

# Prefrontal cortical thinning in HIV infection is associated with impaired striatal functioning

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**Abstract** While cortical thinning has been associated with HIV infection, it is unclear whether this reflects a direct effect of the virus, whether it is related to disruption of subcortical function or whether it is better explained by epiphenomena, such as drug abuse or comorbid medical conditions. The present study investigated the relationship between cortical thickness and subcortical function in HIV+ patients. Specifically, we examined the relationship between prefrontal cortical thickness and striatal function. Twenty-three largely treatment naïve, non-substance abusing HIV+ participants and 19 healthy controls matched for age, gender, and educational status were included. Cortical morphometry was performed using FreeSurfer

software analysis. Striatal function was measured during an fMRI stop-signal anticipation task known to engage the striatum. Any cortical regions showing significant thinning were entered as dependent variables into a single linear regression model which included subcortical function, age, CD4 count, and a measure of global cognitive performance as independent predictors. The only cortical region that was significantly reduced after correction for multiple comparisons was the right superior frontal gyrus. Striatal activity was found to independently predict superior frontal gyral cortical thickness. While cortical thinning in HIV infection is likely multifactorial, viral induced subcortical dysfunction appears to play a role.

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## Introduction

HIV infection produces a typical fronto-subcortical pattern of neuropsychiatric impairment, (Navia et al. 1986), characterized by specific motor (Hardy and Hinhn 2002), cognitive (Antinori et al. 2007), and behavioral symptoms (Castellon et al. 1998). Despite the widespread availability of combination antiretroviral therapy (cART), HIV infection continues to have a negative impact on cognitive function in up to 52 % of infected individuals (Heaton et al. 2010). HIV is thought to enter the brain via infected monocytes in the early stage of illness (An et al. 1999) and to concentrate primarily in subcortical regions, such as the striatum (Wiley et al. 1998). Here, it is thought to cause synapto-dendritic damage (Moore et al. 2006)/apoptosis either by the induction of neuroinflammation (Desplats et al. 2013) or due to direct toxic effects of viral proteins,

such as tat (Bruce-Keller et al. 2003) and GP120 proteins (Agrawal et al. 2010).

Neuroimaging studies consistently report generalized cortical volume loss in patients with HIV infection (Elovaara et al. 1990; Chang et al. 2011; Pfefferbaum et al. 2012). Additionally, in keeping with the clinical features of subcortical dementia, imaging studies have reported loss of gray matter in the basal ganglia (Elovaara et al. 1990; Aylward et al. 1993; Ances et al. 2012), and subcortical volume reductions have been found even in patients receiving cART treatment (Ances et al. 2012). These volume reductions have been related to viral load (Dewey et al. 2010) as well as the AIDS dementia complex stage (Aylward et al. 1993). It is surprising, therefore, that other studies have not found striatal atrophy in HIV+ patients (Melrose et al. 2008; Heaps et al. 2010). This is all the more unexpected given that frontal striatal dysfunction was consistently found in HIV patients in a recent meta-analysis of working memory studies (Ernst et al. 2002) as well as in studies of episodic memory (Maki et al. 2009) and delay discounting paradigms (Meade et al. 2011). Striatal dysfunction has also been shown to be specifically affected in a simple motor paradigm (Ances et al. 2011), reward processing (du Plessis et al. 2015a) as well as with an inhibition task (du Plessis et al. 2015b). Furthermore, a fMRI study in HIV patients has demonstrated reduced functional connectivity between subcortical and cortical regions, in the presence of normal striatal volumes (Melrose et al. 2008). Thus, the exact relationship between structural and functional changes observed in HIV remains to be determined. Taken together, these findings suggest that it may be that structural and functional imaging techniques are sensitive to different aspects of HIV-related neuropathology.

There are several possible explanations for the cortical thinning reported in HIV infection. First, it could be a direct consequence of viral infection in cortical structures. Second, indirect viral mediated immune processes may be involved (Thompson et al. 2005). Third, epiphenomena such as substance abuse (Jernigan et al. 2005) and age (Ances et al. 2012) should be considered. Finally, cortical thickness reductions could be secondary to the observed subcortical dysfunction in these patients. To understand how subcortical pathology could influence cortical morphology (Draganski et al. 2008), the functional relationship of these two systems needs to be considered. Current thinking is that the cortex and basal ganglia are connected in parallel, as functionally segregated circuits (Alexander and Crutcher 1990). This is based on anatomical (Middleton and Strick 2002), functional connectivity (Zandbelt and Vink 2010) and probabilistic tracking studies (Draganski et al. 2008). Being functionally connected in this manner, it is reasonable to propose that subcortical dysfunction caused by direct viral infection could

result in reductions in cortical thickness in areas that are functionally connected.

