Donders Graduate School for Cognitive Neuroscience

Master of Science Programme

MSc Thesis

The effect of HIV infection on frontostriatal inhibitory control in the era of combined antiretroviral therapy

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Abstract

Studies on brain activity and connectivity in Human Immunodeficiency Virus (HIV) suggest that frontostriatal dysfunction plays a role in HIV-associated cognitive deficits. However, almost no research has been done to investigate frontostriatal functioning in a HIV population that is virally suppressed with combined antiretroviral therapy (cART). In this study, 27 HIV-positive participants, stable on cART and with an undetectable viral load, performed a stop signal anticipation task (SSAT) while being scanned with functional MRI (fMRI). This task activates the striatum during reactive inhibition (i.e. outright stopping of a response) and engages the frontostriatal network during proactive inhibition (i.e. anticipation of stopping). Results showed normal striatal activity in HIV+ participants during both reactive and proactive inhibition. During proactive inhibition, HIV+ participants showed less reaction time slowing during anticipation of a stop signal. This was paralleled in the brain by decreased dynamic activation in the right inferior frontal gyrus (IFG) with increased stop-signal probability, as well as decreased functional connectivity between the right striatum and the right IFG. These results suggest normal striatal functioning in a virally suppressed HIV population, but dysfunctional frontal activity and decreased frontostriatal connectivity. These findings serve as a stepping stone to research that distinguishes between the effects of HIV-infection and cART on frontostriatal functioning.

Keywords: HIV, response inhibition, fMRI, striatum, inferior frontal gyrus, cART

Introduction

Human Immunodeficiency Virus (HIV) affects the brain in an early stage of infection. With the introduction of combined antiretroviral therapy (cART) the life expectancy of people living with HIV is now close to that of the general population (Samji et al., 2013). However, neuroinflammation and mild forms of HIV associated neurocognitive disorder remain common (Chang, Holt, Yakupov, Jiang, & Ernst, 2013). Previous functional MRI (fMRI) studies have shown that a dysfunctional frontostriatal brain network may contribute to cognitive deficits in HIV. For example, studies report increased frontal activity during a working memory task (Chang et al., 2001), decreased activation in the caudate and prefrontal cortex during semantic event sequencing (Melrose, Tinaz, Boer Castelo, Courtney, & Stern, 2008), decreased striatal activity during reward processing (Du Plessis et al., 2014) and decreased resting-state connectivity of the frontostriatal network (Ortega, Brier, & Ances, 2015).

It remains unclear to what extent antiretroviral medication contributes to dysfunction in the frontostriatal network. In the past it has been suggested that cART has a neurotoxic effect and can cause impaired functioning of the frontal cortex (Chang, Yakupov, Nakama, Stokes, & Ernst, 2008). However, more recent studies suggest that this dysfunction is caused by the virus, indicating a beneficial effect of medication instead of a harmful one. Furthermore, these studies suggest that frontal areas benefit from medication, but not as much as striatal areas (Brier et al., 2015; Ortega, Brier, & Ances, 2015). Postmortem studies show that HIV is predominantly found in the striatum, which might explain why viral suppression is more effective here than in the frontal cortex (Wiley et al., 1998).

A key function of the frontostriatal network is response inhibition; the ability to suppress prepotent responses or impulses. Response inhibition involves activation of the striatum during

outright stopping of a response (i.e. reactive inhibition) and activation of the striatum and the inferior frontal gyrus (IFG) during anticipation of stopping a response (i.e. proactive inhibition). To date, research on inhibition in HIV individuals has found decreased striatal activity and normal cortical activation during inhibition (Du Plessis et al., 2015). This South-African study investigated a medication naïve HIV population consisting of mostly women in their early thirties. These findings on frontostriatal functioning during inhibition in HIV-infection may not be representative for the European and North-American HIV-infected population. This population consists of mostly men who take cART and are on average older than study populations from Africa (Samji et al., 2013). Replication of previously conducted research (Du Plessis et al., 2015) in a Western population may therefore lead to different outcomes. Moreover, little research has been conducted with regard to functional connectivity of the frontostriatal network in HIV-infection. This information is relevant in order to find out how HIV-infection influences frontostriatal communication.

Here, we investigate the impact of HIV-infection on frontostriatal functioning. To this aim, we have obtained fMRI data from 27 HIV-positive subjects. Participants performed a stop signal anticipation task (SSAT; Zandbelt & Vink, 2010) that measures both reactive and proactive inhibition. During this task, participants had to give timed responses in reaction to a GO-signal with occasional STOP-signals occurring at fixed probabilities, indicating that response had to be inhibited. By investigating predefined regions of interest (ROIs; obtained from Zandbelt & Vink, 2010) in the frontostriatal network (i.e. the right striatum and the right IFG), we aimed to investigate activity and connectivity in this network in HIV-infection.

