

Decreased brain dopaminergic transporters in HIV-associated dementia patients

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Summary

HIV has a propensity to invade subcortical regions of the brain, which may lead to a subcortical dementia termed HIV-cognitive motor complex. Therefore, we aimed to assess whether dopamine (DA) D2 receptors and transporters (DAT) are affected in the basal ganglia of subjects with HIV, and how these changes relate to dementia status. Fifteen HIV subjects (age 44.5 ± 11 years; CD4 $185 \pm 130/\text{mm}^3$) and 13 seronegative controls (42 ± 12 years) were evaluated with PET to assess availability of DAT ($[^{11}\text{C}]$ cocaine) and DA D2 receptor ($[^{11}\text{C}]$ raclopride). HIV patients with associated dementia (HAD), but not those without dementia (ND) had significantly lower DAT availability in putamen (-19.3% , $P = 0.009$) and ventral

striatum (-13.6% , $P = 0.03$) compared with seronegative controls. Higher plasma viral load in the HIV dementia patients correlated with lower DAT in the caudate ($r = -0.7$, $P = 0.02$) and putamen ($r = -0.69$, $P = 0.03$). DA D2 receptor availability, however, showed mild and non-significant decreases in HIV patients. These results provide the first evidence of DA terminal injury in HIV dementia patients, and suggest that decreased DAT may contribute to the pathogenesis of HIV dementia. The greater DAT decrease in the putamen than in the caudate parallels that observed in Parkinson's disease. The inverse relationship between viral burden and DAT availability further supports HIV-mediated neurotoxicity to dopaminergic terminals.

Keywords: HIV; dopamine; dementia; PET; cocaine

Abbreviations: CES-D = Center for Epidemiologic Studies—Depression Scale; DA = dopamine; DAT = dopamine transporter; HAD = HIV-associated dementia; ND = non-demented; ROI = region of interest

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Introduction

HIV infection is frequently complicated by CNS dysfunction that manifests predominantly as subcortical dementia. The core symptoms of HIV-associated dementia (HAD) are similar to those seen in subjects with frontal–striatal dysfunction, such as in Parkinson's disease (Berger and Nath, 1997). Studies using MRI (Aylward *et al.*, 1993; Berger *et al.*, 2000) and PET with fluorodeoxyglucose (Rottenberg *et al.*, 1996) suggest that the basal ganglia are particularly vulnerable to HIV infection. Neuropathology also confirms that HIV has the propensity to invade subcortical brain areas, particularly the basal ganglia (Kure *et al.*, 1990). Since dopaminergic terminals are located in the basal ganglia, HIV may damage dopamine (DA) neurons. Neuronal injury may result from HIV neurotoxic proteins and a complex cascade of cytokines,

excitotoxins, and free radicals triggered by HIV-infected or immune-stimulated brain macrophages and astrocytes (Kaul *et al.*, 2001).

Dopaminergic dysfunction as the pathogenesis of HAD has been suggested by findings of decreased CSF DA in HIV patients with or without neurocognitive signs (Berger *et al.*, 1994), and decreased homovanillic acid (a DA metabolite) in patients with advanced AIDS dementia (Larsson *et al.*, 1991). Patients with HIV dementia complex also exhibit an increased likelihood of developing acute onset parkinsonism and dystonia when treated with dopamine antagonists (Hriso *et al.*, 1991). The purpose of this study was to assess the brain dopamine function in the brains of patients infected with HIV. PET with $[^{11}\text{C}]$ cocaine and $[^{11}\text{C}]$ raclopride were used

to assess dopaminergic function in the HIV infected subjects. [^{11}C]Cocaine binding allowed the assessment of the presynaptic DA transporter availability (Volkow *et al.*, 1999), while [^{11}C]raclopride assessed DA D2 receptor availability, which mostly reflect postsynaptic sites (Volkow *et al.*, 1996; Wang *et al.*, 1999). We hypothesize that the neurotoxic effects of HIV will lead to injury in the dopaminergic terminals, hence decreased DAT and decreased presynaptic [^{11}C]cocaine binding. However, up-regulation of postsynaptic DA D2 receptors may occur to compensate for decreased DA innervation.

