−0.707* (p=0.05)
HIV-1 VL in FC vs average domain *T* scores	8	r_s=−0.905** (p=0.002)
HIV-1 VL in FC6 vs attention/work memory	7	r_s=−0.775* (p=0.041)
HIV-1 VL in caudate vs attention/work memory	5	r_s=−0.894* (p=0.041)
HIV-1 VL in GP vs learning domain	4	r_s=−0.949 (p=0.051)

*Correlations are significant at the level of 0.05 (two-tailed)

**Correlations are significant at 0.01 level (two-tailed)

severely impaired in some cognitive domains, and patients who were diagnosed with probable or possible HAD (MSK dementia rating 1–4) or MCMD had lower *T* scores (<20 and <35) in more than two NP domains. In some cases, the *T* scores were low in three to seven domains of NP functions (Table 5, Fig. 1). However, strong correlations were found between *T* scores (ranging between r_s=0.369, p=0.045 and r_s=0.923, p=0.000) among different NP domains in HIV-1-infected patients.

Discussion

In this study, we found that the decreased availability of dopamine in different brain regions of HIV-1+ individuals (compared with that in HIV-negative individuals) was correlated with the lower level of performance in some of the NP functions (*T* scores <19 reflecting severe impairment and *T* scores >20 to <40 reflecting mild to moderate impairment; Table 5) assessed prior to death of HIV-1+ individuals. For example, the available DA concentration in the SN (45% lower than that of the HIV-negative controls) correlated significantly with the lower level of performance in the speed of information processing and learning as well as memory and average domains, whereas the changes in HVA as both lower and higher concentration in different brain regions were found to have significant relationships with the level of performance in different NP domains. For instance, HVA concentrations in BG (22.5% lower relative to that in HIV-negative individuals) were strongly correlated with the level of performance in motor functions, and with no decrease in SN, caudate nucleus (CN), and putamen, HVA concentration correlated moderately to strongly with performance in motor domain, speed of information processing, and attention/working memory (Table 4). While HVA levels in FC6 correlated moderately with attention working memory, no correlation was detected between DA and HVA concentrations in the other FC regions and between the levels of performance in any NP function.

We also found several inverse correlations between HIVRNA levels and the level of performance in NP domains that approached statistical significance, such as between HIVRNA levels in FC and motor and learning domains *T* scores, whereas HIVRNA levels in FC6 were negatively correlated with attention/working memory domain *T* scores. In some individuals, a strong correlation between HIVRNA levels in FC and a decline in overall NP performance (average domain *T* scores, Table 4) were also found. Correlations between DA, HVA, and HIVRNA levels in each brain region were evaluated with the available data for antemortem measures of NP functions. The elapsed time between NP evaluation and death of majority of HIV-1-infected individuals was between 1 and 8 months (mean, 5.40±5.42). One individual who was infected with HIV-1 for 17 years and was treated with HAART had an elapsed time of 19 months. However, the longer elapsed time in this individual was not specifically found to influence the overall outcome of the relationship between NP evaluation scores and DA and HVA levels in