Hypotheses

Basic task execution

First, we investigate basic response execution by examining primary motor cortex activation and reaction times on GO-signals in a context in which there are no STOP-signals. We hypothesize that HIV-infection does not have an effect on motor cortex activation and that reaction times are increased, as this was also found in previous research in HIV individuals using the same task (Du Plessis et al., 2015).

Reactive inhibition

Second, we hypothesize that HIV-infection does not have an effect on striatal activity during reactive inhibition as a result of viral suppression with medication (Brier et al., 2015), because reactive inhibition is for an important part achieved by motor cortex suppression through striatal activation. As a result, we hypothesize that HIV-infection does not have an effect on reaction time during reactive inhibition, as measured with stop signal reaction time (SSRT).

Proactive inhibition

Third, we hypothesize that HIV has no effect on striatal activity during proactive inhibition, also as a result of viral suppression of the striatum with medication (Brier et al., 2015). We hypothesize that if cART is less effective in cortical regions (Ortega, Brier & Ances, 2015), such as the inferior frontal gyrus (IFG), then we expect to find less activity in the IFG during proactive inhibition. We hypothesize that this will result in less reaction time slowing during anticipation of a stop signal. Furthermore, we expect that this is paralleled by decreased

connectivity between the striatum and the IFG, as this is the main network involved in proactive inhibition (Zandbelt & Vink, 2010).

Methods

Participants

27 right-handed men between the age of 25 and 50 with a HIV positive status were included in the study (HIV+ group). All participants were stable on cART. Participants were recruited from the infectious diseases outpatient department at the University Medical Center Utrecht (UMCU). They were informed about the study during a regular check-up. Before participating, all participants gave their informed consent. A blood sample was taken from each participant to determine viral load and number of CD4 immune cells (see Table 1). These parameters are used to indicate disease severity in HIV. All participants had an undetectable viral load, meaning that there were less than 50 copies of the virus per milliliter blood sample (copies/ml), and a CD4 count above the AIDS defining count of 200 cells/ml. We used control data from other research conducted at the UMCU, resulting in a selection of 32 suitable right-handed healthy men between the age of 25 and 57 (HIV- group).

Main exclusion criteria for participation in this study were: (a) major depression in the past year and/or use of antidepressant drugs, (b) opportunistic infection in the central nervous system now or in the past, (c) acute or chronic hepatitis C infection now or in the past 12 months, (d) history of neurologic disease, (e) active psychiatric disorder, (f) history of alcohol or drug abuse according to the DSM-V.

Stop Signal Anticipation Task

The task performed by the participants in the MR scanner was a Stop-Signal Anticipation Task (SSAT; Zandbelt & Vink, 2010) displayed in Figure 1. Three horizontal lines were displayed on the screen. The task consisted of two trial types: GO-trials and STOP-trials. The goal was to stop a moving vertical bar as close to the middle line as possible (GO-trial). The bar was stopped with a button response of the right thumb. The vertical bar would reach the middle line at 800 ms. During a STOP-trial the bar would stop moving before reaching this line (i.e. the stop signal). In that case, participants were instructed to refrain from pushing the button. The color of the middle line indicated the chance that the vertical bar would stop moving. There were five stop-signal probabilities: 0% (green), 17% (yellow), 20% (amber), 25% (orange) and 33% (red). Initially, the stop-signal was set at 550 ms after the start of the trial, but was adjusted according to performance. When the participant was not able to successfully inhibit a response, trial difficulty was decreased by increasing the stop-signal onset time with steps of 25 ms. Conversely, when a participant successfully refrained from responding to a stop-signal the delay between the start and the stop-signal was decreased with 25 ms. This was to ensure an equal amount of successful and unsuccessful STOP-trials. In total there were 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%,

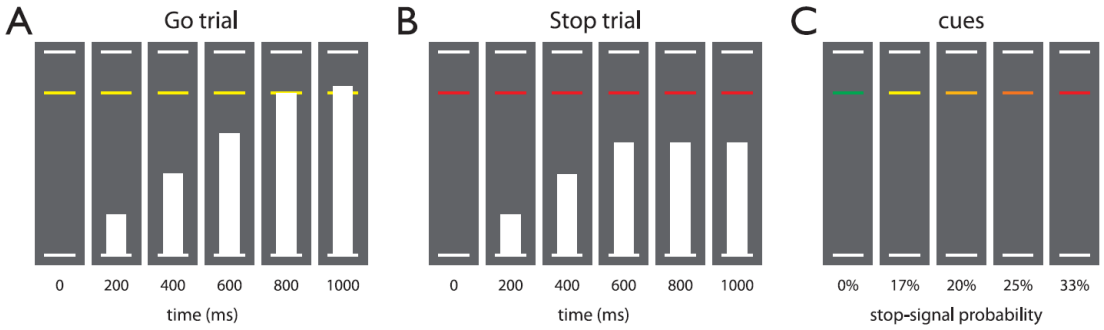

Figure 1. The Stop Signal Anticipation Task. The task consisted of GO-trials (A) and STOP-trials (B). The color of the middle horizontal line gave an indication of the stop-signal probability (C).

