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Imaging Serotonergic Transmission with [^{11}C]DASB-PET in Depressed and Non-Depressed Patients Infected with HIV

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Abstract

Introduction—Site-selective imaging can provide significant insight into the mechanism of HIV-associated neurological disease. The goal of this study was to evaluate the involvement of serotonergic transmission in HIV-associated depression using [^{11}C]DASB, a serotonin transporter (5-HTT)-specific radiopharmaceutical for positron emission tomography (PET).

Methods—9 depressed HIV+ subjects (HIV-D), 9 nondepressed HIV+ subjects (HIV-ND) and 7 healthy controls (HC) underwent an MRI scan and a [^{11}C]DASB-PET scan. The outcome measure was 5-HTT binding potential normalized to nondisplaceable tissue radioligand (BP_{ND}).

Results—HIV-ND subjects had lower mean regional 5-HTT BP_{ND} estimates across regions, compared to HC, while HIV-D subjects demonstrated higher mean regional binding values than HIV-ND subjects in most regions. Prior to correction for the false discovery rate, HIV-ND had significantly lower BP_{ND} values compared to HC subjects in two regions (insula and anterior cingulate) and all HIV+ patients had significantly lower binding than HC in all regions except for the midbrain, thalamus and pons. After correction for the false discovery rate, only the insula showed significantly lower binding in HIV+ subjects compared to HC ($P < 0.0045$). Despite a significant difference in the duration of illness between the HIV-D and HIV-ND groups, there was no definite correlation between the duration of illness and BP_{ND}.

Conclusion—Lower [^{11}C]DASB binding in HIV+ patients compared to HC may reflect serotonergic neuronal loss as a component of generalized HIV-associated neurodegeneration. Higher mean regional BP_{ND} values in HIV-D compared to HIV-ND subjects could reflect increased density of 5-HTT, leading to increased clearance of serotonin from the synapse, which could account, in part, for symptoms of depression. The lack of correlation between duration of illness and binding argues against these findings being the result of differential neurodegeneration only. Our findings suggest a possible role for dysregulated serotonergic transmission in HIV-associated depression.

Keywords

neuroAIDS; serotonin; 5-HTT; positron emission tomography; molecular imaging

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Introduction

Neuropsychiatric symptoms, including depression, are very common and well-recognized in the setting of HIV infection (Cruess et al., 2003; Repetto et al., 2003; Starace et al., 2002; Trepanier et al., 2005). In fact, a meta-analysis of the relationship between HIV infection and risk for depressive disorders found that HIV-seropositive (HIV+) individuals were twice as likely to be diagnosed with major depression as HIV-negative individuals (Ciesla and Roberts, 2001). Besides its known direct negative effects, depression in HIV+ patients is associated with increased substance abuse (Kalichman et al., 1997), poor treatment adherence (Catz et al., 2000; Safren et al., 2001), and worse viral control (Horberg et al., 2007). Also, untreated depression in HIV+ individuals can promote risk-taking behavior leading to further spread of the disease (Dursun and Reveley, 1995; Kopnisky et al., 2004). Because of the abovementioned reasons, recognizing and treating depression becomes of utmost importance in this patient population.

The involvement of the serotonergic system in the pathophysiology of HIV-associated mood disorders, namely depression, has long been suspected (Dube et al., 2005; Dursun and Reveley, 1995). HIV+ depressed patients respond to antidepressant therapy, including selective serotonin reuptake inhibitors (SSRIs) (Elliott et al., 1998; Rabkin et al., 1999; Schwartz and McDaniel, 1999). However, neither the mechanism by which depression arises in those patients, nor exploration of appropriate diagnostic and treatment regimens has been adequately addressed. There have been no neuroreceptor or neurotransmitter imaging studies targeting the serotonergic system in the setting of neuroAIDS (neurological disorders that result primarily from damage to the central and peripheral nervous system by HIV).

One way of evaluating the serotonergic system is through evaluation of serotonin transporter (5-hydroxytryptamine transporter or 5-HTT) integrity, especially in view of the successful treatment of depressed patients with SSRIs (Elliott et al., 1998; Rabkin et al., 1999; Schwartz and McDaniel, 1999). That is especially true in the case of HIV+ individuals since SSRIs are recommended as first line treatment for depression due to their superior side effect profile (Caballero and Nahata, 2005; Elliott et al., 1999). One way to evaluate serotonergic transmission noninvasively in human subjects is through imaging with positron emission tomography (PET).

(3-^{11}C-Amino-4-(2-dimethylaminomethylphenylsulfanyl) benzonitrile) ([^{11}C]DASB), a relatively new radiopharmaceutical for 5-HTT, was found to be superior to other radioligands such as [^{11}C]McN5652 and [^{123}I]β-CIT due to its fast kinetics, reversibility, higher selectivity and greater specific binding (Ginovart et al., 2001; Ichise et al., 2003; Wilson et al., 2002), as well as higher reproducibility (Frankle et al., 2006; Kim et al., 2006). Unlike the previously described radioligands, [^{11}C]DASB shows 1,200-fold selectivity for 5-HTT versus norepinephrine transporter or dopamine transporter sites. Currently [^{11}C]DASB represents the best option among radiopharmaceuticals for imaging 5-HTT (Meyer, 2007). [^{11}C]DASB has been used by several groups in the setting of major depression (Bhagwagar et al., 2007; Cannon et al., 2007; Meyer, 2007; Meyer et al., 2004), bipolar disorder (Cannon et al., 2006), alcoholism (Brown et al., 2007), tryptophan depletion (Praschak-Rieder et al., 2005), as well as in occupancy studies of different SSRIs (Voineskos et al., 2007) (Parsey et al., 2006b; Takano et al., 2006a; Takano et al., 2006b). However, serotonergic transmission has not been imaged with [^{11}C]DASB, or any other radiopharmaceutical, in the context of HIV-associated mood disorders.

