Adaptive Working Memory Training Improved Brain Function in Human Immunodeficiency Virus–Seropositive Patients

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Objective: We aimed to evaluate the effectiveness of an adaptive working memory (WM) training (WMT) program, the corresponding neural correlates, and *LMX*1A-rs4657412 polymorphism on the adaptive WMT, in human immunodeficiency virus (HIV) participants compared to seronegative (SN) controls.

Methods: A total of 201 of 206 qualified participants completed baseline assessments before randomization to 25 sessions of adaptive WMT or nonadaptive WMT. A total of 74 of 76 (34 HIV, 42 SN) completed adaptive WMT and all 40 completed nonadaptive WMT (20 HIV, 20 SN) and were assessed after 1 month, and 55 adaptive WMT participants were also assessed after 6 months. Nontrained near-transfer WM tests (Digit-Span, Spatial-Span), self-reported executive functioning, and functional magnetic resonance images during 1-back and 2-back tasks were performed at baseline and each follow-up visit, and *LMX*1A-rs4657412 was genotyped in all participants.

Results: Although HIV participants had slightly lower cognitive performance and start index than SN at baseline, both groups improved on improvement index ($>$30%; false discovery rate [FDR] corrected $p < 0.0008$) and nontrained WM tests after adaptive WMT (FDR corrected, $p \leq 0.001$), but not after nonadaptive WMT (training by training type corrected, $p = 0.01$ to $p = 0.05$) 1 month later. HIV participants (especially *LMX*1A-G carriers) also had poorer self-reported executive functioning than SN, but both groups reported improvements after adaptive WMT (Global: training FDR corrected, $p = 0.004$), and only HIV participants improved after nonadaptive WMT. HIV participants also had greater frontal activation than SN at baseline, but brain activation decreased in both groups at 1 and 6 months after adaptive WMT (FDR corrected, $p < 0.0001$), with normalization of brain activation in HIV participants, especially the *LMX*1A-AA carriers (*LMX*1A genotype by HIV status, cluster-corrected-$p < 0.0001$).

Interpretation: Adaptive WMT, but not nonadaptive WMT, improved WM performance in both SN and HIV participants, and the accompanied decreased or normalized brain activation suggest improved neural efficiency, especially in HIV-*LMX*1A-AA carriers who might have greater dopaminergic reserve. These findings suggest that adaptive WMT may be an effective adjunctive therapy for WM deficits in HIV participants.

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Incidence of human immunodeficiency virus (HIV)-associated dementia declined dramatically since the introduction of potent combination antiretroviral therapy; however, milder forms of HIV-associated neurocognitive disorders (HAND) persist in 20% to 50% of HIV-infected individuals.[1,2] HAND leads to both functional and occupational disabilities, which are often exacerbated by comorbid factors, such as coinfections and ongoing substance abuse.[3,4] Even with milder forms of HAND, the cost of care for these patients may double in the next 20 years, primarily for residential care.[5] Given that more HIV individuals are at risk for HAND attributed to aging,[6] developing effective treatments for these patients is critical. However, multiple pharmacological trials targeting neuroprotection or enhancing monoamines (eg, memantine, minocycline, and selegiline) were conducted with no clear efficacy for cognitive improvements.[1] To address this urgent problem, we performed a comprehensive study to evaluate how a computerized working memory (WM) training (WMT) program might improve brain function in HIV-infected, compared to seronegative (SN), individuals.

WM deficits are common in HIV patients.[7–9] WM is defined as the cognitive skill involved in retaining and manipulating information "online" over short periods of time. Therefore, WM is necessary for concentration, maintaining awareness, and is crucial for learning, executive function, and ultimately for all daily life activities. WM deficits can result in HAND and may lead to unemployment and dependence in activities of daily living,[10] self-reported cognitive complaints,[11] and poorer medication adherence.[12]

Here, we evaluated a computerized adaptive WMT program (Cogmed®) that improved cognition in children with attention deficit hyperactivity disorder (ADHD),[13] preterm born children,[14,15] adults with stroke,[16] acquired brain injury,[17,18] and normal aging.[19] We aimed to (1) determine whether adaptive, but not nonadaptive, WMT would lead to improved brain function on trained and near-transfer nontrained WM tests and self-reported executive function at 1 month after training, and whether the gain from adaptive WMT is maintained at 6 months in participants with or without HIV infection. (2) To assess the neural correlates of adaptive WMT, we performed blood-oxygenated-level–dependent (BOLD) functional magnetic resonance (MR) imaging (MRI) (fMRI) to evaluate changes in the neural network at 1 and 6 months after the training. Based on previous work, we expect HIV patients to show a baseline reorganized or adapted WM network, with lesser activation within the normal WM network, but greater activation in the reserve networks, compared to controls.[20–24] After the adaptive WMT, improved efficiency in the neural networks would lead to decreased activation in the extent and magnitude of the BOLD signal in both groups. (3) Furthermore, given that WM deficits may be related to reduced dopaminergic function in HIV patients,[25–27] we also explored whether polymorphisms of LIM homeobox transcription factor-1-alpha gene (*LMX*1A-rs4657412), which codes for a factor that maintains dopaminergic neurons,[28] would modulate the adaptive WMT effects. Polymorphisms of *LMX*1A were associated with dopaminergic disorders, such as Parkinson's disease[29] or schizophrenia,[30] and recently with WMT effects.[31] Based on previous work,[31] we predicted that rs4657412-AA carriers would show greater adaptive WMT effects than the G carriers, particularly for those with normal cognition.

Materials and Methods

The study (ClinicalTrails.gov-NCT02602418) was approved by the Committees on Human Studies at the University of Hawaii and the Queen's Medical Center. Participants were recruited from the local community (September 2010–December 2015), screened by telephone (n = 436), and evaluated with detailed medical and neuropsychiatric examinations (n = 219) to ensure that they fulfilled the study criteria[32] (n = 206; Fig 1). Participants were men or women of any ethnicity, ages ≥18 years, who provided written informed consents. HIV participants had documented HIV seropositivity and were stable on antiretroviral medications for ≥6 months or remained off treatment during the study. SN controls were confirmed seronegative for HIV and matched demographically to the HIV participants. Participants were excluded if they had any confounding medical or neuropsychiatric disorders, or contraindications for MR studies.[32]

A total of 201 of 206 qualified participants completed baseline neuropsychological testing, MRI scans, provided blood samples for DNA, and were randomized to adaptive or nonadaptive WMT. A total of 173 of 201 started training; 76 (34 HIV, 42 SN) completed adaptive WMT and 40 (20 HIV, 20 SN) completed nonadaptive WMT (Table 1). A total of 74 adaptive WMT (33 HIV, 41 SN) and all 40 nonadaptive WMT participants were assessed 1 month after training and 55 adaptive WMT participants (26 HIV, 29 SN) were additionally assessed 6 months later. A total of 12 (5 HIV, 7 SN) participants who completed the nonadaptive WMT also completed the adaptive WMT (ie, crossover subgroup).

Cognitive Assessments

Before the training, each participant was assessed for estimated verbal intelligence quotient (IQ), full-scale IQ, and completed tests within the seven cognitive domains required to diagnose HAND[33] (Table 2). At each visit, all participants were assessed with nontrained near-transfer WM tests (Digit-Span and Letter-Number Sequencing from Wechsler Adult Intelligence Scale-Fourth Edition, and Spatial-Span from the Wechsler Memory
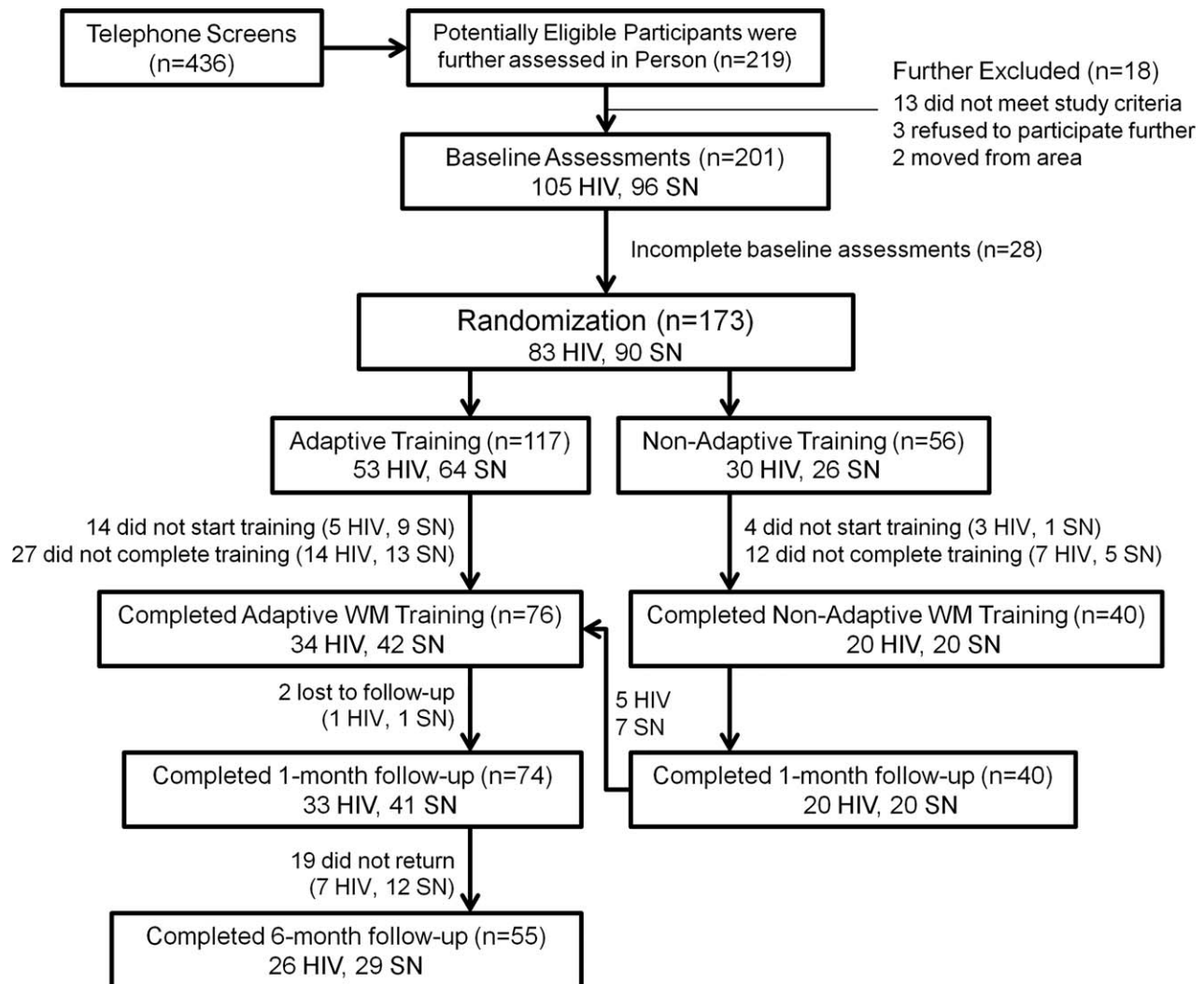
FIGURE 1: CONSORT diagram showing the number of participants at each stage of the study. CONSORT = CONsolidated Standards Of Reporting Trials; HIV = human immunodeficiency virus; SN, seronegative controls; WM – working memory.

Scale-Third Edition) and for depressive symptoms (Centers for Epidemiologic Studies-Depression Scale; CES-D) and self-reported executive function in everyday life (Behavior Rating Inventory of Executive Function-Adult Version; BRIEF-A).