n=12; 25%, *n*=18; 33%, *n*=24), presented in a single run in pseudorandom order. Participants practiced the task before the MRI session to ensure that they understood the task.

The task instruction in the HIV+ group alternated between 'stopping the bar as close to the middle line as possible' and 'stopping the bar on the middle line', whereas participants in the HIV- group all received the latter instruction. Therefore, response time measurements were adjusted for task instruction.

Behavioral Statistical Analysis

In accordance with previous research (Zandbelt & Vink, 2010; Vink et al., 2014; Du Plessis et al., 2015) reactive inhibition was measured in terms of Stop Signal Reaction Time (SSRT) and accuracy on STOP-trials. Proactive response performance was calculated as the slope of reaction time increase on GO-trials as a function of stop-signal probability and accuracy on GO-trials with more than 0% stop-signal probability. All behavioral statistics were performed using univariate analyses, adjusted for task instruction.

Functional MRI acquisition

Imaging was performed on a 3.0 Tesla Philips Achieva system (Philips Medical Systems, Best, The Netherlands) at the UMCU using an eight channel sensitivity-encoding (SENSE) parallel-imaging head coil. Whole brain T2*-weighted two dimensional echo planar images (EPI) with blood-oxygen level-dependent (BOLD) contrast were acquired (622 volumes, 30 slices per volume interleaved acquisition, repetition time [TR] = 1600 ms, echo time [TE] = 23.5 ms, field of view [FOV] = 256x232 mm, flip angle = 72.5°, 4 mm slice thickness, 4 mm isotropic voxels). For within-subject image registration a T1-weighted structural scan was acquired for

each subject (192 slices, TR = 7.9 ms, TE = 4.5 ms, FOV = 256x232x192 mm, flip angle = 8°, 1 mm isotropic voxels).

Functional MRI analysis

Image data were preprocessed and analyzed using SPM5 (Statistical Parametric Mapping; www.fil.ion.ucl.ac.uk/spm5). Functional images were slice time corrected, realigned, co-registered to the anatomical image, segmented and normalized. Images were then smoothed using a Gaussian filter of 8 mm isotropic full-width half-maximum (FWHM) and were high-pass filtered to remove low-frequency drift.

The fMRI data were modeled voxelwise using a general linear model (GLM). The following regressors were included in the model: failed STOP-trials, successful STOP-trials and GO-trials with stop signal probability > 0%. For GO-trials with stop-signal probability > 0% response time and stop-signal probability level were included as parametric regressors. Rest blocks were also modeled so that 0% stop-signal probability trials served as baseline.

For each participant, we computed the same contrast images as has been done in previous research using the same task (Vink et al., 2014; Du Plessis et al, 2015): (1) Baseline activation on GO-trials with 0% stop-signal probability to measure response execution, (2) activation during successful STOP-trials versus unsuccessful STOP-trials (to investigate reactive inhibition), (3) activation during successful STOP-trials versus GO-trials with 0% stop-signal probability (also to investigate reactive inhibition), (4) the parametric effect of stop-signal probability on GO-signal activation (to investigate proactive inhibition) and (5) activation during GO-trials with >0% stop-signal probability versus GO-trials with 0% stop-signal probability (also to investigate proactive inhibition).

Group activation differences were assessed in predefined regions of interest (ROIs). These ROIs are based on activation maps acquired in a previous experiment with healthy volunteers performing the SSAT (Zandbelt & Vink, 2010). The 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). ROIs included frontostriatal regions, such as the right striatum and the right inferior frontal gyrus (IFG) for reactive and proactive inhibition as well as motor cortex areas.

Functional connectivity

A psychophysiological interaction (PPI) analysis was conducted to assess whether there was an effect of HIV status on functional connectivity between frontal and striatal areas during proactive inhibition. The seed was a 4 mm radius sphere in the right striatum (MNI coordinates around center of mass: [20 12 0]). A PPI analysis was conducted to investigate functional coupling between the right striatum and the right IFG during GO-trials with a stop-signal probability > 0% (i.e. the psychological factor). The location of this PPI was obtained from previous research using the same task (Vink et al., 2014).

