

EEG event related potentials in sustained, focused and divided attention tasks: Potential biomarkers for cognitive impairment in HIV patients



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HIGHLIGHTS

- Neurophysiological measures of attention differentiated individuals with HIV from healthy controls.
- HIV ERPs showed increased amplitude of P200 and decreased amplitude of the late positive potential.
- The increase in P200 amplitude was positively correlated with duration of HIV infection.

ABSTRACT

Objectives: The objective of this study was to assess the usability of event-related-potentials (ERPs) during sustained, focused, and divided attention tasks as biomarkers for cognitive decline in HIV patients.

Methods: EEG was acquired using a mobile/wireless 9-channel system in 39 persons with HIV, with well-controlled immune function and 63 healthy control participants (HCs) during three ERP tasks: sustained attention, focused attention, and divided attention.

Results: The HIV-group evidenced smaller late positive potential (LPP) and larger P200 amplitudes across the tasks compared to the HC group. P200 amplitude was correlated ($r = 0.56$) with the estimated duration of infection. Both groups showed higher P200 and LPP amplitudes in response to infrequent stimuli; this effect was not significantly different between groups. In the sustained attention task, the HIV-group showed significantly slower reaction time than controls while maintaining the same level of accuracy. In the divided attention task, the HIV-group showed a trend towards faster/less accurate responses.

Conclusions: HIV seropositive participants receiving anti-retroviral treatment (ART) demonstrated significantly larger P200 amplitude during three different attention tasks. This may reflect attentional deficits characterized by over-attending to non-target/distracting stimuli.

Significance: These findings demonstrate the potential benefits of EEG-ERP metrics derived from attention tasks as neurocognitive biomarkers for HIV. This approach may reveal underlying causes of attentional deficits in HIV patients.

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1. Introduction

Human immunodeficiency virus (HIV) has been shown to induce neuropathological changes including both structural and functional deficiencies detected with neuroimaging in the majority of patients over the course of the infection (O'Connor et al., 2018; Alakkas et al., 2019). HIV enters the central nervous system (CNS)

soon after infection resulting in multiple neuropathological alterations (O'Connor et al., 2018; Gelman, 2015). Advances in anti-retroviral therapies (ART) have significantly improved patients' life expectancy and quality of life through reduction of viral load with concomitant decreases in both encephalitis and opportunistic central nervous system (CNS) infections (Babiloni et al., 2014, 2016a; Nakagawa et al., 2013). HIV-associated neurocognitive disorders (HAND) have also been mitigated with ART (Ances and Clifford, 2008; Clifford, 2008; Williams et al., 2012). However, it is estimated that as many as 45% of patients still suffer from neurocognitive disorders despite well-controlled immune function (Heaton

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et al. 2011), often with sub-clinical symptoms that go unobserved by the patients themselves (Cysique et al., 2009; Chiao et al., 2013). There is substantial evidence that these impairments affect essential activities of daily living (Heaton et al., 1996, 2004; Hinkin et al., 2004, 2007; van Gorp et al., 2007), including automobile driving (Marcotte et al., 1999, 2003, 2004, 2006).

Post-mortem investigations of the patients diagnosed with mild to moderate HAND have not revealed any consistent pathoanatomical changes, suggesting that the neuropathological correlates of HAND, unlike those observed in other neurodegenerative diseases such as Alzheimer's and Lewy Body dementias, may be linked to abnormalities in synaptic transmission, neurotransmitter regulation, or neural plasticity that are more difficult to detect with histopathological methods (Gelman et al., 2013). These abnormalities may be fully or partially reversible with various treatments designed to affect neurometabolic functions. Therefore, novel treatments for HAND will require early and sensitive assessment methods to optimize treatment protocols and provide an opportunity for early intervention.

The current method for evaluating HAND relies on the Frascati criteria (Alford et al., 2019). Based on those criteria, a positive HAND diagnosis is made if a patient is more than one standard deviation below normative neuropsychology test scores in at least two of the following cognitive domains: attention, executive function, learning, memory, processing speed and motor function. However, given the potential concerns for sensitivity and specificity (Gisslén et al. 2011) of these methods and the presence of confounding variables, EEG biomarkers may complement neuropsychological measures by detecting cognitive decline at the neurophysiological level.

Since EEG reflects postsynaptic currents directly, EEG-based measures such as event related potentials (ERPs) show promise in helping track subtle neuropathological changes associated with cognitive decline. These measures can be used to assess the efficacy of novel interventions and benefit the overall clinical management of HIV patients (Picton et al., 2000; Clifford, 2008; Babiloni et al., 2016b, 2016a). For example, studies suggest that ERPs could reveal early functional abnormalities in HIV patients before they become apparent in clinical assessments or structural MRI (Comi et al., 1996; Polich et al., 2000; Fernández-Cruz and Fellows, 2017).

ERP components reflect a variety of neurofunctional processes in the brain as they unfold across different temporal stages. While early components (50 to 200 ms post-stimulus) are sensitive to the sensory characteristics of the stimuli, they can also be influenced to some extent by arousal and attention (Hillyard et al., 1973; Coles et al., 1995). The late ERP components which include the P300, N400, P600, and Late Positive Potential (LPP) are thought to reflect several aspects of cognitive processing including feature evaluation, memory matching, attention, semantic integration, and response selection and execution (Hillyard and Kutas, 1983; Polich and Kok, 1995; Nunez, 2006; Luck, 2014). Both P300 and LPP components are known to be influenced by stimulus novelty, presentation frequency, as well as the presence or absence of a requirement for user response. Multiple reports suggest abnormal amplitude and latency of the LPP is associated with cognitive decline (Polich et al., 1986, 2000; Polich and Kok, 1995; Olichney et al., 2002a, 2002b; Fernández-Cruz and Fellows, 2017). Furthermore, these measures have been shown to reliably distinguish cognitive decline due to neurodegenerative diseases including Alzheimer's and Lewy Body dementias from those associated with normal aging (Babiloni et al., 2004; Olichney et al., 2008; Fernández-Cruz and Fellows, 2017; Waninger et al., 2018).

