Journal of the International Neuropsychological Society (2015), **21**, 722–731.

doi:10.1017/S1355617715000971

HIV Infection Is Associated with Impaired Striatal Function during Inhibition with Normal Cortical Functioning on Functional MRI

Stéfan du Plessis,[1] Matthijs Vink,[2] John A. Joska,[3] Eleni Koutsilieri,[4] Asif Bagadia,[5] Dan J Stein,[3,6] AND Robin Emsley[1]

[1]Department of Psychiatry, 2nd Floor Clinical Building, Faculty of Heath Sciences, University of Stellenbosch, Fransie van Zijl Avenue, Tygerberg, Cape Town, South Africa
[2]Brain Center Rudolf Magnus, CG Utrecht, The Netherlands
[3]Department of Psychiatry, University of Cape Town, J-Block, Groote Schuur Hospital, Observatory, Cape Town
[4]Institute for Virology and Immunobiology, University of Würzburg, Würzburg, Germany
[5]Department of Radiology, 5th Floor Clinical Building, Faculty of Heath Sciences, University of Stellenbosch, Fransie van Zijl Avenue, Tygerberg, Cape Town, South Africa
[6]Medical Research Council (Unit on Anxiety and Stress Disorders), 2nd Floor Clinical Building, Faculty of Heath Sciences, University of Stellenbosch, Tygerberg, Cape Town, South Africa

(RECEIVED March 25, 2015; FINAL REVISION August 11, 2015; ACCEPTED September 14, 2015; FIRST PUBLISHED ONLINE October 5, 2015)

Abstract

The aim of the present study was to investigate the effect of HIV infection on cortical and subcortical regions of the frontal-striatal system involved in the inhibition of voluntary movement. Functional MRI (fMRI) studies suggest that human immunodeficiency virus (HIV) infection is associated with frontostriatal dysfunction. While frontostriatal systems play a key role in behavioral inhibition, there are to our knowledge no fMRI studies investigating the potential impact of HIV on systems involved during the inhibition of voluntary movement. A total of 17 combined antiretroviral therapy (cART) naïve HIV+ participants as well as 18 age, gender, ethnic, education matched healthy controls performed a modified version of the stop-signal paradigm. This paradigm assessed behavior as well as functional brain activity associated with motor execution, reactive inhibition (outright stopping) and proactive inhibition (anticipatory response slowing before stopping). HIV+ participants showed significantly slower responses during motor execution compared to healthy controls, whereas they had normal proactive response slowing. Putamen hypoactivation was evident in the HIV+ participants based on successful stopping, indicating subcortical dysfunction during reactive inhibition. HIV+ participants showed normal cortical functioning during proactive inhibition. Our data provide evidence that HIV infection is associated with subcortical dysfunction during reactive inhibition, accompanied by relatively normal higher cortical functioning during proactive inhibition. This suggests that HIV infection may primarily involve basic striatal-mediated control processes in cART naïve participants. (*JINS*, 2015, *21*, 722–731)

Keywords: Brain, Inhibition, Dementia, fMRI, Putamen, HIV

INTRODUCTION

It is well recognized that the human immunodeficiency virus (HIV) invades the brain early in the course of infection, and is thought to cause neurocognitive impairment in up to 52% of patients (An, Groves, Gray, & Scaravilli, 1999; Heaton et al., 2010). The typical neuropsychological disorder associated with untreated HIV infection is best described as a "subcortical" or "fronto-subcortical" dementia, as it involves cognitive (e.g., memory impairment, with relative sparing of recognition) (Grant, 2008), neuropsychiatric (e.g., motivation, emotional control, social behavior) (Castellon, Hinkin, Wood, & Yarema, 1998; Paul et al., 2005), and motor symptomatology (e.g., motor slowing) (Hardy & Hinhn, 2002). Postmortem studies show that HIV has a predilection for the striatum as well as the white matter tracts connecting for the striatum with the cortex (Langford et al., 2002; Wiley et al., 1998).

Past studies have consistently shown impaired function associated with frontostriatal circuits involved in visual attention and working memory (Chang et al., 2001; Ernst, Chang, Jovicich, Ames, & Arnold, 2002), episodic memory (Castelo, Sherman, Courtney, Melrose, & Stern, 2006), delay discounting (Meade, Lowen, MacLean, Key, & Lukas, 2011), and a monetary incentive delay task (Plessis et al., 2015). Furthermore, frontostriatal function loss is already

Correspondence and reprint requests to: Stéfan du Plessis, Department of Psychiatry, 2nd Floor Clinical Building, Faculty of Heath Sciences, University of Stellenbosch, Fransie van Zijl Avenue, Tygerberg, Cape Town, 7505 South Africa. E-mail: stefandup@sun.ac.za

observed during rest (Ortega, Brier, & Ances, 2015; Thomas, Brier, Snyder, Vaida, & Ances, 2013) and during simple motor paradigms (Ances et al., 2011). However, to date the impact of inhibitory control over voluntary movement has not been investigated. Such control entails concerted activation of both frontal regions and the striatum (Zandbelt & Vink, 2010). As HIV is known to involve the motor system clinically (Hardy & Hinhn, 2002), it is important to investigate how HIV impacts the various subsystems of this network involved in the control over the motor system.

Response inhibition represents a major component of frontostriatal functioning (Aron, 2011). Although cognitive neuropsychological measures have demonstrated potential abnormalities of response inhibition in terms of Stroop task performance (Hinkin, Castellon, Hardy, Granholm, & Siegle, 1999), the potential impact of HIV on the function of frontostriatal brain systems related to response inhibition has yet to be studied. Inhibition involves several sub processes, among which are (1) motor execution (i.e., GO responses), (2) outright stopping as an immediate reaction to a STOP signal (i.e., reactive inhibition) (Mink, 1996; Vink et al., 2005), and (3) higher order cortical functions involved in proactive anticipation of stopping (i.e., proactive inhibition) (Aron, 2011; Vink et al., 2005; Zandbelt & Vink, 2010).

In a previous study in healthy volunteers, a modified version of a Stop Signal Anticipation Task (SSAT) was used to investigate cortical and subcortical functions involved in the inhibition of voluntary movement (see Figure 1). During this task, subjects were required to give timed GO responses with occasional STOP signals occurring at fixed probabilities. The probability of a STOP signal occurring was explicitly stated to allow participants to adjust their responses proactively. GO responses in the absence of STOP signals served as a baseline, and they mainly activated the primary motor cortex. The striatum was found not to be active during these baseline responses, as these involve simple button presses. The putamen, however, was found to be active bilaterally during successful STOP trials (i.e., reactive inhibition) (Zandbelt & Vink, 2010). Furthermore, it was found that proactive inhibition evoked activation in both frontal and striatal regions to facilitate STOP performance by slowing down GO responses. Proactive inhibition specifically engaged the right inferior frontal gyrus, bilateral parietal gyri, and the right striatum (Zandbelt & Vink, 2010).