Within the seed-region the first eigenvariate of the BOLD signal was calculated for each participant and adjusted for average task activation and head motion. Next, we calculated the interaction between the psychological factor and activity in the seed region. Finally, second-level analyses were performed to test the effect of HIV status on functional connectivity within the frontostriatal network.

Results

Demographics

The demographic characteristics of the HIV+ and the HIV- group are displayed in Table 1. All behavioral results described below were adjusted for task instruction (also see Supplementary Table 1).

Table 1. Demographic characteristics of the HIV-infected (HIV+) group and the healthy control (HIV-) group

	HIV+	HIV-	Test-statistic	p-value
Age in years	41.3 (6.7)	38.8 (10.5)	T = 1.07	0.29
Duration of HIV-infection in years	7.5 (5.4)	-		
CD4 cells	634 (194)	-		
Nadir CD4 cells	255 (112)	-		

Note: Age, duration of HIV-infection, CD4 cells and nadir CD4 cells data represent mean +/- standard deviation. CD4 cells and nadir CD4 (lowest CD4 ever) are displayed in cells/mL

Basic task execution

Behavioral results

The HIV+ group was faster on GO-trials with 0% stop-signal probability, although this result was not statistically significant after correction for task instruction (HIV+: M =790, SD = 32; HIV-: M = 810, SD =14; $F(1,56) = 3.72$, $p = .06$). Because the mean reaction time of the HIV+ group was below 800 ms, we performed additional analyses on the subgroup of HIV+ participants that received the same task instructions as the HIV- group (also see Supplementary Table 2). This revealed that the HIV+ group was actually slower on basic response execution (M =826, SD = 21; $t(38) = 2.54$, $p = .02$), indicating motor response slowing in this group. The HIV+ group and the HIV- group were equally accurate on GO-trials with 0% stop-signal probability ($F(1,56) = 1.81$, $p = .18$). This indicates that the HIV+ group was able to perform the basic response task.

fMRI results

Activation in the primary motor cortex during basic task execution (GO-trials with a 0% stop-signal probability versus rest) did not differ between the HIV+ and the HIV- group ($t(41) = 0.73$, $p = .47$; for 16 of 32 healthy controls data was available). This indicates normal motor cortex functioning in the HIV+ group during basic timed responses.

Reactive inhibition

Behavioral results

The speed of reactive inhibition (expressed by SSRT in ms) differed significantly between the HIV+ and the HIV- group ($F(1,56) = 46.17$, $p < .001$), the HIV+ group being on average faster than the HIV- group (HIV+: $M = 305$, $SD = 18$; HIV-: $M = 331$, $SD = 17$). Both groups were equally accurate on STOP-trials ($F(1,56) = 0.29$, $p = .59$). This result was expected as the stop signal was adjusted according to performance (see Methods).

fMRI results

Results are displayed in Figure 2. We found no significant difference between the HIV+ group and the HIV- group on activation in the right striatum during successful STOP-trials versus unsuccessful STOP-trials ($t(57) = -1.17$, $p = .25$). Both groups showed an equal decrease in left primary motor cortex activation ($t(57) = -0.16$, $p = .87$), indicating that motor activity was suppressed during reactive inhibition. These results indicate that the HIV+ group showed normal activation during reactive inhibition.

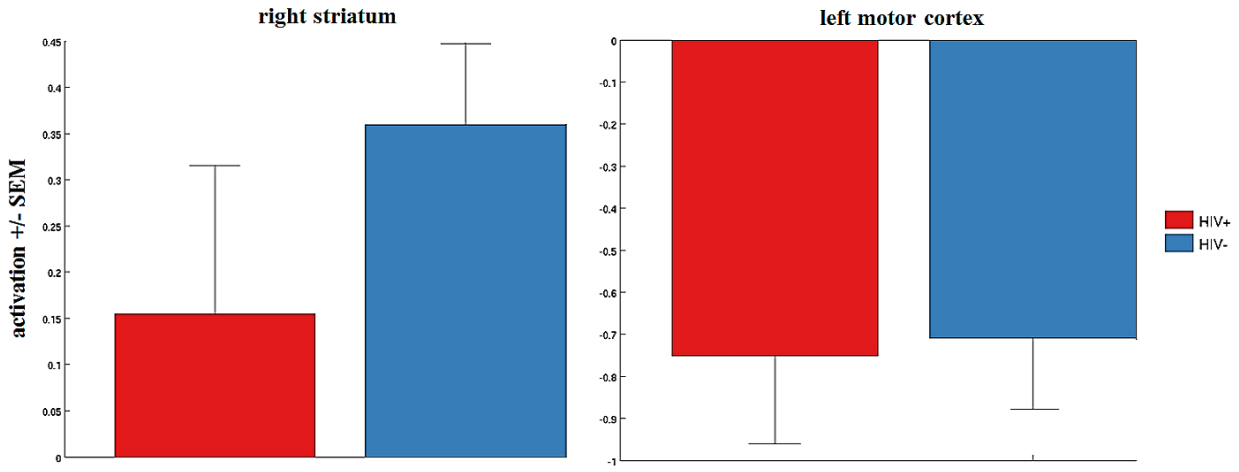

Figure 2. Right striatum and left motor cortex activation during successful STOP-trials versus unsuccessful STOP-trials (reactive inhibition) +/- standard error of the mean for the HIV+ and the HIV- group

