HIV infection results in ventral–striatal reward system hypo-activation during cue processing

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Objective: Functional MRI has thus far demonstrated that HIV has an impact on frontal–striatal systems involved in executive functioning. The potential impact of HIV on frontal–striatal systems involved in reward processing has yet to be examined by functional MRI. This study therefore aims to investigate the effects of HIV infection on reward processing by examining the function of the ventral–striatal reward system during a monetary incentive delay task.

Design: This is a cross-sectional case-control study.

Methods: Eighteen combined antiretroviral therapy-naive HIV-positive (HIV+) participants, as well as 16 matched healthy controls, performed a monetary incentive delay task. This paradigm assesses behaviour as well as functional brain activity-associated reward anticipation and reward outcome.

Results: HIV+ participants showed a general decrease in activation associated with both neutral as well as potentially rewarding cues in their ventral striatum. We found normal activity related to reward outcome in the orbito-frontal cortex. Despite HIV+ participants' reaction times being significantly slower when independently measured from the reward paradigm, this performance deficit normalized during the performance of the reward task.

Conclusion: HIV caused a decrease in activity during cue processing in the ventral striatum, with normal cortical functioning during reward outcome processing. Our results therefore suggest that HIV not only has an impact on fronto-striatal systems involved in executive functioning, but also has a direct impact on the function of the ventral–striatal reward system.

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Keywords: brain, functional MRI, HIV, motivation, reward, ventral striatum

Introduction

HIV enters the brain in the early stage of infection [1], and even in the era of combined antiretroviral therapy (cART), HIV causes neurocognitive impairment in up to half of the individuals [2]. Functional imaging studies have demonstrated that HIV affects the functioning of the fronto-striatal network, a key system involved in executive functioning [3,4]. The effect of HIV on the fronto-striatal network could, at least in part, be due to high concentrations of viral RNA accumulating in the striatum and the surrounding areas early on during infection [5]. More specifically, striatal dopamine neurons may be particularly sensitive to viral effects [6,7]. This could either be caused directly by toxic effects of viral proteins such as GP120 [8] or tat [9], or indirectly by means of the de-regulation of the host immune system [10].

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As striatal function plays an important role in reward processing [11–14], HIV could potentially interfere with the function of the ventral–striatal reward system. Behavioural evidence thus far has indicated that HIV may affect reward processing [15,16]. For example, HIV-positive (HIV+) substance-dependent individuals exhibit greater risky decision-making behaviour on a gambling task [16]. HIV+ participants favoured relatively larger payoffs, which incurred infrequent large penalties. While controls also selected these payoffs, they quickly learned to avoid them. HIV infection was thought to play a role in this behavioural deficit, as although half of the participants were classified as having past drug dependence, few met criteria for current drug dependence. Furthermore, controlling for these factors did not affect the final results. Although such behavioural studies provide evidence for an affect of HIV on reward processing, the effect of HIV in the absence of drug abuse on the function of the ventral–striatal reward system remains to be demonstrated.

Here, we investigated the effects of HIV on the function of the ventral–striatal reward system. Eighteen drug and non-smoking medication (cART)-naive HIV+ participants and 16 matched controls performed a modified version of the monetary incentive delay task while being scanned with functional MRI (fMRI) [17,18]. This task has been shown to reliably activate the ventral–striatum during reward anticipation and the orbito-frontal cortex (OFC) during reward outcome [18–20].

In healthy controls, there is an increase in the ventral–striatal activity during the presentation of reward cues relative to the activity present during neutral cues [14,18]. HIV infection has been associated with hypoactive functional striatal responses, as well as a decreased baseline cerebral blood flow on past neuroimaging studies [21,22, unpublished data]. We therefore predicted that HIV infection is more likely to result in a general decrease in activity in the ventral striatum during reward neutral and reward cues, rather than a specific effect on any given cue.

We also predicted a normal cortical response during reward processing, as we have previously found evidence for an isolated effect of HIV on the striatal regions in our sample population [unpublished data]. As reward outcome tends to activate primarily cortical regions such as the OFC [17], we therefore predicted normal activity in this region in HIV+ participants during reward outcome.