In an effort to gain further understanding of the mechanism of depression in HIV, specifically to study the potential contribution of serotonergic disruption, we used [^{11}C]DASB-PET to compare three different groups of subjects: HIV+ depressed patients (HIV-D), HIV+ non-

depressed patients (HIV-ND) and healthy non-depressed controls (HC). Our underlying hypothesis was that HIV-D subjects would demonstrate higher binding of [^{11}C]DASB compared to HIV-ND, similar to what has been shown in most [^{11}C]DASB-PET studies in the literature, which have evaluated a variety of depressive psychiatric diseases (Bhagwagar et al., 2007; Cannon et al., 2006; Cannon et al., 2007; Meyer et al., 2004; Takano et al., 2007). We thought that the depressive symptoms could be related to higher 5-HTT density/activity resulting in lower intrasynaptic serotonin levels, as has been previously suggested (Meyer, 2007). We also wanted to assess whether there was any correlation between [^{11}C]DASB binding and the 5-HTT-linked polymorphic region (5-HTTLPR) genotype, according to the suggested genetic theory of depression (Pezawas et al., 2005).

Methods

Patients

HIV+ patients were recruited from the Johns Hopkins Hospital HIV/AIDS Service (Moore Clinic) Psychiatric Clinic. The control population was recruited from the general population through advertisement approved by our Institutional Review Board (IRB).

Exclusion criteria included a history of SSRI use within one year prior to entry, history of current or past opportunistic central nervous system (CNS) infection at the start of the study, history or concurrent clinical evidence of a psychotic disorder (e.g. schizophrenia), history of chronic neurological disorder such as multiple sclerosis or epilepsy or structural CNS abnormalities such as stroke or arteriovenous malformation, history of present or recent (within the last year prior to the study) drug dependence, including use of cocaine, methamphetamine, opiates, barbiturates, or alcohol. All subjects provided written consent as approved by the Johns Hopkins Hospital IRB.

Our final study population consisted of seven HC (age range: 23-53, mean = 39.9 ±7.8), nine HIV-ND subjects (age range: 36-55, mean=47.2 ± 4) and nine HIV-D subjects (age range: 29-54, mean=42.4 ± 5.6). There was no significant difference in the age range between the three groups of patients [$P = 0.18$, one-way analysis of variance (ANOVA)].

All of our HIV+ patients were being treated with highly active antiretroviral therapy (HAART) at the time of recruitment except for two subjects in each group. The four patients who were not treated with HAART at the time of the study, however, had received HAART in the recent past. The CD4 counts of the patients at the time of recruitment varied from 270 to 467. There were no significant differences in the CD4 counts between the HIV-D and HIV-ND groups ($P > 0.05$, unpaired, two-tailed t-test). Four patients in the HIV-D group and four patients in the HIV-ND group admitted to prior drug abuse, however all were free of drug use for at least one year prior to the study. Three patients in the HIV-D group admitted to past use of alcohol, with no alcohol use for at least one year prior to the study.

Psychiatric evaluation

Written informed consent was obtained from each participant by trained study members. Participants (HIV+ and healthy controls) who fulfilled all inclusion criteria were required to complete the symptom checklist-90-R (SCL-90-R), a self-reported, 90-item assessment of psychological distress and symptoms in nine areas: somatization, obsessive-compulsive personality, interpersonal sensitivity, depression, anxiety, aggression, phobia, paranoid ideation, and psychoticism (Derogatis, 1992). Each item is rated on a Likert scale indicating level of distress ranging from (0) “not at all” to (4) “extremely.” The depression assessment on the SCL-90-R is comprised of 10 items. The SCL-90-R serves as an effective tool for initial evaluation of symptoms and as a method of tracking changes in symptoms in response to

treatment (Derogatis, 1997; Holi et al., 1998; Knekt et al., 2008; Schmitz et al., 2001; Skydsbjerg et al., 2001). The diagnosis of current depressed state was further determined by the administration of a Structured Clinical Interview for DSM IV diagnosis (SCID) by a psychiatrist (Spitzer et al., 1992). The SCID has been used in clinical and research settings and has been found to be reliable in several research studies (Williams et al., 1992). Where there was disagreement between depression status as determined by the SCID and the SCL-90-R, depression status as determined by the SCID was used.

We recruited 19 HIV+ subjects and seven HC subjects for this study. One HIV+ patient had inconsistent psychiatric test results, and markedly decreased uptake of [^{11}C]DASB in the brain, comparable to reported levels seen in patients treated with SSRIs (~ 15 – 20% of normal uptake) (Meyer, 2007; Takano et al., 2006a; Takano et al., 2006b; Voineskos et al., 2007), despite denial of their use. When we compared the BP_{ND} values of that patient to all HIV+ patients, these were at least two standard deviations lower than the mean values, in all high binding areas. Therefore, we considered this patient an outlier and excluded those BP_{ND} results from the final analysis.