WMT (Cogmed® RM; www.cogmed.com)

Each participant had to complete 20 to 25 sessions in 5–8 weeks. Each session required 30 to 40 minutes and had 8 of 12 possible modules (15 trials each) targeting verbal and visuo-spatial WM. The primarily verbal WM training comprised four modules with various combinations of numbers or letters that were paired with lamps that lit up in different sequences. The visuospatial WMT included eight modules with various combinations of lamps that lit up and objects that rotated, moved, or required sorting. The participants had to recall the sequences with or without cues, and in forward or reverse order. These tasks became increasingly difficult, adapting to the participants' performance (adaptive WMT) or remained at the same difficulty level (nonadaptive WMT). An improvement index was generated only for the adaptive WMT, based on one visuospatial (visual data link) and one verbal WM (input module with or without lid) task trained.

MRI/fMRI

All scans were performed in a 3-Tesla MR scanner (TimTrio; Siemens Medical Solutions, Erlangen, Germany). Structural MRI included a sagittal three-dimensional magnetization prepared rapid gradient echo (repetition time/echo time [TR/TE]/inversion time [TI] = 2,200/4.47/1,000 ms; 1-average; $256 \times 256 \times 160$ matrix, GeneRalized Autocalibrating Partial Parallel Acquisition = 2) and an axial fluid attenuated inversion recovery FLAIR sequence (TR/TE/TI = 9,100/84/2,500 ms; 1-average; $204 \times 256 \times 44$ matrix). An experienced neurologist (LC) reviewed all structural scans to exclude those with major abnormalities. BOLD-fMRI were performed during two WM tasks (1-back and 2-back) after brief training, with two single-shot gradient-echo echo planar imaging time series (TE/TR = 30/3,000 ms; 3-mm slices; 1-mm gap; 46 axial slices; 64^2

TABLE 1. Participant Characteristics at Baseline (mean ± SE)					
	SN Controls (n = 62)		HIV⁺ Participants (n = 54)		p (*t* tests, χ^2, one-way ANOVA)
	Nonadaptive (n = 20)	Adaptive (n = 42)	Nonadaptive (n = 20)	Adaptive (n = 34)	
Age (yr)	52.1 ± 2.3	52.6 ± 1.7	57.0 ± 1.9	50.3 ± 1.9	0.17
No. male sex (%)	19 (95)	36 (86)	18 (90)	32 (94)	0.55
% race (Asian/White/ American Indian/ Pacific Islander/Black or African American/ more than one race)	25/50/0/ 20/0/5	24/57/0/ 9.5/0/9.5	5/70/0/ 10/0/15	12/67/ 3/3/6/9	0.30
Index of social position[a]	35.4 ± 3.9	38.5 ± 2.5	34.7 ± 3.8	40.9 ± 2.9	0.51
CES-D scale score[b]	8.1 ± 1.6	8.7 ± 1.2	8.9 ± 2.2	8.6 ± 1.3	0.99
*LMX*1A frequency (% AA)[c]	14 (70)	25 (61)	7 (37)	12 (36)	**0.03**
Karnofsky score (0–100)	98.9 ± 0.8	100 ± 0.0	94.2 ± 2.2	92.1 ± 1.7	**0.0004**
HIV disease severity					
Duration of HIV diagnosis (months)			195 ± 27	192 ± 17.1	0.92
No. on antiretroviral medications (%)			19 (95)	33 (97)	0.70
No. with undetectable virus (%)[d]			14 (70)	29 (85)	0.18
Log viral load (copies/mL)[e]			1.67 ± 0.12	1.73 ± 0.16	0.81
CD4 (no./mm³)			613.9 ± 96.5	552.4 ± 42.4	0.51
Nadir CD4 (no./mm³)			295.6 ± 75.9	203.5 ± 27.4	0.18

[a]Index of social position was assessed using the Hollingshead Four Factor Index of Social Position.
[b]CES-D: Center for Epidemiological Studies–Depression Scale.
[c]*LMX*1A-genotype not available from 3 participants (2 refused, 1 had ambiguous data; 1 adaptive SN, 1 adaptive HIV, and 1 HIV crossover).
[d]Undetectable viral load: < 75 copies/mL.
[e]Log viral load calculated only for the 11 subjects with detectable viral load.
SE = standard error; HIV = human immunodeficiency virus; SN, seronegative controls; ANOVA = analysis of variance.

matrix; 192-mm field of view; 82 time points; and a vendor-provided prospective acquisition correction for head motion for real-time fMRI). The MRI trigger pulse was synchronized to a custom-stimulus software written in Matlab (The MathWorks, Inc., Natick, MA). Participants responded with a button push if the letter repeated on consecutive screens (1-back), or 2-screens before (2-back), providing reaction time and accuracy. Only scans with task accuracy >70% and motion < 1 mm and <1 degree were accepted. Spatial distortion correction was performed during image reconstruction using point-spread function mapping.[34]

In total, 312 fMRI scans were analyzed, 171 scans from the 1-back task at baseline and 1 month (36 SN, 28 HIV) and additionally at 6 months (24 SN, 19 HIV), and 141 scans from the 2-back task at baseline and 1 month (32 SN, 20 HIV) and additionally 6 months (21 SN, 16 HIV) after adaptive WMT.

Genotyping for LMX1A
DNA was extracted from whole blood collected in ethylenedia-minetetraacetic acid tubes using DNeasy Blood & Tissue Kit (catalog no. 69506; Qiagen Inc, Valencia, CA). Restriction fragment length polymorphism polymerase chain reaction analysis was used to determine the *LMX*1A polymorphism at rs4657412 as described.[32] Although the genotype distribution did not deviate from Hardy-Weinberg equilibrium, AA was less prevalent in the HIV groups (Table 1), contrary to the higher A frequency 0.6805/1600 (www.hapmap.org).

Statistical Analyses
Demographic and cognitive variables were analyzed using SAS software (version 9.3; SAS Institute Inc, Cary, NC). First, repeated-measures analysis of covariance (ANCOVA) was used to evaluate the cognitive outcomes, with HIV serostatus and *LMX*1A genotype (AA vs GG/GA) as between-participant

TABLE 2. Baseline Cognitive Performance and Training Indices (mean ± SE)

	SN Controls (n = 62)		HIV+ Participants (n = 54)		p (one-way ANOVA, χ^2 or unpaired t tests)
	Nonadaptive (n = 20)	Adaptive (n = 42)	Nonadaptive (n = 20)	Adaptive (n = 34)	
Education (yr)	15.5 ± 0.6	14.6 ± 0.4	14.9 ± 0.6	14.2 ± 0.4	0.31
Estimated verbal IQ[a]	111.6 ± 1.3	110.3 ± 1.4	108.2 ± 2.0	106.5 ± 1.5	0.10
Full-scale IQ[b]	111.4 ± 3.3	109.6 ± 4.7	110.3 ± 3.6	105.6 ± 2.0	0.38
HIV dementia scale (0–16)	14.8 ± 0.4	15.0 ± 0.2	13.2 ± 0.7	14.0 ± 0.4	**0.03**
Cognitive domain Z-scores at baseline[c]					
Fluency Z-score	0.10 ± 0.10	0.07 ± 0.06	−0.15 ± 0.10	−0.02 ± 0.08	0.22
Executive function Z-score	−0.13 ± 0.08	−0.06 ± 0.07	−0.21 ± 0.10	−0.18 ± 0.08	0.54
Speed Z-score	−0.18 ± 0.13	−0.05 ± 0.05	−0.48 ± 0.14	−0.23 ± 0.06	**0.006**
Attention Z-score	0.01 ± 0.10	0.07 ± 0.06	−0.48 ± 0.12	−0.20 ± 0.07	**0.02**
Learning Z-score	0.26 ± 0.23	0.35 ± 0.14	−0.30 ± 0.39	0.02 ± 0.15	0.16
Memory Z-score	0.38 ± 0.20	0.33 ± 0.12	−0.17 ± 0.35	0.06 ± 0.15	0.20
Motor Z-score	−0.27 ± 0.20	−0.12 ± 0.14	−0.38 ± 0.24	0.08 ± 0.17	0.31
Global Z-score	−0.04 ± 0.12	0.08 ± 0.09	−0.27 ± 0.17	−0.27 ± 0.11	0.06
No. HAND or HAND equivalent[d] (%)	3 (15)	8 (19)	8 (40)	7 (21)	0.13
Assessments from the working memory training program					
Sessions trained (No.)	24.8 ± 0.2	24.7 ± 0.1	24.5 ± 0.3	24.2 ± 0.3	0.25
Start index	NA	88 ± 2.2	NA	81 ± 1.8	**0.005**
Maximum index	NA	116 ± 3.4	NA	105 ± 2.7	**0.005**
Index of improvement (%)	NA	28 ± 2 (33)	NA	25 ± 2 (32)	0.08

[a]Verbal intelligence quotient (IQ) was estimated from the Wechsler Test of Adult Reading.
[b]Full-scale IQ was calculated from the Wechsler Adult Intelligence Scale, 4th edition.
[c]Z-scores are derived from a normative database of 481 seronegative healthy controls studied with the same test battery below (56 for the Delis-Kaplan Executive Function System [DKEFS]) and are adjusted for age and education.

- Fluency: DKEFS or Ruff Figural Design Fluency and Verbal Fluency (with letters FAS).
- Executive Functions: DKEFS-Color Word Interference or Stroop Interference and Trail Making Test B.
- Speed of information processing: Symbol Digit, DKEFS Trail-making Number Sequencing or Trail Making Test A, DKEFS Color Naming or Stroop Color Naming, and California Computerized Assessment Package (CalCAP) Simple Reaction Time.
- Attention/working memory: Arithmetic from Wechsler Adult Intelligence Scale-VI, Digit Span Backward, Letter-Number Sequencing, Arithmetic, and Paced Auditory Serial Addition Test 1.
- Learning: Rey Auditory Verbal Learning Test Trial 5; Rey-Osterrieth Complex Figure Test-Immediate Recall.
- Memory: Rey Auditory Verbal Learning Test Delayed Recall (Trial 7); Rey Complex Figure-Delayed Recall.
- Motor Skills: Grooved Pegboard Dominant and Nondominant hands.