Methods and materials

Participants

Participants were drawn from a larger study cohort described elsewhere [unpublished data]. The participants were recruited from a community primary health clinic in Khayelitsha, Cape Town, South Africa. They provided written informed consent after having received a complete description of the study in their first language (Xhosa), in accordance with procedures approved by the Health Research Ethics Committee (HREC) of Stellenbosch University and the University of Cape Town, Cape Town, South Africa.

Controls were confirmed to be HIV-negative on enzyme-linked immunosorbent assay (ELISA). Both participants and controls were screened using the Mini-International Neuropsychiatric Interview (MINI) 6.0.0/MINI-PLUS 6.0.0 [23]. Participants were excluded if they had a general medical condition that could confound the diagnosis of HIV-associated neurocognitive disorder (HAND), a history of substance abuse on the Substance Abuse and Mental Illness Symptoms Screener (SAMISS) questionnaire [24], a Kreek-McHugh-Schluger-Kellogg (KMSK) score for smoking greater than 1 [25], or if they were currently receiving treatment for tuberculosis. All participants were right-handed as confirmed by the Edinburgh Handedness Inventory [26].

Laboratory measures were performed within 2 weeks of neuroimaging. HIV+ participants received a $CD4^+$ cell count, HIV viral load, rapid plasma reagin for syphilis (RPR) and thyroid-stimulating hormone (TSH) level. HIV-ELISA or high plasma viral load confirmed the HIV serostatus. Controls were confirmed negative with HIV-ELISA performed within 2 weeks of neuroimaging.

All the scans were examined by a radiologist for intracranial pathology that could potentially confound results. Neuropsychological testing assessed the following cognitive domains: motor ability, memory function, learning, attention, speed of information processing, abstract thinking, executive function and working memory. Raw test scores were converted to t scores by means of a normative control group to calculate a global deficit score (GDS) to ascertain the level of HIV-associated neurocognitive impairment in the present sample [27].

Monetary incentive delay task

The task used [18,28,29] in the present study is based on the original monetary incentive delay (MID) task by Knutson *et al.* [14] (see Fig. 1). Potentially rewarding trials ($n = 30$) were indicated with a smiling face, and neutral trials ($n = 30$) were indicated with a neutral face at the onset of each trial. A fixation star followed the reward cue. Following the anticipation cue, a target was presented, requiring patients to react as fast as possible by button press using their right (dominant) index finger. All participants were instructed to respond to a target regardless of the trial type. Reward outcome was presented at the end of each trial. During a practice session prior to the main task, the participant's quickest reaction time was recorded to act as a baseline in order to