Table 5 Assessment of neuropsychological domains

#	Patient ID	Gender	Years of HIV	Age at death	Neurocognition (MSK rating)	ABST-TS	INFOPROC-TS	ATTN-TS	LERN-TS	MEM-TS	VERB-TS	MOTOR-TS	AVERG-TS
1	1052	F	2	48	Prob HAD (4)[a]		12.00		19.00	19.00	19.00		17.30
2	2074	M	3	37	Prob MCMD (1)[a]	36.00	29.70	36.00	31.00	27.50	41.00	23.50	31.30
3	6050	M	5	41	Prob HAD (2)[a]	33.00	36.50	53.00	23.50	23.50	39.00		31.50
4	6073	M	6	49	Possib HAD (3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
5	6007	M	9	34	Prob HAD (2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
6	1021	F	5	41	NPI alcoh (2)	40.50		41.00	38.00	41.00	35.00	44.50	40.90
7	2066	M	5	35	Prob HAD (2)								
8	4056	M	2	37	Possib HAD (3)[a]	40.50		29.00	21.50	19.00	34.00	16.50	25.90
9	4013	M	6	43	Prob HAD (2)[a]	31.00		22.00	43.50	36.00	22.00	42.00	33.10
10	1013	M	9	58	Prob HAD (2)[a]	19.00		22.50	33.00	28.50	47.00	14.50	25.30
11	2033	F	3	58	Prob HAD (2)[a]	28.00		34.00	33.00	41.50	34.00	13.00	29.60
12	6037	M	7	41	Prob HAD (2)[a]	25.00		28.00	29.00	37.50	47.00	14.50	30.60
13	6052	M	4	39	Possib HAD (3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
14	6009	M	5	53	Prob HAD (2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
15	6011	M	10	50	Possib HAD (3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
16	4049	M	9	44	Possib HAD (2)[a]	40.00		35.50	21.50	19.00	46.00	26.50	32.40
17	5057	M	12	38	No imp	52.50		49.50	54.00	53.00	57.00	46.00	50.10
18	D0012KE	M	9	33	Prob HAD (1) HIVE[a]	14.50	24.33	33.00	22.00	21.50	28.00	6.00	21.07
19	D0020LP	F	10	35	Prob HAD (2)[a]	45.50	45.67	37.50	38.50	37.50	44.00	20.00	38.50
20	D0027RL	M	6	50	Possib MCMD (1)	47.50	50.67	69.00	34.50	38.50	61.00	45.50	48.78
21	G0035KG	F	2	43	Impaired/dementia?	40.00	45.67	34.00	47.00	40.00	45.00	35.50	41.40
22	G0061AD	M	17	33	Possib HAD (?)[a]	34.50	39.33	39.00	23.50	26.50	46.00	24.50	32.84
23	G0068BS	M	5	31	Prob MCMD (2)	52.50	54.33	45.00	55.00	50.00	31.00	35.50	47.85
24	G0076EG	M	14	49	NP imp (2) unk cause[a]	40.00	36.00	42.00	21.50	23.00	28.00	26.50	30.76
25	H0007GA	M	8	45	Prob MCMD (1)	38.00	47.33	46.00	47.00	47.00	44.00	34.50	43.64
26	10095	MSM	6	42	Prob MCMD (2)	41.00	38.00	43.00	36.00	42.00	38.00	32.00	38.00
27	10045	F	8	31	Possib HAD (2)[a]	35.00	29.00	37.00	24.00	31.00	20.00	14.00	27.00
28	CE124	M	17	55	NP imp	31.00	47.00	43.00	99.00	N/A	41.00	19.00	43.00
29	CE144	M	13	47	MCMD (1)	41.00	46.00	43.00	37.00	43.00	59.00	30.00	42.00
30	CE150	M	15	42	Prob MCMD (no score)	42.00	44.00	41.00	25.00	22.00	57.00	39.00	38.00
31	CA110	M	21	43	Possib HAD (no score)[a]	27.00	26.00	20.00	22.00	22.00	19.00	14.00	22.00
32	CB164	M	<1	35	NP imp (no score)	53.00	46.00	47.00	48.00	45.00	45.00	16.00	43.00
33	CA236	M	7	34	Normal	48.00	47.00	49.00	57.00	53.00	56.00	49.00	51.00
34	CA163	M	21	46	Normal	48.00	49.00	34.00	42.00	52.00	39.00	63.00	47.00
35	CE116	M	12	46	Possib MCMD	N/A	N/A	31.00	24.00	27.00	17.00	24.00	25.00
36	CC120	M	6	45	Possib HAD (3)[a]	20.00	23.00	33.00	22.00	25.00	32.00	16.00	23.00
37	CC116	M	11	32	No DX	48.00	43.00	47.00	29.00	33.00	54.00	33.00	40.00

Table 5 (continued)

