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ORIGINAL RESEARCH

Underlying Neural Mechanisms of Cognitive Improvement in Fronto-striatal Response Inhibition in People Living with HIV Switching Off Efavirenz: A Randomized Controlled BOLD fMRI Trial

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ABSTRACT

***Introduction*:** It is unclear whether neurotoxicity due to the antiretroviral drug efavirenz (EFV) results in neurocognitive impairment in people living with HIV (PLWH). Previously, we found that discontinuing EFV was associated with improved processing speed and attention on neuropsychological assessment. In this imaging study, we investigate potential neural mechanisms underlying this cognitive improvement using a BOLD fMRI task assessing cortical and subcortical functioning.

***Methods*:** Asymptomatic adult PLWH stable on emtricitabine/tenofovirdisoproxil/efavirenz were randomly (1:2) assigned to continue their regimen ($n=12$) or to switch to emtricitabine/tenofovirdisoproxil/rilpivirine ($n=28$). At baseline and after 12 weeks, both groups performed the Stop-Signal Anticipation Task, which tests

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reactive and proactive inhibition (indicative of subcortical and cortical functioning, respectively), involving executive functioning, working memory, and attention. Behavior and BOLD fMRI activation levels related to processing speed and attention Z-scores were assessed in 17 pre-defined brain regions.

Results: Both groups had comparable patient and clinical characteristics. Reactive inhibition behavioral responses improved for both groups on week 12, with other responses unchanged. Between-group activation did not differ significantly. For reactive inhibition, positive Pearson coefficients were observed for the change in BOLD fMRI activation levels and change in processing speed and attention Z-scores in all 17 regions in participants switched to emtricitabine/tenofovir disoproxil/rilpivirine, whereas in the control group, negative correlation coefficients were observed in 10/17 and 13/17 regions, respectively. No differential pattern was observed for proactive inhibition.

Conclusion: Potential neural mechanisms underlying cognitive improvement after discontinuing EFV in PLWH were found in subcortical functioning, with our findings suggesting that EFV's effect on attention and processing speed is, at least partially, mediated by reactive inhibition.

Trial Registration: Clinicaltrials.gov identifier [NCT02308332].

Keywords: HIV; HIV-associated neurocognitive disorders (HAND); Neurocognition; BOLD functional MRI; Efavirenz; Response inhibition

Key Summary Points

It is unclear whether neurotoxicity due to the antiretroviral drug efavirenz (EFV) results in neurocognitive impairment in people living with HIV (PLWH).

In this study, we investigate potential neural mechanisms underlying cognitive improvement in attention and processing speed previously found during neuropsychological assessment, using a BOLD fMRI task assessing cortical and subcortical functioning in 17 pre-defined brain regions.

For reactive inhibition activation (indicative of subcortical functioning), positive Pearson coefficients for the change in BOLD fMRI activation levels and change in processing speed and attention Z-scores were observed in all 17 regions in participants switched to emtricitabine/tenofovir disoproxil/rilpivirine, whereas in the control group, negative correlation coefficients were observed in 10/17 and 13/17 regions, respectively. No differential between-group pattern was observed for proactive inhibition.

Potential neural mechanisms underlying cognitive improvement after discontinuing EFV in PLWH were found in subcortical functioning, with our findings suggesting that EFV's effect on attention and processing speed is, at least partially, mediated by reactive inhibition.

INTRODUCTION

Although the advent of combination antiretroviral therapy (cART) has resulted in a significant increase in the life expectancy of people living with HIV (PLWH), the burden of disease due to comorbidities remains substantial [1, 2]. A common comorbidity with a major impact on quality of life is the presence of HIV-associated neurocognitive disorders (HAND) [3, 4]. The etiology of HAND has not been fully elucidated, with several proposed mechanisms including

previous irreversible nervous system damage prior to cART initiation; neuronal damage due to persistent HIV replication in the central nervous system (CNS) compartment, despite effective replication control in the plasma compartment; continued immune activation in the CNS; the presence of non-infectious comorbidities resulting in additional neurological damage; and neurotoxicity due to antiretroviral therapy itself [5, 6]. Although the incidence of the most severe form of HAND, HIV-associated dementia, substantially decreased after cART introduction, milder forms persisted, despite viral suppression and immune reconstitution [7]. Moreover, the pattern of HAND differs, with PLWH in the pre-cART era having more impairments in motor skills, cognitive speed, and verbal fluency, while those in the cART era having more memory (learning) and executive function impairments [7].

One of the antiretroviral agents most often implicated is efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor (NNRTI) [8]. EFV is currently recommended in World Health Organization guidelines as alternative first-line treatment, is still one of the most prescribed antiretroviral drugs globally, and is expected to continue to be widely used, with forecast analyses showing ten million PLWH (i.e., 25% of the total HIV-positive population) using EFV in 2025 [9, 10]. Despite its widespread use, EFV is notorious for neurocognitive side effects such as dizziness or insomnia and has frequently been associated with neurocognitive impairment, although the latter remains a topic of debate as studies report conflicting findings [11–17].

Neurocognitive impairment due to HAND is traditionally investigated by neuropsychological assessment (NPA). In the ESCAPE-trial, we showed that discontinuing EFV in asymptomatic PLWH resulted in an improvement in the cognitive domains attention and processing speed, as assessed by NPA [18]. However, the NPA findings reflect an overall effect in cognitive domains and it therefore remains unclear which neural mechanisms in the brain underlie the cognitive improvement. One way to assess this is blood oxygenated level dependent (BOLD) functional magnetic resonance imaging (fMRI). BOLD fMRI can detect local changes in cerebral blood flow and oxygenation that reflect regional neuronal activity. BOLD fMRI is more sensitive in assessing the impact of cART on neurocognition than NPA alone, as it can reliably detect early changes in the brain in the absence of symptomatic neurocognitive impairment [19–21]. Therefore, by using both diagnostic modalities, it is possible to link cognitive changes assessed by NPA to more localized BOLD fMRI findings and investigate potential underlying neural mechanisms of neurocognitive improvement.