In the present study, we investigated the relationship between cortical thickness and subcortical function in HIV+ patients compared to healthy controls. Specifically, we examined the relationship between prefrontal cortical thickness and striatal function, since HIV has been shown to affect the frontostriatal system specifically (du Plessis et al. 2013). We predicted that the striatal hypofunction we have shown in a group of HIV+ participants in a previously published analysis would be related to frontal atrophy in the same group. For the fMRI, we selected an inhibition task that we previously used to demonstrate that the striatum, particularly the putamen, is hypoactive in HIV+ participants (i.e., during successful versus unsuccessful STOPs), whereas frontal functioning was not affected during proactive inhibition (du Plessis et al. 2015b). The morphometric measures for the new analysis in the same cohort, were obtained using the standard Desikan–Killiany Atlas in FreeSurfer to generate regions of interest (Desikan et al. 2006).

These include a number of bilateral prefrontal regions. In particular, activity in the right inferior and superior frontal gyrus is normally functionally coupled with activity in the left putamen (Zandbelt and Vink 2010) during the correct versus incorrect STOPs BOLD contrast.

## Methods and materials

### Participants

The study was approved by the Health Research Ethics Committee (HREC) of Stellenbosch University and the Human Research Ethics Committee of the University of Cape Town, Cape Town, South Africa. Prior to 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. A total of 23 HIV+ participants were included in the study together with 19 gender, education, and ethnicity matched healthy controls. The controls were HIV negative, as confirmed by the enzyme-linked immunosorbent assay (ELISA).

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 physical examination 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 according to the Kreek–McHugh–Schluger–Kellogg (KMSK) scale (Kellogg et al. 2003); current active 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 one 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 composite global deficit score (GDS) 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 two weeks of neuroimaging: CD<sub>4</sub> count, HIV viral load, rapid plasma reagin for syphilis (RPR), and thyroid stimulating hormone (TSH) level. Urinary drug screen was performed on all participants prior to undergoing the MRI assessments. 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.

### Image acquisition

All scans were acquired on a 3T Siemens Allegra at the Combined Universities Brain Imaging Centre (CUBIC). For the study of brain morphology, a T1 ME-MPRAGE-weighted structural scan was acquired (TR = 2530 ms; TE<sub>1</sub> = 1.53 ms TE<sub>2</sub> = 3.21 ms, TE<sub>3</sub> = 4.89 ms, TE<sub>4</sub> = 6.57 ms, flip-angle: 7°, FOV: 256 mm, 128 slices, 1 mm isotropic voxel size) (van der Kouwe et al. 2008).

### Structural imaging analysis

#### *Preprocessing of structural scans*

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>). As FreeSurfer is computationally intensive, reconstructions were performed utilizing custom batching scripts, on the Centre for High Performance Computing (CHPC) Rosebank, Cape Town, Sun Intel Nehalem cluster (<http://www.chpc.ac.za/>).

Scans were processed and analyzed using FreeSurfer stable release version 5.1. The technical details of these procedures are described in prior publications (Dale et al.

1999). Briefly, slices were resampled to a three-dimensional image with 1-mm isotropic voxels. Non-uniform intensity normalization was then performed, and images were registered to the Montreal Neurological Institute (MNI) space. A second normalization step was performed with a different algorithm in which control points were automatically identified and normalized to a standard intensity value. This was followed by an automated skull strip procedure. Gross brain anatomy was then delineated into cortical and subcortical labels. All scans were visually checked for errors in Talaraich transformation, skull stripping as well as segmentation and corrected if possible.