We chose to investigate a cART naïve cohort for two reasons. First, it allowed us to investigate the impact of the illness on brain function without the confounding effects of medication. Indeed, cART has been shown to potentially confound the effects of HIV on the frontostriatal system, leaving its true impact uncertain (Chang, Yakupov, Nakama, Stokes, & Ernst, 2007). Second, unmedicated HIV-positive patients continue to form an important part of patients seen in clinical settings in sub-Saharan countries (Reda & Biadgilign, 2012). For example individuals in Sub-Saharan Africa are generally only eligible for cART with CD4 counts of 350 or 500 cells/mL. Also, many eligible individuals do not access care for various reasons and a substantial number default form care after 12 months (15–20%) (Fox & Rosen, 2010). Therefore, the effect of illness in the absence of cART remains an important question in these settings.

The aim of the present study was to investigate the effect of HIV infection on cortical and subcortical regions of the frontal-striatal system involved in the inhibition of voluntary movement. To this end, 22 cART naive HIV+ and 18 matched controls performed a stop signal anticipation task while being scanned with functional MRI.

We hypothesized that HIV infection would have the following effects: (1) motor execution as measured by baseline timed GO responses would be increased, as HIV infection often involves psychomotor slowing (Hardy & Hinhn, 2002; Navia, Jordan, & Price, 1986); (2) reactive inhibition time as measured by the speed of inhibition, that is, STOP signal reaction time (SSRT) (Logan, Cowan, & Davis, 1984) would be increased, similar to findings in other subcortical dementia's such as Parkinson's disease (Gauggel, Rieger, & Feghoff, 2004); (3) subcortical dysfunction as evidenced by hypofunction in the putamen during reactive inhibition would be demonstrated (Zandbelt, van Buuren, Kahn, & Vink, 2011); and (4) compromised higher cortical functioning would be reflected in the participants' inability to proactively increase their response times in anticipation of

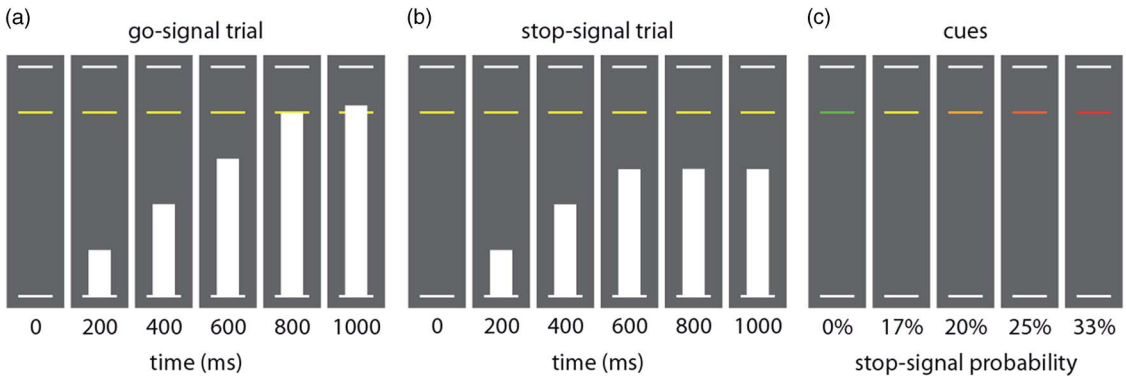

Fig. 1. The Stop Signal Anticipation Task. There are two types of trials: (a) GO signal trials interspersed with (b) occasional STOP signal trials. (c) A changing color cue indicates the stop-signal probability, which varies from trial to trial.

https://doi.org/10.1017/S1355617715000971 Published online by Cambridge University Press

STOP signals, as well as in associated cortical activation deficits in the inferior frontal gyrus during proactive inhibition (Zandbelt et al., 2011).

METHOD

Participants

The study was approved by the Health Research Ethics Committee of Stellenbosch University and the Human Research Ethics Committee of the University of Cape Town, Cape Town, South Africa. Before enrolment, all participants provided written consent after receiving a full description of this study. Our sample was recruited from a medically stable clinic-attending population during routine HIV care and testing at Site C primary health care clinic, in Khayelitsha, Cape Town, South Africa. A total of 22 HIV+ participants were included in the study together with 18 gender, education, ethnicity, and age-matched healthy controls. The controls were HIV negative as confirmed by the enzyme-linked immunosorbent assay. All HIV+ patients included in the study were cART naïve.

Participants were screened using the Mini International Neuropsychiatric Interview (MINI) 6.0.0/MINI-PLUS 6.0.0. (Sheehan et al., 1998). All HIV+ participants received a full medical examination by a clinician and were excluded if there was a current comorbid psychiatric/neurological or general medical condition that could confound the diagnosis of HIV associated neurocognitive disorders (HAND); any history of substance use/abuse as assessed by the Substance Abuse and Mental Illness Symptoms Screener (SAMISS) screening questionnaire (Pence et al., 2005); a score for smoking greater than 1 as confirmed by the Kreek-McHugh-Schluger-Kellogg (KMSK) scale (Kellogg et al., 2003); were pregnant as confirmed by a urine pregnancy test; or were currently receiving treatment for tuberculosis. All participants were right handed as confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971).

HIV+ participants underwent detailed neuropsychological assessment within two weeks of neuroimaging and controls within 1 year for characterization purposes only. The test battery assessed the following cognitive domains: abstraction/ executive function, memory, learning, speed of information processing, verbal fluency, motor and sensory/ perception (Grant, 2008). From these scores, a Global Deficit composite score was derived (Carey et al., 2004) using normative data from a larger parent study (Joska et al., 2010).

The following laboratory measures were performed in the HIV+ participants within 2 weeks of neuroimaging: CD_4 count, HIV viral load, Rapid Plasma Reagin for syphilis and thyroid stimulating hormone level. All participants received a urinary drug screen before being scanned. In view of the fact patient reports of duration of infection are highly unreliable in our present population we relied on pre-treatment CD4 count (as a proxy for nadir) and viral load as an estimation of disease progression as all participants were cART naive and being treated for the first time. While hepatitis C co-infection has been associated with increased risk and severity of cognitive impairment in HAND, participants were not screened as it is not endemic to the region (Amin et al., 2004). An experienced radiologist reviewed all of the scans for intracranial pathology that could potentially confound functional imaging measurement results.

Functional MRI

All scans were acquired on a 3 Tesla Siemens Allegra at the Combined Universities Brain Imaging Centre (CUBIC). During MRI image acquisition, 622 whole-brain two-dimensional-echo planar imaging images [repetition time (TR) = 1600 ms; echo time (TE) = 23 ms; flip-angle: 72.5 degrees; field of view (FOV): 256 × 256; 30 slices; 4 mm isotropic voxels) were acquired. Trial-by trial variability was accounted for by setting the total task length to 17 min. Excess scans were discarded.

For image registration, a T1 ME-MPRAGE weighted structural scan was acquired (TR = 2530 ms; TE_1 = 1.53 ms; TE_2 = 3.21, ms; TE_3 = 4.89 ms; TE_4 = 6.57 ms; flip-angle: 7 degrees; FOV: 256 mm; 128 slices; 1 mm isotropic voxel size) (van der Kouwe, Benner, Salat, & Fischl, 2008).