Previous research has shown that HIV infection primarily impairs the fronto-striatal network and, more specifically, subcortical functioning [19, 22]. Combined with EFV's propensity for neurocognitive side effects and demonstrated in vitro neurotoxicity, the fronto-striatal network may thus be at increased risk for additional neurotoxic damage [23, 24]. Prior studies support this hypothesis, showing altered fronto-striatal activation after discontinuing EFV in both adult and adolescent PLWH [25, 26]. The Stop-Signal Anticipation Task (SSAT) is an event-related fMRI task that has been shown to reliably test executive functioning, working memory, and attention [27, 28]. It tests response inhibition, one of the main functions of the fronto-striatal network, which reflects the ability to suppress irrelevant or interfering information or impulses [27, 29]. It consists of several subprocesses, such as motor execution, outright stopping as an immediate reaction to a STOP signal (i.e., reactive inhibition) and proactive anticipation of stopping (i.e., proactive inhibition), with reactive and proactive inhibition indicative of subcortical and cortical functioning, respectively [27, 29].

We hypothesized that, as a result of HIV infection impairing subcortical functioning and rendering it potentially susceptible to neurotoxic damage of EFV, subcortical and not cortical functioning would be affected. A potential neural mechanism underlying the cognitive improvement observed for attention and processing speed after discontinuing EFV might therefore be found in improved reactive inhibition. To investigate this, we performed a subanalysis of the ESCAPE trial and combined task-based BOLD fMRI, in the form of the SSAT, with NPA findings. Participants stable on the single-tablet regimen

emtricitabine/tenofovirdisoproxil fumarate/efavirenz (FTC/TDF/EFV) were randomly allocated to continue FTC/TDF/EFV or to switch to emtricitabine/tenofovirdisoproxil fumarate/rilpivirine (FTC/TDF/RPV). As our entire study population used EFV at the onset of the trial, we specifically studied the effect of EFV by discontinuation in one group. NPA and BOLD fMRI scans were performed at baseline and after 12 weeks.

METHODS

Participants

The present study is a subanalysis of the ESCAPE (Effect of SwitChing AtriPla to Eviplera on neurocognitive and emotional functioning) trial, which was conducted at two major HIV treatment centers in the Netherlands (OLVG (Amsterdam) and Universitair Medisch Centrum Utrecht (Utrecht)) from 2015 until its completion in 2017 [18]. Strict inclusion and exclusion criteria were chosen to ensure a homogenous study population as PLWH exhibit greater variability with respect to fMRI measurements, and fMRI results can be readily influenced by confounding factors [30, 31]. To summarize, asymptomatic male PLWH aged 25–50 years stable on FTC/TDF/EFV for over 6 months were included. Prospective participants were excluded in case of an active psychiatric or neurological disorder, an active or past central nervous system infection, or a history or evidence of alcohol or drug abuse as assessed by the Drug Abuse Screening Test [32]. During the trial, participants with a viral load (VL) of greater than 200 copies/mL were excluded from analysis, as we judged this might interfere with fMRI results. For the full list of inclusion and exclusion criteria, see the published study [18].

The trial was reviewed and approved by the Medical Research Ethics Committee of the UMC Utrecht, performed in accordance with the Declaration of Helsinki and registered at Clinicaltrials.gov [NCT02308332]. Findings were reported in accordance with the CONSORT guideline [33]. The trial was funded by Gilead Sciences. The funder had no role in trial design, data collection or analysis, or in the preparation of the manuscript. Data were collected by the investigators with the use of case report forms. All participants provided written informed consent. The data and corresponding analysis code that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available because of privacy and ethical restrictions.

Study Design and Procedures

Participants on FTC/TDF/EFV were randomly assigned in a 2:1 ratio, using computer-generated block randomization with a variable block size (range 3–9), to switch to FTC/TDF/RPV or to continue taking FTC/TDF/EFV. A study nurse, not involved in the study, generated the random assignment sequence and allocated participants. FTC/TDF/RPV was chosen for the switch group as it is a single-tablet regimen comprising the same backbone and a similar NNRTI anchor drug as FTC/TDF/EFV. Head-to-head comparison between RPV and EFV in the ECHO and THRIVE trials showed significantly fewer neuropsychiatric side effects, though they still were present in the RPV study groups [34]. Participants were instructed to take one tablet daily and, in the case of FTC/TDF/RPV, with a significant amount of food. The NPA was performed by neuropsychologists who were unaware of the assigned treatment. Researchers performing the fMRI scan and participants were not blinded, as we believed that their knowledge of the treatment would not affect our objective outcome of fMRI brain activity.

All participants had fMRI scans at baseline and after 12 weeks. The MRI scans were reviewed by a radiologist for intracranial pathology. Cognition was examined by way of NPA and it was ascertained whether the distribution of potentially confounding asymptomatic neurocognitive impairment, as defined by the Frascati criteria, was comparable between groups [3]. Routine blood samples were obtained to assess laboratory abnormalities and confirm virologic suppression. Participants switching to FTC/TDF/RPV had two additional routine outpatient visits after 2 and 4 weeks to monitor for