[d]HIV-associated neurological disorder (HAND) subtype distribution (SN-nonadaptive: 1 asymptomatic neurocognitive impairment [ANI], 2 minor neurocognitive disorder [MND]; SN-adaptive: 6 ANI, 2 MND); HIV-nonadaptive: 1 ANI, 5 MND, 2 HIV-associated dementia [HAD]; HIV-adaptive: 2 ANI, 3 MND, 2 HAD).
SE = standard error; HIV = human immunodeficiency virus; SN, seronegative controls; NA, not applicable; ANOVA = analysis of variance.

factors and training effect (baseline, 1 month, and 6 months) as a within-participant factor. Three way [HIV serostatus by genotype by training, or HIV serostatus by training by training type (adaptive vs. nonadaptive)], and two-way (HIV serostatus by training, or genotype by training) interaction models were performed with age, sex, Index of Social Position (ISP), and

crossover effect as covariates. Second, ANCOVA models with significant contrasts of interest were repeated using an inverse probability weighting method, which uses a weighted generalized estimating equations (GEE) method in SAS for analyzing longitudinal data with missing observations, enabling adjustment of model estimates for subject dropouts (https://support.sas.com/resources/papers/proceedings14/SAS166-2014.pdf). All *p* values from both models were adjusted for false discovery rate
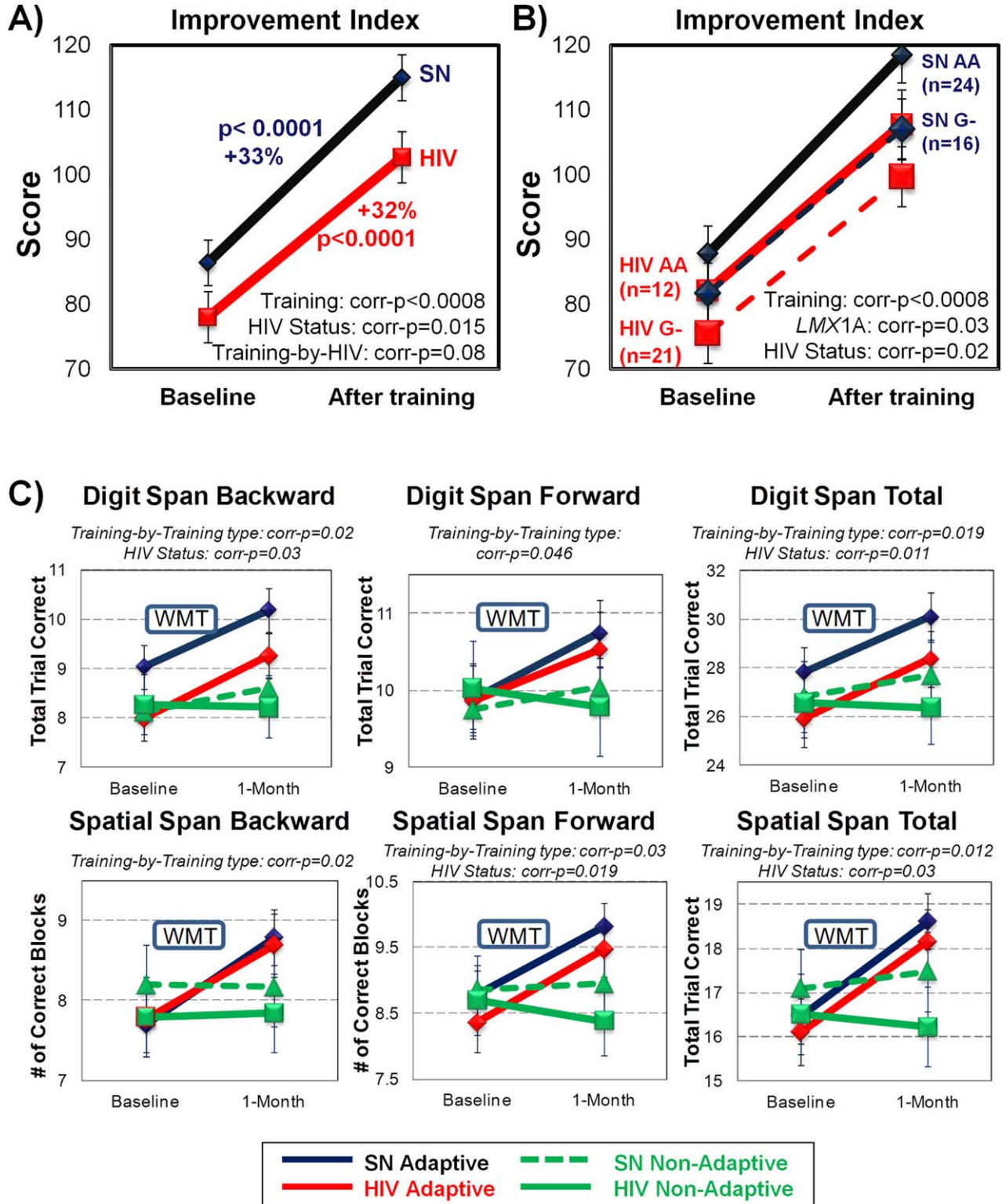

FIGURE 2.

(FDR) using Benjamini-Hochberg procedure. fMRI time series were analyzed with SPM8 software (Wellcome Department of Cognitive Neurology, London, UK). Preprocessing steps involved realignment, spatial normalization to MNI152 atlas, smoothing with an 8-mm full width at half maximum isotropic kernel, segmentation, and coregistration as reported previously.[23,24] In a first-level analysis, statistical maps reflecting the difference in activation between time points (eg, 1 month–baseline, 6 months–baseline) were calculated for each participant and task using a fixed-effects model. Each participant's output from the fixed-effects analysis (t-image) was included in a subsequent random-effects 2×2 ANCOVA, using serostatus and genotype as categorical variables (main and interaction term) and participants' age, sex, ISP, and crossover effect as covariates (same covariates used for each time point). The statistical threshold for Statistical Parametric Mapping (SPM) analyses was set at an FDR cluster corrected p value < 0.05 and an extent threshold of 100 voxels. SPM findings were illustrated using extracted regional percent change in BOLD signal from significant clusters (0.729 cm^3 centered at cluster maxima). No masking procedure was used in the SPM analyses. The relationships between cognitive improvements and extracted BOLD signals from regions with significant changes after adaptive WMT were explored using Pearson correlations.

Results

Participant Characteristics

The four participant groups had similar age, sex, racial distribution, socioeconomic status (ISP), and depressive symptoms. The two HIV groups also had similar CD4 cell counts (>500/mm^3), nadir CD4 cell counts, duration of HIV diagnosis (~16 years), and proportion with undetectable virus (70–85%), but lower prevalence of LMX1A-AA genotype and Karnofsky scores compared to SN controls (Table 1). At baseline, despite the similar education and intelligence (estimated verbal IQ and full-scale IQ), the HIV groups had lower HIV dementia scale scores, lower speed and attention

Z-scores, and nonsignificantly higher rates of HAND compared to SN controls (Table 2).

Furthermore, compared to training completers who returned at 1 month, participants who dropped out during training (41 adaptive WMT, 16 nonadaptive WMT) had similar age, sex proportion, education, ISP, and %SN, but lower estimated verbal IQs (adaptive completers vs dropouts, $p = 0.03$), lower full-scale IQ (in both adaptive and nonadaptive groups, $p = 0.05$), more depressive symptoms (nonadaptive completers vs dropouts, $p = 0.04$) and a higher percentage with HAND (combined adaptive and nonadaptive completers vs dropouts, $p = 0.004$).

Effects of Adaptive WMT and Nonadaptive WMT on Trained and Nontrained WM Tasks

All groups completed near-maximum 25 sessions (Table 2). HIV participants had lower start and maximum indices than SN controls (HIV serostatus, $p = 0.005$); however, both groups showed significant and similar improvement indices on adaptive WMT ($+32$–33%; training corrected-$p < 0.0008$; Fig 2A; Table 2). On the nontrained WM tests, HIV participants had lower performance than SN, especially for Digit-Span Backward and Spatial-Span Forward (Fig 2C). However, both groups showed significant transfer of training gain to Digit-Span and Spatial-Span tasks after adaptive WMT, but not after nonadaptive WMT, at 1 month (training by training type corrected-$p = 0.01$–0.05; Fig 2C). The adaptive WMT groups were able to maintain the gain 6 months later on Digit-Span Backward and Total (Fig 3A, top row) and to a lesser extent on Spatial-Span tasks (Fig 3B, bottom row).

Association of LMX1A Genotype on Adaptive WMT, Transfer of Training, and Maintenance of Gain

Both SN and HIV participants with LMX1A-AA genotype had higher start and maximum indices than their

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FIGURE 2: Improvements After Adaptive WMT and Comparisons of Adaptive WMT and Nonadaptive WMT 1 Month Later on Nontrained WM Tasks. p values are from the inverse proportional weighting, using the generalized estimating equations (GEE) method, including baseline longitudinal data from the dropout subjects; categorical factors included HIV serostatus (A), HIV serostatus and $LMX1A$ (B), and HIV serostatus and training type (C). Covariates included age, sex, index of social position, and crossover effects from the 12 subjects that had nonadaptive WMT before baseline adaptive WMT; furthermore, given that the dropout subjects also had higher depression scores, lower FSIQ and higher proportion with HAND compared to the completers, the GEE model additionally adjusted for CES-D, FSIQ, and HAND status. All p values were also FDR corrected. (A) The HIV group (red line, n = 34) had a lower start index than SN controls (black line: n = 42) at baseline, but both groups showed similar gains after the WMT; hence, the max index remains higher in SN than HIV. (B) When subjects were stratified by LMX1A genotypes, both groups with the GG/GA genotypes (dotted lines: 16 SN and 21 HIV) showed a lower start index than those with AA genotype (solid lines, 24 SN and 12 HIV). However, all four groups showed similarly strong indices of improvement. (C) Top Row: Digit-Span Tests: Both HIV and SN groups showed improved performance after adaptive WMT (black and red lines), but not after nonadaptive WMT (green lines), on Digit-Span Backward (Training by training type, FDR corrected, $p = 0.02$), Digit-Span Forward (Training by training type, FDR corrected, $p = 0.05$), and Digit-Span Total (Training by training type, FDR corrected $p = 0.02$). HIV subjects also had lower performance on Digit-Span Backward and Total and Spatial-Span Forward and Total. CES-D = Center for Epidemiological Studies–Depression Scale; FDR = false discovery rate; FSIQ = full-scale IQ; HAND = HIV-associated neurological disorder; HIV = human immunodeficiency virus; SN, seronegative controls; WMT = working memory training.