Among the other seven HC and 18 HIV+ patients, there was a 96% concordance rate in the diagnosis of depression between the SCID and SCL-90R. One out of 25 participants (4 %) had a positive diagnosis of depression on the SCID but was not depressed as assessed by the SCL-90. In that case, a diagnosis of depression assessed by the SCID was upheld and the patient was placed in the depressed category. In total, out of 18 HIV+ subjects, nine were classified as depressed. Thus, our group included seven HC, nine HIV-D, and nine HIV-ND subjects.

No one in either the patient or control population was being treated for depression at the time of the PET scan. Once a patient was diagnosed with depression based on the SCID and psychiatric evaluation, the PET scan was obtained within a few days and treatment, if deemed necessary, was initiated immediately thereafter.

Magnetic resonance imaging

All subjects underwent magnetic resonance (MR) imaging using a 1.5T Signa Advantage system (GE Medical Systems, Milwaukee, WI, USA) and a three-dimensional (3D) spoiled gradient recalled acquisition in the steady state (SPGR) sequence with the following parameters: repetition time = 50 ms, echo time = 5 ms, flip angle = 45 degrees, number of excitations = 1, field of view = 24 × 24 cm, slice thickness = 1.5 mm, and reconstruction matrix of 256 × 256, yielding an in-plane pixel size of 0.93 × 0.93 mm. MR scans were used to identify regions of interest (ROIs) for midbrain, caudate, putamen, thalamus, hippocampus, anterior cingulate gyrus, posterior cingulate gyrus, dorsolateral prefrontal cortex, ventromedial prefrontal cortex, insula and pons. ROIs were also drawn in the cerebellar cortex to be used as a reference region. The vermis was carefully excluded from the cerebellar ROIs as it is known to contain higher levels of HRRT (Meyer, 2007). ROIs were then transferred to the dynamic PET data to generate tissue time-activity curves (TACs).

The MR images were reviewed by two neuroradiologists and no focal masses or lesions were seen to suggest a superimposed infectious or malignant process. None of the patients were clinically suspected to have an opportunistic infection at the time of imaging.

PET imaging

A thermoplastic mask was fitted to each subject's face for the purpose of immobilization and positioning during scanning. PET images were acquired on a CPS/CTI High Resolution Research Tomograph (HRRT), head-only camera, with axial spatial resolution (FWHM) of 2.4 mm, and an in-plane resolution of 2.4 - 2.8 mm (Wienhard et al., 2002). This device acquires

207 simultaneous slices of 1.22 mm thickness. The axial and transaxial fields of view are 24.0 cm and 31.2 cm, respectively. To calculate the degree of attenuation correction for the emission scans, a six minute transmission scan was obtained with a ^{137}CS (γ energy = 662 keV) source prior to radiotracer injection. The attenuation map obtained with ^{137}CS was converted using a lookup table to estimate attenuation coefficients for 511 keV photons.

PET image acquisition protocol—[^{11}C]DASB (734 ± 41 MBq) was prepared in high specific radioactivity (285 ± 159 GBq/μmol) and delivered intravenously. There were no significant differences in injected dose or specific radioactivity between HC, HIV-ND, and HIV-D subjects ($P > 0.05$, one-way ANOVA). Dynamic PET studies consisted of a 22 frame protocol (3 × 20 sec, 2 × 30 sec, 2 × 60 sec, 3 × 120 sec, 8 × 300 sec, 4 × 600 sec) with a total scan duration of 90 min. PET scans were reconstructed using the ordered-subsets expectation maximum (OSEM) algorithm, in a 31 × 31 cm field of view and a 256 × 256 pixel matrix with a pixel size of 1.2 × 1.2 mm. PET frames were corrected for radioactive decay.

PET data analysis—To correct for minimal degrees of head movement, the PET frames from four min until the end of the study were coregistered to an early mean image that was created by averaging the frames from 1.5 - 10 min. PET to PET coregistration was performed using the normalized mutual information method and the realign function in SPM2 (Wellcome Department of Cognitive Neurology, London, UK). After realignment of the image frames, a mean PET image (20 - 90 min) was used for MR-PET coregistration, which was also performed using SPM2. MR scans were used to identify ROIs as described above. Regions were then transferred to the dynamic PET data to generate tissue TACs. ANALYZE™ software (Mayo Foundation, Rochester, MN) was used for processing ROIs and TACs.

The outcome measure in this study is the 5-HTT binding potential normalized to non-displaceable tissue radioligand (BP_{ND}), which was estimated using a simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996) with cerebellum applied as a reference region. For target (i.e. non-reference) regions, SRTM provides an estimate of relative delivery (R_1), reference tissue clearance (k_2^r), and BP_{ND}. As noted previously (Wu and Carson, 2002), parameter estimation with SRTM can be stabilized by constraining the value of k_2^r to be identical across regions. In our implementation, SRTM was fitted simultaneously to 11 tissue regions with coupling of k_2^r using an in house program written in C++ (Endres C J et al., 2003). For each subject data set the regression provided R_1 and BP_{ND} for all 11 target regions, as well as k_2^r, giving a total of 23 estimated parameters.