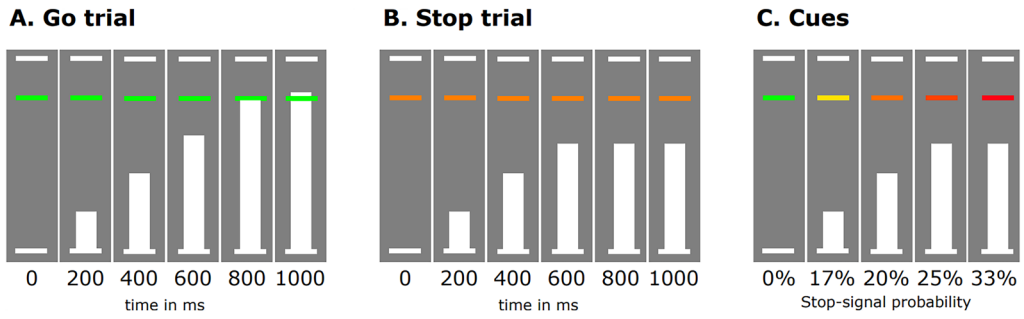

Fig. 1 Schematic representation of the Stop-Signal Anticipation task. Three horizontal lines were displayed during the task. A bar moved from the bottom line to the top in 1000 ms. At 800 ms the bar reached the middle colored line and had to be stopped (GO trials, **A**). In a small proportion of trials, the bar stopped moving on its own before reaching the middle colored line, requiring the stop response to be withheld (STOP trials, **B**). The color of the middle line indicated the stop signal probability (**C**) [27]

side effects and obtain blood samples. Lastly, participants completed multiple questionnaires at baseline and week 12, including the Hospital Anxiety and Depression Scale (HADS) and Patient Reported Outcome Measurement Information System (PROMIS) questionnaires testing depression, anxiety, and sleep disorders. The HADS questionnaire consisted of a 7-item scale with a maximum of 21 points, with score of 11 points or more indicating a probable mood disorder. The raw PROMIS questionnaire scores for depression, anxiety, and sleep disorders were transformed into T-scores with a mean of 50 and a standard deviation of 10. For full information on these and other study questionnaires used, see the published study [18].

NPA

The NPA consisted of 16 subtests and tested for seven cognitive domains [18]. The tests were specifically selected to detect minimal changes in neurocognitive performance, as our study population was asymptomatic. For attention and processing speed, the Letter-Number-Sequencing WAIS-IV NL, Paced Auditory Serial Addition Test, Digit Symbol WAIS-IV NL, Symbol Search WAIS-IV NL, and Trailmaking Test part A were used [35–37].

Stop Signal Anticipation Task

Participants performed the SSAT, a task based on the theory by Logan and Cowan [27, 38]. They postulated that a response, either starting or stopping, is the result of a race between the "GO" and "STOP" brain processes. If the STOP process is finished before the GO process reaches the execution threshold, the GO response is stopped.

The task and experimental procedures are the same as previously described by Zandbelt and Vink [27]. The experiment was performed using Presentation® software (Version 14.6, www.neurobs.com). In short, participants were presented with three background lines (Fig. 1). On each trial, a bar moved at a constant speed from the bottom towards the top bar, reaching the middle line in 800 ms. On GO trials, participants were asked to stop the bar as close as possible to the middle line, by pressing a button. If the bar passed the top line after 1000 ms, the GO trial was considered a failure. STOP trials were identical to GO trials, except that the bar stopped moving automatically before the middle bar, indicating a STOP signal. Participants were then required to withhold the button press (i.e., reactive response inhibition). To measure proactive response inhibition, the probability that a STOP signal would appear was manipulated across trials and could be anticipated on the basis of the

color of the middle line. There were five STOP signal probability levels: 0% (green), 17% (yellow), 20% (amber), 25% (orange), and 33% (red). The interval between start of a trial and the STOP signal, the stop signal delay (SSD), was initially 550 ms and varied for each STOP signal according to the participant's performance. In case of a successful STOP trial, the trial difficulty was increased as the SSD was raised by 25 ms. If the STOP trial was unsuccessful, the SSD was reduced with the same time limit, ensuring an equal amount of successful and unsuccessful STOP trials. The intertrial interval was kept at 1000 ms. In total, 414 GO trials (0%, $n=234$; 17%, $n=30$; 20%, $n=48$; 25%, $n=54$; 33%, $n=48$) and 60 STOP trials (17%, $n=6$; 20%, $n=12$; 25%, $n=18$; 33%, $n=24$) were presented in a single run in pseudorandom order.

All participants received standardized training in task performance before scanning. They were instructed that the GO and STOP trials were equally important and that it would not always be possible to suppress a response when a STOP signal occurred. We informed them that a STOP signal would never occur on a trial with a green cue and that they were more likely in the context of, in consecutive order, yellow, amber, orange, and red cues. The total task duration was 16 m 36 s.

Behavioral Data Analysis

Motor execution was studied using the response time and accuracy of GO trials with no possibility of a STOP signal (0%). Reactive inhibition was analyzed using the stop signal reaction time (SSRT), which was computed according to the integration method and calculated across all STOP signal probability levels (17–33%) [38]. The SSRT reflects the latency of the inhibition process and better reactive inhibition is indicated by a smaller SSRT.

Proactive inhibition is the anticipation of stopping based on the STOP signal probability and was measured as the slope of the mean response time to increasing STOP signal probability (0–33%). In general, participants slow their response as the STOP probability increases, resulting in larger response times. When proactive inhibition is impaired, participants thus show a reduced effect of the STOP signal probability on their response times, reflected by a less steep slope [27]. Repeated measures analyses of variance (ANOVA) were conducted on the mean response times, response accuracy, and on the slope of the response time to stop signal probability, with the STOP signal probabilities, group (FTC/TDF/RPV versus FTC/TDF/EFV), and time (baseline versus 12 weeks) as factors.