corresponding *LMX*1A-G carriers (*LMX*1A corrected-$p = 0.03$; Fig 2B), but both groups with both genotypes showed similar improvement indices (AA, $+ 31.2–34.9\%$; GG/GA, $+ 31.0–32.0\%$; training corrected-$p < 0.0008$; Fig 2B). Similarly, independent of HIV serostatus and compared to G carriers, AA participants had better performance at 1 month for Digit-Span Forward (*LMX*1A by training corrected-$p = 0.02$) and were able to maintain better performance at 6 months on Digit-Span Backward (*LMX*1A by training corrected-$p = 0.05$; Fig 3A,
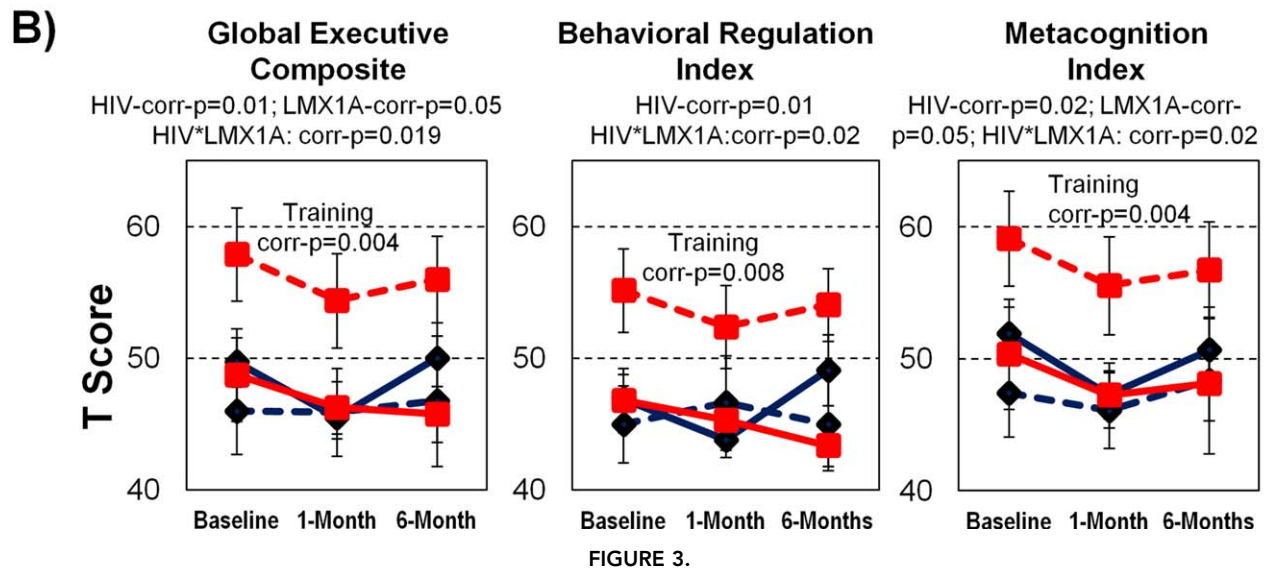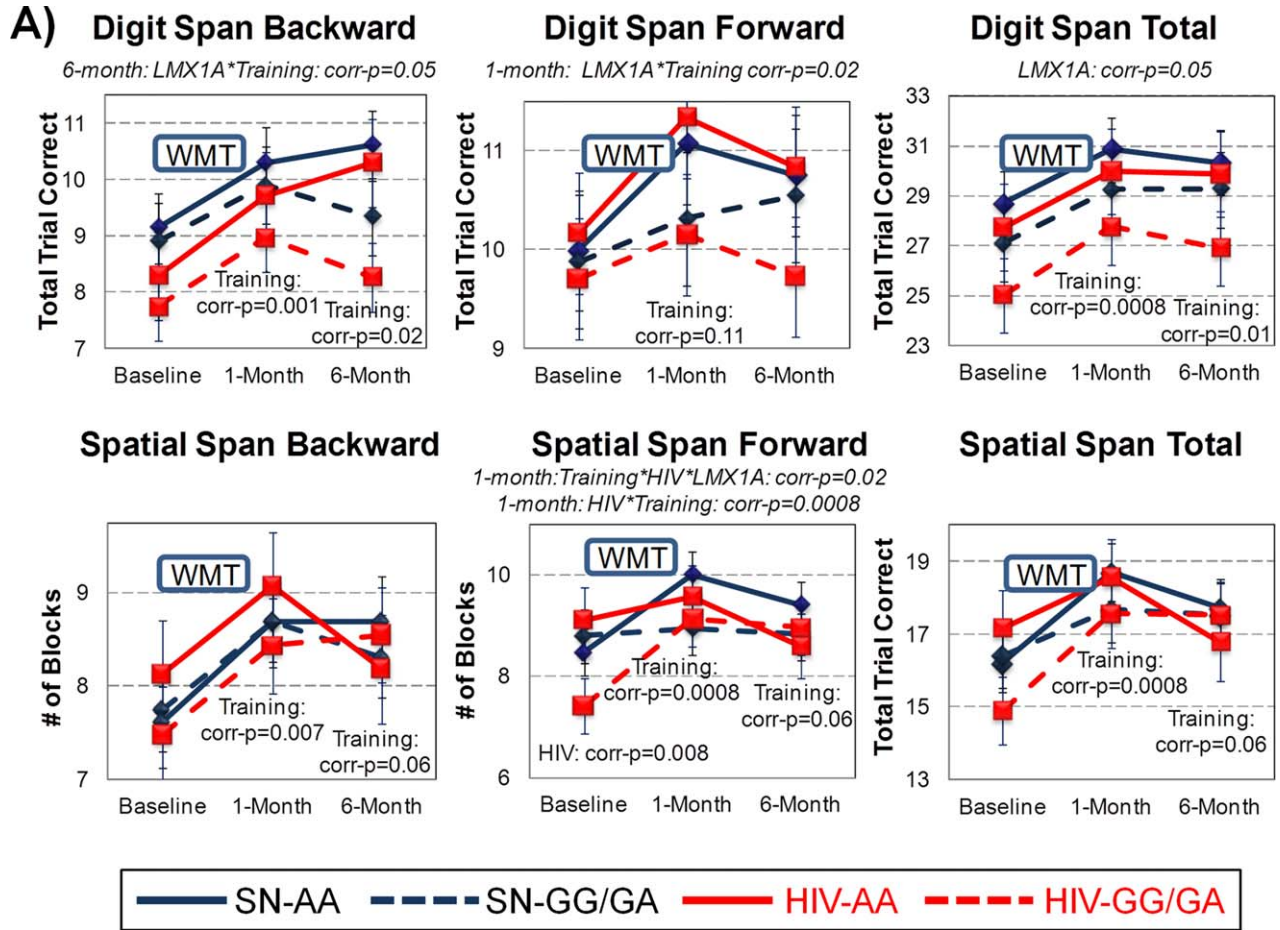

FIGURE 3.

top row). In addition, all participants with AA genotype had greater gain on Digit-Span Sequence and Longest Digit-Span Sequence (*LMX*1A by training, $p = 0.003$ for both, data not shown). In contrast, on Spatial-Span tests, no genotype group difference was found on training effects: however, whereas HIV-*LMX*1A-G carriers improved at 1 month, HIV-*LMX*1A AA showed lesser gain at 1 month on Spatial-Span Forward (HIV × *LMX*1A × training corrected-$p = 0.02$; Fig 3A, bottom row).

Effects of Adaptive WMT and Nonadaptive WMT on Self-Reported Executive Functioning (BRIEF-A)

On BRIEF-A, HIV participants reported overall poorer executive functioning than SN controls (higher scores for all three composite measures; however, these differences were driven by HIV-*LMX*1A-G carriers, who had poorer executive functioning than the other participant groups across all three time points; HIV by *LMX*1A corrected-$p \leq 0.02$; Fig 3B). Notably, all participant groups' executive functioning scores were below clinical significance (T-scores > 65).

At 1 month, both SN and HIV groups reported improved functioning after adaptive WMT; however, HIV participants also reported decreased T-scores after nonadaptive WMT at 1 month (Behavioral Regulation Index or BRI: HIV by training type, $p = 0.04$; Global Executive Composite: HIV by training type, $p = 0.05$; Metacognition Index: HIV by training type, $p = 0.08$; data not illustrated).

Participants who completed the adaptive WMT and were followed for 6 months showed improved T-scores on all three composite measures only at 1 month: Global Executive Composite (training corrected-$p = 0.004$), BRI (training corrected-$p = 0.008$), and Metacognition Index (training corrected-$p = 0.004$; Fig 3B). The Metacognition Index included improved subscales for Initiate ($p = 0.008$), WM ($p = 0.001$), Plan-Organize ($p = 0.004$), Task-Monitor ($p = 0.006$), and Organization of Materials ($p = 0.008$).

fMRI Results

BASELINE ACTIVATION AND GROUP COMPARISONS. On structural MRIs, only 7 participants (2 HIV, 5 SN) had incidental findings of small- to medium-sized cerebellar subarachnoid cysts, which should not affect brain activation. On fMRI, both groups showed typical robust activation patterns during the 1-back and 2-back WM tasks[20,22] (Figs 4 and 5). On the 1-back task, HIV participants showed greater activation than SN controls (FDR corrected, $p < 0.0001$) in frontal regions, with local maxima at the left cingulate gyrus (Brodmann's area [BA] 24), left medial frontal gyrus (BA 6), and right middle frontal gyrus (BA 9; Supplementary Table 1). However, HIV participants also activated less than SN (FDR corrected, $p = 0.003$) in the left brainstem (pons and substantia nigra), and bilateral cingulate gyri (BA 23; Supplementary Table 1). Similarly, on the 2-back task, HIV participants had greater activation than SN (FDR corrected, $p = 0.002$; Supplementary Table **2**) also in the frontal regions, with maximal activation in the left cingulate gyrus (BA 32), right medial frontal gyrus (BA 6), and right precentral gyrus (BA 4), but no less activation than SN in any brain region.

Training Effects on Brain Activation at 1 Month After Adaptive WMT

At 1 month after adaptive WMT, on the 1-back task, HIV participants continued to show greater activation than SN controls (FDR corrected, $p = 0.0003$) in the left postcentral gyrus (BA 3 and BA 5) and right insula (Supplementary Table 1). However, HIV participants showed only a trend for greater changes (decreases) on the 1-back task than controls at 1 month in bilateral cerebellar regions (Supplementary Table 1). On the 2-back task, both SN and HIV groups showed similar activation 1 month after adaptive WMT (data not shown) and less activation 1 month after adaptive WMT compared to