Using BP_{ND} as a reliable measure strongly depends on the ability to identify a brain region free of specific 5-HTT, i.e., a reference region. It was recently shown that although there are no brain regions completely devoid of 5-HTT, the concentration in the cerebellum is very low (Kish et al., 2005) and the cerebellum has frequently been applied as a reference region for the use of this radioligand (Meyer et al., 2004; Meyer et al., 2001; Talbot et al., 2005).

Genotyping

The 5-HTT gene promoter polymorphism was determined by DNA polymerase chain reaction (PCR) using flanking primers GCC AGC ACC TAA CCC CTA AT (forward) and AGG GAG ATC CTG GGA GAG (reverse). DNA was isolated using a QIAamp DNA blood kit (Quiagen, Valencia, CA, USA). After collection, the blood was spun at 4,000 rpm for 10 min. The plasma was discarded and 200 μL of packed cells were used for DNA extraction. PCR was performed in a 20 μL reaction containing 2 μL of 10 × buffer, 2 μL (~100 ng) sample DNA, 50 mM $MgSO_4$, 10 mM dNTPs, 0.1 μL (20 uM) of each primer, 14.7 μL H_2O and 1 μL Taq DNA polymerase (Roche, Indianapolis, IN, USA). DNA was denatured at 94 °C for 5 min and subjected to 30 PCR cycles at 94 °C (30 sec), 55 °C (30 sec) and 72 °C (30 sec) with a final

extension step of 5 min at 72 °C. After PCR, samples were digested at 37° for two to three hours with Msp1, and were subsequently analyzed by a 1.5% agarose gel. Alleles were designated short (S: 206 bp) and long (La: 249 bp, Lg: 148 bp, 101 bp).

Statistics

One-way ANOVA with Bonferroni correction was applied to each region separately. For each region, that procedure generated significance (*P*) values for the three possible comparisons between controls, HIV-D, and HIV-ND. The resulting *P*-values for each comparison were compiled for all regions. The *P*-values were then corrected for multiple comparisons using the False Discovery Rate (FDR) method. The uncorrected *P*-values are also reported.

We also computed the volume weighted BP_{ND} using all 11 regions, yielding a single composite measure of [^{11}C]DASB binding for each subject. We then calculated the mean BP_{ND} values for each group and performed one-way ANOVA comparison on the three groups of patients. We also used a t-test (unpaired, 2-tailed) to compare HC and HIV_{tot}.

To evaluate the effect of (5-HTTLPR) genotype on [^{11}C]DASB binding, we used the Mann-Whitney U test to compare BP_{ND} values in HIV+ patients carrying two La alleles (La/La) (n=4), and HIV+ patients carrying at least one S allele (n=7).

Results

Our final study population consisted of seven HC, nine HIV-ND subjects and nine HIV-D subjects. With respect to the mean regional BP_{ND} values, we noticed a trend of decreased binding in all regions when comparing HIV-ND to HC subjects. There was also a trend of increased binding in HIV-D subjects compared to HIV-ND subjects in all regions except for three low binding areas (the posterior cingulate gyrus, dorsolateral prefrontal and ventromedial prefrontal cortex) that showed comparable values (Figure 1).

We performed one-way ANOVA to determine whether there were any significant differences in the BP_{ND} values between the three groups. To protect from type I error, i.e., an artifact due to multiple comparisons, we corrected for the FDR. We found that HIV-ND subjects had significantly lower BP_{ND} values compared to controls in two regions (insula and anterior cingulate), prior to FDR correction. After correction, differences previously demonstrated in the insula and anterior cingulate gyrus lost significance (Table 1). No significant differences were noted between HIV-D and HC or between HIV-D and HIV-ND, before or after FDR correction.

We then compared all HIV+ patients (HIV-D and HIV-ND) to HC. A significantly lower binding in HIV+ patients was seen in all regions except for the midbrain, thalamus and pons, prior to FDR correction. After correction for FDR, only the insula showed significantly lower binding in HIV+ subjects compared to HC ($P < 0.0045$) (Table 2).

As measured by Cohen's d, in comparing controls with all HIV+ subjects, the effect size of [^{11}C]DASB binding in the insula was 1.46. With a sample population of 25 subjects (seven controls, 18 HIV+), the decreased [^{11}C]DASB binding in insula was significant and survived FDR correction. Note that in comparing controls to the HIV-ND group, there were four regions (thalamus, anterior cingulate, insula, pons) that similarly had effect sizes greater than 1.4, however, with a sample population of only 16 subjects (seven controls, nine HIV-ND), those results did not survive FDR correction. The implication is that for those comparisons to achieve significance following FDR correction, nine additional subjects (either controls or HIV-ND) would be needed as that would give a total sample population of 25 subjects.

When we compared the volume weighted BP_{ND} for each subject, we found that the differences between HC and HIV-ND were significant ($P = 0.008$) and survived Bonferroni correction for comparison across the three groups. The differences between HC and HIV-D did not reach significance ($P = 0.09$). Similarly, there were no significant differences between HIV-ND and HIV-D ($P = 0.33$). We then compared HC and HIV_{tot} subjects using a t-test (unpaired, 2-tailed) and found significant differences with $P = 0.012$.