Functional MRI

Image Acquisition

MRI scans were acquired using a 3.0 T Philips Achieva MRI scanner (Philips Medical Systems, Best, the Netherlands) in the UMC Utrecht. An eight-channel sensitivity-encoding (SENSE) parallel-imaging head coil was used to acquire the images. Head motion was restricted using a vacuum cushion and foam wedges. Whole-brain T2-weighted echo planar images with BOLD contrast, oriented in a transverse plane tilted 20° over the left–right axis, were acquired in a single run (622 volumes; 30 slices per volume; repetition time 1600 ms; echo time 23.5 ms; field of view 256 × 208 mm × 256 mm; flip angle 72.5°; 64 × 64 matrix; 4 × 4 mm in-plane resolution; 4 mm slice thickness SENSE factor 2.4 (anterior–posterior)). We discarded the first six images to allow for T1 equilibration effects. A whole-brain three-dimensional fast field echo T1-weighted scan (185 slices; repetition time 8.4 ms; echo time 3.8 ms; flip angle 8°; field of view 288 × 252 × 185 mm; voxel size 1 mm isotropic) was acquired for within-subject registration purposes.

Image Pre-processing

Image data were analyzed with SPM (https://www.fil.ion.ucl.ac.uk/spm/). Pre-processing and first-level statistical analyses were performed as described previously [27]. In short, pre-processing included correction for differences in slice timing, realignment to correct for head motion, spatial normalization according to the Montreal Neurological Institute template brain and spatial

(8 × 8 × 8mm) smoothing to account for inter-individual differences in neuroanatomy. Head motion parameters were analyzed to ensure that the maximum motion did not exceed a pre-defined threshold (scan-to-scan > 3 mm) [39]. If this threshold was exceeded, the MRI scan was considered of insufficient quality and the participant was excluded from the analysis.

Individual Analyses

Each participant's pre-processed fMRI data were high-pass filtered (cutoff 128 Hz) to remove low-frequency drifts and were modelled voxel-wise using a general linear model. The following events were included as regressors: timed GO trials with STOP signal probability above 0%, successful STOP signal trials, and unsuccessful STOP signal trials. For the GO trials with a STOP signal probability above 0%, we included a parametric regressor modelling the STOP signal probability level and variation in response time. In addition, GO trials with 0% STOP signal probability and activity were also modelled. We computed two contrast images for each participant: activation during successful STOP trials versus unsuccessful STOP trials (to assess reactive inhibition) and the parametric effect of STOP signal probability on GO trial activation (to assess proactive inhibition).

Region of Interest Analyses

Differences in activation between groups were assessed in pre-defined regions of interest (ROIs), using mask-based activation maps acquired in a previous experiment in healthy controls performing the same task (Fig. 2) [27]. These 17 ROIs were defined using a cluster-level threshold (cluster-defining threshold of $p < 0.001$, cluster probability of $p < 0.05$, family-wise error corrected for multiple comparisons). Mean activation levels during reactive and proactive inhibition were calculated over the ROIs as defined by the a priori masks. For both reactive and proactive inhibition, the correlation between the change in BOLD fMRI activation levels and change in processing speed and attention Z-scores was examined in the 17 ROIs in both groups using both the Pearson and Spearman correlation coefficient. These coefficients were then compared to examine a differential pattern after switching from FTC/TDF/EFV to FTC/TDF/RPV versus continuing with FTC/TDF/EFV. Using a multivariate analysis of variance (MANOVA) and using Pillai's trace, groupwise differences in the overall change in BOLD fMRI activation between baseline and 12 weeks after therapy switch in the 17 regions were also assessed. A two-sided alpha level of 0.05 was used and statistical analyses were conducted using SPSS version 25.0 (IBM Corp. Armonk. NY).

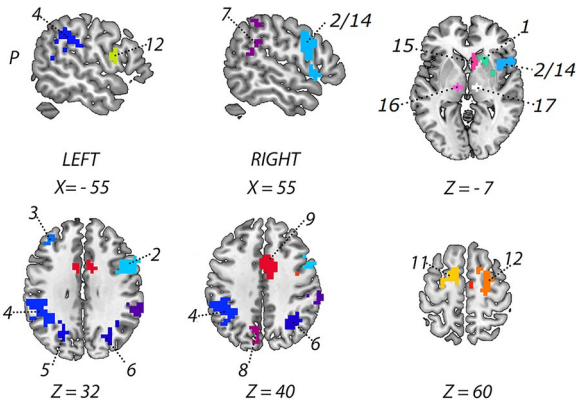

Fig. 2 Regions used to assess activation levels related to reactive and proactive inhibition after discontinuing EFV. Regions were (1) right striatum; (2) right inferior frontal cortex ventral; (3) left middle frontal gyrus; (4) left temporoparietal junction; (5) left superior parietal gyrus; (6) right superior parietal gyrus; (7) right temporoparietal junction; (8) left precuneus; (9) anterior cingulate gyrus; (10) right superior frontal gyrus; (11) left superior frontal gyrus; (12) left inferior frontal gyrus; (13) right anterior insula; (14) right inferior frontal cortex dorsal; (15) right caudate; (16) left subthalamic nucleus; (17) right subthalamic nucleus

RESULTS

Demographics

A total of 59 potential participants were screened for inclusion, of which one participant was a screen failure due to not meeting eligibility criteria (Fig. 3). The remaining 58