FIGURE 3: (A) Effects of adaptive WMT, HIV serostatus, and *LMX*1A genotype on nontrained near-transfer WM tasks. Top row: On the Digit-Span Tasks, all subjects showed WMT training effects from baseline to 1 (backward, forward, and total) and 6 months after WMT (backward and total). Furthermore, at 6 months, those with AA genotype (solid lines) showed better performance overall and trends for better training effects (*LMX*1A × training interactions) than those with the GG/GA genotypes (dotted lines), especially on the backward task. Bottom row: On the Spatial-Span Tasks, subjects also showed significant training effects at 1 month, but on the Forward task, the training effect differed based on genotype and HIV status. Analyses were performed using the inverse proportional weighting generalized estimating equations method for analyzing longitudinal data that have missing follow-up observations, with training effect across time as a repeated measure, *LMX*1A and HIV serostatus as categorical factors, and the same four covariates as in Figure 2 (all *p* values are FDR corrected). Data are from seronegative (SN; 24 AA, 16 GG/GA) and HIV-positive (12 AA, 21 GG/GA) subjects. (All data are presented as least-square means and standard errors.) **(B)** Effects of adaptive WMT, HIV serostatus, and *LMX*1A on composite scores of the Behavior Rating Inventory of Executive Function-Adult Version. Data are from 41 SN subjects (24 AA, 15 GG/GA, and 2 unavailable) and 32 HIV subjects (11 AA, 20 GG/GA, and 1 unavailable). HIV subjects with GG/GA genotypes (red dotted line) had higher T-scores, indicating more difficulty with executive function compared to the other three subject groups. The statistical model and covariates were the same as those in 3A, and *p* values are FDR corrected. FDR = false discovery rate; HIV = human immunodeficiency virus; WM = working memory; WMT = working memory training.
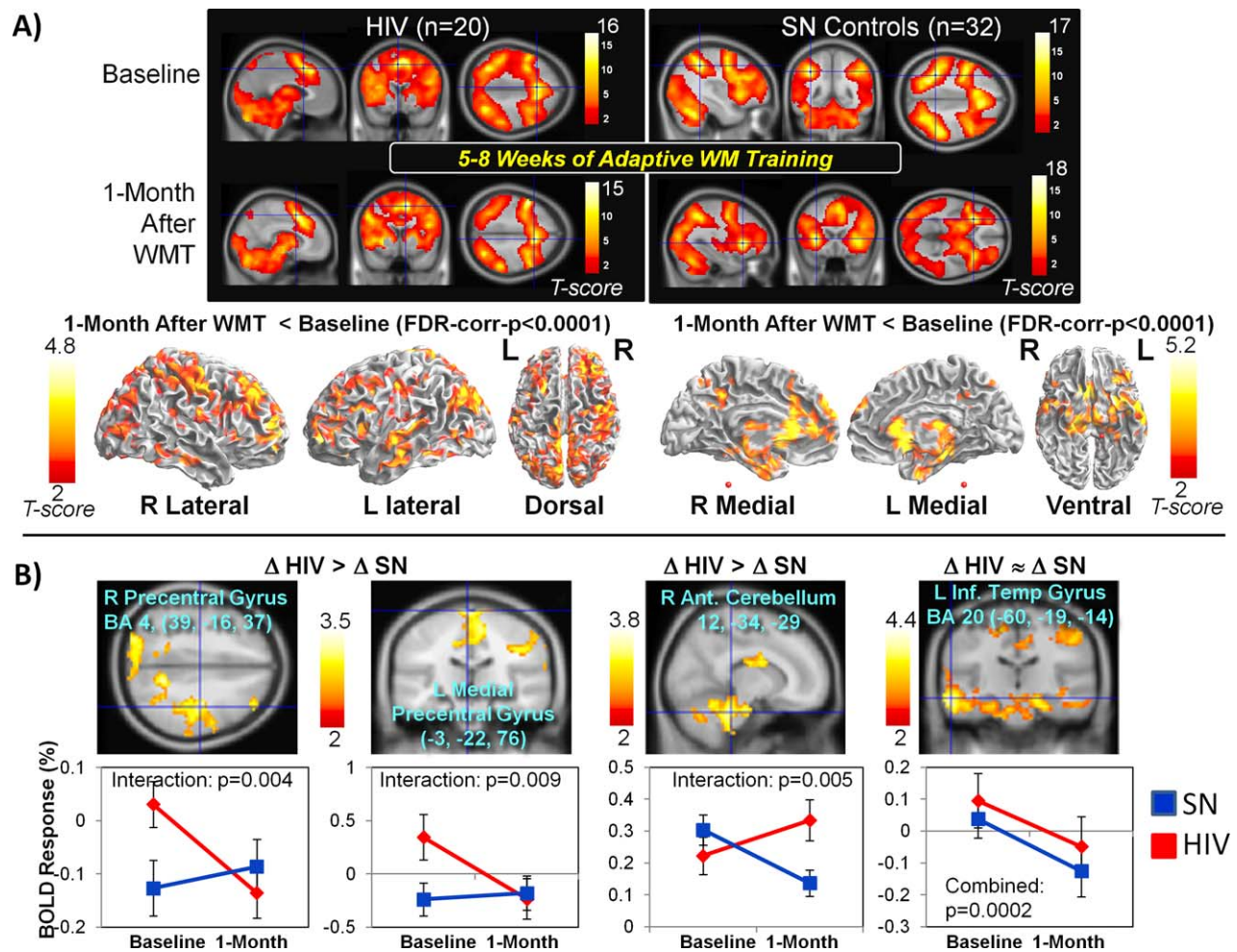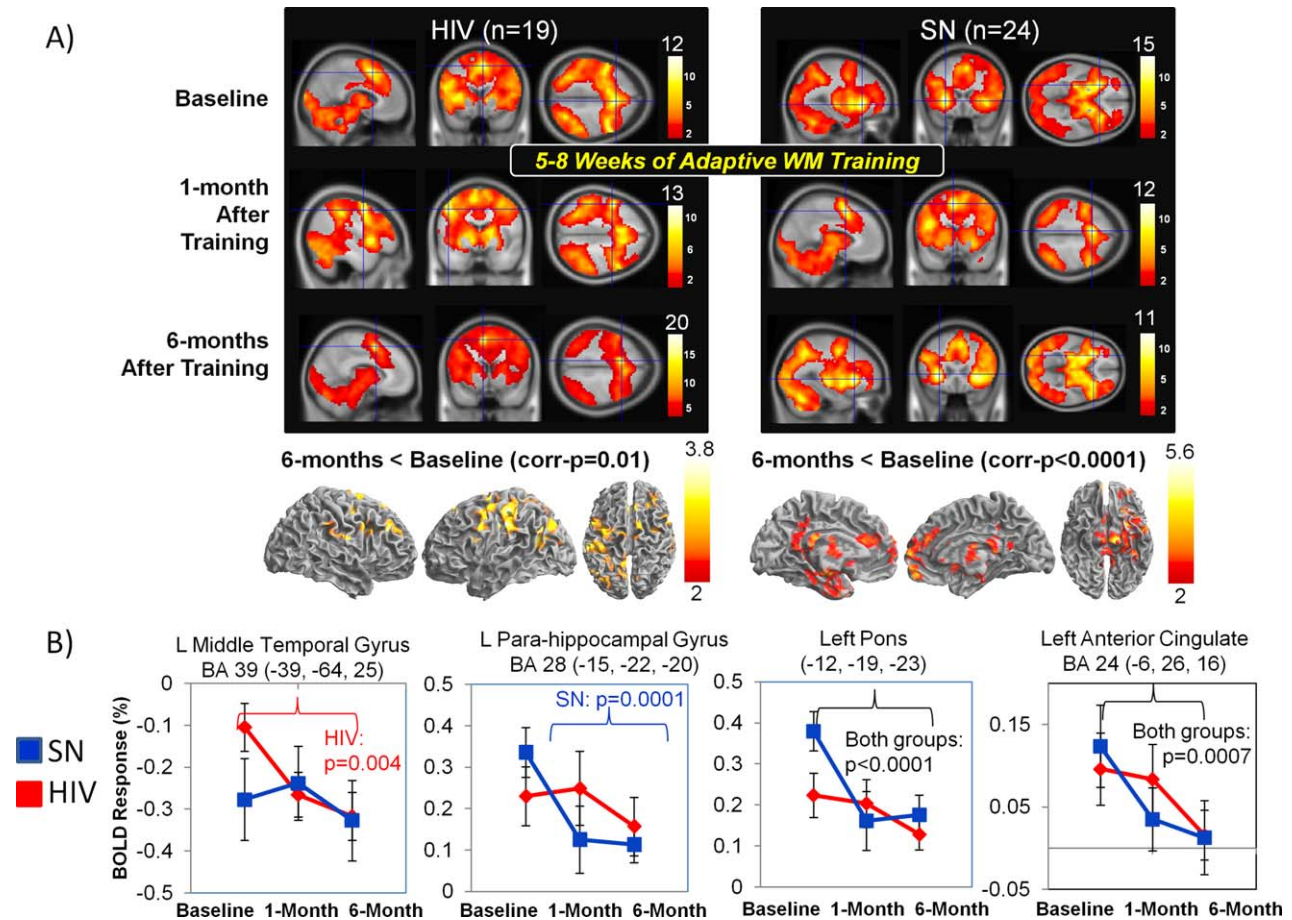
FIGURE 4: Changes in brain activation during a working memory (WM) task (2-back) before and 1 month after adaptive WM training (WMT). (A) Relative to baseline, both groups showed significant decreases in brain activation 1 month after WMT. Top panels: Brain activation (t-maps) in HIV and SN groups at baseline and 1 month after WMT. Bottom: On the surface p-maps, note the significantly decreased activation throughout the dorsal and bilateral cortical brain regions in the HIV subjects, whereas seronegative (SN) controls show significantly decreased activation in bilateral anterior cingulate regions as well as the ventral and medial regions of the brain. (B) Top row: Renderings of t-scores for the difference (reduction) in activation at 1 month compared to baseline. Bottom line-graphs: BOLD signal changes in select brain regions for SN (blue) and HIV (red) subjects at baseline and 1 month. Comparisons were tested using repeated-measures ANCOVA (same four covariates as in Fig 2); with cluster minimum > 100 voxels and threshold minimum T > 2.1. ANCOVA = analysis of covariance; BOLD blood-oxygen-level dependent; FDR = false discovery rate; HIV = human immunodeficiency virus; L = left; R = right.

baseline in multiple brain regions (FDR corrected, $p < 0.0001$; Supplementary Table 2; Fig 4). However, brain regions with decreased activation during the 2-back task differed between HIV and SN groups. Whereas the HIV group showed marked and extensively decreased activation in bilateral dorsal prefrontal and parietal regions (Fig 4), especially right frontal regions (FDR corrected, $p < 0.0001$; Supplementary Table 2), SN controls showed decreases primarily in medial and subcortical regions (FDR corrected, $p < 0.0001$; Fig 4), including the left posterior cerebellar tonsil, left medial frontal gyrus, and left caudate (Supplementary Table 2). Consequently, 1 month after adaptive WMT, HIV participants showed greater decreases on the 2-back task than SN in

frontal brain regions (FDR corrected, $p = 0.02–0.001$), whereas SN controls showed greater decreases in the pons and cerebellar regions (FDR corrected, $p = 0.01$; Supplementary Table 2; Fig 4). However, both groups showed similar decreases after training compared to baseline in left postcentral, left precuneus, and left inferior temporal gyri (Supplementary Table 2; Fig 4).

NEURAL CORRELATES OF MAINTENANCE OF TRAINING EFFECTS AT 6 MONTHS AFTER ADAPTIVE WMT.

One hundred twenty-nine fMRI scans from 24 SN and 19 HIV participants who had complete and usable data sets at all three time points were analyzed. These SN and HIV groups had similar activation patterns (Fig
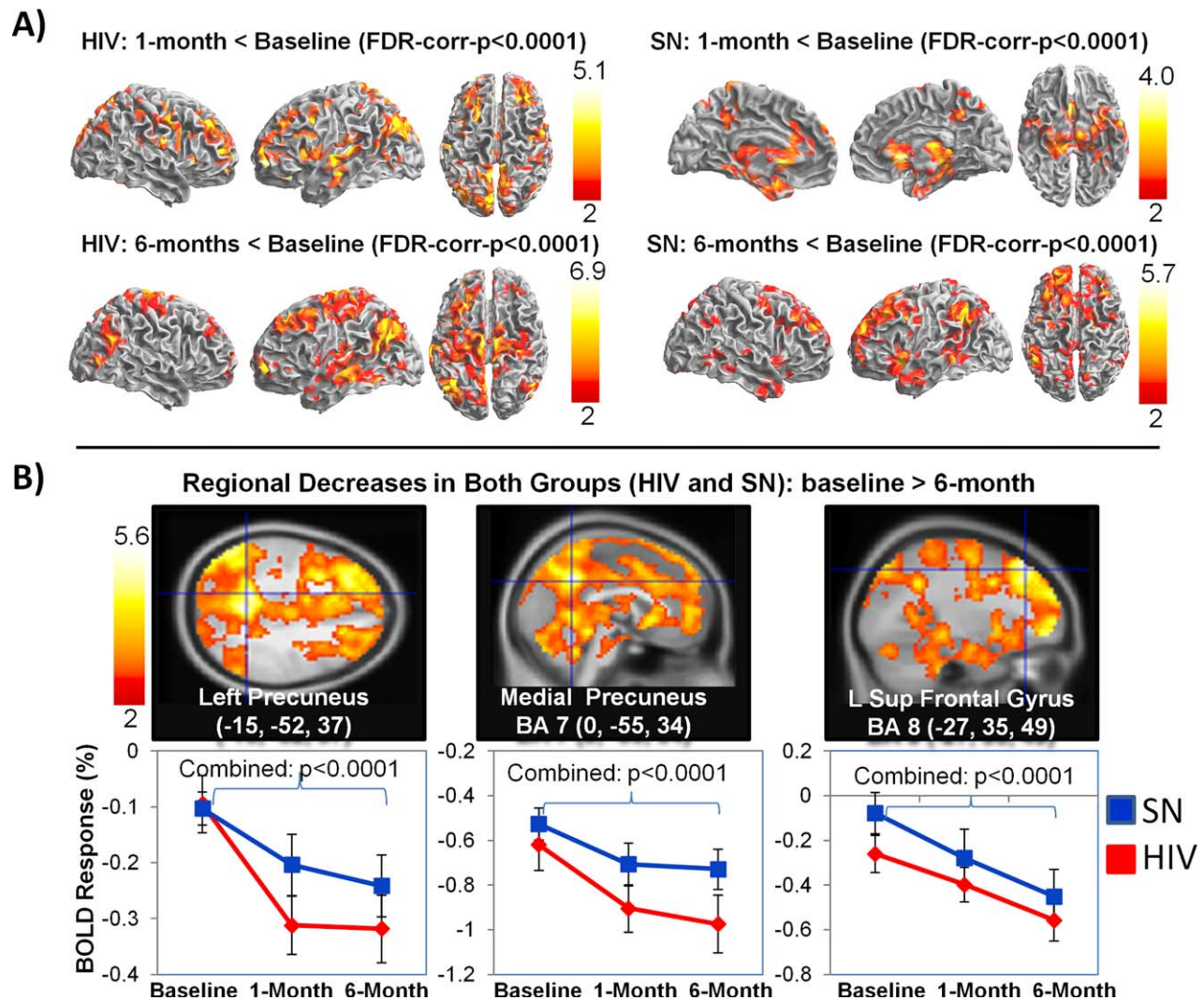
FIGURE 5: Changes in brain activation during working memory (1-back) at baseline, 1 month, and 6 months after adaptive working memory training (data are from 19 HIV and 24 seronegative or SN with all three time points). (A) Top panels: Activation patterns at each time point for both groups. Bottom panels: Surface t-maps showing similar results from the full cohort; significant decreases in brain activation were observed within each group at 6 months. HIV subjects primarily showed decreases in the right frontal and left parietal and temporal regions, whereas SN subjects had decreases predominantly in subcortical regions, with cluster maxima at the left pons, left anterior cingulate, and right medial frontal regions. (B) Line graphs showing BOLD signals extracted from regions of interest centered at select cluster maxima, showing significantly decreased brain activation either in HIV subjects (red), SN (blue), or in both groups at 6 months (see also Supplementary Table 2). Comparisons were tested using repeated-measures ANCOVA (same four covariates as in Fig 2), with cluster minimum >100 voxels and threshold minimum T >2.1. ANCOVA = analysis of covariance; BA = Brodmann's area; BOLD blood-oxygen-level dependent; HIV = human immunodeficiency virus; L = left.