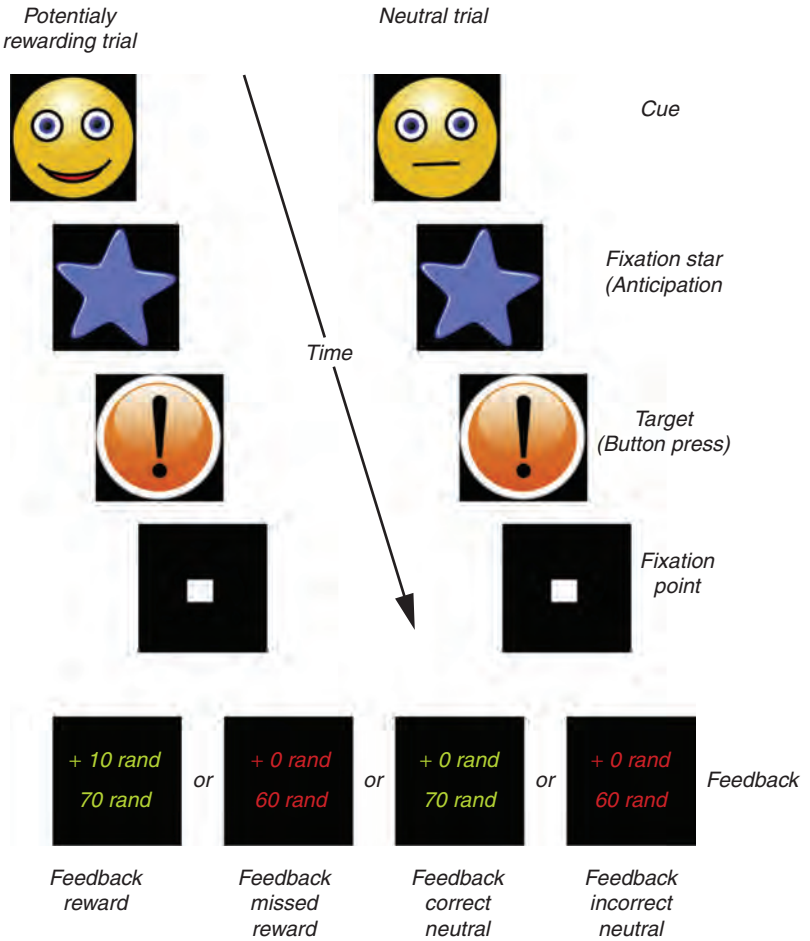

Fig. 1. Schematic representation of the Monetary Incentive Delay task [17,18].

vary the task difficulty. In 50% of the trials, the target was presented for the duration of the individual time limit + 200 ms, enabling participants to be successful in these trials. In the other trials, the time limit was decreased with 150 ms, to make sure that participants could not respond in time.

This ensured adequate power to compare rewarded and non-rewarded trials, as well as ensuring all participants received an equal reward amount (Target R150 ZAR).

To reduce collinearity between anticipation of reward and reward outcome, the anticipation cue time and the inter-trial interval time were varied (mean duration 3286 ms, range 779–6729 ms; mean duration 3535 ms, range 1029–6979 ms, respectively). In this way, the blood oxygen level-dependent (BOLD) signal in response to reward anticipation could be modelled independently from that of the reward outcome [18,20]. The complete task therefore consisted of 60 trials, with a mean duration of 9571 ms (range 4946–16107 ms), resulting in a total task duration of 9 min 35 s.

A response time independent of the reward paradigm was also obtained using the simple response time from the California Computerized Assessment Package (CALCAP) [30].

Behavioural data analysis

Repeated-measures analysis of variance (ANOVA) was performed to test for effects of condition (reward trials and neutral trials) and group (HIV+ participants and controls) on response time, as well as response accuracy. The reward amount was compared between groups using a two-sample *t* test.

Functional MRI

Measurements

Measurements Scans were acquired on a 3T Siemens Allegra at the Combined Universities Brain Imaging Centre (CUBIC). Six hundred and twenty-two whole-brain 2D-EPI 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 in about 16 min. 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 isotropic voxel size) [31].

Image pre-processing

Image data were analysed using SPM8 (http://www.fil.ion. ucl.ac.uk/spm/software/spm8/). Pre-processing and first-level statistical analyses were performed as previously described [18]. In brief, pre-processing involved correction for slice timing differences, re-alignment to correct for head motion, spatial normalization to the Montreal Neurological Institute template brain and spatial smoothing to accommodate inter-individual differences in neuro-anatomy. Head motion parameters were analysed to ensure that the maximum motion did not exceed a predefined threshold (scan-to-scan >3 mm).

Individual analyses

The pre-processed time-series data for each individual were analysed using a general linear model (GLM) analysis. The model consisted of six factors of interest, representing haemodynamic changes time-locked to anticipation during and after the presentation of the reward cue (reward anticipation), anticipation during and after a neutral cue (neutral anticipation), feedback reflecting a positive monetary reward outcome (reward outcome), feedback reflecting no reward, feedback reflecting a correct response in a neutral trial (neutral correct outcome) and feedback reflecting an incorrect response in a neutral trial (Fig. 1). The onset of the factors modelling anticipation (duration range 1529–7479 ms) was at the presentation of the cue, whereas the onset of the factors modelling feedback (duration 2000 ms) was at the presentation of the target, including the button press to the target and the subsequent feedback (Fig. 1). Motion parameters from the realignment procedure were included as factors of no interest. Low-frequency drifts were removed from the signal by applying a high-pass filter with a cut-off frequency of 128 s.

For each participant, we generated statistical maps for each of the conditions, as well as the following contrasts: reward anticipation versus neutral anticipation and reward outcome versus neutral correct outcome.