#### *Structural regions of interest analysis*

Initially we compared whole brain cortical volumes as well as subcortical volumes, corrected for total intracranial volume (Buckner et al. 2004) between groups to ascertain the general impact of HIV on brain volume in our sample. Then, we subdivided the frontal lobes into regions using standard FreeSurfer regions of interest (Desikan et al. 2006) for their cortical thickness measures. We specifically selected the frontal lobe regions as they are functionally connected to both right and left putamen activation during successful inhibition (Zandbelt and Vink 2010). Apart from playing an important role in executive functions, such as response inhibition (Zandbelt and Vink 2010) and working memory [i.e., rostral middle frontal gyrus (Kikinis et al. 2010)], these regions also play an important role in functions associated with motivational control, such as reward processing [i.e., rostral anterior cingulate, lateral orbitofrontal gyrus, medial orbitofrontal gyrus (Hoogendam et al. 2013)]. The following frontal regions were included: bilateral rostral anterior cingulate thickness, medial orbitofrontal thickness, pars opercularis thickness, superior frontal thickness, lateral orbitofrontal thickness, and rostral middle frontal thickness. To limit the number of comparisons, we restricted our a priori analysis to these regions. The regions were compared between groups using a two sample *t* test. All statistical tests were corrected for multiple comparisons using the Bonferroni method.

### Stop-signal anticipation fMRI task

During the fMRI experiment, participants performed the STOP-signal anticipation task (Zandbelt and Vink 2010). Not all participants recruited in the present study could be included in a combined functional and structural analysis due to poor structural and/or poor fMRI data quality (see “Demographics” section). The present set of patients, therefore, represent a new subsample of data previously reported on (du Plessis et al. 2015b).

## Functional imaging analysis

### *Image preprocessing*

Image data were modeled using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). Preprocessing and first-level statistical analyses were performed as previously described (Zandbelt and Vink 2010). In brief, preprocessing involved correction for slice timing differences, realignment to correct for head motion, spatial normalization to the Montreal Neurological Institute template brain, and spatial smoothing to accommodate inter-individual differences in functional and gyral anatomy during inter-subject averaging. Head motion parameters were analyzed to ensure that the maximum motion did not exceed a pre-defined threshold (scan-to-scan >3 mm) (Van Dijk et al. 2012).

### *Individual fMRI analyses*

The fMRI data were modeled voxel-wise, using a general linear model, in which successful STOP-signal trials and failed STOP-signal trials events were included as regressors. The fMRI data were high-pass filtered (cutoff 128 s) to remove low-frequency drifts. For each participant, we computed a contrast image of activation during successful STOP-signal trials versus failed STOP-signal trials.

### *Regions of interest analyses*

As previously described (du Plessis et al. 2015b), group activation differences in the left and right putamen were determined by a region-of-interest analysis in predefined a priori regions, defined by a previous experiment (Zandbelt and 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  $p < 0.001$ , cluster probability of  $p < 0.05$ , family-wise error corrected for multiple comparisons). For each participant, the mean activation level (expressed as percent signal change) during the contrasts of interest specific to successful STOP-signal trials versus failed STOP-signal trials was calculated over all the voxels of each ROI.

### *Regression analysis*

Brain regions showing significant cortical thinning were entered into a linear regression model as the dependant variable. Contralateral left putamen activation during successful versus unsuccessful stops was entered as a predictor as it has been previously shown to be primarily associated with right superior frontal lobe activity during inhibition

(Zandbelt and Vink 2010). Age, CD4 count, and GDS scores were also included in the model, as they are known to affect cortical thickness (Thompson et al. 2005; Schnack et al. 2015). We did not include subcortical volume measures, as there were no differences between patients and controls. Viral load was also not included, as there were two missing data points. Finally, we did not compare cortical activation with cortical thickness as we found no differences in cortical function between HIV+ participants and controls in our previously reported fMRI results in this cohort (du Plessis et al. 2015b).

### *Post hoc exploratory correlation analysis*

Lastly, we wished to clarify whether the relationship between striatal activation and frontal cortical thinning was specific to these regions or whether it represents part of a more general association between frontal cortical structure and subcortical function. To this end, we performed an uncorrected correlation analyses between all of the FreeSurfer regions known to be related to response inhibition.