Methods

Subjects

Written informed consent approved by the Brookhaven National Laboratory Institutional Review Board was obtained from each participant prior to the study. Fifteen (three female and 12 male) HIV subjects, 44.5 ± 10.9 (25–65) years of age, and 13 (three female and 10 male) healthy seronegative control subjects, 42.1 ± 11.5 (26–61) years of age, with similar socio-economic background were enrolled after a detailed screening procedure to ensure their eligibility for the study. Each subject was interviewed and had a neuropsychiatric examination by a neurologist (LC), screening blood tests (complete blood count, chemistry panel, prothrombin time/partial thromboplastin time, hepatitis A, B and C testing, HIV test if the status is not known within the last 6 months), urine tests (urinalysis, drug screen and pregnancy test if female), and an ECG. In addition, HIV patients were additionally assessed with Karnofsky scores, HIV dementia scale, and AIDS dementia staging according to the Memorial Sloan Kettering system (Aronow *et al.*, 1988), and for possible depressive symptoms, the Center for Epidemiologic Studies—Depression scale (CES-D).

HIV subjects were either HAD or non-demented (ND). HIV subjects fulfilled the following inclusion criteria: (i) 20 years or older; (ii) seropositive for HIV; (iii) HIV–cognitive motor complex according to the American Academy of Neurology (American Academy of Neurology AIDS Task Force Working Group, 1991), including both minor cognitive motor disorder (AIDS dementia stage 0.5) and HAD (AIDS dementia stage ≥ 1); (iv) $\text{CD4} < 500/\text{mm}^3$ within the past 6 months; (v) on no antiretroviral medication or stable on an antiretroviral regimen for at least 8 weeks prior to the study; (vi) able to provide written informed consent; (vii) education level eighth grade or above. Control subjects also fulfilled inclusion criteria (i), (vi) and (vii) and had to be seronegative for HIV, and on no medications except for vitamins. Subjects in both groups were excluded if they had any of the following criteria: (i) past or present history of psychiatric illness which may confound the analysis of the study (e.g. schizophrenia, major depression); (ii) presence of opportunistic brain lesions (e.g. toxoplasmosis, lymphoma or progressive multifocal leucoencephalopathy); (iii) confounding neurological disorder (e.g. multiple sclerosis, Parkinson's disease, degenerative brain diseases, or neoplasms); (iv) severe hepatic or renal dysfunction; (v) present or past history of drug dependence (including phencyclidine, cocaine, methamphetamine, opiates, inhalants, barbiturates, or alcohol), or nicotine use more than one pack per day; (vi) positive urine toxicology screen or positive pregnancy test if female; (vii) head trauma with loss of consciousness > 30 min.

PET scanning

PET scans were performed with a Siemens EXACT HR + (Knoxville, TN, USA) tomograph (resolution $4.5 \times 4.5 \times 2.4$ mm FWHM, 63 slices). Two tracers, [^{11}C]raclopride and [^{11}C]cocaine, were administered to each subject with at least 2 h between scans. Procedures for subject positioning and scanning protocol were as described previously (Wang *et al.*, 1999). Briefly, for [^{11}C]raclopride, dynamic scans were started immediately after intravenous injection of 3–8 mCi (specific activity > 0.25 Ci/ μmol at the time of injection) for a total of 60 min (Wang *et al.*, 1999). For [^{11}C]cocaine, dynamic scans were started immediately after intravenous injection of 3–8 mCi (specific activity > 0.25 Ci/ μmol at the time of injection) for a total of 54 min.

Data analysis

Image analysis and regions of interest (ROI) placement were performed by a rater (G.J.W.) who was blinded to the clinical information of the patients and subjects. ROI in basal ganglia (caudate, putamen and ventral striatum) and cerebellum in both hemispheres were drawn directly on an emission image that represented the sum of images obtained between 10 and 60 min for [^{11}C]raclopride, and between 10 and 54 minutes for [^{11}C]cocaine. ROIs for basal ganglia were obtained bilaterally from the three planes where they were best identified. Right and left cerebellar regions were drawn in the three planes 1.0, 1.4 and 1.8 cm above the canthomeatal line. These regions were then projected into dynamic images to generate time–activity curves for striatum and cerebellum. Average values for the basal ganglia and cerebellar regions were computed from three slices where the regions were obtained. The measure B_{max}/K_D , the ratio of the distribution volume in basal ganglia to that in cerebellum minus 1, was obtained using a graphical analysis method without blood sampling technique for reversible systems [Logan Plots (Logan *et al.*, 1996)]. The measures were used to quantify the DA transporter and D2 receptor availability, which are the numbers of transporters or receptors that are free to bind to the radiotracer.