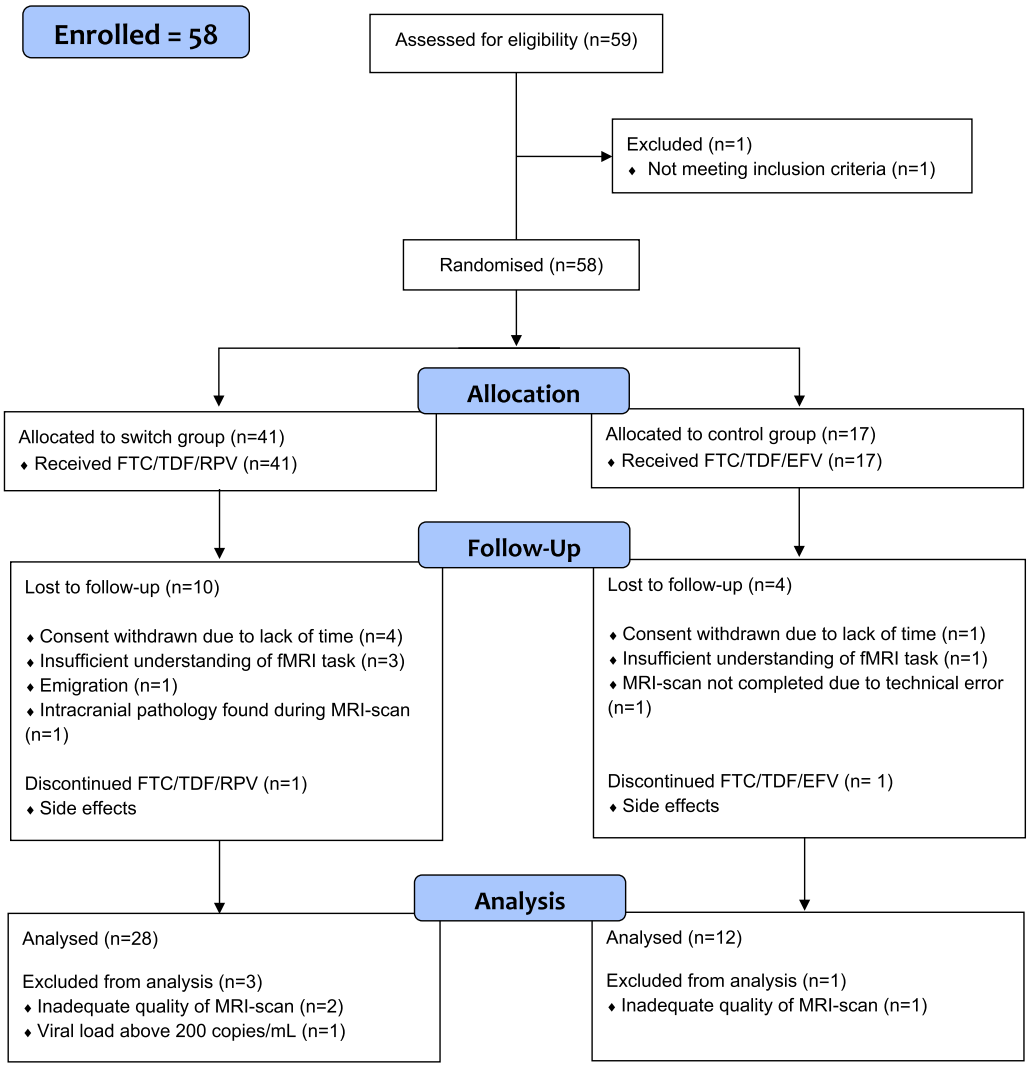

Fig. 3 Trial flowchart of participants enrolled and included in our analysis. *EFV* efavirenz, *fMRI* functional magnetic resonance imaging, *FTC* emtricitabine, *RPV* rilpivirine, *TDF* tenofovirdisoproxil fumarate

participants were randomized (2:1), with 41 assigned to the switch group and 17 to the control group. Of these, 18 participants were lost to follow-up or excluded from analysis for reasons indicated in the flowchart (with 1 participant in each group discontinuing because of side effects), leaving 28 and 12 participants in the switch and control group for analysis. These 40 participants had a median age of 43.37 (IQR 35.47–47.23) years, were all male, and had 16.50 (IQR 16.00–17.00) median years of education (Table 1). The median time since HIV and on EFV was, respectively, 96.80 (IQR 62.02–121.15) and 62.00 (IQR 32.53–78.00) months, with 38 (95%) and 39 (97.5%) of participants virologically suppressed at baseline and after 12 weeks.

Behavioral Analyses

Motor Execution

In order to assess the effect of discontinuing EFV on response inhibition, we first evaluated

Table 1 Characteristics of the study participants according to study arm

	FTC/TDF/RPV (switch)		FTC/TDF/EFV (control)	
	n **= 28**	**(IQR)/(%)**	***n*** **= 12**	**(IQR)/(%)**
Demographics				
Age (years)	42.68	35.47–47.23	44.19	36.64–48.20
Gender (male)	28	100	12	100
BMI (kg/m^2)	24.90	22.05–27.13	25.25	22.31–26.68
Education (years)	16.00	16.00–17.00	17.00	16.00–17.75
Clinical characteristics				
Time since HIV diagnosis (months)	95.95	49.95–118.02	102.50	74.45–137.94
Time on EFV (months)[a]	64.00	33.93–77.90	55.00	22.60–86.00
Time on cART (months)[a]	64.00	38.82–77.90	55.00	22.60–86.00
ANI at baseline	7	25.00	3	25.00
Co-medication				
0	17	60.7	7	58.3
1	8	28.6	4	33.3
2 or more	3	10.7	1	8.3
Biochemical characteristics				
Nadir CD4 (cells/mm^3)[a]	299.50	220.50–341.25	241.00	145.25–367.50
Baseline CD4	619.50	470.50–804.25	688.00	547.00–783.75
Baseline VL < 50 (copies/mL)	27	96.4	11	91.7
Baseline VL 50–200	1	3.6	1	8.3
CD4 at week 12[a]	650.50	520.50–740.00	638.00	566.00–820.25
VL < 50 at week 12	28	100	11	91.7
VL 50–200 at week 12	0	0	1	8.3
Baseline questionnaire results		(SD)		(SD)
HADS–anxiety[a]	2.92	2.63	3.27	3.35
HADS–depression[a]	1.92	2.78	2.36	3.11
PROMIS–anxiety[a]	46.70	7.35	48.25	6.97
PROMIS–depression[a]	45.70	8.24	45.73	9.99
PROMIS–sleep disorder[a]	47.63	8.16	45.59	5.78