Stop-Signal Anticipation Functional MRI Task

During the functional MRI (fMRI) experiment, participants performed the STOP signal anticipation task (Zandbelt & Vink, 2010). The experiment was performed using Presentation® software (Version 14.6, www.neurobs.com). The task is based on original work by Logan et al. (1984) who proposed a horse-race model, suggesting that a response, either GO or STOP, is a result from a race between the GO process and the STOP process. The response is stopped when the STOP process finished before the GO process reaches execution threshold (Logan & Cowan, 1984). The task and experimental procedures were identical to those described before (Zandbelt & Vink, 2010). All participants received standardized training in task performance before scanning by a trained technician in their first language (isiXhosa).

During task performance, participants were presented with three background lines. In each trial, a bar moved at a constant speed from the bottom line to the top line, passing the middle line within 800 milliseconds (ms). On GO trials, participants were required to stop the bar with a button press using their right index finger, as close to the middle/colored line as possible. Should the bar reach the top line after 1000 ms, the GO trial was considered a failure. The inter-trial interval was kept at 1000 ms. On STOP signal trials the bar stopped on its own, indicating a STOP signal. During STOP trials the participant was required to withhold the button press (reactive response inhibition).

To measure proactive response inhibition, the probability of the stop signal was explicitly indicated to the participant by the color of the middle line. This allowed a participant to proactively anticipate a STOP signal in each STOP trial, by taking the stop-signal probability into account. There were

https://doi.org/10.1017/S1355617715000971 Published online by Cambridge University Press

five stop-signal probability levels: 0% (green), 17% (yellow), 20% (amber), 25% (orange), and 33% (red). In total, 414 go trials (0%, $n = 234$; 17%, $n = 30$; 20%, $n = 48$; 25%, $n = 54$; 33%, $n = 48$) and 60 stop trials (17%, $n = 6$; 20%, $n = 12$; 25%, $n = 18$; 33%, $n = 24$) were presented in a single run in pseudorandom order.

The STOP signal delay (SSD), the interval between start of a trial and the STOP signal, was initially 550 ms and varied for each STOP signal according to a staircase procedure. That is, should a STOP trial be successful, the trial difficulty was increased by increasing the STOP signal delay by 25 ms. Should a STOP trial be unsuccessful, trial difficulty was decreased in the same manner. This technique assured an equal amount of successful and unsuccessful STOP trials. For more details on the SSAT, see Zandbelt and Vink (2010).

Motor Execution: Baseline GO Reaction Time

Timed baseline GO responses were measured in the absence of the possibility of a STOP signal. To explore speeded responses in terms of simple reaction time we included the California Computerized Assessment Package (CALCAP) in our neuropsychological assessment battery (Miller, Satz, & Visscher, 1991).

Reactive Inhibition

Reactive inhibition was studied in terms of the SSRT (Logan et al., 1984; Zandbelt & Vink, 2010), which was calculated according to the integration method (Logan & Cowan, 1984) and pooled across all STOP signal probability levels.

Proactive Inhibition

In keeping with previous studies (Vink et al., 2005, 2014; Zandbelt & Vink, 2010), proactive inhibition was measured as the effect of STOP signal probability on GO signal response time. Impaired proactive inhibition is evidenced by a reduced effect of STOP signal probability on GO signal response time (Vink et al., 2005, 2014; Zandbelt & Vink, 2010). This indicates a weaker anticipation of a STOP signal. Statistical analysis of proactive inhibition consisted of a repeated measures analysis of variance on mean GO signal response times, with STOP signal probability and HIV serostatus as factors.

fMRI Data Analysis

Image data were modeled using SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8/). Preprocessing and first-level statistical analyses were performed as previously described (Zandbelt & Vink, 2010). Preprocessing involved correction for slice timing differences by resampling all slices in time relative to the middle slice using Fourier interpolation. Re-alignment to the mean image was performed using fourth-degree B-spline interpolation to correct for head motion. Head motion parameters were analyzed to ensure that the maximum motion did not exceed a predefined threshold (scan-to-scan >3 mm) (Van Dijk, Sabuncu, & Buckner, 2012). Spatial normalization was performed using linear and non-linear deformations to the Montreal Neurological Institute template brain, and spatial smoothing using a 6-mm full-width at half-maximum Gaussian kernel to accommodate inter-individual differences in neuro-anatomy.

The fMRI data were modeled voxel-wise, using a general linear model, in which the following events were included as regressors: Timed GO signal trials with STOP signal probability >0%, successful STOP signal trials and failed STOP signal trials. For GO signal trials with a STOP probability above 0%, we also included a parametric regressor modelling the STOP signal probability level as well as variations in response time. GO baseline (0% STOP probability) as well as activity during rest was explicitly modelled.

The fMRI data were high-pass filtered (cut-off 128 Hz) to remove low-frequency drifts. For each participant, we computed four contrast images: (1) Baseline GO-activation, to measure motor response initiation, (2) activation during successful STOP signal trials *versus* failed STOP signal trials (to assess reactive inhibition), (3) activation during successful STOP signal trials *versus* GO signal trials in the 0% STOP signal probability context (also to assess reactive inhibition), and (4) the parametric effect of STOP signal probability on GO signal activation (to assess proactive inhibition). We computed two contrasts for reactive inhibition because there is no consensus currently, on which contrast is most appropriate for investigating reactive inhibition.

We assessed group activation differences in predefined *a priori* regions of interest (ROIs), based on activation maps acquired in a previous experiment (Zandbelt & Vink, 2010), in which an independent sample of healthy volunteers performed the same task. These ROIs were defined using a cluster-level threshold (cluster-defining threshold $p < .001$, cluster probability of $p < .05$, family-wise error corrected for multiple comparisons). They included the primary motor cortex as activated during baseline GO responses; the right striatum during reactive inhibition and the right inferior frontal gyrus during proactive inhibition. We chose the right inferior frontal gyrus as our primary region of interest during proactive inhibition, as the inferior frontal regions have been shown to be affected by HIV in tasks of visual attention and working memory (Plessis et al., 2014). An exploratory voxel wise whole-brain analysis was also performed for each of the above contrasts, testing for group differences using independent sample *t*-tests (family-wise error corrected for multiple comparisons).

RESULTS

Demographics

Forty participants were initially recruited into the study. We excluded five patients for the following reasons: Tested positive for benzodiazepines ($n = 1$); Did not receive a full physical examination ($n = 1$); Problems with response box

https://doi.org/10.1017/S1355617715000971 Published online by Cambridge University Press

Table 1. Demographic characteristics of the diagnostics groups.

	HIV ($N = 17$)	HC ($N = 18$)	Test Statisticstatistic	p-Value
Gender (M/F)	2/15	3/15	$\chi^2 = 0.172$	0.679
Mean Age age (years)	31 ± 4.1	28 ± 5.3	T = −2.00	0.054
Education (years)	12 (10.8–12)	12 ± (11–12)	U = 128	0.424
Viral Load load (copies/ml)	51065.4 ± 62034.4			
CD_4 (cells/μl)	392 ± 211.8			
Participants with AIDS defining CD_4 count	7			
GDS (Summary summary Scorescore)	0.21 (0.07–0.36)	0.14 (0.07–0.3)	U = 275	0.44

Note. Age, viral load, and CD_4 data represent mean ± SD. Education and GDS data represent median and interquartile range between 25th and 75th centiles. AIDS defining CD_4 count of 350 cells/μl used.
F, female; M, male; GDS: Global Deficit Score (22); HC: Hhealthy Ccontrols, HIV: HIV+ participants. AIDS defining CD_4 count of 350 cells/μl used.