Considering the range of scores obtained using the SCL-90 test, we evaluated for possible correlation between scores (both general test scores and individual symptomatology scores) and BP_{ND} values in the three subject groups. The results were not statistically significant.

We attempted to relate the 5-HTT BP_{ND} with the 5-HTT-linked polymorphic region (5-HTTLPR) genotype in HIV+ patients (n = 16 patients). We found that four patients carried two La alleles (La/La), and seven patients carried at least one S allele (one S/S, five La/S and one Lg/S). No significant allelic association was found with the BP_{ND} values. There was no difference in BP_{ND} between patients who were carriers of the La/La genotype compared to carriers of at least one S allele in any region (Mann-Whitney U test, $P > 0.05$ in all regions) (Table 3). We did not include the healthy controls in this comparison.

Upon reviewing the demographics of the three groups of subjects, we noticed that disease duration in HIV-D patients was significantly shorter than that in HIV-ND subjects (unpaired t-test, $P = 0.014$). That raised a question as to whether the decreased 5-HTT binding in depressed patients was solely due to longer disease duration, which could be reflective of advanced neuronal loss in that population rather than a genuine difference in 5-HTT density. To assess the effect of disease duration we used a linear regression model plotting mean BP_{ND} values against duration of disease in all regions, in all HIV+ patients, irrespective of the presence of depression. None of the 11 regions demonstrated significance, indicating that BP_{ND} estimates are unrelated to disease duration. Representative plots of BP_{ND} vs. disease duration in two brain regions are shown in Figure 2.

Discussion

The incidence of neuronal injury in patients with HIV-1 infection, namely HIV-associated dementia (HAD), has decreased after the introduction of HAART (McArthur et al., 2003). However, CNS involvement with HIV is becoming more prevalent since most medications comprising HAART do not cross the blood-brain barrier (BBB), while infected macrophages carrying the virus can (Buckner et al., 2006). Once inside the brain, virus is shed from the invading macrophages to infect the resident microglial cells and astrocytes, resulting in the production of multiple neurotoxins, which along with viral proteins, eventually result in a cascade of neuronal injury that culminates in apoptosis and neurodegeneration (Kaul and Lipton, 2006). Cerebral volume loss ensues, and is a well-recognized late-stage manifestation of neuroAIDS (Stout et al., 1998). Accordingly, HIV-associated neuronal injury should affect different neurotransmitter systems indiscriminantly. The resulting symptomatology would depend upon which neurotransmitter systems were most heavily involved. For example, nigrostriatal dopaminergic degeneration is thought to occur in HIV infected patients with secondary psychomotor slowing, apathy and motor disorders similar to the bradykinesia and postural and gait abnormalities observed in late Parkinson's disease (Koutsilieri et al., 2002), (Wang et al., 2004). In addition, studies evaluating dopaminergic function in monkeys affected with the simian immunodeficiency virus (SIV) demonstrated reduced dopamine content in brains of the infected monkeys compared to uninfected animals (Jenuwein et al., 2004; Nosheny et al., 2006). Similarly, cognitive and memory impairment in HAD seems to be related to cholinergic (Farr et al., 2002) and glutamatergic system dysfunction (Fernandes et al., 2007; Wang et al., 2003). One would expect the serotonergic system to be affected similarly.

Since 5-HTT is thought to be one facet of serotonergic transmission that reflects the integrity of this transmitter system, (McCann et al., 1998; McCann et al., 2005; Reneman et al., 2001; Szabo et al., 2002) one would expect 5-HTT binding to decrease in the setting of global serotonergic neuronal degeneration, such as with HIV infection. We found the 5-HTT BP_{ND} estimates in HIV+ patients to be lower than in HC. That was most clearly demonstrated in the insula, which showed a significant difference even after correction for the false discovery rate (FDR). These findings support the presence of serotonergic neuronal dysfunction in neuroAIDS.

The significance of the finding in the insula is however unclear. Based on our own data and published autoradiography results (Varnas et al., 2004), the insula is not among the high [^{11}C] DASB binding areas but still shows BP_{ND} values higher than most other cortical areas. Also, we are not aware of any increased susceptibility of the insula to the degenerative effects of HIV infection, when compared to the other regions. Consequently, we do not believe that there is a regional significance associated with the finding in the insula. We rather believe that there is a general reduction in 5-HTT density in HIV+ patients that would probably yield statistically significant differences of [^{11}C]DASB binding in other regions as well, if a larger sample size were used.

In the group of HIV+ patients, HIV-D subjects trended toward higher mean regional 5-HTT BP_{ND} estimates than HIV-ND subjects, in most regions. In previous studies evaluating [^{11}C] DASB binding in depressed patients, the most common outcome was increased binding in depression (Cannon et al., 2007), bipolar disease (Cannon et al., 2006; Cannon et al., 2007) or in association with neuroticism (Takano et al., 2007) and dysfunctional attitudes (Meyer et al., 2004). One possible explanation for that trend is that increased 5-HTT density results in increased reuptake of serotonin into the presynaptic neuron, with secondary decreased synaptic levels of the transmitter. Decreased or increased synaptic serotonin levels are known to be associated with depression, such as demonstrated in studies of acute tryptophan depletion (decreased serotonin) (Bell et al., 2005; Hood et al., 2005) or fenfluramine administration (increased serotonin) (Lichtenberg et al., 1992).