Region-of-interest analyses

Primary analyses were performed in one region of interest (ROI): the combined bilateral ventral striatum for anticipation and combined bilateral OFC for reward outcome, on the basis of previous findings by Knutson *et al.* [17]. These regions were defined using the Automated Anatomical Labeling-Atlas [32] and the Oxford-GSK-Imanova Striatal Connectivity Atlas for the ventral striatum [33]. For each participant, the mean activation level (expressed as percentage signal change) during the contrasts of interest specific to reward anticipation and reward outcome (reward anticipation, neutral anticipation, reward outcome and neutral correct outcome) was calculated over all the voxels of each ROI. These values were used in a repeated-measures ANOVA, testing for main and group effects in activation levels between neutral versus potentially rewarding trials, reward anticipation versus reward outcome, as well as correct neutral trials versus positive reward outcome.

To determine whether activity was related to clinical measures, we performed a regression analysis in HIV+ participants with activation as a dependent variable, and GDS, viral load, age and sex as predictors.

Whole-brain analysis

In addition to the ROI analysis, whole-brain group-wise analyses were performed, to test for differences outside the predefined ROIs. Group-activation maps were thresholded at a family-wise error (FWE)-corrected cluster level of P equal to 0.05 (cluster-defining threshold of $P = 0.001$, critical cluster size of 26 for reward outcome and 33 for reward anticipation, respectively). These parameters were determined using SPM5 and a script (CorrClusTh.m, to be found on http://www2.warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/scripts/spm), which uses estimated smoothness [estimated full width at half maximum (FWHM): $3.56 \times 3.65 \times 3.46$ voxels] and random field theory to determine the corrected thresholds.

Results

Demographics

Twenty-two HIV+ participants and 18 matched controls were included in the present study. Two HIV+ participants were excluded due to poor task comprehension. One HIV+ participant and two controls were excluded due to poor scan quality as assessed by motion parameters (>3 mm movement), as well as in-house quality assessment software checking for regional signal-to-noise dropout [34–36]. One HIV+ participant screened positive for benzodiazepines prior to scanning. After these exclusions, 18 HIV+ participants and 16 healthy controls were included in the final analysis (see Table 1).

The groups did not differ with regards to sex, age or education level. All participants were from a similar socio-economic background. All HIV+ participants were ambulant and healthy enough to participate in the fMRI task. No potentially confounding intra-cranial pathology was found on inspection of the MRI scans.

Behaviour results

As expected, there was a main effect of condition on reaction time, with both groups reacting significantly faster on potentially rewarding trials than neutral trials [$F(1, 32) = 4.25$, $P = 0.04$]. There was no group-by-condition interaction effect during the performance of

Table 1. Demographic characteristics of the diagnostics groups.

	HIV ($N=18$)	HC ($N=16$)	Test statistic	P^*
Sex (M/F)	2/16	1/15	$\chi^2=0.249$	1.000
Mean age (years)	32 ± 4.6	28 ± 5.2	$T=-2.363$	0.096
Education (years)	11 (10–12)	12 (11–12)	$U=111$	1.000
Viral load (copies/ml)	24936.3 ± 31877.4			
$CD4^+$ (cells/μl)	433 ± 199			
Participants with AIDS-defining $CD4^+$ cell count	7			
GDS (summary score)	0.21 (0.07–0.36)	0.17 (0.07–0.36)	$U=86$	1.000

Age, viral load and $CD4^+$ data represent mean ± SD. Education and GDS data represent median and inter-quartile range between the 25th and 75th centiles. AIDS-defining $CD4^+$ cell count of 350 cells/μl used. F, female; GDS, Global Deficit Score [22]; HC, healthy controls; HIV, HIV-positive participants; M, male.
*P values reported are adjusted using the Bonferroni correction for multiple comparisons.

the reward task [$F(1, 32)=0.71$, $P=0.40$], indicating that both groups had a similar decrease in response time during potentially rewarding trials. Finally, there was no main effect of group [$F(1, 34)=0.97$, $P=0.33$], indicating that both groups responded equally fast. This was unexpected as we have previously reported that these HIV+ participants had significantly slower simple response times on CALCAP [$t(27)=-2.937$, $P=0.007$].