## Results

### Demographics

Twenty-five HIV+ participants and 19 matching controls were initially included in the study. Two HIV+ participants and one control were excluded from the structural analysis due to poor scan quality. Thus, 23 HIV+ participants and 18 healthy controls were included in the final structural analysis (see Table 1). A further six HIV+ participants were excluded from the regression analysis for the following reasons: Tested positive for benzodiazepines ( $n = 1$ ); uncertainty regarding general medical condition ( $n = 1$ ); technical problems with the response box ( $n = 2$ ); poor scan quality on their functional scans ( $n = 1$ ); and missing data ( $n = 1$ ).

The groups did not differ with regards to age, gender, educational level or final GDS score (see Table 1). All subjects were from a similar socioeconomic background. All of the HIV+ participants were ambulant and healthy enough to participate in the fMRI task. No intracranial pathology was found on inspection of the MRI scans.

### Imaging results

#### *Structural regions of interest analysis*

Compared to healthy volunteers, the HIV+ participants showed a smaller total cortical volumes [ $t(39) = 3.14$ ,  $p = 0.003$ ], suggestive of general cortical atrophy. However, no differences were found in subcortical volumes

**Table 1** Demographic characteristics of the diagnostics groups

	HIV ( <i>N</i> = 23)	HC ( <i>N</i> = 18)	Test statistic	<i>P</i> *
Gender (M/F)	4/19	3/15	$\chi^2 = 0.004$	1.000
Age (years)	31 (27–34)	30 (22–32)	$U = 127$	0.14
Education (years)	11 (10–12)	12 (11–12)	$U = 179.5$	1.000
Viral load (copies/ml)	42,364 ± 55,376			
CD <sub>4</sub> (cells/μl)	401 ± 207			
Participants with AIDS defining CD <sub>4</sub> count	9			
GDS (Summary Score)	0.15 (0.05–0.3)	0.133 (0–0.36)	$U = 160$	1.000
On cART	2			

Age, viral load, and CD<sub>4</sub> data represent mean ± SD. Education and GDS data represent median and interquartile range between 25th and 75th centiles

*F* female, *M* male, *GDS* Global Deficit Score (22), *HC* healthy controls, *HIV* HIV+ participants, *AIDS* CD<sub>4</sub> count of 350 cells/μl used, *cART* combined antiretroviral therapy

\* *P* values are adjusted for multiple comparisons using the Bonferroni method

between the groups [ $t(39) = 1.14$ ,  $p = 0.26$ ]. Specifically, we found no differences in right [ $t(39) = 0.453$ ,  $p = 0.653$ ] or left [ $t(39) = 0.381$ ,  $p = 0.705$ ] putamen volumes.

For the cortical thickness measures, the only region of interest to be significantly reduced compared with healthy controls after Bonferroni correction was the right superior frontal gyrus [ $t(39) = 3.15$ ,  $p = 0.003$ ]. At an uncorrected threshold of  $p = 0.05$ , we found reduced cortical thickness in patients in the right medial orbitofrontal gyrus [ $t(39) = 2.56$ ,  $p = 0.01$ ], left pars opercularis [ $t(39) = 2.07$ ,  $p = 0.05$ ], left [ $t(39) = 1.98$ ,  $p = 0.05$ ] superior frontal gyrus as well as left [ $t(39) = 2.62$ ,  $p = 0.01$ ] rostral and right [ $t(39) = 2.05$ ,  $p = 0.05$ ] middle frontal gyrus. This suggests a trend to overall frontal cortical thickness reductions in HIV (see Table 2).

### Functional regions of interest analysis

#### Successful inhibition

We found hypo-activation in the left [ $t(32) = 2.279$ ,  $p = 0.029$ ] as well as the right [ $t(32) = 2.233$ ,  $p = 0.033$ ] putamen in this particular subsample confirming our results from our previous analysis in the larger cohort (du Plessis et al. 2015b).

#### Regression analysis

Reduced right superior frontal gyral thickness in the HIV+ group was predicted by a decrease in left putamen BOLD activity ( $\beta = 0.381$ ,  $p = 0.033$ ), as well as by lower GDS score ( $\beta = -0.531$ ,  $p = 0.003$ ), more advanced age ( $\beta = -0.381$ ,  $p = 0.030$ ), and lower CD4 count ( $\beta = 0.543$ ,  $p = 0.004$ ). Together, these predictors accounted for 76.5 % of the total variance [ $R^2 = 0.765$ ,  $R^2_{\text{adjusted}} = 0.687$ ,  $F(4,12) = 9.763$ ,  $p = 0.001$ ] (Fig. 1).