#	Patient ID	Gender	Years of HIV	Age at death	Neurocognition (MSK rating)	ABST-TS	INFOPROC-TS	ATTN-TS	LERN-TS	MEM-TS	VERB-TS	MOTOR-TS	AVERG-TS
38	CC147	M	6	50	MCMD	-	52.00	45.00	27.00	24.00		36.00	36.00
					Mean±SD→	37.7±10.22	39.63±10.93	39.0±10.00	35.25±16.08	33.82±11.02	39.52±12.58	28.47±13.42	35.25±9.22
						Mini=14.50	Mini=12.00	Mini=20.00	Mini=19.00	Mini=19.00	Mini=17.00	Mini=6.00	Mini=17.30
						Max=53.00	Max=54.33	Max=69.00	Max=99.00	Max=53.0	Max=61.00	Max=63.00	Max=51.00
						N=29	*N*=23	*N*=31	*N*=32	*N*=31	*N*=31	*N*=30	*N*=32
43	3002 HIV−	M	N/A	70	HIV-neg normal	61.00	N/A	54.00	53.00	50.00	53.00	N/A	54.80
46	3015 HIV−	F	N/A	79	HIV-neg normal	48		50	41	38.5	63	46	47

Data presented are *T* scores for each domain. *T* scores in HIV-1+ individuals for different NP domains were provided by the NNTC centers. *T* scores for two HIV-negative individuals (#43 and #46) with normal NP functions are also presented. NNTC-Key for NP deficits with respect to *T* scores: 40+=0 (normal); 39–35=1 (mild); 34–30=2 (mild to moderate); 29–25=3 (moderate); 24–20=4 (moderate to severe); <19=5 (severe). The elapsed time for NP assessment and death for majority of individuals was within 1–8 months. However, increased elapsed time (for example, 19 months for #28) was not found to have a specific impact on NP evaluation scores or on the levels of DA and HVA in the brain regions (FC, BG, SN; DA $\log_{10}$ picogram per gram tissue=0.322, 0.403, 1.017, respectively, and HVA $\log_{10}$ nanogram per gram tissue=0.738, 1.67, and 1.9, respectively; data from Kumar et al. 2009) and was within the range of other HIV-1+ individuals. NP performance suggested moderate impairment in abstr/exec function (*T* scores=31) and severe impairment in motor function (*T* scores=19), indicating the effect of decreased dopaminergic availability. *N/A* data not available

[a] Patients with HAD who had dementia score of 2–4, performed poorly in two to seven NP domains

the postmortem brain regions (see caption, Table 5). It is to be pointed out that samples of all brain regions from each individual were not available for quantifying DA, HVA, and HIVRNA levels, and the corresponding data for all NP measures were also not available for each HIV-1+ individual.

With regards to dopamine depletion in the CNS and its relationship with impairment in NP functions in HIV-1-infected individuals, we anticipated (based on our proposed hypothesis) that a decrease in the availability of DA in BG regions, particularly, 53% decrease in putamen, 47% in the caudate, 45% in SN, and 24% in globus pallidus (compared with that in the same brain regions of HIV-negative individuals) as well as low levels of DA found in the fronto-cortical motor regions of HIV-1 infected individuals, would significantly affect the level of performance in motor functions, memory, and attention/working memory as well as other NP functions, since it is well recognized that optimum levels of DA and dopaminergic activity in these brain regions are required in the modulation of these cognitive functions (Borozoski et al. 1979; Previc 1999). Findings from other studies suggest that dopaminergic activity in the frontal lobe and basal ganglia region, specifically, in the caudate and putamen is associated with regulation of motor functions and initiation and maintenance of working memory and mathematical and other complex planning and reasoning tasks and that these functions are dependent on the availability of optimum concentration of dopamine for neurotransmission (Owen et al. 1996; Nieoullon 2002; Grahn et al. 2009). However, we found that among the brain regions of HIV-1+ individuals, depletion of dopamine levels in SN was correlated with the lower performance in the speed of information processing, verbal fluency, learning, and memory. This may be due to the fact that the SN (pars compacta) is the main site of dopamine synthesis, and after synthesis, DA is transported to the other subcortical and fronto-cortical regions (caudate, putamen, globus pallidus, and the FC areas) via the nigro-striatal and fronto-striatal neuronal network of axonal and synapto-dendritic projections. In patients with PD, deficits of DA in the SN caused by degeneration of dopamine-producing neurons, as well as disruption of dopaminergic pathways in the subcortical regions leading to interruption of transport and neurotransmission, have been related with neurocognitive impairment (Bernheimer et al. 1973; Hornykiewicz 1998). Recent studies also suggest that variable degree of substantial loss of DA in the brain striatal region, including caudate, putamen (89–98%), and specifically the loss of DA in the subregions of GP (51–82%), is associated with cognitive deficits, particularly with the subtypes of motor dysfunctions (Rajput et al. 2008).