5), but were not different at 6 months after adaptive WMT for both the 1-back and 2-back tasks (data not shown). On the 1-back task, both groups showed significantly decreased brain activation from baseline to 6 months after training (Supplementary Table 2; Fig 5). Again, regional changes in brain activation after adaptive WMT were different between the groups. HIV participants showed decreases (FDR corrected, $p = 0.01$) primarily in dorsal and lateral cortical regions, with maxima in the left middle temporal gyrus (BA 39; Fig 5), right medial frontal gyrus (BA 6), and left postcentral gyrus (BA 3). Conversely, SN participants showed significant decreases (FDR corrected, $p < 0.0001$) primarily in ventromedial regions, with maxima in the left parahippocampal gyrus (BA 28; Fig 5) and left middle temporal

gyrus (BA 21; Supplementary Table 2). However, some brain regions showed significant decreases in both groups, such as the left pons, left anterior cingulate gyrus (BA 24), and the right medial frontal gyrus (BA 11; Supplementary Table 2; Fig 5).

On the 2-back task, for the 37 participants who had all three time points, both groups showed decreased brain activation at 1 month and further at 6 months after WMT compared to baseline (Supplementary Table 2; Fig 6). At 1 month after adaptive WMT, this subcohort showed similar findings as all participants, with greater decreased brain activation in HIV participants than in SN controls, maximally at the precentral and left medial precentral regions (Supplementary Table 2; Fig 6). At 6 months after adaptive WMT, all
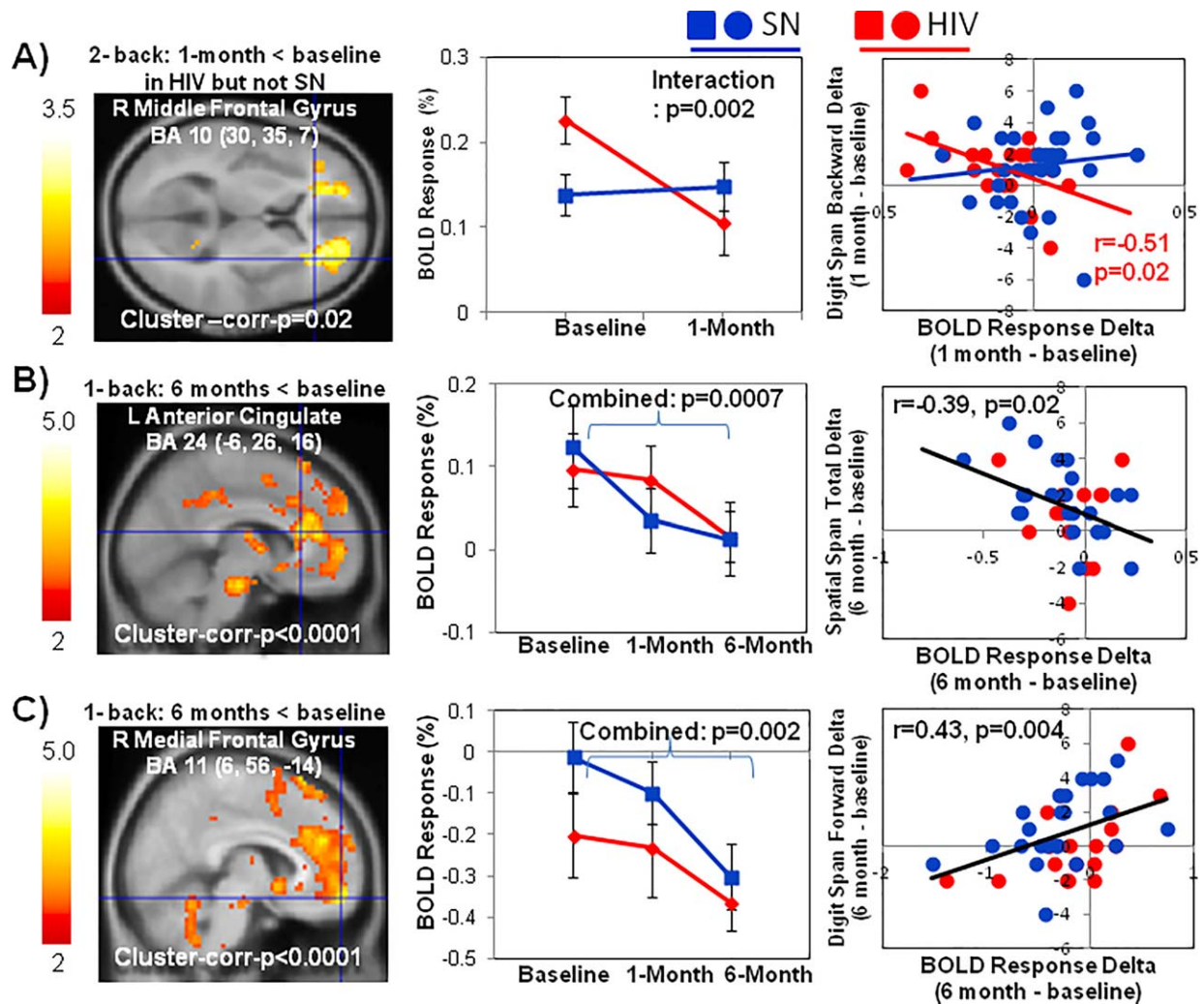
FIGURE 6: Changes in brain activation during WM (2-back) at baseline, 1 month, and 6 months after adaptive WM training (in the two groups with data at all three time points, 21 SN and 16 HIV, for this task). (A) Similar to results from the full cohort, significant decreases in brain activation at 1 month were observed within each group, primarily in the right frontal, left parietal, and temporal regions in HIV subjects, but in subcortical regions in HIV subjects. However, when the BOLD signal was compared between 6 months after WMT and baseline, the spatial pattern was similar for HIV and SN subjects, with decreases primarily in cortical regions. (B) BOLD signals extracted from ROIs centered at the cluster maxima at left and medial precuneus, and left superior frontal gyrus, showing significantly decreased brain activation in both groups at 6 months (see also Supplementary Table 3). Comparisons were tested using repeated-measure ANCOVA (same four covariates as in Fig 2), with cluster minimum >100 voxels and threshold minimum T >2.1. ANCOVA = analysis of covariance; BA = Brodmann's area; BOLD blood-oxygen-level dependent; FDR = false discovery rate; HIV = human immunodeficiency virus; L Sup = left superior; SN, seronegative; WM = working memory; WMT = working memory training.

participants showed further decreases in brain activation. Although the greatest decreases occurred at different coordinates in HIV participants (BA 6, 8, 31) compared to SN controls (BA 25, 32, 40; Supplementary Table 2), the 6-month changes did not differ between the two groups (Fig 6B). Both groups combined showed decreased activation at 6 months compared to baseline in a widely distributed cluster (FDR corrected $p < 0.0001$), maximally in the left and medial precuneus, as well as left superior frontal gyrus (Supplementary Table 2; Fig 6B).

Correlations Between Changes in BOLD Signals and Improvements on Nontrained WM Tasks

Exploratory analyses were performed to evaluate changes in regional BOLD signal with performance on near-transfer WM tests that showed training effects. At 1 month after adaptive WMT, HIV participants, but not SN controls, showed decreased brain activation on the 2-back task in the right middle frontal gyrus (BA 10; interaction, $p = 0.002$), which correlated with improved score on the Digit-Span Backward in the HIV participants ($r = -0.51$; $p = 0.02$; Fig 7A). At 6 months after adaptive WMT, both groups showed
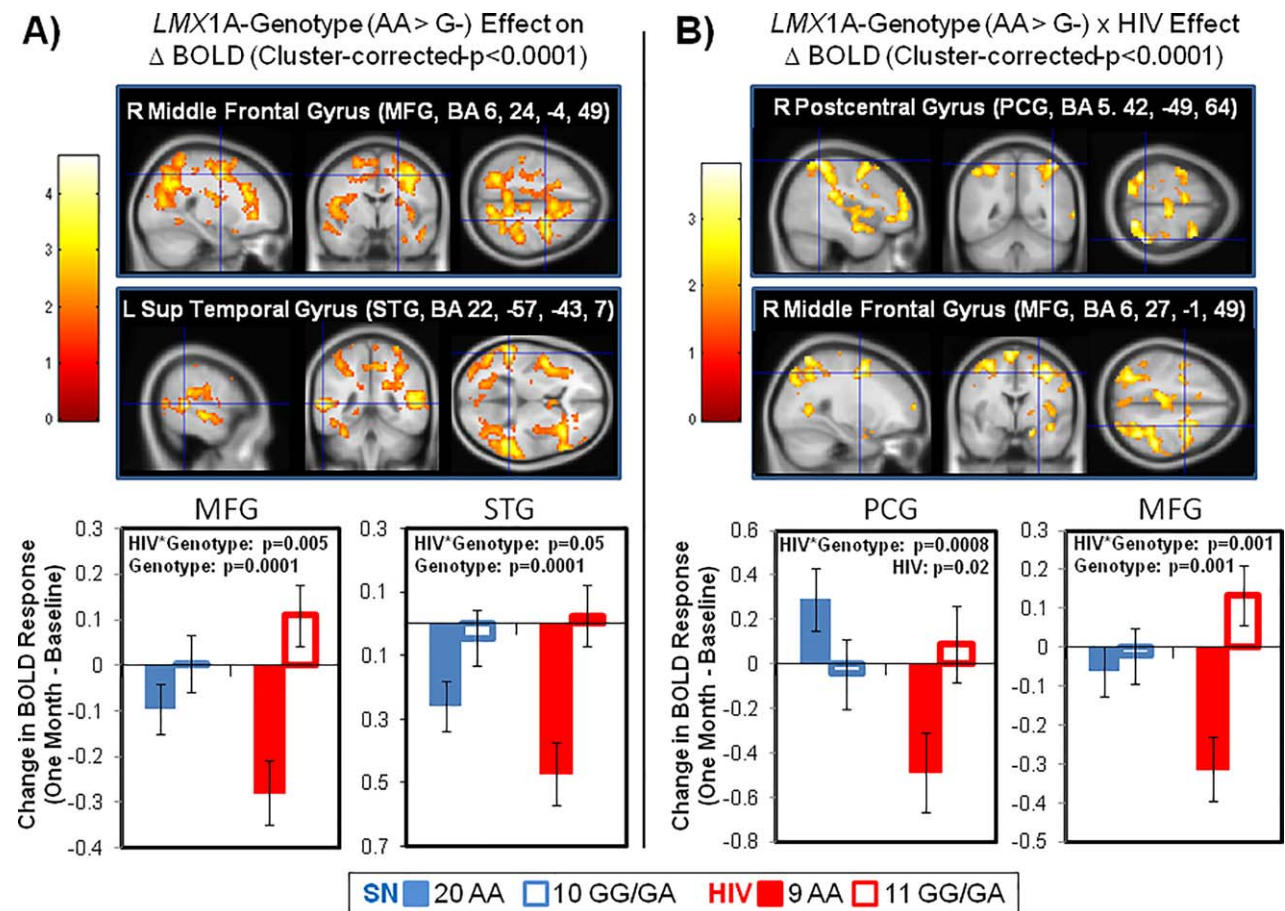
FIGURE 7: Changes in brain activation during working memory (WM) tasks (1-back and 2-back) correlated with improvements on WM after adaptive WM training (WMT). (A) At 1 month after WMT, HIV subjects, but not seronegative (SN) controls, showed decreased brain activation on the 2-back task in the right middle frontal gyrus; the decreased activation correlated with improved score on the Digit-Span Backward task in HIV subjects (red dots and line; r = –0.51; *p* = 0.02). (B) At 6 months after WMT, both HIV and SN controls showed a decrease in activation in the left anterior cingulate (BA 24) during the 1-back task, which correlated with improvements on the Spatial-Span Total scores across both groups (r = –0.39; *p* = 0.02; HIV: red, SN: blue). (C) Also at 6-months after WMT, both groups showed further deactivation in the right medial frontal gyrus (BA 11) during the 1-back task. Across both groups, those with lesser additional deactivation showed greater improvement on the Digit-Span Forward task (r = 0.43; *p* = 0.004). BA = Brodmann's area; BOLD blood-oxygen-level dependent; HIV = human immunodeficiency virus; L = left; R = right.