As expected, there was a main effect of condition on task accuracy [$F(1, 32)=32.79$, $P<0.001$], with both groups showing significantly more accurate responses on potentially rewarding trials, compared to neutral trials. There was no significant group-by-condition interaction effect [$F(1, 32)=0.451$, $P=0.507$] or a main effect of group [$F(1, 32)=0.042$, $P=0.839$], confirming similar task performance of the HIV+ participants compared to the controls. As task difficulty was adjusted according to individual performance levels, both groups received an equal amount of reward [HIV: $M=137\pm15$, control: $M=140\pm12$, $t(32)=0.613$, $P=0.544$].

Imaging results

Reward processing in the ventral striatum

As expected, there was a significant main effect of condition in the ventral striatum [$F(1, 32)=4.927$, $P=0.034$], indicating an increase of ventral–striatal activity from neutral to reward cues. This did not differ between the two groups [group-by-condition interaction: $F(1, 32)=0.287$, $P=0.596$]. There was, however, a significant main group effect of condition in the ventral striatum [$F(1, 32)=5.81$, $P=0.02$] (see Fig. 2), with HIV+ patients showing less activation during both neutral and reward cues.

In a further exploratory analysis, we investigated activity related to reward outcome, comparing activity during neutral correct and successful reward outcome trials in the ventral striatum. As expected, there was no main effect of condition in the ventral striatum [$F(1, 32)=1.938$, $P=0.174$]. There was no group-by-condition interaction effect [$F(1, 32)=0.311$, $P=0.581$], nor a main effect of group [$F(1, 32)=0.051$, $P=0.822$]. This demonstrates that HIV has a specific impact on ventral–striatal reward cue processing and not a general effect on striatal blood flow.

Reward processing in the orbito-frontal cortex

As expected, there was a significant main effect of condition in the OFC [$F(1, 32)=48.924$, $P<0.001$], indicating an increase from neutral correct outcome to reward outcome in the OFC. There was no interaction effect between group and condition [$F(1, 32)=0.779$, $P=0.384$]. There was also no main effect of group [$F(1, 32)=1.457$, $P=0.236$].

Whole-brain analysis

To investigate whether there were activation differences outside the predefined regions, we performed whole-brain analyses (see Fig. 3). Whole-brain analysis revealed no results that survived multiple comparisons correction for reward anticipation (contrast: reward anticipation

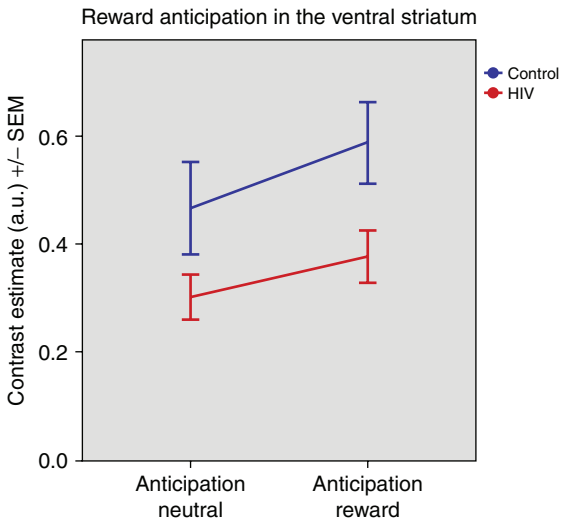

Fig. 2. Line graph showing repeated measures analysis of activity in the ventral striatum in the anticipatory period during neutral and rewarded trials in HIV+ participants and controls. HIV+, HIV-positive.

versus neutral anticipation). On a more liberal threshold [$P = 0.001$ (uncorrected)], reward anticipation-related activity was found in the striatum, thalamus and several frontal, temporal and parietal areas. Reward outcome-related activity (contrast: reward outcome versus neutral correct outcome) was mainly found in the bilateral OFC, anterior cingulate gyrus, left hippocampal and parahippocampal gyri (FWE-corrected $P = 0.05$, cluster-defining threshold of 26). This is comparable to what has been previously found in the literature [14,18]. No between-group differences were found on whole-brain analysis.

Regression analyses

None of the clinical variables was found to significantly predict activity during reward anticipation or reward outcome in the ventral striatum or OFC.