($n = 2$); Poor scan quality leading to failure in pre-processing ($n = 1$). One healthy control was excluded to excessive movement (6.7 mm between scan movement) with a notable drop in signal to noise as assessed with in house quality assessment software (Geissler et al., 2007; Stöcker et al., 2005). Therefore, 17 HIV+ participants and 18 healthy controls were included in the final analysis (see Table 1).

The groups did not differ with regard to age, gender, ethnicity, or education level. All HIV participants were ambulant and healthy enough to participate in the experiment. No significant pathology was found on the structural MRI scans. As expected, most of the present sample is female as the HIV+ population of sub-Saharan Africa consists mostly of women infected by heterosexual contact (UNAIDS, 2012).

Behavioral Results

Motor execution

Response times for baseline GO trials (a STOP signal probability of 0%) were close to the target response time of 800 ms (794 ± 7 ms), for controls, whereas HIV+ participants were significantly slower (M = 827 ± 8; $t(33) = -3.067$; $p = .004$; $r = 0.471$). Reaction time assessment according to CALCAP confirmed that HIV participants showed significant signs of motor slowing (Control: M = 295 ± 16 ms; HIV: M = 367 ± 19 ms; $t(32) = -2.818$; $p = .008$; $r = 0.446$). Despite this slow baseline response speed, there was no difference in baseline GO accuracy between groups (Control: M = 96 ± 0.6; HIV: M = 96 ± 0.7; $t(33) = 0.673$; $p = .506$; $r = 0.116$), indicating that all subjects were able to perform the basic task regardless of baseline response speed.

Reactive inhibition

The speed of reactive inhibition (SSRT) did not differ between the groups (Control: M = 270 ± 3 ms; HIV: M = 267 ± 6 ms; $t(33) = 0.429$; $p = .670$; $r = 0.075$). As STOP errors were manipulated according to subject performance as previously described (Pence et al., 2005; Zandbelt & Vink, 2010), there was no difference in STOP related errors ($t(33) = -1.191$; $p = .242$; $r = 0.203$).

Proactive inhibition

There was a significant main effect of STOP probability on reaction time regardless of disease status, showing response slowing as the STOP probability increased ($F(2.1,70.4) = 16.808$; $p < .001$) in trials where a STOP signal could occur (see Figure 2). Although there was no significant group by STOP probability interaction ($F(2.1,70.4) = 1.516$; $p = .226$), there was a trend toward a group effect ($F(1,33) = 3.235$; $p = .081$). This shows that both groups were able to slow down their responses proactively during GO trials in which a STOP signal could occur, with the HIV+ group being on average slower than controls.

On further analysis, both groups showed, as expected, a main effect of response slowing relative to baseline ($F(1,33) = 31.171$; $p < .001$). There was no group by response speed interaction, indicating that both groups showed an equal amount of proactive slowing relative to their own baseline ($F(1,33) = 2.42$; $p = .129$). Finally, HIV+ had the same accuracy on GO trials where a STOP signal could occur (Control: M = 97 ± 0.5%; HIV: M = 95 ± 0.8%; $t(33) = 1.745$;

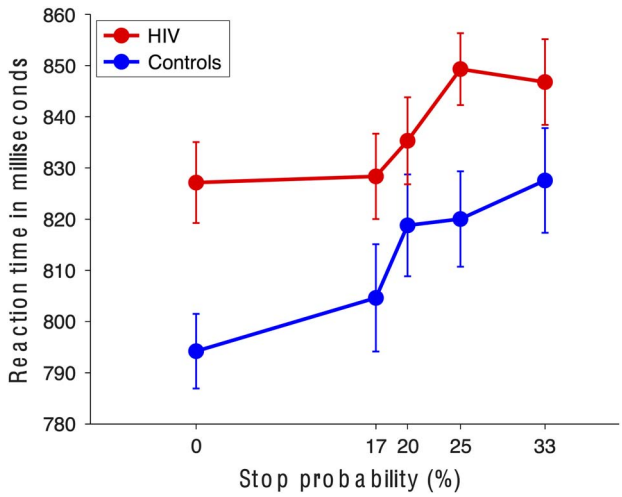

Fig. 2. Effect of stop-signal probability on go-signal response time across groups with error bars indicating the standard error of the mean.

https://doi.org/10.1017/S1355617715000971 Published online by Cambridge University Press

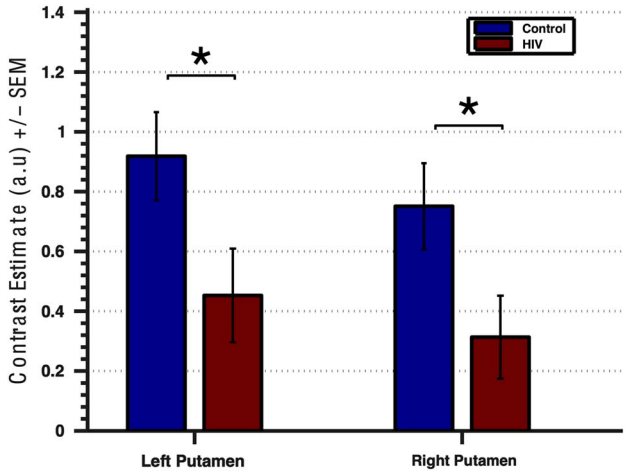

Fig. 3. Putamen activation during reactive inhibition in both HIV+ participants and seronegative controls.

$p = .090$; $r = 0.291$). Both groups had a STOP accuracy close to the target of 50%, indicating that the stepwise difficulty adjustment during STOP trials were successful (Control: $M = 51 \pm 1.5\%$; HIV: $M = 54 \pm 1\%$; $t(33) = -1.522$; $p = .137$). It should be noted that, as the difficulty was adjusted according to individual performance, we expected no difference in STOP accuracy.

fMRI Results

Motor execution

Both groups showed equal activation in the motor cortex on baseline GO responses, indicating normal motor cortical function during the timed responses ($t(33) = 0.320$; $p = .751$; $r = 0.056$).

Reactive inhibition

When comparing successful STOPs *versus* unsuccessful STOPs, we found hypo-activation in the right putamen ($t(33) = 2.157$; $p = .038$; $r = 0.352$) in the HIV+ group during this task. Further exploratory ROI analysis revealed the same effect to be present in the left putamen ($t(33) = 2.136$; $p = .040$; $r = 0.348$) (see Figure 3). No further differences were found on an exploratory whole brain analysis (see Figure 4). An exploratory regression analysis with putamen activation as dependent variable and global deficit score, viral load, and age as predictors, revealed no further significant results in the HIV+ group. We did not find any significant correlations between cognitive domain scores and reactive inhibition activation (see Table 2).