decreased activation in left anterior cingulate (BA 24) during the 1-back task, which correlated with improvements on the Spatial-Span Total scores (r = –0.39; *p* = 0.02; Fig 7B). Furthermore, at 6 months, both groups showed further deactivation in the right medial frontal gyrus (BA 11) during the 1-back task; however, those with lesser additional deactivation showed greater improvement on the Digit-Span Forward (r = 0.43; *p* = 0.004, Fig 7C).

LMX1A Genotype Effects on Brain Activation During WM Tasks

At 1 month after adaptive WMT, no genotype group differences were found on changes in brain activation with

the 1-back task. However, on the 2-back task, all participants with *LMX*1A-AA genotype showed decreased brain activation compared to baseline, whereas the G carriers showed little change or slight increases after 1 month (cluster FDR corrected, *p* < 0.0001; Fig 8A). Genotype differences were larger in HIV participants, in right insula (BA 13; *p* < 0.0001, not shown), right middle frontal gyrus (BA 6; HIV by genotype, *p* = 0.005), and left superior temporal gyrus (BA 22; HIV by genotype, *p* = 0.05; Fig 8A). Stronger HIV by genotype effect was observed on changes in brain activation on the 2-back task after 1 month (cluster FDR corrected, *p* = 0.0001), maximally in the right postcentral gyrus (BA 5; HIV by

FIGURE 8: Changes in brain activation during WM (2-back) before and 1 month after adaptive WM training in relation to *LMX*1A genotype and HIV serostatus. These results are from two-way ANCOVA with HIV serostatus and genotype (*LMX*1A-AA vs *LMX*1A-GG/GA) as factors and age, sex, index of social position, and crossover (after placebo training) as covariates. SPM maps show significant clusters of *LMX*1A-genotype effects or *LMX*1A × HIV interactions on BOLD signal changes; values in the bar graphs are extracted from major cluster maxima shown in the upper panels. Changes in BOLD response are shown as least square means and standard errors. (A) SPM t-maps showing genotype effects regardless of HIV serostatus. Subjects with *LMX*1A-AA genotype showed greater decreases in BOLD signals compared to G-carriers (cluster corrected, *p* < 0.0001), especially in right middle frontal gyrus (24, –4, 49, Brodmann area 6) and left superior temporal gyrus (–57, –43, 7, Brodmann area 22). (B) Whereas HIV subjects with the *LMX*1A-AA genotype showed significant decreases in BOLD signals, SN subjects showed increases or no change in BOLD signals in the parietal and frontal regions. Bar graphs show region of interest data extracted from the cluster shown in SPM maps above (cluster corrected, *p* = 0.0001; 4,623 voxels; T-max, 3.81). ANCOVA = analysis of covariance; BA = Brodmann's area; BOLD blood-oxygen-level dependent; HIV = human immunodeficiency virus; L = left; R = right; SN, seronegative; WM = working memory.

genotype, *p* = 0.0008), and right middle frontal gyrus (BA 6; HIV by genotype, *p* = 0.001; Fig 8B). Genotype effects were not evaluated at 6 months because of the small sample size.

Discussion

WM improved, both on trained and nontrained WM tasks, in all participants 1 month after adaptive WMT, but not after nonadaptive WMT. All participants also reported fewer symptoms on executive functioning after the adaptive WMT; however, HIV participants reported improvement even after the nonadaptive WMT. This is the first study to show improved (decreased) brain activation on BOLD-fMRI, suggesting improved neural

efficiency in HIV-patients 1 month and further at 6 months after adaptive WMT. However, the decreased activation occurred in higher cortical regions in HIV patients, but primarily in subcortical regions in SN controls, attributed to normalization of the initially reorganized neural networks in patients with HIV-associated brain injury.[20,21,24] Furthermore, better overall WM performance and the greater improvement on brain activation in those with *LMX*1A-AA genotype likely reflect greater dopaminergic reserve. Last, the correlations between improvements in nontrained WM performance and changes in regional brain activation further suggest that adaptive WMT is associated with improved neural efficiency that led to improved WM.

Improved WM After Adaptive WMT

The four groups did not have HAND at the group level and had similar proportions of individuals with HAND or HAND equivalent. However, the HIV group had lower attention/WM and speed Z-scores than SN at baseline, which is typical among neuroasymptomatic HIV patients.[9,11] Although participants with HIV had a lower start index and a similar improvement index as those with SN after adaptive WMT (>30%), their max index was higher than the start index of SN controls. Improved WM after adaptive WMT (with Cogmed®) was reported in patients with nonprogressive acquired brain injury,[17] WM deficits after stroke,[16] patients in rehabilitation with impaired WM,[17] and college students with ADHD and learning disability.[35] However, WMT or other cognitive training in elderly with amnestic mild cognitive impairment[19] or those with multiple sclerosis[36] appeared to show lesser gain, greater variability in the training effect, or lesser generalized effects to other cognitive domains. Collectively, these studies indicate that adaptive WMT may be more efficacious in patients with nonprogressive WM deficits than in those with ongoing brain injury, such as our participants without HAND. The improved WM after adaptive WMT in our HIV participants also parallels the improved maze learning and attention in a pilot study of HIV-infected children in Africa, using Captain's Log computerized cognitive rehabilitation therapy configured for attention and memory skills.[37] However, an active control group was not included in this pediatric study, and the children also did not show improvements on some of the WM and learning tasks, which was attributed to the low number of training sessions.[37] In addition to the improved WM from the program, our participants also improved on several nontrained, near-transfer WM tests (Digit-Span and Spatial-Span tests) at 1 month and mostly maintained at 6 months after adaptive WMT, similar to the patients with brain injury[18] or WM deficits.[17]

Subjective Improvements on Executive Function After WMT

On BRIEF-A, HIV participants reported more problems than SN in behavioral regulation, but both groups improved on their executive functioning 1 and 6 months after the adaptive WMT, which suggest that adaptive WMT may improve overall executive function. However, our HIV participants also reported similar improvements after the nonadaptive WMT, which suggest a placebo effect in these participants. These results are consistent with fewer problems in daily life after adaptive WMT in patients with acquired brain injury.[18] Likewise, a meta-analysis showed generalized, but moderate, improvements in everyday functioning, particularly reduced inattention, after the same adaptive WMT program.[38] Improved overall cognitive performance is not surprising given that WM is essential for many tasks in everyday functioning; however, more objective measures of executive function would minimize variability from self-reports as in BRIEF-A. Improved WM efficiency and everyday functioning also may contribute to fewer depressive symptoms and lesser fatigue after WMT,[17] which should be evaluated in HIV patients in future studies.

LMX1A Genotype on Baseline Cognitive Function, WMT Gain, and BRIEF-A

Consistent with an earlier study,[31] our participants with LMX1A-rs4657412-AA genotype had higher start and max indices, but similar improvement index, compared to the G carriers. Our LMX1A-AA participants also tended to improve more than G carriers on near-transfer verbal, but not spatial, WM tests[31] 1 month after the adaptive WMT and maintained higher performance even 6 months later. These findings are also analogous to the greater gain on backward Digit-Span and visuospatial grid tasks in healthy A carriers compared to CC carriers of the dopamine receptor D2-rs2283265 gene.[39] Given that WM is mediated by dopaminergic receptors,[40] and those with LMX1A-AA genotype likely had higher basal dopaminergic tone and greater number of dopaminergic terminals, our AA participants might have had greater WM capacity that enabled their greater improvement on verbal WM after adaptive WMT. Furthermore, the poorer self-reported executive function found only in HIV participants without the LMX1A-AA genotype also indicates that lower WM capacity might lead to more challenges in everyday functioning.

BOLD-fMRI Findings

At baseline, HIV participants showed a reorganized neural network compared to SN participants even on the relatively simple 1-back task, with greater activation in the medial and lateral frontal regions, but lesser activation in brainstem and bilateral cingulate gyri, which are consistent with previous studies of WM and sustained attention tasks in HIV participants.[20,22,23,41] Similarly, on the 2-back task, the greater activation in bilateral medial frontal regions and the right precentral gyrus is also consistent with greater usage of the reserve attention network, or increased attentional modulation for this more-difficult task in HIV patients.[21,24]

One month after adaptive WMT, HIV participants continued to show greater activation in left postcentral gyrus and right insula on the 1-back task than controls, indicating persistence of lesser neural efficiency.

Nonetheless, the decreased activation on the 2-back task 1 month after WMT indicates that both groups became more efficient. However, changes in activation were regionally different for the two groups and likely reflect the abnormal baseline neural networks in HIV participants, who typically show hyperactivation in the contralateral (left) caudate and frontal regions,[42] lesser striatal-frontal connectivity,[43] reduced dopamine transporters,[26,27] and greater atrophy in subcortical structures.[44] The greater decreased activation predominantly in the cortical regions in our HIV participants also indicate lesser requirement of the "top-down" attention network.[24] In contrast, SN controls showed improved "bottom-up" networks after adaptive WMT, suggesting that the processing might have become more automated.[45] However, the decreased brain activation after adaptive WMT in our participants contrasts with the increased striatal BOLD signals following adaptive WMT in healthy individuals[46] and in children with ADHD.[47] These discrepant findings might reflect differences in the participant populations and experimental conditions.

Furthermore, both groups showed persistent or further decreased brain activation at 6 months compared to baseline for both the 1-back and 2-back tasks, which suggests continued improvements in efficiency of neural processing. This continued improvement again involved primarily the top-down dorsal frontal and postcentral regions in HIV participants, and bottom-up ventral parahippocampal and temporal regions, in SN controls. Greater activation suggesting lesser efficiency of the top-down dorsal or prefrontal regions was also observed in HIV-infected women, especially in those with the catechol-O-methyltransferase–Val/Val genotype and lesser dopamine degradation.[48] Although all participants with LMX1A-AA genotypes showed similar training effects and transfer of gain to other WM tasks, decreased or normalized brain activation in the frontal brain regions after adaptive WMT was most pronounced in HIV-LMX1A-AA participants. These HIV-LMX1A-AA participants might have a greater dopaminergic reserve and hence greater neural plasticity compared to the G carriers.