Proactive inhibition

Behavioral results

Proactive inhibition was measured as the amount of reaction time slowing on GO-trials as a function of stop-signal probability. The HIV+ group showed significantly less reaction time slowing compared to the HIV- group ($F(1,56) = 15.67$, $p < .001$). This suggests that people in the HIV+ group did not slow down their reaction in response to increased stop-signal probability in the same way as the HIV- group, indicating less anticipation of increased stop chance. However, people in the HIV+ and the HIV- group were equally accurate on GO-trials with >0% stop signal probability ($F(1,56) = 0.36$, $p = .55$), suggesting that the HIV+ participants were able to adequately respond to GO-trials with increased stop-signal probability.

fMRI results

Results are displayed in Figure 3 (for a representation of the data in bar plots see Supplementary Figure 1). A regression analysis showed that the main effect of stop-signal probability was significant for right striatum activation ($F(1,57) = 7.88$, $p = .01$) and right IFG

activation (F(1,57) = 7.90, p = .01). This indicates that activity in these areas increased with an increase in stop-signal probability. The main effect of group was not significant for right striatum activation (F(1,57) = 0.16, p = .69) and for right IFG activation (F(1,57) = 0.15, p = .70). The group by stop-signal probability interaction was not significant for right striatum activation (F(1,57) = 0.23, p = .63), but there was a significant interaction for right IFG activation (F(1,57) = 5.61, p = .02). This indicates that the effect of stop-signal probability on right IFG activation was driven by the HIV- group. Post-hoc analyses support this; the HIV- group showed a significant effect of stop-signal probability compared to baseline GO-trial activity in the right IFG (t(31) = -4.58, p < .001), whereas the HIV+ group did not (t(26) = 0.13, p = .90).

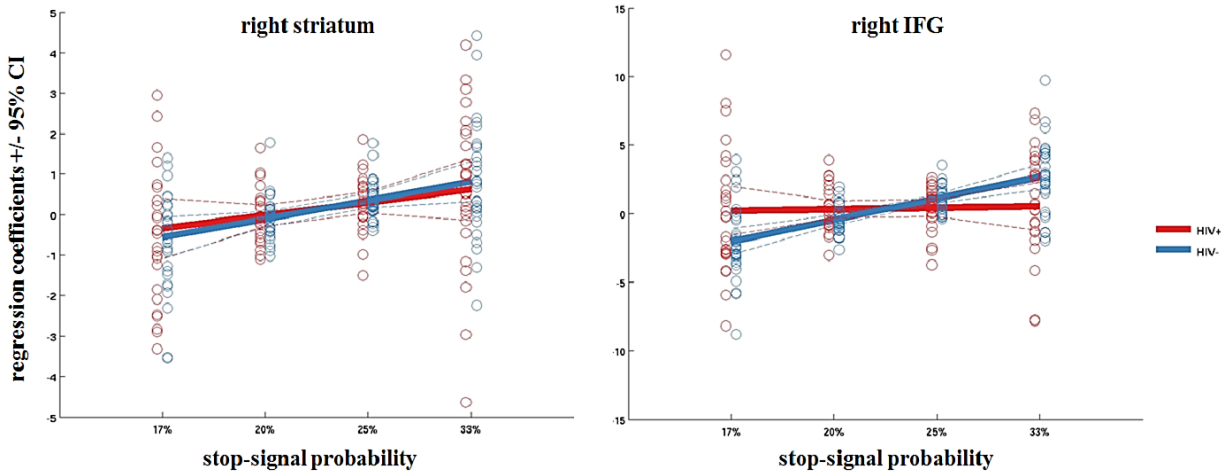

Figure 3. Regression coefficients (+/- 95% confidence interval) of right striatum and right IFG activation for stop-signal probability > 0% for the HIV+ and the HIV- group. IFG = inferior frontal gyrus

Functional connectivity results

Results are displayed in Figure 4. A PPI analysis revealed a significant decrease in connectivity between the right striatum and the right IFG in the HIV+ group during GO-trials with > 0% stop-signal probability ($t(57) = -2.04$, $p = .05$ [$p = .046$]). These results indicate that the right striatum became weaker connected with the right IFG during proactive inhibition in the HIV+ group than in the HIV- group.