Discussion

Here, we investigated brain activity during reward processing in 18 HIV+ substance and cART-naive participants and 16 matched controls using fMRI. To our knowledge, this is the first study to investigate the effects of HIV on fronto-striatal functioning during reward processing. Importantly, both groups were substance and cART-naive. As predicted, HIV+ participants showed a general decrease in ventral–striatal activity during anticipation for both neutral and potentially rewarding trials, when compared to controls. The increase in activity related to reward outcome in the OFC did not differ between the two groups. Despite HIV+ participants' reaction times being significantly slower at baseline, this performance deficit normalized during the performance of the reward task. These findings suggest that HIV has an impact on the function of the ventral striatum during cue processing, with a relative sparing of the cortical function. Striatal dysfunction during cue processing was present despite HIV+ participants still being able to speed up their responses in anticipation of a potential reward, indicating that the impact of HIV is not limited to striatally mediated executive function, but extends to reward processing.

We found a decrease in ventral–striatal activity during cue processing in HIV+ participants. It is well known that HIV's impact on brain function often results in a clinical fronto-striatal dementia [37]. Past functional studies have shown general striatal dysfunction, with hypo-activity in the putamen during reactive inhibition [unpublished data], caudate hypo-activity during semantic event sequencing [22], as well as a general decrease in resting cerebral blood flow in the striatum on arterial spin labeling [21]. Our data extend these findings by showing an HIV-related decrease in activity in the ventral–striatal reward system during cue processing. Given the limitations of BOLD fMRI [38], a potential explanation for a general decrease in regional BOLD signal is that the consequences of HIV infection, such as neuro-inflammation [10], does not affect neural activity *per se*, but rather causes a general change in haemodynamics in the striatum [39]. This is unlikely to be the case, given that we find no decrease in the ventral–striatal activity during reward feedback in HIV. We therefore have shown that HIV does not only affect striatal functions associated with executive functioning such as the inhibition of voluntary movement [unpublished data] or semantic event sequencing [22], but also reward processing. Previous studies in the behavioural impact of HIV have been potentially confounded by past drug dependence [16]. Our findings further support behavioural studies reporting abnormal behaviour on gambling tasks [16] in HIV infection in the absence of illicit drug use/abuse, as cue processing is vital in predicting future rewards. For example, hypo-activation during ventral–striatal anticipatory activity has been associated with impulsive decision-making in alcohol dependence, as well as pathological gambling [40,41].

Our data show that HIV does not result in a specific deficit during the anticipation of reward cues, but also during activity related to neutral cues. Nevertheless, it is likely that a disruption in general cue processing could potentially result in abnormal reward-based decision-making. This could include risky decision-making with respect to sexual behaviour, aggression, substance abuse and potentially a decreased capacity to appreciate the long-term benefits of using and staying on treatment. Importantly, as our sample has no reported drug use, abnormal reward-related behavior in the HIV+ population is unlikely to be explained by the effects of drug abuse alone [15,42].

We found normal activity in the cortical regions known to be active during reward outcome [17]. This finding is consistent with our previous work which suggested that sub-cortical function is primarily affected in the present sample population [unpublished data]. This negative finding is seemingly at odds with other functional studies, which generally demonstrate HIV-induced hyper-activation in the cortex during working memory, as well as during visual attention tasks [4,43–45]. A possible explanation for why some studies found cortical dysfunction when we have not is that these studies differ from our present sample in terms of patient age and cART use. The additional effect of cART, as well as the effect of aging, has been associated with increases in cortical activation in HIV infection in their own right [46,47]. More importantly, participants from our sample population were all newly diagnosed, just prior to the initiation of treatment. This would suggest that HIV could have a different impact on cortical function after treatment [46]. This will have to be confirmed with further prospective studies utilizing fMRI tasks that reliably engage the cortex and the striatum.