Statistical analysis

Differences in B_{max}/K_D of DA transporters and D2 receptors in the striatum between HIV and controls subjects were tested using the independent samples *t* test (two-tailed). The relationship between B_{max}/K_D of DA transporters or D2 DA receptors and clinical variables (CD4, viral load, HIV dementia scale and AIDS–dementia complex stage) and other possible covariates (e.g. CES-D) were explored using linear regression analyses.

Results

Clinical assessments

Table 1 shows the clinical parameters in the HIV patients. The HAD and ND groups had similar age, gender proportion, education and CD4 counts. However, the nadir CD4 count was lower and the duration of HIV diagnosis was longer in the HAD group compared with the ND group. The 10 HIV patients with dementia had a mean AIDS dementia stage of 1.5 ± 0.5 (five with stage 1 and five with stage 2 dementia), and the non-demented (ND) HIV patients all had AIDS dementia stage 0.5. Although none of the HIV patients

Table 1 Clinical characteristics of HIV patients (mean \pm SD)

	HAD (n = 10)	ND (n = 5)	P value*
Age (years)	46.6 \pm 11.6	40.2 \pm 9.0	0.30
Female/male	2/8	1/4	
Education (years)	13.6 \pm 2.0	13.9 \pm 1.4	0.77
CD4 (no./mm ³)	187 \pm 149	181 \pm 93	0.94
Nadir CD4 (no./mm ³)	46 \pm 74	144 \pm 73	0.03
HIV RNA (copies/ml)	127 539 \pm 173 403	39 661 \pm 105 413	0.24
Log HIV RNA	4.2 \pm 1.4	2.9 \pm 1.4	0.11
Duration of HIV diagnosis (months)	107 \pm 57	41 \pm 47	0.04
MMSE (0–30)	28.2 \pm 1.2	29.6 \pm 0.5	0.03
HIV dementia scale (0–16)	12.8 \pm 2.8	13.9 \pm 1.0	0.46
Karnofsky score (0–100)	82 \pm 6	90 \pm 0	0.02
AIDS dementia stage (0–4)	1.5 \pm 0.5	0.5 \pm 0	0.001

*P values are from unpaired *t*-tests. MMSE = Mini-Mental State Examination.

Table 2 Average left and right *D* values (mean \pm SD) of dopamine receptor (¹¹C]raclopride) and transporter (¹¹C]cocaine) availability (B_{max}/K_D) in controls and HIV subjects

	Seronegative controls (n = 13)	HAD (n = 10)	ND (n = 5)	P values*			
				ANOVA	HAD versus seronegative	ND versus seronegative	HAD versus ND
Caudate							
[¹¹ C]cocaine	0.75 \pm 0.08	0.66 \pm 0.16 (–12.0%)	0.72 \pm 0.13 (–4%)	0.30	0.38	0.74	0.38
[¹¹ C]raclopride	2.43 \pm 0.27	2.26 \pm 0.33 (–7.0%)	2.38 \pm 0.38 (–2.1%)	0.43	0.20	0.80	0.46
Putamen							
[¹¹ C]cocaine	0.92 \pm 0.10	0.74 \pm 0.20 (–19.6%)	0.88 \pm 0.14 (–4.3%)	0.02	0.009	0.65	0.09
[¹¹ C]raclopride	3.00 \pm 0.25	2.77 \pm 0.52 (–7.7%)	2.85 \pm 0.30 (–5.0%)	0.36	0.17	0.47	0.70
Ventral striatum							
[¹¹ C]cocaine	0.70 \pm 0.09	0.61 \pm 0.09 (–12.9%)	0.70 \pm 0.11 (0%)	0.05	0.03	0.95	0.07
[¹¹ C]raclopride	2.30 \pm 0.34	2.27 \pm 0.42 (–1.3%)	2.29 \pm 0.46 (–0.4%)	0.99	0.90	0.99	0.92
Ratio of putamen/caudate							
[¹¹ C]cocaine	1.24 \pm 0.09	1.11 \pm 0.18	1.24 \pm 0.18	0.11	0.05	0.99	0.13

*P values for analysis of variance (ANOVA) are from comparisons between seronegative controls, HAD and ND; P values for the other comparisons are from *post hoc* Fisher's PLSD.

were clinically depressed or required antidepressant medications, they had more depressive symptoms than the control subjects, as measured by the CES-D (5.7 \pm 4.2 versus 16.3 \pm 7.6, $P = 0.0003$). However, both HIV groups showed similar CES-D scores and similar performance on the HIV dementia scale. The Mini-Mental Status Examination scores and Karnofsky scores were both slightly lower in the HAD group compared with the ND group. Although none of the subjects abused illegal drugs, nicotine use (<1 pack/day) was more common in the HIV subjects ($n = 5$) compared with controls ($n = 1$).