Table 1 continued

All categorical data are expressed as frequency (percentage) and continuous data are expressed as median (interquartile range) or mean (standard deviation, SD)

ANI asymptomatic neurocognitive impairment (according to the Frascati criteria [3]); *BMI* body mass index; *cART* combination antiretroviral therapy; *FTC/TDF/EFV* emtricitabine/ tenofovirdisoproxil fumarate/ efavirenz; *FTC/TDF/RPV* emtricitabine/tenofovirdisoproxil fumarate/rilpivirine; *HADS* hospital anxiety and depression scale; *PROMIS* patient reported outcome measurement information system; *VL* viral load

[a]Missing data: time on EFV (1 control, 2.5%), time on cART (1 control, 2.5%), nadir CD4 (2 switch participants, 5.0%), CD4 at week 12 (2 switch participants, 5.0%), HADS questionnaire (1 control, 2.5%), and 3 switch participants (7.5%), PROMIS questionnaire, 1 control (2.5%) and 2 switch participants, 5.0%)

motor execution in the two groups. Response time for baseline GO trials (with a STOP signal probability of 0%) was similar between groups at both time points ($F_{1,38} = 0.65$, $p = 0.43$), with no group-by-time interaction effect ($F_{1,38} = 0.44$, $p = 0.51$) nor main group effect ($F_{1,38} = 0.38$, $p = 0.54$). Similar results were found for response accuracy.

Reactive Inhibition

Next, we evaluated reactive inhibition behavioral outcomes after discontinuing EFV. Both groups responded significantly faster during incorrect STOP trials compared to successful GO trials at both time points ($F_{1,38} = 126.33$, $p < 0.001$; $F_{1,38} = 103.34$, $p < 0.001$), indicating that the underlying assumption of the SSAT task (i.e., the race between the "STOP" and "GO" brain processes model) was valid [38]. Surprisingly, we found that the speed of reactive inhibition (SSRT) improved in both groups over time ($F_{1,38} = 6.84$, $p = 0.01$), with the mean SSRT of the switch and control groups decreasing by 8.61 ms and 6.80 ms, respectively. There was no group-by-time interaction ($F_{1,38} = 0.09$, $p = 0.76$) nor main group effect ($F_{1,38} = 1.30$, $p = 0.26$). Response accuracy of pooled STOP trials was also found to improve for both groups ($F_{1,38} = 4.28$, $p = 0.05$), but no group-by-time interaction effect ($F_{1,38} = 0.17$, $p = 0.68$) nor main group effect ($F_{1,38} = 0.04$, $p = 0.84$) was observed. The latter result was expected as we manipulated the stop signal delay according to individual performance to ensure a similar number of successful trials.

Proactive Inhibition

We then examined proactive inhibition behavioral outcomes. A significant main effect of STOP probability was found at both time points ($F_{2.39,93.19} = 12.26$, $p < 0.001$; $F_{1.69,65.82} = 6.10$, $p = 0.01$), indicating participants adequately performed the task by slowing their response with increased probability for a STOP signal. No main effect on proactive inhibition was found, as the slopes of the mean response times in STOP trials with an increasing STOP probability were similar over time ($F_{1,38} = 0.08$, $p = 0.78$). Additionally, there was no group-by-time interaction effect ($F_{1,38} = 0.12$, $p = 0.73$) nor main group effect ($F_{1,38} = 0.95$, $p = 0.34$).

Functional ROI Analyses

Reactive Inhibition

Afterwards, we assessed reactive inhibition activation. Positive Pearson coefficients were observed for the change in BOLD fMRI activation levels and change in processing speed and attention Z-scores in all 17 ROIs in participants switching from FTC/TDF/EFV to FTC/TDF/RPV, whereas in the control group continuing FTC/TDF/EFV, negative correlation coefficients were observed in 10/17 and 13/17 ROIs, respectively (Table 2). A similar pattern was observed for the Spearman coefficients (Supplementary Table S1). No statistically significant MANOVA effect was observed of discontinuing EFV on the overall change in reactive inhibition BOLD fMRI activation between baseline and

Table 2 Pearson correlation coefficients between the change in BOLD fMRI activation for reactive inhibition and the change in attention or processing speed NPA Z-scores per ROI, stratified in the intervention (switching from FTC/TDF/EFV to FTC/TDF/RPV) and the control group (continuing FTC/TDF/EFV)