To determine whether striatal activation was related to cortical thickness in the other frontal regions that did not show significant thinning, we also sought correlations between putamen activation and these other regions of interest. We did not correct for multiple comparisons in this additional exploratory analysis. Significant positive correlations were found between task-related putamen BOLD activity during inhibition and cortical thickness in 9 out of our 12 frontal lobe regions of interest for the left and 3 out of 12 for the right putamen (see Table 3).

### Discussion

In this study, we investigated the relationship between prefrontal cortical thickness and striatal function in 23 HIV+ participants and 18 matched healthy controls. To the best of our knowledge, this is the first study to explore the relationship between subcortical function and cortical thickness in HIV infection. Our main finding was that decreased striatal activity was associated with reduced prefrontal cortical thickness in a region that is involved in inhibition, i.e., the superior frontal gyrus. Rather than being an isolated association with the superior frontal gyrus, our uncorrected post hoc analyses suggest that this was part of a general trend toward reduced cortical thickness being related to decreased striatal function. While we cannot infer causality from our findings, one possible explanation is that the frontal cortical thinning is a consequence of viral induced striatal hypofunction. This would be consistent with neuropathological evidence suggesting that HIV concentrates primarily in subcortical regions, such as the striatum (Wiley et al. 1998), and would also explain the typical pre-treatment clinical presentation of a subcortical dementia (Navia et al. 1986). However, an alternative explanation that should be kept in mind is that cortical

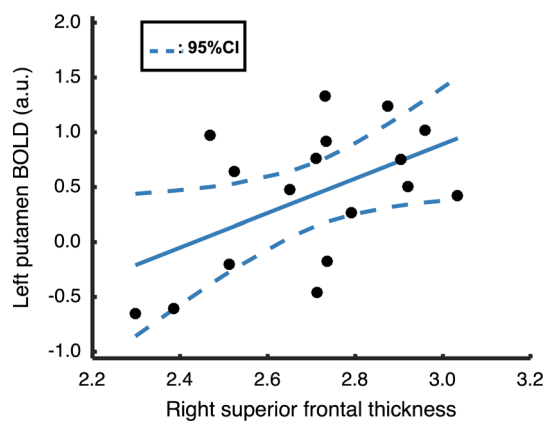


**Table 2** Group differences comparing total gray matter volume, subcortical volume, and region of interest cortical thickness

FreeSurfer region of interest	HIV	Controls	Std. error difference	<i>P</i>
Subcortical gray matter volume (mm <sup>3</sup> )	1185.34	1228.38	37.89	0.26
Total gray matter volume (mm <sup>3</sup> )	4060.03	4345.17	90.88	0.003**
Total intra-cranial volume (mm <sup>3</sup> )	1,387,129.69	1,357,170.04	40,345.38	0.46
Left rostral anterior cingulate thickness (mm)	2.74	2.85	0.10	0.32
Right rostral anterior cingulate thickness (mm)	2.56	2.63	0.07	0.34
Left medial orbitofrontal thickness (mm)	2.51	2.53	0.08	0.81
Right medial orbitofrontal thickness (mm)	2.34	2.49	0.06	0.01**
Left pars opercularis thickness (mm)	2.46	2.60	0.07	0.04*
Right pars opercularis thickness (mm)	2.55	2.68	0.07	0.09
Left superior frontal thickness (mm)	2.77	2.90	0.07	0.05*
Right superior frontal thickness (mm)	2.69	2.87	0.06	0.003**
Left lateral orbitofrontal thickness (mm)	2.59	2.70	0.07	0.13
Right lateral orbitofrontal thickness (mm)	2.54	2.54	0.07	0.98
Left rostral middle frontal thickness (mm)	2.23	2.36	0.05	0.01**
Right rostral middle frontal thickness (mm)	2.25	2.35	0.05	0.05*

\*\* Significant at the 0.01 level

\* Significant at the 0.05 level



**Fig. 1** Scatterplot showing a significant linear relationship between subcortical function loss and right superior frontal cortical thinning in HIV+ participants. *CI* confidence interval

thinning is a consequence of a more global insult of HIV on the brain, and that striatal hypofunction is secondary to this process. Our study confirms previous findings that a decreased CD4 count is associated with reductions in cortical thickness (Stout et al. 1998; Thompson et al. 2005). Also, as with previous functional imaging (Ances et al. 2010), we were able to show that our findings were independent of age-related changes. However, as our sample is relatively young, future work in older populations should further investigate the effects of age on brain function and morphology in HIV infection. Taken together, our results suggest that cortical thinning in HIV infection is likely multifactorial, and that in addition to factors such as

immune status, age, and substance abuse, striatal dysfunction may be an important factor to consider.