In HIV-1-infected individuals, degeneration of dopamine-producing neurons in the pars compacta of SN has been found in the postmortem brains (Reyes et al. 1991; Itoh et al.

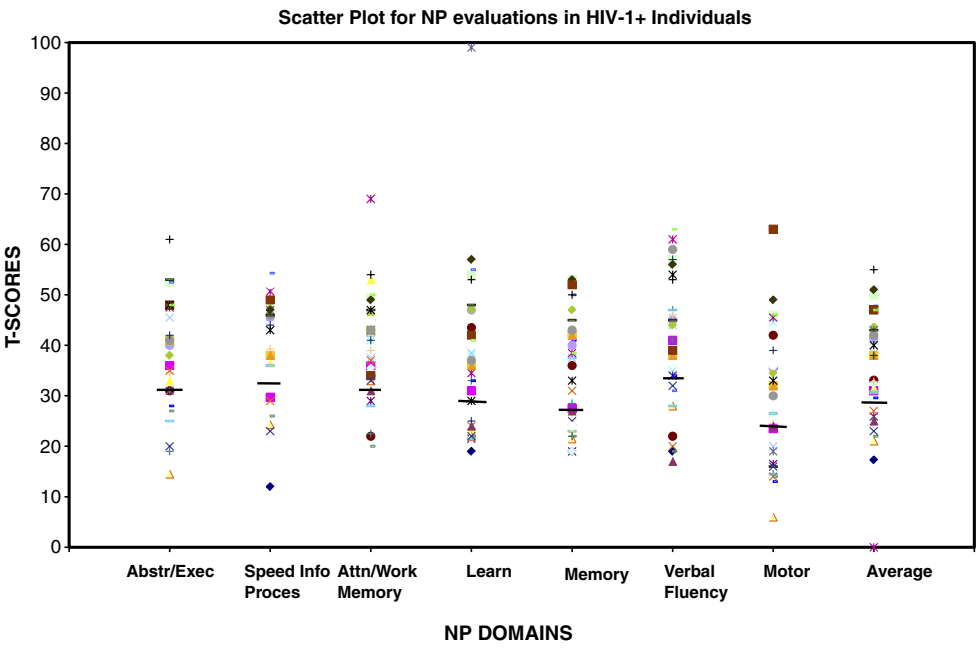

Fig. 1 Scatter plot showing evaluation of neuropsychological (NP) performance as *T* scores (*Y-axis*) for different NP domains (*X-axis*) assessed in HIV-1+ individuals during their life. Each *symbol* on the *vertical line* above the specific NP domain represents *T* score of each individual. The *horizontal bars* represent the mean value of *T* scores in each NP variable. Although a few individuals (with HAD) performed poorly in more than two NP domains (*T* scores <35 and <20), the average score indicated mild to moderate overall impairment in NP functions

2000), which may account for the overall depletion of DA in the CNS. These findings are also consistent with our findings of decreased concentration of DA in the SN as well as in the other brain regions of HIV-1+ individuals and its relationship with impairment in the performance of the speed of information processing, verbal fluency, learning, memory, and motor tasks found in the present study. Further evidence of HIV-1-associated neurodegenerative changes, including disruption in the neuronal network such as dendritic simplification and reduced synaptic density in the FC region of the postmortem brains, were also found to relate with the antemortem measures of global cognitive decline (Masliah et al. 1997; Everall et al. 1999). However, with respect to changes in HVA concentration, we found that the lower levels of HVA (the metabolite of DA) in BG, FC, and FC4, as well as minimum change in the levels of HVA in the SN or higher levels in putamen, caudate, and globus pallidus were strongly correlated with the level of performance in motor functions, speed of information processing, and attention/working memory in HIV-1+ individuals (Table 4). These findings suggest that in these brain regions of HIV-1 infected individuals, an increase in HVA levels may be the result of an increased metabolic activity of DA, which may also contribute to a decrease in the availability of DA, and that the relationship we found between HVA and cognitive deficits may in fact be a reflection of the decreased DA availability for neurotransmission.