All but one HIV patient, who was medication-naive, were treated on stable antiretroviral medications; duration of treatment on current regimen was 24.9 \pm 25.8 months. None of the patients had resting tremor. However, three HIV patients showed mild signs of movement disorder and all three were in the HAD group. Two of these patients had intermittent choreiform movements in bilateral extremities and mild

diffusely increased tone. The subject with the lowest DAT also had mildly increased rigidity in his left upper and lower extremities, moderate postural instability and micrographia. All three of these subjects also had mild bradykinesia.

Dopamine transporter and receptor levels

The HIV subjects with dementia showed significantly lower DA transporters availability (B_{max}/K_D) bilaterally compared with the seronegative controls in the putamen (–19.6%, $P = 0.009$) and in the ventral striatum (–12.9%, $P = 0.03$), but only mild and non-significant decreases in the caudate (Table 2, Fig. 1). Therefore, the ratio of DAT availability in the putamen to the caudate was significantly lower in the HAD group compared with controls ($P = 0.05$). DAT loss showed no difference between right and left hemisphere and was averaged for comparisons. The ND HIV patients, however, showed no significant decreases in DAT in the

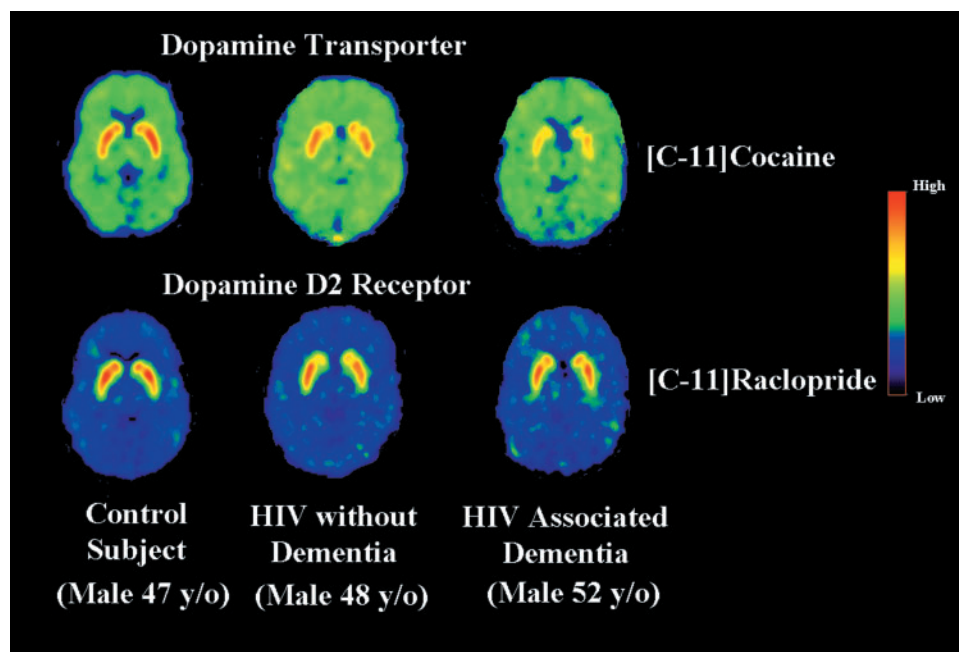


Fig. 1 Distribution volume ratio images of PET with [^{11}C]cocaine (DA transporter, top row) and [^{11}C]raclopride (DA D2 receptor, bottom row) in a 47-year-old control subject (left), a 48-year-old ND subject (right) and a 52-year-old HAD subject (middle), at the level of the basal ganglia. The images are scaled with respect to the maximum value obtained in the control subject and presented using the rainbow scale (red colour = high value, violet = low value).

basal ganglia. DA D2 receptor availability did not differ between the HIV and the control subjects in any of the regions (Table 2, Figs 1 and 2). Figure 2 shows the DA transporter availability and the DA D2 receptor availability (B_{max}/K_D) values for the control subjects and two HIV groups.