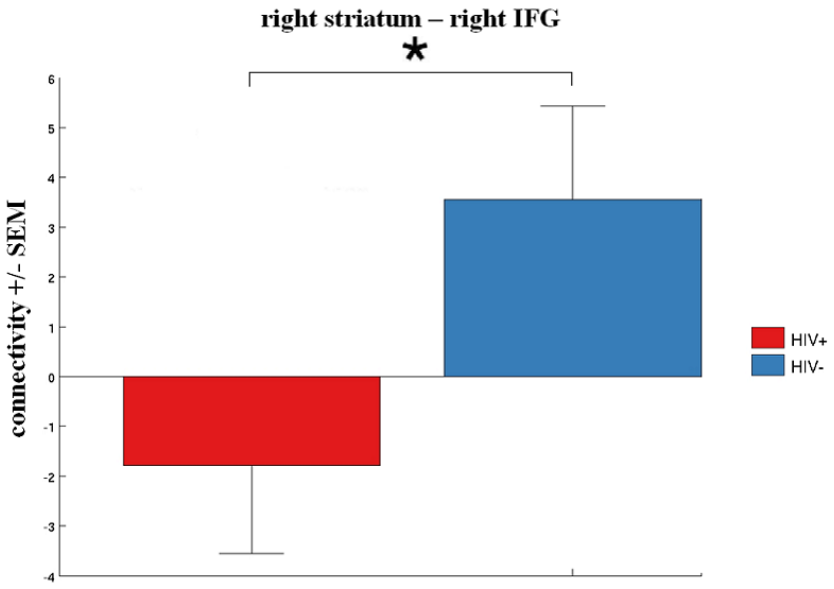

Figure 4. Functional connectivity between the right striatum and the right IFG during proactive inhibition (+/- standard error of the mean). IFG = inferior frontal gyrus. * Significant at $p < .05$

Discussion

Here, we investigated the effect of HIV-infection on behavior and frontostriatal network activity and connectivity during reactive (outright stopping) and proactive (anticipation of stopping) inhibition. 27 HIV-infected men, stable on cART and with an undetectable viral load, were compared to healthy controls. Participants performed a Stop Signal Anticipation Task (Zandbelt & Vink, 2010) that measures response inhibition. HIV+ participants were slower on

basic task execution and showed decreased speed of stopping compared to the control group. There were no differences in accuracy during task execution. Furthermore, the HIV+ group showed less reaction time slowing in response to increased stop-signal probability compared to the HIV- group. No differences between groups were found on striatal activation during both reactive and proactive inhibition. Both groups were equally able to suppress motor cortex activation in response to a stop signal. During proactive inhibition, the HIV+ group showed less dynamic activation of the right IFG in response to increased stop-signal probability. Furthermore, decreased functional connectivity between the right striatum and the right IFG was seen in the HIV+ group during proactive inhibition. Overall, these results suggest dysfunctional frontal activity and frontostriatal connectivity, but normal striatal activity in a HIV-infected population stable on cART and with an undetectable viral load.

Behavior

The HIV+ group was slower on basic task execution (GO-trials with 0% stop-signal probability). This finding replicates the results found in earlier research that also found response slowing (Du Plessis et al., 2015), indicating motor slowing in HIV-infection. In contradiction with our expectations, the HIV+ group had a faster SSRT than the control group. This was not found in previous research (Du Plessis et al., 2015). A possible explanation for this is that the HIV+ group adopted a different strategy during STOP-trials. Instead of focusing on the external cue (i.e. the colored line that indicated a stop-signal probability), this group might have merely focused on the moving bar, not taking into account stop-signal probability.

When investigating proactive inhibition we found less reaction time slowing in response to increased stop-signal probability in the HIV+ group. Increased reaction time in response to

higher stop-signal probability is associated with stop-signal anticipation. The results in this study therefore indicate an inability of the HIV+ group to anticipate an upcoming stop signal. Interestingly, a similar pattern of inadequate stop-signal anticipation was found in children (Vink et al., 2014). In children, the prefrontal cortex is not yet fully developed (Casey, Jones & Hare, 2008), which suggests that deficiencies in this area underlie the differences in proactive inhibition between HIV+ participants and the healthy control group.