Although metabolites of DA in the human brain include HVA and 3,4-dihydroxy-phenylacetic acid (DOPAC), we measured only HVA since HVA is the major metabolite of DA, and its concentration in the human brain regions is many-fold higher than that of DOPAC. Since DOPAC is an intermediary metabolite and is formed when DA is oxidized by the enzyme monoamine oxidase A (MAO-A) in one of the two pathways of DA metabolism. DOPAC is then converted to HVA by the enzyme catecholamine methyl transferase (COMT). In the second pathway of DA metabolism, methylation by COMT converts DA to methoxytyramine, and MAO-A converts 3-methoxytyramine to 3-methoxy-4-hydroxyphenylacetic acid (HVA). Since HVA is the end product of both pathways of DA metabolism and reflects the complete turnover of DA, its concentration is much higher than that of DOPAC which is only a fraction of that of HVA (Van Kammen et al. 1986). Moreover, HVA is more stable in the brain tissues and is the most frequently used and accepted approach for measurement of DA metabolism in the brain tissues and cerebrospinal fluid (Wilk and Stanley 1978; Walsh et al. 1982), and the levels of HVA are found to reflect the activity of dopaminergic neurons, particularly in the basal ganglia region.

Moreover, our findings of a significant decrease in the availability of DA in different brain regions (putamen, caudate, and to a lesser extent in the globus pallidus and frontocortical areas) of HIV-1-infected individuals and poor performance in some of the NP functions (learning, memory, motor functions, speed of information processing, and attention/working memory) are also consistent with the findings from other recent studies that used positron emission tomography (PET) and found a decrease in the availability of dopamine transporters in the putamen and caudate of HIV-1-infected patients, which was related with poor performance in psychomotor speed and attention and working memory (Chang et al. 2008; Wang et al. 2004). Furthermore, degenerative changes in the CNS were also found in studies using MRI, showing reduced volume as

well as blood flow in the basal ganglia, particularly in the caudate of HIV-1+ patients with neurocognitive impairment, compared with those with no impairment and HIV-negative controls (Aylward et al. 1993; Ances et al. 2006). The volume loss has also been reported in the white matter and specific gray matter in the basal ganglia regions, including caudate, putamen, and globus pallidus in HIV-1-infected individuals with greater severity of neurocognitive impairment (Aylward et al. 1995). Other studies using cytochemical techniques on postmortem cortical and subcortical brain regions of HIV-1-infected individuals found that the neurodegenerative changes in the markers of presynaptic terminals and neuronal cell bodies and dendrites (synaptophysin and microtubule-associated protein-2, respectively) were variable in the midfrontal cortex, the hippocampus, and particularly in the putamen. These markers were found to be predictors of neurodegeneration and were related with a unique variation in the severity of deficits in antemortem measures of NP impairment, suggesting that the variable disruption of the overall connection between cortical and subcortical regions may lead to varying degrees of severity in NP impairment (Moore et al. 2005).

Although our findings of decreased availability of dopamine in different brain regions of the basal ganglia (SN, putamen, caudate, and GP) as well as frontal cortex and its relationship with lower level of performance in some of the NP functions concur with the findings from the above-mentioned PET and MRI studies showing HIV-1-associated damage to subcortical and cortical regions, decreased dopaminergic activity, and NP impairment, it is not clear why there was a lack of significant correlation between the overall decrease in DA concentrations in different brain regions and the severity of neurocognitive impairment in those with probable and possible HAD and probable and possible MCMD, despite the fact that these individuals had high dementia ratings for HAD (MSK, 2–4) and scored poorly in two to seven NP domains, and in some cases in all seven domains, compared with those who had MCMD or had no impairment (Table 5).