Delta BOLD fMRI activation in:	Control group (12)		Intervention group (28)		Control group (12)		Intervention group (28)	
	Delta attention		Delta attention		Delta processing speed		Delta processing speed	
	Pearson	*p* value	Pearson	*p* value	Pearson	*p* value	Pearson	*p* value
(1) Right striatum	0.266	0.403	0.419	0.026*	− 0.065	0.841	0.229	0.242
(2) Right inferior frontal cortex ventral	− 0.113	0.726	0.422	0.025*	− 0.218	0.496	0.171	0.385
(3) Left middle frontal gyrus	− 0.230	0.472	0.396	0.037*	− 0.135	0.676	0.070	0.724
(4) Left temporoparietal junction	− 0.321	0.309	0.484	0.009*	− 0.038	0.906	0.139	0.481
(5) Left superior parietal gyrus	− 0.433	0.159	0.410	0.030*	− 0.171	0.596	0.328	0.088
(6) Right superior parietal gyrus	− 0.315	0.318	0.375	0.049*	− 0.241	0.451	0.177	0.368
(7) Right temporoparietal junction	− 0.114	0.723	0.542	0.003*	− 0.222	0.488	0.187	0.340
(8) Left precuneus	− 0.479	0.115	0.521	0.005*	− 0.036	0.911	0.087	0.660
(9) Anterior cingulate gyrus	0.078	0.809	0.199	0.310	0.018	0.957	0.427	0.024
(10) Right superior frontal gyrus	0.260	0.414	0.444	0.018*	0.042	0.896	0.104	0.600
(11) Left superior frontal gyrus	0.140	0.665	0.547	0.003*	0.121	0.708	0.177	0.368
(12) Left inferior frontal gyrus	0.133	0.680	0.343	0.074	− 0.038	0.907	0.208	0.287
(13) Right anterior insula	− 0.234	0.465	0.383	0.044	− 0.302	0.340	0.271	0.163
(14) Right inferior frontal cortex dorsal	− 0.211	0.510	0.463	0.013	− 0.318	0.314	0.161	0.414
(15) Right caudate	− 0.179	0.579	0.112	0.569	− 0.092	0.777	0.313	0.104
(16) Left subthalamic nucleus	0.069	0.830	0.117	0.553	− 0.343	0.275	0.345	0.072
(17) Right subthalamic nucleus	0.075	0.817	0.088	0.657	− 0.464	0.129	0.466	0.013*

*Results significant at a $p = 0.05$ value

12 weeks after therapy in the 17 ROIs (Pillai's trace = 0.384, $F_{17,22} = 0.81$, $p = 0.67$).

In none of the 17 ROIs were significant group-wise differences observed in the overall change in reactive inhibition BOLD fMRI activation between baseline and 12 weeks after therapy.

Proactive Inhibition

Finally, we assessed proactive inhibition activation. No apparent differential between-group pattern was observed regarding the Pearson coefficients for the change in BOLD fMRI activation levels and change in processing speed and attention Z-scores in participants switching from FTC/TDF/EFV to FTC/TDF/RPV versus the controls continuing FTC/TDF/EFV (Table 3). Similarly, for the Spearman coefficients, no discernable differential pattern was observed (Supplementary Table S3). No statistically significant MANOVA effect was observed of discontinuing EFV on the overall change in proactive inhibition BOLD fMRI activation between baseline and 12 weeks after therapy in the 17 ROIs (Pillai's trace = 0.294, $F_{17,22} = 0.54$, $p = 0.90$).

Table 3 Pearson correlation coefficients between change in BOLD fMRI activation for proactive inhibition and change in attention or processing speed NPA Z-scores per ROI, stratified in the intervention (switching from FTC/TDF/EFV to FTC/TDF/RPV) and the control group (continuing FTC/TDF/EFV)

Delta BOLD fMRI activation in:	Control group (12)		Intervention group (28)		Control group (12)		Intervention group (28)	
	Delta attention		Delta attention		Delta processing speed		Delta processing speed	
	Pearson	*p* value	Pearson	*p* value	Pearson	*p* value	Pearson	*p* value
(1) Right striatum	− 0.325	0.303	− 0.236	0.226	− 0.103	0.751	− 0.152	0.440
(2) Right inferior frontal cortex ventral	− 0.192	0.550	− 0.378	0.047*	− 0.129	0.690	− 0.265	0.173
(3) Left middle frontal gyrus	− 0.201	0.530	0.043	0.827	− 0.157	0.626	− 0.065	0.744
(4) Left temporoparietal junction	− 0.367	0.241	− 0.078	0.694	− 0.240	0.453	− 0.204	0.298
(5) Left superior parietal gyrus	0.045	0.889	− 0.171	0.385	− 0.179	0.578	− 0.041	0.837
(6) Right superior parietal gyrus	− 0.184	0.566	− 0.272	0.162	− 0.211	0.510	− 0.115	0.560
(7) Right temporoparietal junction	− 0.320	0.311	− 0.278	0.152	− 0.180	0.575	− 0.145	0.460
(8) Left precuneus	− 0.200	0.534	− 0.261	0.180	0.099	0.759	0.090	0.651
(9) Anterior cingulate gyrus	0.073	0.823	− 0.277	0.154	0.337	0.285	− 0.143	0.468
(10) Right superior frontal gyrus	0.069	0.832	− 0.199	0.310	− 0.255	0.423	− 0.005	0.982
(11) Left superior frontal gyrus	− 0.401	0.197	− 0,067	0,735	− 0.202	0.529	0.068	0.730
(12) Left inferior frontal gyrus	− 0.140	0.665	− 0.187	0.340	− 0.201	0.532	− 0.155	0.431
(13) Right anterior insula	− 0.026	0.936	− 0.396	0.037*	− 0.323	0.306	0.070	0.725
(14) Right inferior frontal cortex dorsal	0.022	0.945	− 0.222	0.257	− 0.215	0.503	− 0.056	0.779
(15) Right caudate	0.121	0.708	− 0.208	0.288	0.173	0.590	0.034	0.864
(16) Left subthalamic nucleus	− 0.298	0.348	− 0.118	0.548	− 0.536	0.072	− 0.166	0.397
(17) Right subthalamic nucleus	− 0.222	0.489	− 0.140	0.477	− 0.383	0.219	− 0.143	0.466

*Results significant at a $p = 0.05$ value

DISCUSSION

This multicenter BOLD fMRI randomized controlled trial (RCT) was, to our knowledge, the first to investigate underlying neural mechanisms of cognitive improvement after discontinuing EFV in fronto-striatal response inhibition by combining NPA and BOLD fMRI findings. Potential neural mechanisms were found in subcortical functioning, with functional imaging revealing a differential pattern between study groups regarding the change in reactive inhibition fMRI activation and change in processing speed and attention Z-scores. No group-wise differences were found after discontinuing EFV and no apparent between-group differential pattern was observed for proactive inhibition.