How can we explain the etiology of a putatively increased 5-HTT density in our depressed patient population? The genetic explanation is attractive, due to the known genetic susceptibility component in depression (Pezawas et al., 2005). Supporting the genetic theory, evaluation of the 5-HTTLPR genotype demonstrated that there was probably a correlation between the allelic composition of 5-HTTLPR and the incidence of depression (Cao et al., 2007; Cervilla et al., 2006; Dorado et al., 2007; Gonda et al., 2007; Hayden et al., 2008; Lee et al., 2005; Must et al., 2007). Two main alleles are recognized for the 5-HTTLPR genotype: Short (S), and long (L). The long allele was later stratified into two alleles: La and Lg, based on an A > G substitution in the 5-HTTLPR. However, a functional similarity was noted between Lg and S (Gallinat et al., 2007). The exact relationship between the genotype, expression of 5-HTT and psychiatric/depressive symptomatology however has not been elucidated, with contradictory results seen in the psychiatric literature. However, it seems that the short allele is most frequently implicated with depression, (Cao et al., 2007; Cervilla et al., 2006; Dorado et al., 2007; Hayden et al., 2008; Must et al., 2007), anxiety and posttraumatic stress disorder (Gonda et al., 2007; Lee et al., 2005) (Pezawas et al., 2005). Correlative imaging studies are less numerous but still yielded contradictory results. In one such study evaluating 19 healthy volunteers, four La/La homozygotes demonstrated a 25% increase in 5-HTT density in the midbrain as compared to carriers of at least one S allele, using [^{11}C]DASB as the radiopharmaceutical (Reimold et al., 2007). Another group of investigators found that 5-HTTLPR long (a/g) polymorphism influences 5-HTT density leading to higher putamen [^{11}C] DASB BP in healthy La/La carriers of Caucasian ancestry (Praschak-Rieder et al., 2007). On the other hand, no difference in 5-HTT BP by genotype in healthy volunteers or in subjects

with major depressive disorder was demonstrated in another study (Parsey et al., 2006a). Further clarification in larger studies is needed. We were not able to determine a significant relationship between the 5-HTTLPR genotype and [^{11}C]DASB BP_{ND} values in our small (n = 18) HIV+ population. This is probably due to the fact that our sample size is underpowered to detect any differences, especially considering that a significant association of the S allele with depression was only demonstrated in large scale studies including hundreds of patients and healthy controls (Cao et al., 2007; Cervilla et al., 2006; Dorado et al., 2007).

Still, in the setting of HIV infection, depressed patients may have a predisposition to depression related to higher than normal 5-HTT density. However, since HIV+ patients have lower baseline 5-HTT density (probably due to neuronal degeneration), a pseudo-normalization phenomenon may have occurred in our HIV-D population, with 5-HTT binding almost reaching the same level as that of healthy non-depressed controls. Indeed, the mean regional BP_{ND} values in the HIV-D population were between values seen in HC and those in HIV-ND patients, in almost all regions (Figure 1).

In a recent review concerning imaging of 5-HTT during major depressive disease, the author described four possible models to explain the abnormal 5-HTT binding in these patients, two of which he thought were plausible (Meyer, 2007). The first one is that of a lesion model where destruction of nerve terminals would lead to a reduction in regional 5-HTT binding potential. That is in concordance with our theory of neuronal degeneration in HIV being responsible for lower [^{11}C]DASB binding. In that model decreased 5-HTT density reflects neuronal density. The second plausible model suggested by Meyer is that of increased clearance of serotonin through increased 5-HTT density. That is in concordance with our finding of increased [^{11}C]DASB binding in the depressed subpopulation of HIV+ patients compared to the non-depressed group.

An alternative explanation for higher BP_{ND} values in HIV-D patients compared to HIV-ND subjects is that of baseline decreased intrasynaptic serotonin levels of depressed patients resulting in less competition with [^{11}C]DASB for the transporter sites, and secondarily increased [^{11}C]DASB binding. That however is unlikely since it has been shown that only very high levels of endogenous serotonin can affect 5-HTT binding levels by [^{11}C]DASB in animal studies (Ginovart et al., 2003; Lundquist et al., 2005). Also, tryptophan depletion did not result in a difference in regional 5-HTT BP (Talbot et al., 2005) (Praschak-Rieder et al., 2005). Accordingly, we do not believe that lower synaptic 5-HT levels could have accounted for our findings.

Longer duration of disease in the non-depressed population, associated with advanced serotonergic neuronal degeneration, could have resulted in lower [^{11}C]DASB BP_{ND} values. It is known that duration of disease correlates with neuronal degeneration and volume loss (Stout et al., 1998). In our subject population, HIV-ND subjects had a longer duration of illness compared to HIV-D subjects ($P < 0.05$). However, when we accounted for the effect of duration of disease on [^{11}C]DASB binding in the HIV+ population, irrespective of the diagnosis of depression, no correlation emerged. That suggests that duration of disease is unlikely to have affected our results. Furthermore, duration of disease is a relatively inaccurate measurement since the original infection is not always immediately recognized, and in many patients the diagnosis of HIV occurs years after the original infection.