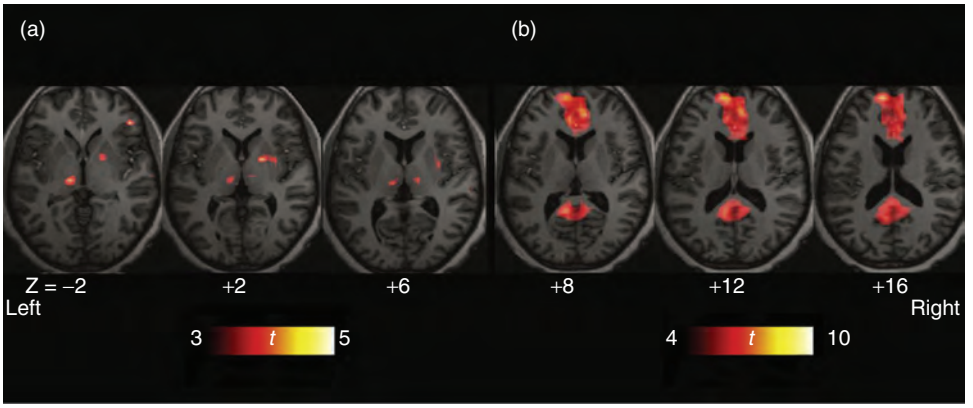

Fig. 3. Whole-brain activation during reward anticipation and reward outcome in HIV+ as well as HIV− controls while performing a Monetary Incentive Delay task [17,18]. One-sample *t* tests of (a) reward anticipation versus neutral anticipation are displayed at an activation threshold of $P = 0.001$ (uncorrected). (b) Reward outcome versus neutral correct outcome are FWE-corrected ($P = 0.05$) with a cluster-defining threshold of 26. FWE, family-wise error; HIV+, HIV-positive; HIV−, HIV-negative.

Both controls and HIV+ participants showed significantly faster response times as well as increased response accuracy between neutral trials and potentially rewarding trials. This is in keeping with behavioural responses previously reported in healthy control populations [18]. This indicates task comprehension in both the groups. Furthermore, the HIV+ participants are still able to anticipate potentially rewarding trials. The fact that HIV+ participants did not show generally slower responses than controls is surprising, given that we did indeed find slower simple response times acquired independent of the fMRI task. Although it is well known that HIV infection is associated with reaction time slowing [48], here we show that this response slowing could normalize during situations with a positive motivational valence. This implicates at least, in part, deficient reward processing in response time slowing in HIV.

As we have used a relatively simple reward task that utilizes only one level of reward, we cannot rule out the possibility that HIV+ participants will start showing slower behavioural responses with increased task complexity with multiple levels of reward, as well as the inclusion of punishment trials. We chose to utilize a simpler task to ensure that reward anticipation would not be influenced by a lack of task comprehension. As the present task was successfully utilized in children as young as 10 years, who demonstrated no measurable differences in response accuracy from those of adults, we believe that the task was simple enough not to confound performance in the present study [18]. As our task involved on an average a 50% failure rate, factors such as participant frustration could potentially have differed between the groups. Task accuracy was, however, not significantly different in the present sample, and therefore differences in levels of group frustration should have been minimal.

As our sample largely consisted of female participants, special mention should be made on the possible influence of sex on our findings. It has been postulated that women are differentially at risk for the development of HAND, due to potentially different prevalence of risk factors such as poverty, differences in substance abuse and prevalence of mental health disorders [49–52]. Studies performed thus far have indeed found a small HIV serostatus-by-sex interaction on cognition, with HIV-related comorbidities having a much larger impact [50,52]. The only functional study performed thus far in a largely female cohort did indeed report hippocampal dysfunction in women, but could potentially have been confounded by substance abuse [51]. In the present study, we confirm an impact of HIV on brain function in HIV+ women, and extend these results by demonstrating a functional impact of HIV in the absence of a history of drug use, severe comorbid psychopathology (i.e. major depression), as well as differences in demographic variables, which we controlled for with a strict sample selection.

HIV caused a decrease in activity during cue processing in the ventral striatum, with normal cortical functioning during reward outcome processing. Our results therefore suggest that HIV not only has an impact on the fronto-striatal systems involved in executive functioning, but also has a direct impact on the function of the ventral–striatal reward system.

Acknowledgements

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D.J.S. and R.E. provided feedback on study approach, interpretation of data as well as manuscript review.

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Conflicts of interest

There are no conflicts of interest.

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