Two of the three patients with the lowest DAT had virtually identical DAT loss bilaterally, while the patient with the asymmetrical DAT loss had intermittent movement disorder in his left extremities and slightly greater DAT loss in his right putamen (left, -32% ; right, -34%).

Correlation between dopamine transporters and clinical variables

DA transporter and DA D2 receptor availability did not correlate with CD4 count in HIV subjects. However, the combined ventral striatal DAT from the two groups showed a trend to correlate with nadir CD4 ($r = 0.39$, $P = 0.1$), while DAT in the caudate showed a trend for inverse correlation with log plasma HIV RNA ($r = -0.4$, $P = 0.1$). In the ND subjects, log viral load did not correlate with DAT in any region. However, in HAD patients log viral load correlated with DAT in the putamen ($P = 0.027$) and the caudate ($P = 0.02$), and a trend for correlation in the ventral striatum ($P = 0.07$). The difference in the correlations between log viral load and DAT between the HAD and ND group was significant in the ventral striatum ($P = 0.02$) and showed trends for significance in the putamen ($P = 0.07$). Although the HIV patients had more depressive symptoms, CES-D did not correlate with

DAT or DA D2 availability. Other clinical parameters (duration of HIV, Mini-Mental State Examination, Karnofsky score and HIV dementia scale) also did not correlate with DAT.

Discussion

The major finding of this study is that HIV patients with dementia show decreased dopamine transporters, especially in the putamen, but relatively normal DA D2 receptor availability. In contrast, ND patients had relatively normal DAT and DA D2 receptor availability, although future studies with a larger sample of ND patients are needed to validate these findings. Dopamine transporters are located at presynaptic dopaminergic nerve terminals, while DA D2 receptors are located mostly postsynaptically (Volkow *et al.*, 1996), primarily on striatal GABAergic and cholinergic cells (Scheel-Kruger, 1986) as well as on cortical astroglia (Khan *et al.*, 2001). Therefore, the decreased DAT indicates injury or alteration to the dopaminergic neurons, especially the terminals. Measurements of DAT with PET, however, cannot determine whether DAT loss is due to loss of dopaminergic cell bodies or synapses. Nevertheless, the finding of decreased DAT in HIV extends prior studies of HIV patients that found decreases in CSF dopamine (Berger *et al.*, 1994), CSF dopamine metabolite homovanillic acid (Larsson *et al.*, 1991), and dopaminergic markers in post-mortem brain tissue (i.e. caudate nucleus) (Sardar *et al.*, 1996). This is the first report that documents decreased dopamine function in the living brains of HAD patients.