Moreover, our findings of changes in DA and HVA levels in different brain regions and the variable relationship with the level of NP performance are also consistent with the findings from earlier studies on CSF of HIV-1+ patients. For example, in our study, while decrease in the availability of DA in SN influenced the level of performance in the speed of information processing, verbal fluency, learning, and memory domains and changes in HVA levels in SN, BG, caudate, and putamen influenced other NP functions, including motor, information processing speed, and attention/working memory, studies by Larsson et al. (1991) and Berger et al. (1994) found that decreased levels of DA and HVA in the CSF of HIV-1-infected patients were related with low performance in cognitive and motor functions. Other studies also found that the decreased CSF HVA levels were related with impairment in attention, concentration, and executive functions, although no relationship was found between HVA levels in CSF and deficits in memory (Di Rocco et al. 2000).

Our findings on the relationship between HIVRNA levels in different brain regions and NP functions were not found to be consistent with our proposed hypothesis that the lower levels of HIVRNA in the brain regions will be associated with lesser impairment in NP functions and that higher HIVRNA levels will be related with greater NP impairment. We found on the contrary that despite HAART intervention (majority of individuals in this study had received HAART intervention for variable time periods during life), there was no difference in HIVRNA levels between 33 HAART-treated and five nontreated individuals and that HIV RNA in different brain regions was distributed heterogeneously, with lower levels in the FC regions and higher in the basal ganglia (Kumar et al. 2007). We also did not find the relationship between HIVRNA levels in different brain regions and NP deficits as expected, but on the contrary in some brain regions such as in the frontal cortex, lower HIVRNA levels (compared with that in the other brain regions) was related with lower level of performance in antemortem measures of abstract/executive functions and attention/working memory. In the basal ganglia region, although levels of HIVRNA were higher than that in the FC, there was no direct relationship between HIVRNA and level of NP performance. In individuals with HAD, although decline in performance was seen in three to seven measures of NP domains (Table 5), there was no relationship between the levels of HIVRNA in the basal ganglia region and the level of performance in NP functions in these individuals. Although, HIV-1 is known to have high affinity for the basal ganglia and high viral load has been found in the basal ganglia regions of individuals with cognitive deficits, including those with HAD (Fujimura et al. 1997; Kumar et al. 2007), we did not find correlation between HIVRNA levels in the basal ganglia and performance in any of the NP functions in those with HAD. Findings from other studies also suggest that there is consistent variability in the relationship between HIV-1 viral load in the CNS and neurocognitive deficits (McClernon et al. 2001; Marra et al. 2009), which may be due to the variable distribution of HIV-1 and its impact on neurodegenerating processes in different brain regions. Moreover, findings from previous studies suggest that neurons themselves are not directly infected by HIV-1 (Bagasra et al. 1996; Kolson et al. 1998) and that neurodegenerative changes in the cortical and basal ganglia regions were the result of interaction between neurons and virus-related neurotoxic factors, as well as the virus–host-related neuro-

toxins generated by the extra-neuronal infected cells (microglia and macrophages, as well as astrocytes), which may be the main contributing factors for CNS injury and NP dysfunction (Masliah et al. 1992). The evidence from recent studies also suggest that neurotoxic effects of HIV-1 initiated neuroinflammatory mediators may be acting independently of the level of virus in the CSF or CNS to cause neurocognitive impairment (Kaul and Lipton 2006).

Moreover, HAART has not been found to significantly influence HIV-1 viral load in the CNS (McArthur et al. 1997), primarily due to inadequate CNS penetration of some of the antiretroviral drugs, such as protease inhibitors (Kim et al. 1998; Letendre et al. 2008), and HIV-1 replication in the CNS continues unabated (Enting et al. 1998), as was evident by the lack of difference found in HIVRNA levels (one to six $\log_{10}$ copies per gram tissue) in different brain regions of HAART-treated versus non-HAART-treated individuals (Kumar et al. 2007). Furthermore, the impact of HAART on cognitive functions has remained controversial, showing improvement in performance among some HIV-infected patients and reduced incidence of HIV dementia, but among some HIV-1-infected patients, mild to moderate cognitive impairment is found to persist even after HAART (Sacktor et al. 2002; Robertson et al. 2007). Studies using ^{1}H-MRS have shown that HAART leads to considerable improvement in the brain injury, which is marked by normalization of concentrations of cerebral metabolites, choline and myoinositol (the glial cell activity markers), indicating that HAART may be exerting some influence to contain HIV-1-related damage in the CNS that may contribute to improvement in some NP functions (Chang et al. 1999).