Based on the MRI imaging, no focal abnormalities were seen to suggest a superimposed infectious or malignant process that would entail a disruption of the BBB. Therefore, we do not believe that BBB disruption could have affected our results. Only two patients in each group were not treated with HAART at the time of the study, however they had received HAART in the recent past. There were no significant differences in the CD4 counts between

the HIV-D and HIV-ND groups. No significant differences in disease severity between the two groups were noted based on the clinical evaluation and follow-up. None of the patients were using drugs for at least one year prior to the study, although at least four patients in each group admitted to being previous users. That could have potentially affected our results, however because drug abuse is quite prevalent in the HIV+ population we sampled, it would generally affect both groups (depressed and non-depressed) to the same extent. None of the subjects in this study were treated with SSRIs at the time of the scan or within at least one year prior to the scan, so SSRI uptake will have no confounding effect on these data.

The limitations of our study include a small sample size as well as the discrepancy in duration of disease between the depressed and non-depressed HIV+ subjects. The lack of allelic association with [^{11}C]DASB binding could be due to the small sample size as well. We did not perform a partial volume correction on the data, however we do not believe that partial volume effects have a substantial effect, since all of our studies were performed on the HRRT, which has higher resolution than standard clinical scanners and provides better quantification of binding potential values than the corresponding clinical (HR+) scanner, primarily due to a reduction in partial volume effects (van Velden et al., 2009). Increased age is often accompanied by increased brain atrophy, contributing further to partial volume effects. However, our population was relatively young to be demonstrating age-associated atrophy (mean < 50 years old for each group) and there were no significant differences in ages between the two groups.

In conclusion, our findings suggest a possible role for dysregulated serotonergic transmission in HIV-associated depression. We found consistent trends of lower mean regional [^{11}C]DASB binding in HIV+ patients compared to HC, across most regions, which we believe could reflect serotonergic neuronal loss as a component of generalized HIV-associated neurodegeneration. We also found a consistent trend of higher mean regional BP_{ND} values in HIV-D compared to HIV-ND subjects, which could reflect increased density of 5-HTT, leading to increased clearance of serotonin from the synapse. That could account, in part, for symptoms of depression. However, most of the differences in binding between groups lost significance after correction for FDR, suggesting that further validation of our results with a larger sample size is warranted.

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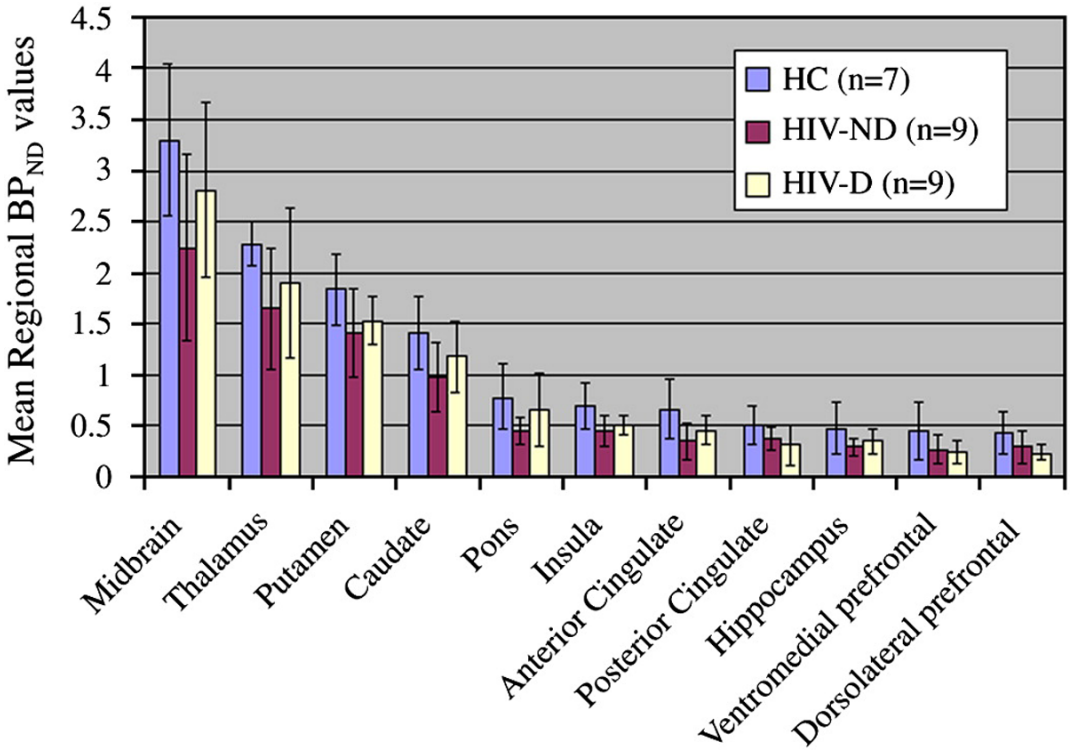

Figure 1.
Mean regional 5-HTT BP_{ND} values in the three groups of subjects: HC, HIV-ND and HIV-D.