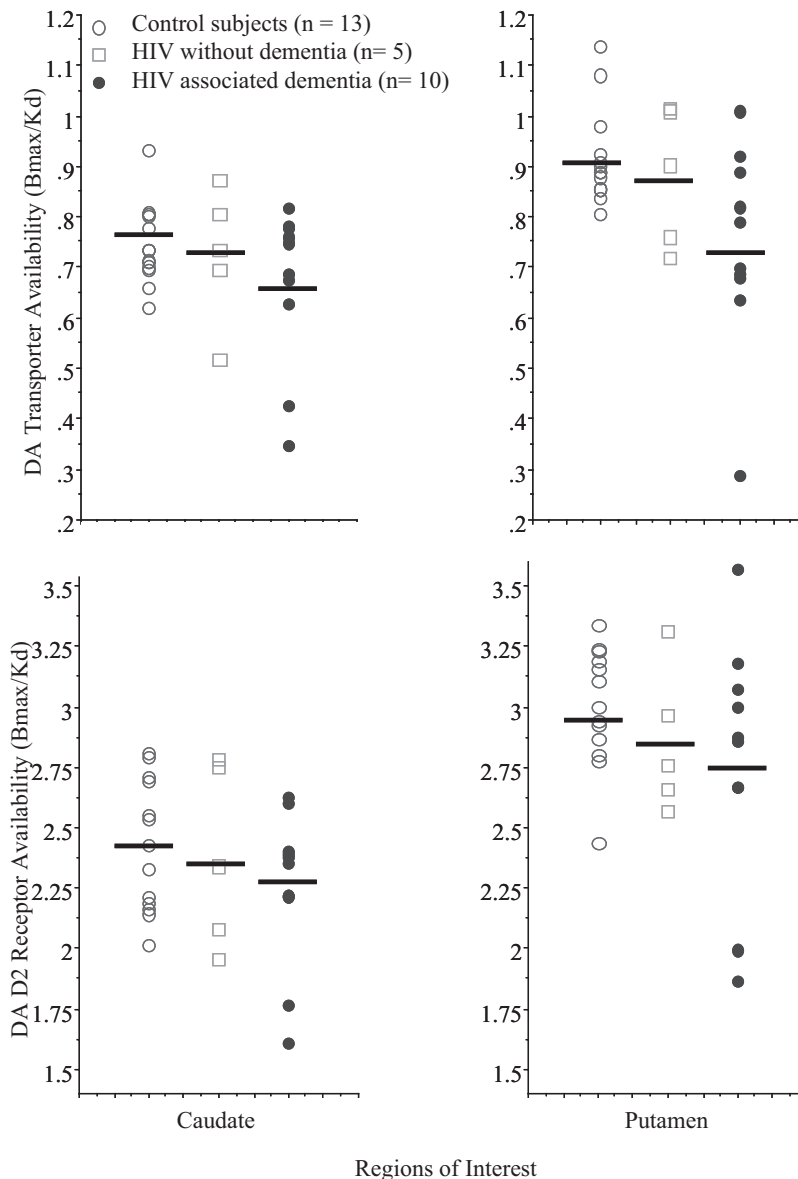


Fig. 2 Individual values for DA transporter and DA D2 receptor availability (B_{max}/K_d) in the HIV and control subjects.

Experimental evidence suggests that HIV proteins (e.g. Tat and gp120) can cause toxicity to dopaminergic neurons *in vitro* and in rodent models (Nath *et al.*, 2000). It is unclear why the dopaminergic neurons appear to be more vulnerable to HIV-induced neurotoxicity. However, neuropathology often shows high HIV viral burden in the basal ganglia (Kure *et al.*, 1990), which has the highest density of dopaminergic terminals. Hence, the DAT on the terminals might be exposed to higher viral load. In our HAD patients, we indeed observed correlations between log viral load and DAT in both the putamen and the caudate. Further clinical evidence that supports the selective vulnerability of the dopaminergic system to HIV neurotoxicity includes reduced basal ganglia volume on MRI (Aylward *et al.*, 1993) and altered striatal glucose metabolism on PET, which was hypermetabolic during early stages and hypometabolic during late stages of HIV

dementia (Rottenberg *et al.*, 1996). An MRI study also found increased gadolinium-enhancement in the basal ganglia of HAD patients, but not in those without dementia, which suggested increased blood–brain barrier permeability as a possible route of viral entry into the brain (Berger *et al.*, 2000). Hence, the lack of correlation between plasma viral load and DAT in the ND patients might be related to their relatively intact blood–brain barrier. Further studies are needed to evaluate the relationship between blood–brain barrier permeability, viral load and DAT availability in HIV patients with and without dementia.

On the neuropathology of AIDS patients, reactive cell changes, multinucleated giant cells and glial–microglial infiltrations also are most often found in the subcortical grey matter (i.e. putamen and caudate) (Kure *et al.*, 1990). These glial elements may further induce neurotoxicity in