Proactive inhibition

We found no difference in function associated with proactive inhibition between groups in the inferior frontal gyrus ($t(33) = -0.036$; $p = .972$; $r = 0.006$). An exploratory whole-brain analysis was also performed, which also showed no group differences. Exploratory analysis revealed no relationship between frontal task activation and cognitive domain scores.

DISCUSSION

In this study, we investigated frontostriatal functioning during an inhibition task that assessed motor execution,

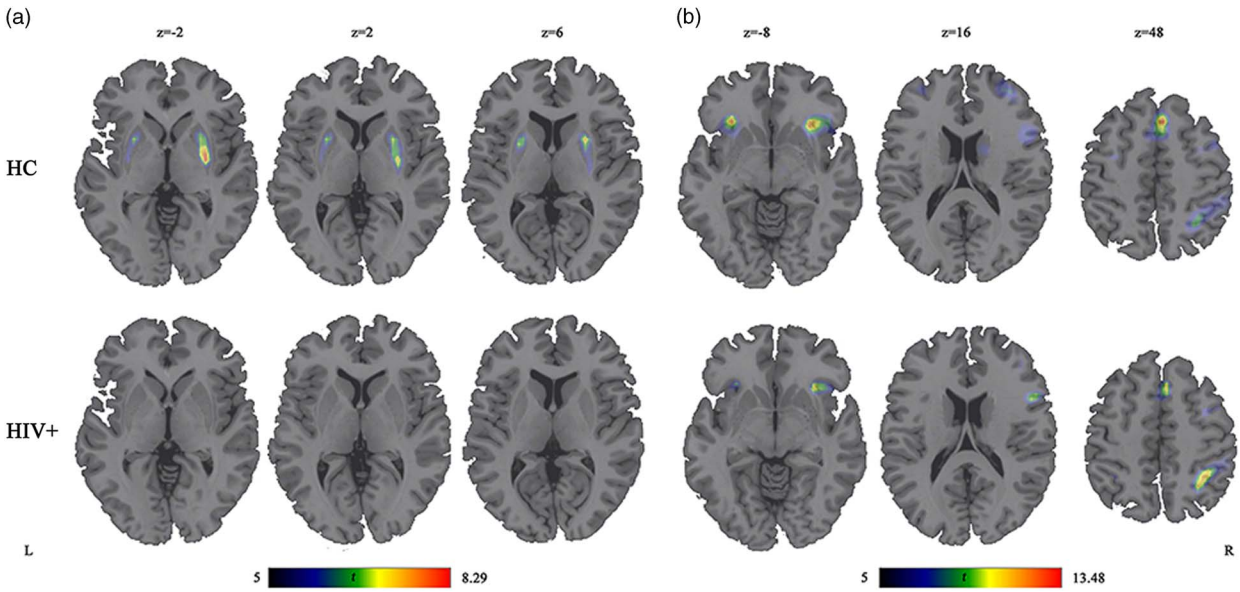

Fig. 4. Whole-brain activation during reactive inhibition in HIV+ participants and healthy control subjects (HC). One-sample *t*-tests of (a) successful STOP signal *versus* failed STOP signal activation and (b) successful STOP signal *versus* GO signal 0% activation, for HIV+ and healthy control subjects. Significant activation clusters ($p < .05$, family-wise error-corrected) are displayed on the normalized and skull-stripped group-average brain (neurological orientation). HC, control subject; L, left; R, right; HIV+, HIV-positive participant.

https://doi.org/10.1017/S1355617715000971 Published online by Cambridge University Press

Table 2. Cognitive domains tested (Mean *Z* value corrected *via* normal control group) as well as Pearson's correlations performed for the left as well as the right putamen activations during reactive inhibition.

Cognitive domain	HIV (N = 17)		*SE*	Left putamen	*p*-Value	Right putamen	*p*-Value
Abstraction/executive function	−.286	+/−	0.235	−.216	.390	−.274	.271
Memory	−.424	+/−	0.202	.061	.810	.059	.815
Learning	.301	+/−	0.183	.072	.776	−.115	.650
Speed of information processing	−.218	+/−	0.193	−.276	.268	−.258	.301
Verbal fluency	.027	+/−	0.173	.050	.845	−.121	.633
Motor	−.205	+/−	0.226	−.311	.209	−.291	.241
Sensory/perception	−.686	+/−	0.391	.037	.888	.129	.623

SE = standard error.

reactive inhibition and proactive inhibition, in 17 cART naïve HIV+ participants and 18 matched healthy controls. The HIV + participants had significantly slower baseline GO reaction times indicating impaired baseline motor execution. Both groups demonstrated similar responses on behavioral measures of reactive inhibition as well as proactive inhibition. During fMRI, however, in HIV+ participants the putamen was found to be hypo-active during reactive inhibition. There were no significant fMRI differences between groups in the cortex during proactive inhibition. This could indicate a relative sparing of higher cortical function with a specific dysfunction of the more basic functions of the basal ganglia in a cART naïve population during reactive inhibition.

We investigated motor execution in terms of timed GO responses and found HIV+ participants to be significantly slower. HIV+ participants displayed a normal inhibition process in terms of speed of inhibition. Given that their timed GO responses were abnormally slow, these findings suggest that the SSRT and the GO process are dependent on different fronto-striatal pathways. This is consistent with animal studies reporting that SSRT is sensitive to cortical lesions and GO reaction time is disrupted by subcortical lesions (Eagle, Baunez, et al., 2007).

The HIV+ group proactively reduced their response speed similar to controls. This indicates that, despite abnormalities found in their baseline GO responses, HIV+ participants could still anticipate STOP signals and slow down their responses to facilitate stopping. As proactive inhibition requires higher cortical regions to appropriately respond to complex environmental cues and successfully communicate this information to the striatum (Zandbelt et al., 2011; Zandbelt & Vink, 2010), it suggests higher cortical functions are largely intact in the present sample.

Our finding of no differences between HIV+ participants and controls in the function of the motor cortex during timed GO responses differs from a previous study in a cART treated group. In the latter study, increased motor cortical activation was found in HIV infected participants using a motor-tapping paradigm (Ances, Roc, Korczykowski, Wolf, & Kolson, 2008). Our finding suggests that the cortex is relatively spared in cART naïve HIV+ individuals (Chang et al., 2007) as seen here during response execution.