Limitations

First, although improvements on nontrained WM tests were observed only in the adaptive WMT groups, the accompanied decreased BOLD signals may be partly attributed to practice effects, as shown in repeated task-activated fMRI scans[49] and in a 1-year follow-up fMRI study of SN controls without training.[23] However, in that follow-up study, HIV neuroasymptomatic participants showed increased, rather than decreased, BOLD signals, suggesting declined efficiency with no practice effects.[23] Future fMRI studies to evaluate brain activation after nonadaptive WMT is needed to delineate WMT from practice effects. Second, the LMX1A genotype subgroups were relatively small. Although participants with the AA genotype tended to show greater improvements than the G carriers, larger subgroups are needed to validate these findings. Third, the improvements on BRIEF-A in the HIV nonadaptive WMT group suggest a placebo effect, and self-reported measures may be less sensitive than objective neuropsychological testing for executive functioning.[50] Last, the high rates of attrition in both adaptive WMT (35%) and nonadaptive WMT (29%) suggest that this WMT program may be too difficult for these individuals, especially the dropouts who had lower IQs, more depressive symptoms, and greater prevalence of HAND, compared to the completers.

Adaptive WMT improved cognition in HIV patients not only on trained tasks, but also on near-transfer nontrained WM tests and self-reported executive functioning at 1 and 6 months after training; they typically achieved performance similar to, or higher than, the baseline performance of SN controls. The decreased brain activation on fMRI suggests that the improved WM is related to a more-efficient WM network. However, these improvements involved different brain regions in SN and HIV participants, showing normalization of the baseline cortical abnormalities in HIV participants, but improved efficiency with more automated subcortical processing in SN individuals. Adaptive WMT appears to be particularly effective for improving WM neural efficiency in HIV patients with LMX1A-AA genotype. Future studies should evaluate whether adaptive WMT may prevent or delay the onset of HAND, and how neuroinflammation and basal dopamine levels might impact HIV patients' ability to improve with cognitive training.

in the data collection for this study, and the statistical consultation from Dr James Davis to assist our reanalyses.

Author Contributions

L.C., G.C.L, T.E., J.S., and E.M. were reponsible for study concept and design. L.C., T.E., T.A., C.S.J, V.D., N.T., C.W., D.C., A.L., and C.O. were reponsible for data acquisition and analysis. L.C., T.E., T.A. C.S.J., V.D. G.C.L., J.S., and C.O. were reponsible for drafting the manuscript and figures.,

Potential Conflicts of Interest

Nothing to report.

References

1. McArthur JC, Steiner J, Sacktor N, Nath A. Human immunodeficiency virus-associated neurocognitive disorders: mind the gap. Ann Neurol 2010;67:699–714.

2. Heaton RK, Clifford DB, Franklin DR, Jr., et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 2010;75:2087–2096.

3. Carey CL, Woods SP, Rippeth JD, et al. Additive deleterious effects of methamphetamine dependence and immunosuppression on neuropsychological functioning in HIV infection. AIDS Behav 2006;10:185–190.

4. Gonzalez R, Jacobus J, Amatya AK, et al. Deficits in complex motor functions, despite no evidence of procedural learning deficits, among HIV+ individuals with history of substance dependence. Neuropsychology 2008;22:776–786.

5. Cysique LA, Bain MP, Brew BJ, Murray JM. The burden of HIV-associated neurocognitive impairment in Australia and its estimates for the future. Sex Health 2011;8:541–550.

6. Becker JT, Lopez OL, Dew MA, Aizenstein HJ. Prevalence of cognitive disorders differs as a function of age in HIV virus infection. AIDS 2004;18(Suppl 1):S11–S18.

7. Law WA, Martin A, Mapou RL, et al. Working Memory in individuals with HIV infection. J Clin Exp Neuropsychol 1994;16:173–182.

8. Bartok JA, Martin EM, Pitrak DL, et al. Working memory deficits in HIV-seropositive drug users. J Int Neuropsychol Soc 1997;3:451–456.

9. Hinkin CH, Hardy DJ, Mason KI, et al. Verbal and spatial working memory performance among HIV-infected adults. J Int Neuropsychol Soc 2002;8:532–538.

10. Heaton RK, Marcotte TD, Mindt MR, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. J Int Neuropsychol Soc 2004;10:317–331.

11. Bassel C, Rourke SB, Halman MH, Smith ML. Working memory performance predicts subjective cognitive complaints in HIV infection. Neuropsychology 2002;16:400–410.

12. Thames AD, Kim MS, Becker BW, et al. Medication and finance management among HIV-infected adults: the impact of age and cognition. J Clin Exp Neuropsychol 2011;33:200–209.

13. Klingberg T, Fernell E, Olesen PJ, et al. Computerized training of working memory in children with ADHD—a randomized, controlled trial. J Am AcadChild Adolesc Psychiatry 2005;44:177–186.

14. Grunewaldt KH, Lohaugen GC, Austeng D, Brubakk AM, Skranes J. Working memory training improves cognitive function in VLBW preschoolers. Pediatrics 2013;131:e747–e754.

15. Lohaugen GC, Antonsen I, Haberg A, et al. Computerized working memory training improves function in adolescents born at extremely low birth weight. J Pediatr 2011;158:555–561.e4.

16. Westerberg H, Jacobaeus H, Hirvikoski T, et al. Computerized working memory training after stroke—a pilot study. Brain Inj 2007;21:21–29.

17. Akerlund E, Esbjornsson E, Sunnerhagen KS, Bjorkdahl A. Can computerized working memory training improve impaired working memory, cognition and psychological health? Brain Inj 2013;27:1649–1657.

18. Bjorkdahl A, Akerlund E, Svensson S, Esbjornsson E. A randomized study of computerized working memory training and effects on functioning in everyday life for patients with brain injury. Brain Inj 2013;27:1658–1665.

19. Vermeij A, Claassen JA, Dautzenberg PL, Kessels RP. Transfer and maintenance effects of online working-memory training in normal ageing and mild cognitive impairment. Neuropsychol Rehabil 2016;26:783–809.

20. Chang L, Speck O, Miller E, et al. Neural correlates of attention and working memory deficits in HIV patients. Neurology 2001;57:1001–1007.

21. Chang L, Tomasi D, Yakupov R, et al. Adaptation of the attention network in human immunodeficiency virus brain injury. Ann Neurol 2004;56:259–272.

22. Tomasi D, Chang L, de Castro Caparelli E, Telang F, Ernst T. The human immunodeficiency virus reduces network capacity: acoustic noise effect. Ann Neurol 2006;59:419–423.

23. Ernst T, Yakupov R, Nakama H, et al. Declined neural efficiency in cognitively stable human immunodeficiency virus patients. Ann Neurol 2009;65:316–325.

24. Chang L, Holt JL, Yakupov R, Jiang CS, Ernst T. Lower cognitive reserve in the aging human immunodeficiency virus-infected brain. Neurobiol Aging 2013;34:1240–1253.

25. Berger JR, Kumar M, Kumar A, Fernandez J, Levin B. Cerebrospinal fluid dopamine in HIV-1 infection. AIDS 1994;8:67–71.

26. Wang GJ, Chang L, Volkow ND, et al. Decreased brain dopaminergic transporters in HIV-associated dementia patients. Brain 2004;127(pt 11):2452–2458.

27. Chang L, Wang GJ, Volkow ND, et al. Decreased brain dopamine transporters are related to cognitive deficits in HIV patients with or without cocaine abuse. Neuroimage 2008;42:869–878.

28. Friling S, Andersson E, Thompson LH, et al. Efficient production of mesencephalic dopamine neurons by Lmx1a expression in embryonic stem cells. Proc Natl Acad Sci U S A 2009;106:7613–7618.

29. Bergman O, Hakansson A, Westberg L, et al. Do polymorphisms in transcription factors LMX1A and LMX1B influence the risk for Parkinson's disease? J Neural Transm 2009;116:333–338.

30. Bergman O, Westberg L, Nilsson LG, Adolfsson R, Eriksson E. Preliminary evidence that polymorphisms in dopamine-related transcription factors LMX1A, LMX1B and PITX3 are associated with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2010;34:1094–1097.

31. Bellander M, Brehmer Y, Westerberg H, et al. Preliminary evidence that allelic variation in the LMX1A gene influences training-related working memory improvement. Neuropsychologia 2011;49:1938–1942.

32. Chang L, Løhaugen GC, Douet V, et al. Neural correlates of working memory training in HIV patients: study protocol for a randomized controlled trial. Trials 2016;17:62.

33. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology 2007;69:1789–1799.

34. Zaitsev M, Hennig J, Speck O. Point spread function mapping with parallel imaging techniques and high acceleration factors: fast, robust, and flexible method for echo-planar imaging distortion correction. Magn Reson Med 2004;52:1156–1166.

35. Gropper RJ, Gotlieb H, Kronitz R, Tannock R. Working memory training in college students with ADHD or LD. J Atten Disord 2014;18:331–345.

36. Hancock LM, Bruce JM, Bruce AS, Lynch SG. Processing speed and working memory training in multiple sclerosis: a double-blind randomized controlled pilot study. J Clin Exp Neuropsychol 2015; 37:113–127.

37. Boivin MJ, Busman RA, Parikh SM, et al. A pilot study of the neuropsychological benefits of computerized cognitive rehabilitation in Ugandan children with HIV. Neuropsychology 2010;24:667–673.

38. Spencer-Smith M, Klingberg T. Benefits of a working memory training program for inattention in daily life: a systematic review and meta-analysis. PLoS One 2015;10:e0119522.

39. Soderqvist S, Matsson H, Peyrard-Janvid M, Kere J, Klingberg T. Polymorphisms in the dopamine receptor 2 gene region influence improvements during working memory training in children and adolescents. J Cogn Neurosci 2014;26:54–62.

40. Goldman-Rakic P. Regional and cellular fractionation of working memory. Proc Natl Acad Sci U S A 1996;93:13473–13480.

41. Caldwell JZ, Gongvatana A, Navia BA, et al. Neural dysregulation during a working memory task in human immunodeficiency virus-seropositive and hepatitis C coinfected individuals. J Neurovirol 2014;20:398–411.

42. Plessis SD, Vink M, Joska JA, et al. HIV infection and the fronto-striatal system: a systematic review and meta-analysis of fMRI studies. AIDS 2014;28:803–811.

43. Melrose RJ, Tinaz S, Castelo JM, Courtney MG, Stern CE. Compromised fronto-striatal functioning in HIV: an fMRI investigation of semantic event sequencing. Behav Brain Res 2008;188:337–347.

44. Chang L, Andres M, Sadino J, et al. Impact of apolipoprotein E epsilon4 and HIV on cognition and brain atrophy: antagonistic pleiotropy and premature brain aging. Neuroimage 2011;58: 1017–1027.

45. Vossel S, Geng JJ, Fink GR. Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. Neuroscientist 2014; 20:150–159.

46. Olesen PJ, Westerberg H, Klingberg T. Increased prefrontal and parietal activity after training of working memory. Nat Neurosci 2004;7:75–79.

47. Stevens MC, Gaynor A, Bessette KL, Pearlson GD. A preliminary study of the effects of working memory training on brain function. Brain imaging Behav 2016;10:387–407.

48. Sundermann EE, Bishop JR, Rubin LH, et al. Genetic predictor of working memory and prefrontal function in women with HIV. J Neurovirol 2015;21:81–91.

49. Tomasi D, Ernst T, Caparelli EC, Chang L. Practice-induced changes of brain function during visual attention: a parametric fMRI study at 4 Tesla. Neuroimage 2004;23:1414–1421.

50. Solsnes AE, Skranes J, Brubakk AM, Lohaugen GC. Executive functions in very-low-birth-weight young adults: a comparison between self-report and neuropsychological test results. J Int Neuropsychol Soc 2014;20:506–515.