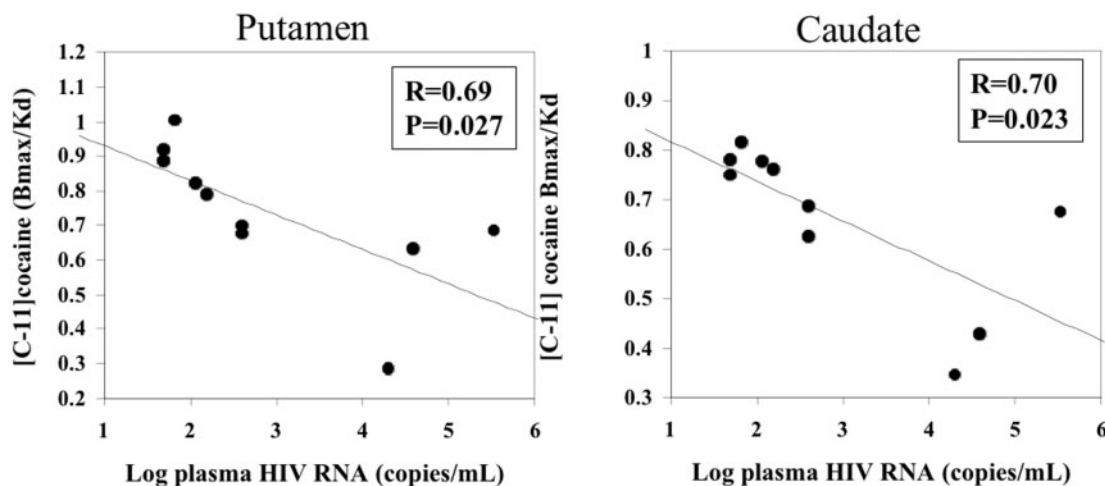


Fig. 3 Correlation between measures of DA transporter availability (B_{\max}/K_d) in the caudate and putamen and log plasma viral load in patients with HAD.

dopaminergic neurons via a cascade of HIV-induced expression of cytokines, chemokines and free radicals (Kaul *et al.*, 2001). Neuronal apoptosis and consequent neuronal loss in HIV indeed have been correlated to microglial activation and axonal damage (Gray *et al.*, 2000). Loss of neurons (up to 25%) in the substantia nigra also has been reported (Reyes *et al.*, 1991). Some studies, however, found primarily decreased dendritic and presynaptic complexities that strongly correlated with abundance of HIV envelope protein (Masliah *et al.*, 1992). Similarly, decreased dopamine levels in the dopaminergic terminal regions, putamen and frontal cortex, rather than in the cell bodies in the substantia nigra, was also observed in a simian immunodeficiency virus model during the early asymptomatic phase (within 8–20 weeks after infection) (Czub *et al.*, 2001). The pattern of DAT reductions in the HIV subjects is not typical of those seen in patients with Parkinson's disease, but shows the parallel finding of greater reduction in the putamen than in the caudate (Miller *et al.*, 1997). This is in contrast to methamphetamine neurotoxicity, which showed greater decreases of DAT in the caudate than in the putamen, both on PET (caudate, –28%; putamen, 21%) (Volkow *et al.*, 2001) and in post-mortem studies (caudate, 61%; putamen, 50%) (Moszczynska *et al.*, 2004). This reverse ratio of DA loss in the caudate and putamen is thought to account for the cognitive rather than motor deficits in chronic methamphetamine abusers (Moszczynska *et al.*, 2004). In Parkinson's disease, striatal DA concentration is typically reduced by up to 70% before clinical signs of parkinsonism are apparent. Although our HIV patients also have greater DAT loss in the putamen (–19%) compared with the caudate (–12%), only three of the subjects with the lowest DAT showed early signs of motor disorders. In patients with Parkinson's disease, reduced DAT is related to the severity of their dementia (i.e. motor and psychomotor slowing, as well as impairment on memory retrieval) (Marie *et al.*, 1999). Future studies using neuropsychological tests are needed to measure possible subtle motor or psychomotor slowing or

attention deficits in these HIV-patients (Miller *et al.*, 1990) and determine whether these cognitive deficits are related to mildly decreased DAT. The present findings, however, support the hypothesis that dopaminergic dysfunction is involved in the pathogenesis of HIV–cognitive motor complex in HIV patients.

The finding of reduced DAT in HIV patients, especially in those with more severe cognitive motor deficits, suggests that these patients may benefit from treatment with dopaminergic agents. One study found improvement on cognitive performance in HIV patients after treatment with methylphenidate (Hinkin *et al.*, 2001). However, recent reports both from *in vitro* and simian immunodeficiency virus models indicate that dopamine and drugs that enhance dopamine levels (e.g. selegiline, levodopa) stimulate viral replication and further exacerbate HIV-induced neurotoxicity (Scheller *et al.*, 2000; Czub *et al.*, 2001). In contrast, antioxidants, such as glutathione, may block some of the dopamine-induced HIV activation (Scheller *et al.*, 2000). Therefore, further studies are needed to explore other approaches for adjunctive therapy using dopaminergic agents, such as the use of dopamine agonists or combined treatments that block the oxidative effects of dopamine-mediated neurotoxicity. In addition, since effective viral suppression appears to correlate with less dopaminergic injury, future studies evaluating HIV patients before and after antiretroviral treatment are needed to determine whether effective viral suppression would lead to recovery of the dopaminergic deficits.

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