As predicted by findings of both clinical (Navia et al., 1986) and post mortem studies (Langford et al., 2002; Wiley et al., 1998), we found subcortical regions to be primarily affected as evidenced by putamen hypofunction during reactive inhibition. Although task based fMRI studies have reported subcortical involvement with HIV infection (Ances et al., 2011; Melrose, Tinaz, Castelo, Courtney, & Stern, 2008) studies differ with regards to the directionality of this involvement. For example, increased activation in the striatum has been reported during a fMRI motor tapping paradigm (Ances et al., 2011) and decreased activity during a semantic event-sequencing task (Melrose et al., 2008). A possible explanation for these differences from the present study could be that behavioral tasks differed between studies. Additionally, a positron emission tomography (PET) study, reported baseline hypometabolism in the basal ganglia in HIV+ participants with moderate motor-slowing, whereas basal ganglia hypermetabolism was found in HIV+ participants with normal motor performance (Giesen et al., 2000). As fMRI studies in HIV often include elderly subjects (Plessis et al., 2014), differences in age across studies could also be a confounding factor, as HIV+ effects on the brain is thought to co-vary with increased age (Ances, Ortega, Vaida, Heaps, & Paul, 2012; Chang, Holt, Yakupov, Jiang, & Ernst, 2013; Holt, Kraft-Terry, & Chang, 2012). Another possible explanation for the directional difference of our data is the effect of cART (Chang et al., 2007), as previous fMRI studies included samples mostly on treatment (Plessis et al., 2014). Furthermore, two arterial spin labelling studies have reported reduced baseline regional cerebral blood flow in the striatum of HIV+ participants, which further supports our finding of hypo-activity of these subcortical structures at baseline (Ances et al., 2006, 2009). Our findings therefore confirm the impact of HIV on the function of the striatum and extend these results by demonstrating striatal hypofunction in a cART naïve sample during reactive inhibition.

We found no difference in cortical activity during proactive inhibition. This is seemingly in contrast to functional studies performed in the past that do indeed find relative cortical hyperactivity in HIV (Chang et al., 2004; Melrose et al., 2008; Plessis et al., 2014). These studies largely included participants on cART treatment, however. As cART

https://doi.org/10.1017/S1355617715000971 Published online by Cambridge University Press

treatment has been shown to be associated with increased cortical activity (Chang et al., 2007), this could serve as a possible explanation for this difference.

We did not find any significant correlations between cognitive test scores and fMRI activation. This is not surprising given that fMRI has been shown to be more sensitive to cerebral pathology than cognitive testing (Ernst et al., 2002). Also, the study may be underpowered due to the small sample size. Further investigation is, therefore, warranted.

The slow GO processes and relatively normal STOP processes found in HIV infection in the present study could be explained on the basis of dopaminergic deregulation: Supportive evidence is forthcoming from animal studies suggesting that dopamine deregulation could result in an abnormally slow motor responses, leaving the speed of inhibition spared relative to controls (Bari, Eagle, Mar, Robinson, & Robbins, 2009; Eagle, Tufft, Goodchild, & Robbins, 2007). Studies performed in rats revealed that neither the administration of the mixed D_1/D_2 receptor antagonist *cis*-flupenthixol (Eagle, Tufft, et al., 2007) nor dopamine-associated transport blockade by GBR-12909 influenced SSRT in a modified version of the SSAT (Bari et al., 2009). However, in the same studies GO reaction time was found to speed up in response to dopamine re-uptake blockade as well as methylphenidate administration (Bari et al., 2009; Eagle, Tufft, et al., 2007). Our finding of a slow GO process in the presence of a normal speed of inhibition indicates that the exact biochemical nature of striatal dysfunction in HIV infection requires further elucidation. As the striatum is modulated by dopaminergic activity (Frank, 2005), the present finding of striatal hypofunction could relate to dopamine deregulation. This could be further investigated by PET using dopamine ligands in conjunction with fMRI functional measurements. Prospective pre- and post-cART prospective studies would help to clarify the striatal and cortical effects of cART (Chang et al., 2007).

A strength of our study is the exclusion of important confounds that could influence fronto-striatal function such as cART (Chang et al., 2007), comorbid depression and substance abuse. The effects of age should also be minimal (Ances et al., 2010; Holt et al., 2012), due to the relatively young age of our cohort. We could not demonstrate a link between slow GO processes and brain function. Although we found normal motor cortical activation in HIV+ participants, we could not rule out differences in other parts of the motor system, as our task involved only simple timed motor responses. We also could not demonstrate a behavioral difference in terms of reactive STOP accuracy, which related to putamen activation. This was due to an inherent limitation of our task design: As putamen activation relies on balanced correct *versus* incorrect STOP factors, task difficulty was adjusted to achieve equal successful and unsuccessful STOP for both groups. We did however demonstrate that the putamen is hypoactive in HIV infection when controlling for task performance in this way. Our study is further limited by a small sample size due to the carefully selected nature of our sample.

Taken together, our findings support the hypothesis that HIV infection primarily affects the basic functions of the putamen during reactive inhibition, with relative sparing of cortical function during proactive inhibition.

ACKNOWLEDGMENTS

The authors thank Dr. Hetta Gouse from the University of Cape Town, as well as Prof. Rob Paul from the University of Missouri-St. Louis, for their assistance in determining the neuropsychological assessment battery as well as giving input into the neuropsychological assessments. The authors also thank Dr. Karen Cloete and Dr. Sanja Kilian from Stellenbosch University for their support in preparation of the manuscript, and Mr. Teboho Linda from the University of Cape Town for assisting in the recruiting of participants. *Financial Disclosures:* S. Du Plessis has received support from a National Research Fund International Research Training Grant (IRTG 1522), as well as support from the Medical Research Council of South Africa, Biological Psychiatry Special Interest Group of the South African Society of Psychiatrists as well as the HIV research Trust (HIVRT14-049). M. Vink, PhD and A. Bagadia have reported no biomedical financial interests or potential conflicts of interest. Joska, PhD has received support from the Medical Research Council of South Africa. E. Koutsilieri, PhD is supported by an EDCTP Strategic Primary Grant (SP. 2011.41304.065.) as well as a "Verein für Parkinson-Forschung" grant. D. Stein, PhD has received research grants and/or consultancy honoraria from Abbott, Astrazeneca, Biocodex, Eli-Lilly, GlaxoSmithKline, Jazz Pharmaceuticals, Johnson & Johnson, Lundbeck, Novartis, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Sun, Takeda, Tikvah, and Wyeth. R. Emsley, PhD has participated in speakers/advisory boards and received honoraria from AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, Lundbeck, Servier, and Otsuka. He has also received research funding from Janssen, Lundbeck and AstraZeneca.

REFERENCES

Amin, J., Kaye, M., Skidmore, S., Pillay, D., Cooper, D.A., & Dore, G.J. (2004). HIV and hepatitis C coinfection within the CAESAR study. *HIV Medicine*, *5*(3), 174–179. http://doi.org/10.1111/j.1468-1293.2004.00207.x

An, S.F., Groves, M., Gray, F., & Scaravilli, F. (1999). Early entry and widespread cellular involvement of HIV-1 DNA in brains of HIV-1 positive asymptomatic individuals. *Journal of Neuropathology and Experimental Neurology*, *58*(11), 1156–1162

Ances, B.M., Ortega, M., Vaida, F., Heaps, J., & Paul, R. (2012). Independent effects of HIV, aging, and HAART on brain volumetric measures. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *59*(5), 469–477. http://doi.org/10.1097/QAI.0b013e318249db17

Ances, B.M., Roc, A.C., Korczykowski, M., Wolf, R.L., & Kolson, D.L. (2008). Combination antiretroviral therapy modulates the blood oxygen level–dependent amplitude in human immunodeficiency virus-seropositive patients. *Journal of Neurovirology*, *14*(5), 418–424. http://doi.org/10.1080/13550280802298112