Our finding of generalized cortical volume reduction in HIV-infected individuals confirms previous studies (Elovaara et al. 1990; Aylward et al. 1993; Thompson et al. 2005; Ances et al. 2010; Dewey et al. 2010). On the other hand, our failure to find evidence of subcortical volume reduction is not consistent with earlier studies reporting subcortical atrophy in HIV (Elovaara et al. 1990; Aylward et al. 1993; Dewey et al. 2010; Ances et al. 2012). However, our results are similar to more recent studies reporting no striatal volume loss (Melrose et al. 2008; Heaps et al. 2012). At face value, these results seem to contradict the long held classification of HIV as primarily a fronto-subcortical neurodegenerative process (Navia et al. 1986). One possible explanation is that the more recent studies included patients identified at an earlier stage of illness. Also, volume reductions due to neuronal damage could possibly be masked by active glial proliferation in these regions, as the striatum is thought to be a site of active viral replication (Wiley et al. 1998).

Our study is limited by a small sample size, which limits our ability to detect more subtle relationships between HIV-induced striatal function and brain morphology. Also, we only used one functional paradigm, therefore limiting our ability to determine whether functional loss in other cortico-striatal circuits is also related to changes in brain morphology. As our sample included participants who were relatively cognitively intact, we could not effectively investigate the potential interaction between cognitive

**Table 3** Correlations between regions of interest and subcortical BOLD activity during reactive inhibition

	Right putamen BOLD	<i>P</i>	Left putamen BOLD	<i>P</i>
Left rostral anterior cingulate thickness	0.398	0.102	0.599 <sup>a</sup>	0.009
Right rostral anterior cingulate thickness	−0.064	0.800	−0.023	0.929
Left medial orbitofrontal thickness	0.045	0.860	0.355	0.148
Right medial orbitofrontal thickness	0.377	0.123	0.583 <sup>b</sup>	0.011
Left pars opercularis thickness	0.490 <sup>b</sup>	0.039	0.541 <sup>b</sup>	0.020
Right pars opercularis thickness	0.295	0.234	0.469 <sup>b</sup>	0.050
Left superior frontal thickness	0.334	0.176	0.523 <sup>b</sup>	0.026
Right superior frontal thickness	0.321	0.194	0.527 <sup>b</sup>	0.024
Left lateral orbitofrontal thickness	0.411	0.090	0.641 <sup>a</sup>	0.004
Right lateral orbitofrontal thickness	0.517 <sup>b</sup>	0.028	0.717 <sup>a</sup>	0.001
Left rostral middle frontal thickness	0.492 <sup>b</sup>	0.038	0.579 <sup>b</sup>	0.012
Right rostral middle frontal thickness	0.306	0.216	0.462	0.054

<sup>a</sup> Correlation is significant at the 0.01 level (two-tailed)

<sup>b</sup> Correlation is significant at the 0.05 level (two-tailed)

impairment, subcortical dysfunction, and cortical atrophy. We did, however, find that, when controlling for cognitive performance, the significant relationship between subcortical dysfunction and frontal cortical thickness persisted. Our sample was carefully selected to control for recognized confounding variables. Although representative of the local clinic-going population, we excluded factors such as severe comorbid depression, the elderly, and a history of substance use/abuse. Although this resulted in a relatively homogenous sample, it also limits the generalizability of our findings. Further studies should investigate the role of such comorbidities.

In conclusion, we have shown that striatal function is related to frontal cortical thickness in HIV infection, even in the presence of normal striatal volumes. This effect was found to be independent of factors such as age, cognitive impairment, and CD4 count.

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#### Compliance with ethical standards

**Conflict of interest** The authors have no conflicts of interest to declare.

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