Neuroimaging

We found no differences in right striatum activation between groups during reactive inhibition. This is in contrast with the results from previous research on inhibition in HIV-infection that found decreased activation in the right putamen (Du Plessis et al., 2015). A possible explanation for this difference between studies is that viral suppression with medication indeed can improve striatal activation (Ortega, Brier, & Ances, 2015). The HIV+ group in this study reached undetectable viral levels with medication use, meaning that there were less than 50 copies/ml of the virus in an individual's blood sample. The predominant presence of HIV in the striatum (Wiley et al., 1998), can possibly be suppressed with cART. This might explain why we found no group differences in behavior and striatal activity during reactive inhibition, as this depends mainly on the striatum (Zandbelt & Vink, 2010).

Proactive inhibition depends mainly on the frontal cortex and frontostriatal connections. In line with our hypotheses, we found differences between groups on frontal activation during proactive inhibition. The HIV+ group showed less dynamic activation of the right IFG in response to increased stop-signal probability. A similar pattern of right IFG activation was found in healthy older adults (age 60-70) in a study on response inhibition using the same task

(Kleerekooper et al., 2016), indicating diminished capacity of the right IFG to increase activation in a situation that requires more effort (i.e. inhibiting a response in a situation with higher stop-signal probability). This result coincides with the idea that efficiency and flexibility of brain processing in people with HIV-infection is comparable to that of 15-20 years older adults (Ances et al., 2010). Furthermore, in our study, decreased functional connectivity was found in the HIV+ group between the right striatum and the right IFG during GO-trials with > 0% stop-signal probability, indicating that there was less communication between these areas during proactive inhibition. Overall, these results suggest a decreased functioning of the right IFG and decreased frontostriatal connectivity in our HIV+ group compared to our HIV- group.

Research conducted in South-Africa did not find differences between HIV-positive individuals and controls on proactive reaction times and frontal brain activation (Du Plessis et al., 2015). We suspect that this discrepancy is not the result of age or gender differences between studies. Although previous research on inhibition in healthy aging suggests that right IFG activation decreases with age, this effect does not seem to become apparent until after the age of 50 (Kleerekooper et al., 2016). Furthermore, it has been suggested that HIV has similar effects on the brain in males and females (Behrman-Lay et al., 2016).

It is possible that impaired cortical activation that was found in the present study is the result of medication induced alterations in brain activity. To date, it remains unclear to what extent antiretroviral medication and HIV independently affect the brain. It has been suggested that cART has a neurotoxic effect on the brain, leading to increased activation (Chang et al., 2008). However, other studies argue that this is a remaining effect of the virus, especially when medication does not effectively penetrate the central nervous system (Ances, Roc, Korczykowski, Wolf, & Kolson, 2008; Brier et al., 2015). Although we did not have information

about the presence of HIV in the brain or in the cerebrospinal fluid, medication was effectively suppressing the virus in the blood. Furthermore, we found decreased activity in the frontal cortex, which is in contrast with the idea that cART causes increased activation of the frontal cortex. This suggests that frontal dysfunction might not be caused by medication, but by detrimental effects of the virus that are suppressed with medication. For example, only within a short time after infection with HIV, dopamine transporter (DAT) and dopamine D2 receptors are diminished (Koutsilieri et al., 2002). These deregulations in the dopamine system are often linked with cognitive impairment in HIV (Wang et al., 2004; Obermann et al., 2009) and are a possible explanation for decreased frontostriatal connectivity. More research is needed to investigate the exact effects of cART on dopaminergic neurotransmission.

Inconsistencies between our study and the South-African study may also originate from differences in HIV subtype between Europe and South Africa. It has been implied that dopaminergic neurotransmission is differentially affected by the subtype predominantly present in Western countries (subtype B) than in the subtype predominantly present in Sub-Saharan African countries (subtype C; Samikkannu et al., 2015).

Limitations

Matched healthy controls were not yet included by the time this article was written. Therefore, this study is considered preliminary. For example, the controls used to compare the HIV+ group with were not matched by substance use, which is on average higher in the HIV population. Furthermore, task instructions varied among participants, which could have led to differences in reaction times although we did adjust for that. Another limitation is that the exact effects of cART on brain function are still uncertain. Although the results of this study indicate

that antiretroviral treatment can improve striatal functioning during inhibition, we did not compare this with an HIV group that did not use medication.

Summary and conclusion

Summarizing, we found no differences in striatal activity in our HIV+ group compared to healthy controls. Although the HIV+ group was able to accurately respond to a stop signal, the group showed less stop-signal anticipation when presented with increased stop-signal probabilities. In the brain, this was paralleled by decreased dynamic activation of the right inferior frontal gyrus (rIFG) and diminished connectivity between the right IFG and the right striatum. These results suggest that combined antiretroviral therapy (cART) can reduce viral effects in the striatum, leading to normal levels of striatal activity. Frontal brain areas, such as the IFG, do not seem to benefit as much from cART as the striatum, resulting in decreased activation and decreased frontostriatal connectivity. The present study can be a stepping stone for research on medication that is not only beneficial for striatal but also for frontal brain functioning in HIV-infection. Now that HIV-infected people can live longer with medication, it is important that future studies distinguish between the effects of antiretroviral medication and remaining viral effects on frontostriatal network functioning, in order to reduce HIV associated cognitive deficits.