Ances, B.M., Roc, A.C., Wang, J., Korczykowski, M., Okawa, J., Stern, J., … Detre, J.A. (2006). Caudate blood flow and volume are reduced in HIV+ neurocognitively impaired patients. *Neurology*, *66*(6), 862–866. http://doi.org/10.1212/01.wnl.0000203524.57993.e2

Ances, B.M., Sisti, D., Vaida, F., Liang, C.L., Leontiev, O., Perthen, J.E., … Ellis, R.J. (2009). Resting cerebral blood flow: A potential biomarker of the effects of HIV in the brain. *Neurology*, *73*(9), 702–708. http://doi.org/10.1212/WNL.0b013e3181b59a97

Ances, B.M., Vaida, F., Cherner, M., Yeh, M.J., Liang, C.L., Gardner, C., … Buxton, R.B. (2011). HIV and chronic methamphetamine dependence affect cerebral blood flow. *Journal of Neuroimmune Pharmacology*, *6*(3), 409–419. http://doi.org/10.1007/s11481-011-9270-y

Ances, B.M., Vaida, F., Yeh, M.J., Liang, C.L., Buxton, R.B., Letendre, S., … McCutchan, J.A. (2010). HIV infection and aging independently affect brain function as measured by functional magnetic resonance imaging. *The Journal of Infectious Diseases*, *201*(3), 336–340. http://doi.org/10.1086/649899

Aron, A.R. (2011). From reactive to proactive and selective control: Developing a richer model for stopping inappropriate responses. *Biological Psychiatry*, *69*(12), e55–e68

Bari, A., Eagle, D.M., Mar, A.C., Robinson, E.S.J., & Robbins, T.W. (2009). Dissociable effects of noradrenaline, dopamine, and serotonin uptake blockade on stop task performance in rats. *Psychopharmacology*, *205*(2), 273–283. http://doi.org/10.1007/s00213-009-1537-0

Carey, C.L., Woods, S.P., Gonzalez, R., Conover, E., Marcotte, T.D., Grant, I., … Heaton, R.K. (2004). Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. *Journal of Clinical and Experimental Neuropsychology*, *26*(3), 307–319. http://doi.org/10.1080/13803390490510031

Castellon, S.A., Hinkin, C.H., Wood, S., & Yarema, K.T. (1998). Apathy, depression, and cognitive performance in HIV-1 infection. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *10*(3), 320–329

Castelo, J.M.B., Sherman, S.J., Courtney, M.G., Melrose, R.J., & Stern, C.E. (2006). Altered hippocampal-prefrontal activation in HIV patients during episodic memory encoding. *Neurology*, *66*(11), 1688–1695. http://doi.org/10.1212/01.wnl.0000218305.09183.70

Chang, L., Holt, J.L., Yakupov, R., Jiang, C.S., & Ernst, T. (2013). Lower cognitive reserve in the aging human immunodeficiency virus-infected brain. *Neurobiology of Aging*, *34*(4), 1240–1253. http://doi.org/10.1016/j.neurobiolaging.2012.10.012

Chang, L., Speck, O., Miller, E.N., Braun, J., Jovicich, J., Koch, C., … Ernst, T. (2001). Neural correlates of attention and working memory deficits in HIV patients. *Neurology*, *57*(6), 1001–1007

Chang, L., Tomasi, D., Yakupov, R., Lozar, C., Arnold, S., Caparelli, E., & Ernst, T. (2004). Adaptation of the attention network in human immunodeficiency virus brain injury. *Annals of Neurology*, *56*(2), 259–272. http://doi.org/10.1002/ana.20190

Chang, L., Yakupov, R., Nakama, H., Stokes, B., & Ernst, T. (2007). Antiretroviral treatment is associated with increased attentional load-dependent brain activation in HIV patients. *Journal of Neuroimmune Pharmacology*, *3*(2), 95–104. http://doi.org/10.1007/s11481-007-9092-0

Eagle, D.M., Baunez, C., Hutcheson, D.M., Lehmann, O., Shah, A.P., & Robbins, T.W. (2007). Stop-signal reaction-time task performance: Role of prefrontal cortex and subthalamic nucleus. *Cerebral Cortex*, *18*(1), 178–188. http://doi.org/10.1093/cercor/bhm044

Eagle, D.M., Tufft, M.R.A., Goodchild, H.L., & Robbins, T.W. (2007). Differential effects of modafinil and methylphenidate on stop-signal reaction time task performance in the rat, and interactions with the dopamine receptor antagonist cis-flupenthixol. *Psychopharmacology*, *192*(2), 193–206. http://doi.org/10.1007/s00213-007-0701-7

Ernst, T., Chang, L., Jovicich, J., Ames, N., & Arnold, S. (2002). Abnormal brain activation on functional MRI in cognitively asymptomatic HIV patients. *Neurology*, *59*(9), 1343–1349

Fox, M.P., & Rosen, S. (2010). Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: Systematic review. *Tropical Medicine & International Health*, *15*, 1–15. http://doi.org/10.1111/j.1365-3156.2010.02508.x

Frank, M.J. (2005). Dynamic dopamine modulation in the basal ganglia: A neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. *Journal of Cognitive Neuroscience*, *17*(1), 51–72. http://doi.org/10.1016/S0028-3932(02)00068-4

Gauggel, S., Rieger, M., & Feghoff, T.-A. (2004). Inhibition of ongoing responses in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *75*(4), 539–544

Geissler, A., Gartus, A., Foki, T., Tahamtan, A.R., Beisteiner, R., & Barth, M. (2007). Contrast-to-noise ratio (CNR) as a quality parameter in fMRI. *Journal of Magnetic Resonance Imaging*, *25*(6), 1263–1270. http://doi.org/10.1002/jmri.20935

Giesen, von, H.J., Antke, C., Hefter, H., Wenserski, F., Seitz, R.J., & Arendt, G. (2000). Potential time course of human immunodeficiency virus type 1-associated minor motor deficits: Electrophysiologic and positron emission tomography findings. *Archives of Neurology*, *57*(11), 1601–1607

Grant, I. (2008). Neurocognitive disturbances in HIV. *International Review of Psychiatry*, *20*(1), 33–47. http://doi.org/10.1080/09540260701877894

Hardy, D.J., & Hinhn, C.H. (2002). Reaction time performance in adults with HIV/AIDS. *Journal of Clinical and Experimental Neuropsychology*, *24*(7), 912–929

Heaton, R.K., Clifford, D.B., Franklin, D.R. Jr, Woods, S.P., Ake, C., Vaida, F., … CHARTER group (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy. *Neurology*, *75*, 2087–2095

Hinkin, C.H., Castellon, S.A., Hardy, D.J., Granholm, E., & Siegle, G. (1999). Computerized and traditional Stroop task dysfunction in HIV-1 infection. *Neuropsychology*, *13*(2), 306–316

Holt, J.L., Kraft-Terry, S.D., & Chang, L. (2012). Neuroimaging studies of the aging HIV-1-infected brain. *Journal of Neurovirology*, *18*(4), 291–302. http://doi.org/10.1007/s13365-012-0114-1