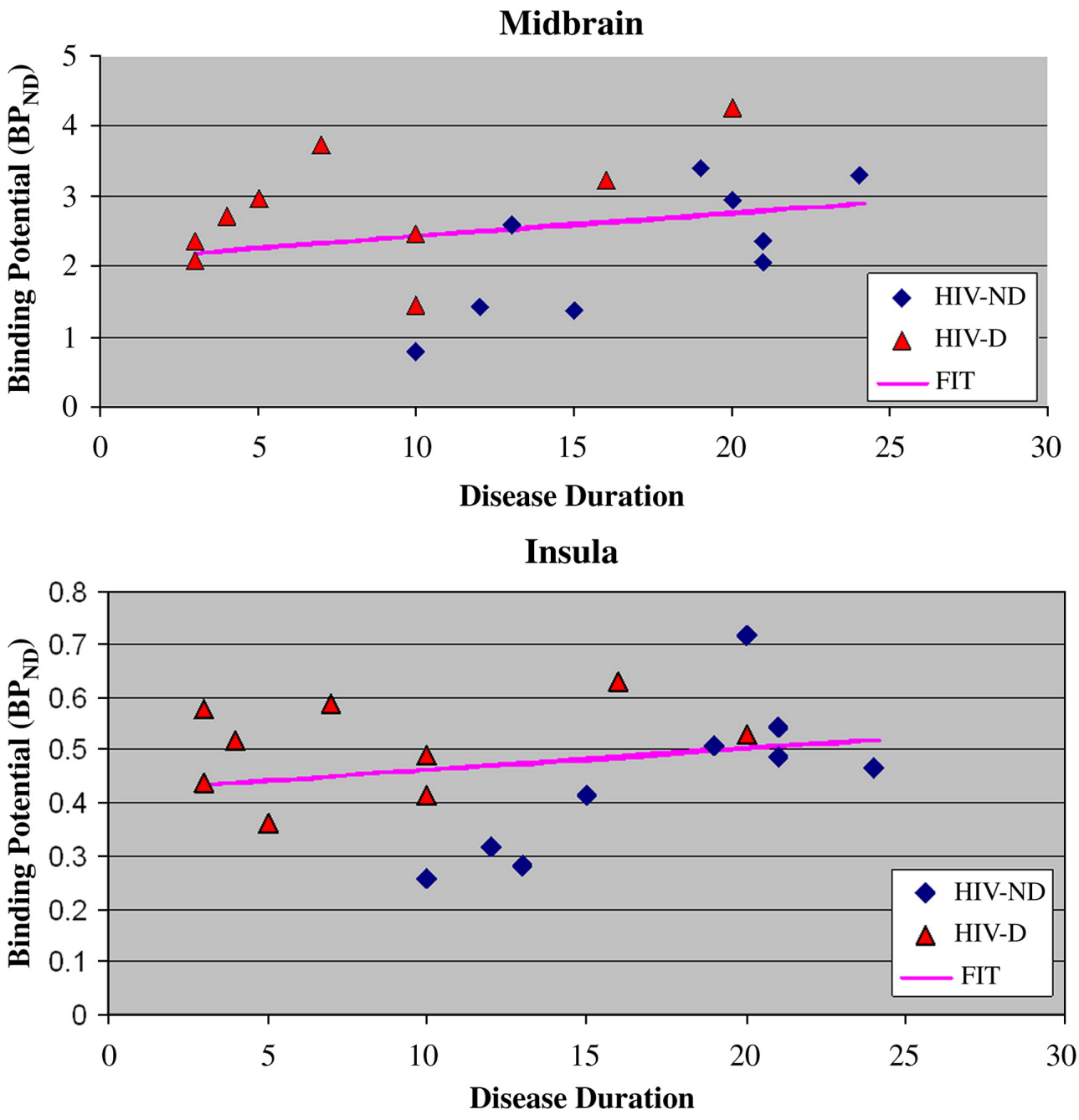

Figure 2.
BP_{ND} vs. disease duration in HIV+ subjects, in two representative brain regions: midbrain and insula.

Table 1

P-values for differences in BP_{ND} estimates between HC and HIV-ND subjects.

	HC vs. HIV-ND	***P*-values thresholds for significance after FDR correction**
Insula	0.014*	0.0045
Anterior cingulate gyrus	0.018*	0.0091
Caudate	0.058	0.0136
Midbrain	0.066	0.0182
Putamen	0.071	0.0227
Pons	0.081	0.0273
Thalamus	0.116	0.0318
Hippocampus	0.126	0.0364
Ventromedial prefrontal cortex	0.160	0.0409
Dorsolateral prefrontal cortex	0.303	0.0455
Posterior cingulate gyrus	0.445	0.0500

* indicates statistically significant *P*-value before correction for false discovery rate (FDR).

Table 2

P-values for differences in BP_{ND} estimates between HC and all HIV+ subjects.

	HC vs HIV_{total}	***P*-values thresholds for significance after FDR correction**
Insula	0.0044*†	0.0045
Anterior cingulate gyrus	0.0105*	0.0091
Ventromedial prefrontal cortex	0.0226*	0.0136
Putamen	0.0251*	0.0182
Dorsolateral prefrontal cortex	0.0262*	0.0227
Caudate	0.0391*	0.0273
Posterior cingulate gyrus	0.0440*	0.0318
Hippocampus	0.0490*	0.0364
Midbrain	0.0564	0.0409
Thalamus	0.0575	0.0455
Pons	0.0855	0.0500

*indicates statistically significant *P*-value before correction for false discovery rate (FDR)

†indicates statistically significant *P*-value after correction for false discovery rate (FDR)