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Supplementary Data

Table 1. Behavioral data for HIV+ on SSAT versus HIV-

	HIV + (n = 27)	HIV – (n = 32)	*F*-statistic	*p*-value
RT GO-trials 0% SSP	790 (32)	810 (14)	3.72	.06
Accuracy GO-trials 0% SSP	98 (2)	98 (2)	1.81	.18
SSRT	304 (18)	330 (17)	46.17	<.001*
Accuracy STOP-trials	42 (7)	45 (6)	0.29	.59
Proactive inhibition	40 (56)	158 (130)	15.67	<.001*
Accuracy GO-trial > 0% SSP	96 (2)	96 (2)	0.36	.55

Note: Reaction times (RT) are represented in ms +/- SD. Accuracy is represented in percentages +/- SD. Proactive inhibition is represented as the slope of RT increase as a function of stop-signal probability +/- SD. SSRT = stop signal reaction time, SSP = stop-signal probability. *Significant at $p < 0.05$

Table 2. Behavioral data for HIV+ subgroup that received the same task instructions on SSAT as HIV-

	HIV + (n = 8)	HIV – (n = 32)	*T*-statistic	*p*-value
RT GO-trials 0% SSP	826 (21)	810 (14)	2.54	.02*
Accuracy GO-trials 0% SSP	97 (3)	98 (2)	-1.22	.23
SSRT	289 (17)	330 (17)	-6.04	<.001*
Accuracy STOP-trials	49 (7)	45 (6)	1.93	.06
Proactive inhibition	56 (64)	158 (130)	-2.13	.04*
Accuracy GO-trial > 0% SSP	95 (3)	96 (2)	-0.50	.62

Note: Reaction times (RT) are represented in ms +/- SD. Accuracy is represented in percentages +/- SD. Proactive inhibition is represented as the slope of RT increase as a function of stop-signal probability +/- SD. SSRT = stop signal reaction time, SSD = stop signal delay, SSP = stop-signal probability. *Significant at $p < 0.05$

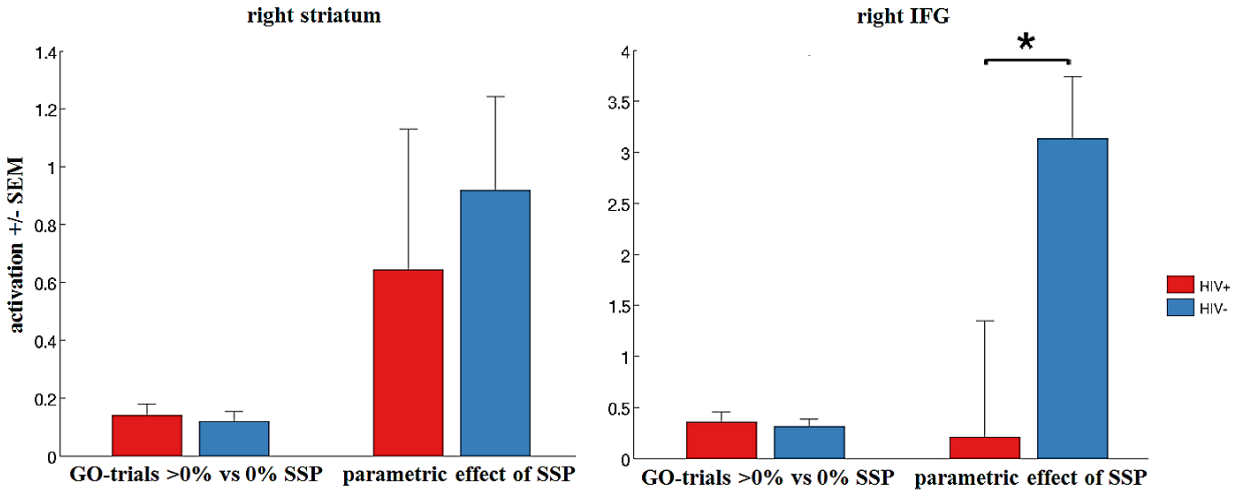

Figure 1. Right striatum and right IFG activation for proactive inhibition (+/- standard error of the mean). Activation during GO-trials with > 0% stop signal probability (SSP) versus GO-trials with 0% stop signal probability and the parametric effect of stop signal probability for the HIV+ and the HIV- group. IFG = inferior frontal gyrus. *Significant at $p < 0.05$