Joska, J.A., Westgarth-Taylor, J., Myer, L., Hoare, J., Thomas, K.G.F., Combrinck, M., … Flisher, A.J. (2010). Characterization of HIV-associated neurocognitive disorders among individuals starting antiretroviral therapy in South Africa. *AIDS and Behavior*, *15*(6), 1197–1203. http://doi.org/10.1007/s10461-010-9744-6

Kellogg, S.H., McHugh, P.F., Bell, K., Schluger, J.H., Schluger, R.P., LaForge, K.S., … Kreek, M.J. (2003). The Kreek-McHugh-Schluger-Kellogg scale: A new, rapid method for quantifying substance abuse and its possible applications. *Drug and Alcohol Dependence*, *69*(2), 137–150

Langford, T.D., Letendre, S.L., Marcotte, T.D., Ellis, R.J., McCutchan, J.A., Grant, I., … HNRC Group (2002). Severe, demyelinating leukoencephalopathy in AIDS patients on antiretroviral therapy. *AIDS*, *16*(7), 1019–1029

Logan, G.D., & Cowan, W.B. (1984). On the ability to inhibit thought and action: A theory of an act of control. *Psychological Review*, *91*(3), 295–327. http://doi.org/10.1037/0033-295X.91.3.295

Logan, G.D., Cowan, W.B., & Davis, K.A. (1984). On the ability to inhibit simple and choice reaction time responses: A model and a method. *Journal of Experimental Psychology: Human Perception and Performance*, *10*(2), 276–291. http://doi.org/10.1037/0096-1523.10.2.276

Meade, C.S., Lowen, S.B., MacLean, R.R., Key, M.D., & Lukas, S.E. (2011). fMRI brain activation during a delay discounting task in HIV-positive adults with and without cocaine dependence. *Psychiatry Research: Neuroimaging*, *192*(3), 167–175. http://doi.org/10.1016/j.pscychresns.2010.12.011

Melrose, R.J., Tinaz, S., Castelo, J.M.B., Courtney, M.G., & Stern, C.E. (2008). Compromised fronto-striatal functioning in HIV: An fMRI investigation of semantic event sequencing. *Behavioural Brain Research*, *188*(2), 337–347. http://doi.org/10.1016/j.bbr.2007.11.021

Miller, E.N., Satz, P., & Visscher, B. (1991). Computerized and conventional neuropsychological assessment of HIV-1-infected homosexual men. *Neurology*, *41*(10), 1608–1616

Mink, J.W. (1996). The basal ganglia: Focused selection and inhibition of competing motor programs. *Progress in Neurobiology*, *50*(4), 381–425

Navia, B.A., Jordan, B.D., & Price, R.W. (1986). The AIDS dementia complex: I. Clinical features. *Annals of Neurology*, *19*(6), 517–524. http://doi.org/10.1002/ana.410190602

Oldfield, R.C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113

Ortega, M., Brier, M.R., & Ances, B.M. (2015). Effects of HIV and combination antiretroviral therapy on cortico-striatal functional connectivity. *AIDS*, *29*(6), 703–712. http://doi.org/10.1097/QAD.0000000000000611

Paul, R., Flanigan, T., Tashima, K., Cohen, R., Lawrence, J., Alt, E., … Hinkin, C. (2005). Apathy correlates with cognitive function but not CD4 status in patients with human immunodeficiency virus. *Journal of Neuropsychiatry and Clinical Neurosciences*, *17*(1), 114

Pence, B.W., Gaynes, B.N., Whetten, K., Eron, J.J., Ryder, R.W., & Miller, W.C. (2005). Validation of a brief screening instrument for substance abuse and mental illness in HIV-positive patients. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *40*(4), 434–444

Plessis, du, S., Vink, M., Joska, J.A., Koutsilieri, E., Bagadia, A., Stein, D.J., & Emsley, R. (2015). HIV infection results in ventral-striatal reward system hypo-activation during cue processing. *AIDS*, *29*(11), 1335–1343. http://doi.org/10.1097/QAD.0000000000000680

Plessis, du, S., Vink, M., Joska, J.A., Koutsilieri, E., Stein, D.J., & Emsley, R. (2014). HIV infection and the fronto-striatal system: A systematic review and meta-analysis of fMRI studies. *AIDS*, *28*, 803–811. http://doi.org/10.1097/QAD.0000000000000151

Reda, A.A., & Biadgilign, S. (2012). Determinants of adherence to antiretroviral therapy among HIV-infected patients in Africa. *AIDS Research and Treatment*, *2012*(4), 1–8. http://doi.org/10.1155/2012/574656

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G.C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59*(Suppl 20), 22–33; quiz 34–57

Stöcker, T., Schneider, F., Klein, M., Habel, U., Kellermann, T., Zilles, K., … Shah, N.J. (2005). Automated quality assurance routines for fMRI data applied to a multicenter study. *Human Brain Mapping*, *25*(2), 237–246. http://doi.org/10.1002/hbm.20096

Thomas, J.B., Brier, M.R., Snyder, A.Z., Vaida, F.F., & Ances, B.M. (2013). Pathways to neurodegeneration: Effects of HIV and aging on resting-state functional connectivity. *Neurology*, *80*(13), 1186–1193. http://doi.org/10.1212/WNL.0b013e318288792b

UNAIDS (2012). *UNAIDS report on the global AIDS epidemic* (pp. 1–106). Geneva: Joint United Nations Program on HIV/AIDS (UNAIDS)

van der Kouwe, A.J.W., Benner, T., Salat, D.H., & Fischl, B. (2008). Brain morphometry with multiecho MPRAGE. *Neuroimage*, *40*(2), 559–569. http://doi.org/10.1016/j.neuroimage.2007.12.025

Van Dijk, K.R.A., Sabuncu, M.R., & Buckner, R.L. (2012). The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage*, *59*(1), 431–438. http://doi.org/10.1016/j.neuroimage.2011.07.044

Vink, M., Kahn, R.S., Raemaekers, M., van den Heuvel, M., Boersma, M., & Ramsey, N.F. (2005). Function of striatum beyond inhibition and execution of motor responses. *Human Brain Mapping*, *25*(3), 336–344. http://doi.org/10.1002/hbm.20111

Vink, M., Zandbelt, B.B., Gladwin, T., Hillegers, M., Hoogendam, J.M., van den Wildenberg, W.P.M., … Kahn, R.S. (2014). Frontostriatal activity and connectivity increase during proactive inhibition across adolescence and early adulthood. *Human Brain Mapping*, *35*(9), 4415–4427. http://doi.org/10.1002/hbm.22483

Wiley, C.A., Soontornniyomkij, V., Radhakrishnan, L., Masliah, E., Mellors, J., Hermann, S.A., … Achim, C.L. (1998). Distribution of brain HIV load in AIDS. *Brain Pathology*, *8*(2), 277–284

Zandbelt, B.B., & Vink, M. (2010). On the role of the striatum in response inhibition. *PLoS One*, *5*(11), e13848. http://doi.org/10.1371/journal.pone.0013848

Zandbelt, B.B., van Buuren, M., Kahn, R.S., & Vink, M. (2011). Reduced proactive inhibition in schizophrenia is related to corticostriatal dysfunction and poor working memory. *Biological Psychiatry*, *70*, 1151–1158