Consistent with our hypothesis that EFV would affect subcortical functioning, no difference in motor execution and proactive inhibition behavioral outcomes was found after stopping EFV. However, to our surprise, we found that for reactive inhibition both groups improved, in the form of improved SSRTs and response accuracy. Although response accuracy

can be practiced, thus seeming a logical explanation, the SSRT cannot be improved through repetition. A previous BOLD fMRI study in PLWH switching from EFV to RPV also observed improved SSRTs and suggested this might reflect a detrimental effect of EFV [25]. However, since this was a before–after study without a control group continuing EFV, our results raise the question of whether the improvement can truly be attributed to EFV, as both our study groups—regardless of EFV switch—improved over time. Another BOLD fMRI study, though cross-sectional in nature and conducted in adolescent PLWH, showed similar SSRTs for those on EFV versus other antiretroviral agents, providing further evidence of EFV most likely not affecting subcortical functioning behavioral outcomes [26]. Finally, it is possible that the SSRT improvement is unrelated to HIV, but since our study did not include a HIV-negative population, we were unable to investigate this. Although we are unsure why the SSRT improved, we believe it is not due to discontinuing EFV and therefore unrelated to our research question.

In line with our hypothesis, we found a differential pattern between the study groups regarding the change in reactive inhibition fMRI activation and change in processing speed and attention Z-scores, with the correlation coefficient being positive for all ROIs for participants who switched to FTC/TDF/RPV versus a negative correlation coefficient for almost all ROIs for the controls. These findings suggest that the neurocognitive changes observed in NPA after discontinuing EFV are, at least in part, mediated by reactive inhibition. Previous research had already shown that HIV infection and cART in general impair neurocognitive systems related to attention and processing speed and here we show that reactive inhibition is involved in this process [40–42]. However, opposite correlation coefficients (i.e., negative versus positive) between groups were not observed in all regions, suggesting that either EFV selectively impacts fronto-striatal regions involved in attention or processing speed or, importantly, that our sample size was ultimately not large enough to detect all differences. As our power calculation was performed for another outcome, this may have led to lack of power for detecting all differences in activation levels. This could also be the case for groupwise differences, of which we found none. Nevertheless, the fact that we do observe a distinctly differential between-group pattern regarding the correlation coefficients in ROIs clearly demonstrates EFV-induced changes in reactive inhibition, but additional research with larger sample sizes is needed to further explore whether these neural mechanisms may serve as markers for neurocognitive impairment.

Proactive inhibition activation was unaffected after discontinuing EFV. Although the aforementioned study evaluating EFV found altered proactive inhibition, it was conducted in adolescent PLWH undergoing active neurodevelopment [26]. Our population consisted of adult asymptomatic men with a longer time since HIV diagnosis and higher level of education and we therefore hypothesized that not cortical but subcortical functioning—since studies already demonstrated this to be impaired by HIV infection—would be affected, which our findings confirmed [22, 43].

The main strength of our study lies in its design, as our RCT design ensured that all known and unknown confounders were similar across groups. Moreover, our control group and longitudinal design allowed us to distinguish practice effects and adequately compare the effect of switching off EFV versus continuing EFV. Furthermore, we used strict inclusion and exclusion criteria which ensured that known fMRI confounding due to variability in gender, age, psychiatric disorders, and drug use was homogenous across participants or reason for exclusion.

Our study has several limitations besides the aforementioned sample size, although ours was still relatively large for a fMRI study, particularly compared to other prospective fMRI studies [15, 25]. A substantial number of participants were lost to follow-up or excluded from analysis, which may have contributed to any lack of power. However, only two participants withdrew because of side effects and other reasons for loss to follow-up or exclusion were not related to our

determinant or outcome, leading us to believe this did not result in bias.

CONCLUSIONS

This study found evidence of potential neural mechanisms underlying cognitive improvement after discontinuing EFV in PLWH in subcortical functioning. Our findings suggest that EFV's effect on attention and processing speed is, at least partially, mediated by reactive inhibition and thus affects these key subcortical areas involved in executive functioning, working memory, and attention.

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Author Contribution. Joop E Arends designed the study. Charlotte S Hakkers wrote the study protocol under supervision of Joop E Arends, Charlotte S Hakkers, and Pascal Pas were responsible for the site work including the recruitment, follow-up and data collection. All authors had access to data. Patrick GA Oomen performed the analysis, interpreted results and drafted the manuscript in close collaboration with Stefan du Pleiss and Berend J van Welzen Patrick GA Oomen, Charlotte S Hakkers, Joop E Arends, Guido EL van der Berk, Pascal Pas, Andy IM Hoepelman, Berend van Welzen, and Stefan du Pleiss contributed to the interpretation of the data, critically reviewed the manuscript and approved the final manuscript.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Joop E Arends has received advisory board fees from ViiV Healthcare. Berend J van Welzen has received a research grant and speaker fees from Gilead Sciences, has received speaker and advisory board fees from ViiV Healthcare: all fees were paid to the institution. J.A. has changed their affiliation after the completion of the manuscript. His current affiliation is Faculty of Health, Medicine and Life Sciences, Maastricht University, Universiteitssingel 40, 6229 ER Maastricht. Berend J. van Welzen is an Editorial Board member of *Infectious Diseases and Therapy*. Berend J. van Welzen was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. For the remaining authors no conflicts of interest are present to be declared.

Ethical Approval. The trial was reviewed and approved by the Medical Research Ethics Committee of the UMC Utrecht, performed in accordance with the Declaration of Helsinki and registered at Clinicaltrials.gov [NCT02308332].

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