With regards to impairment in NP functions caused by HIV-1 infections in the CNS, different domains of NP functions manifest impairment at successive stages of HIV-1 infection, and the domains most severely affected at the initial stage are speed of information processing, attention, learning efficiency, memory, and motor abilities, with deficits in executive functioning and abstraction occurring more often as the disease progresses to AIDS (Heaton et al. 1995). Testing of NP functions is recognized as a valid and sensitive indicator of brain disease, since impairment in different domains of NP functions assessed antemortem in HIV-1-infected individuals has been consistently found to relate with neurodegeneration in the postmortem subcortical and frontostriatal brain systems (Heaton et al. 1995). For example, dysfunctions of frontal cortex at the late stage of HIV disease as a consequence of progressive pathological changes in the basal ganglia are found to be associated with global neurocognitive impairment (Masliah et al. 1997; Everall et al. 1999). Moreover, HIV-1-associated degenerative changes in neuronal projections between the frontal cortex and the basal ganglia, particularly, the caudate nucleus, suggest anatomical similarities between the frontal lobe and subcortical dementias (Cummings 1993).

Furthermore, among HIV-1+ individuals, there is a unique variability in the pattern of decline in different domains of NP functions. For example, in some individuals, HIV-1 results in poor attention, working memory, speed of information processing, learning, executive functions, and motor skills, but the other NP functions are found to remain intact, such as the skills in language, memory (delayed retention), and sensory perception (Heaton et al. 1995; Reger et al. 2002). In a recent report, cluster analysis was found to reveal the variable pattern of NP impairment rates that were neither influenced by demographic variables nor by psychiatric or neuromedical confounds (Dawes et al. 2008), implicating that the patterns of variability may occur partly due to heterogeneity in the patterns of HIV-associated neuropathological changes found in the fronto-striatal brain areas (Masliah et al. 1992; Pomara et al. 2001), and that may result most likely from heterogeneous distribution of HIV-1 RNA in different brain regions (Wiley et al. 1998; Kumar et al. 2007) and production of variable levels of neurotoxic agents.

Although, to the best of our knowledge, this may be the first report to provide evidence that a decrease in the availability of DA in different brain regions of HIV-1+ individuals is related with lower level of performance in some, but not all, NP domains, there are limitations in the study that should be noted: (a) the lack of knowledge on HIV-associated damage to the other neurotransmitter systems including norepinephrine, serotonin, and acetylcholine which in concert with dopamine are involved in functions such as stress-induced learning, emotional responses, and cortical cognitive functions (Luciana et al. 1998; D'Esposito et al. 1995; Giovanni 2010); (b) the small sample size of each brain region for dopaminergic measures, as well as that of the corresponding NP assessment data of all HIV-1+ individuals included in this study. The limited sample size is an important consideration on which many of the observed relations are based, since we found that in a number of instances, substantial positive correlations between DA in specific anatomic regions and relevant cognitive test performance were found (e.g., DA in frontal cortex and performance in the attention/working memory) but were not statistically significant (data not presented). Our failure to find significant relations between DA levels and performance in all NP domains may thus have been due to the low power of our analyses that resulted from our small sample size. A larger sample size in future studies may unravel some of the significant changes in the relationship between decreased DA availability in different brain regions and its impact on performance of NP functions, which were not evident in this study.

In summary, these analyses provide support for the relationship between DA levels in postmortem tissue and antemortem cognitive test performance. Although limited

by our sample size, our results support the possibility that widely observed deficits in cognitive functions seen in individuals with HIV-1 infection are at least in part due to the effect of HIV-1 on the decreased availability of dopamine in different brain regions. The important implication of these findings is to develop treatment strategies for normalizing dopaminergic activity in the CNS that may contribute to improving the cognitive deficits in HIV-1-infected patients and improve the quality of life.

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