The neurobiological mechanisms by which HIV affects electrocortical dynamics, are not fully known. However, consistent EEG differences between healthy individuals and HIV patients (with and without a well-controlled viral load) have been reported in

the literature. Fernández-Cruz and Fellows (2017) summarized a systematic review of such studies published between 1996 and 2016. Across studies, EEG/ERP measures were associated with cognitive test scores, and several longitudinal studies (Babiloni et al., 2015, 2016a, 2016b) suggested that after successful treatment, EEG metrics shifted toward values typically observed in healthy participants. Two primary findings were consistent across all reviewed studies: First, a significant reduction in EEG alpha power was observed for HIV groups recorded during resting state under both eyes open and eyes closed condition (Babiloni et al., 2014, 2015, 2016a, 2016b), and during auditory oddball task (Polich et al. 2000). Second, HIV groups exhibited decreased amplitude and increased latency of the P300 and the Late Positive Potential (LPP) components (Polich et al., 2000; Polich and Basho, 2002; Chao et al., 2004; Bauer, 2011; Olichney et al., 2011; Papaliagkas et al., 2011). Additionally, decreased amplitude and increased latency were also reported for the P100, N100, P200, N200 and N400 components (Fernández-Cruz and Fellows 2017), but these results were reported less frequently. Overall, it has been well established that EEG/ERPs provide important insights into the mechanisms of brain dysfunction in HIV patients (Fernández-Cruz and Fellows 2017, Ishii and Canuet 2014).

The overarching goal of the present study was to contribute to this body of evidence by identifying EEG measures that are both sensitive and specific to HIV infection. The distinguishing feature of the present study is using more complex tasks that require sustaining attention or focusing/dividing it across spatially separate stimuli. A 3-choice vigilance task (3CVT) was used to evaluate sustained attention (Berka et al., 2007; Stikic et al., 2011). While the current study was exploratory in nature, we hypothesized that using 3CVT (which has been used in other indications as well (see e.g. Waninger et al. 2018, Meghdadi et al 2019)), may be useful in detecting attentional deficits that are specific to HAND. Although using novel and more complicated tasks may be beneficial by providing novel ERP measures, it has disadvantages as well. In classical ERP tasks such as auditory oddball paradigm, the associations between ERP component features and cognitive processes have been well studied. However, in novel tasks such as the ones used in this paper, more work is needed to fully understand the implications and functional relevance of these ERP features with respect to specific impairments in cognitive processes.

2. Methods

2.1. Participants

Thirty-nine HIV seropositive individuals (age range 55–74 years; 87.2% male) were recruited at the HIV Neurobehavioral Research Center at the University of California, San Diego (UCSD HNRC). Estimated duration of their HIV infection ranged from 7 to 34 years based on the date of their first HIV positive test they reported during intake. Sixty-three healthy control participants (HC, age 55–87 years; 49.2% male) were recruited from the surrounding San Diego community using flyers and handouts. The two groups were matched on age and years of education (HIV+: 9–20 years, HC: 10–21 years), as shown in Table 1.

Participants were selected after an initial telephone screening to determine their eligibility to participate in cognitive testing and an automobile driving evaluation, the latter provision being relevant to another arm of the study not covered in this manuscript. Participants were included if they agreed to join the study after demonstrating adequate comprehension of informed consent, if they possessed a current driver's license confirmed by the California Department of Motor Vehicles (DMV) on the day of their visit, and if they fulfilled all inclusionary criteria established prior

Table 1
Demographic information of the participants in both groups.

Group	N	Age (mean ± SD)	Gender N(male), N(female)	Years of education (mean ± SD)
HC	63	65.0 ± 8.2	31, 32	15.6 ± 2.7
HIV	39	61.0 ± 4.7	34, 5	15.5 ± 2.9
Total	102	63.7 ± 7.4	65, 37	15.6 ± 2.9

Medication history in HC group: Antidepressant (n = 6), Anxiolytic (n = 1), Opioid (n = 3), Sedative-Hypnotic for Insomnia (n = 1), Antipsychotics (n = 1), Anticonvulsants (for nerve pain or mood) (n = 3).

Medication history in the HIV group: Antidepressant (n = 14), Anxiolytic (n = 9), Opioid (n = 5), Sedative-Hypnotic for Insomnia (n = 7), Antipsychotics (n = 2), Anticonvulsants (for nerve pain or mood) (n = 3), CNS stimulant (n = 1).

to study initiation. Additional exclusion criteria comprised a history of loss of consciousness, e.g. from concussion, that lasted greater than 30 minutes, current substance dependence, psychosis, diagnosis of a cardiovascular, sleep, or pulmonary disorder, opportunistic infections of the CNS, or any neurological disorders other than HIV infection, including self-reported diagnoses of Attention Deficit Hyperactivity Disorder (ADHD), and anxiety-related disorders. Data from three additional participants were excluded from all analyses due to a positive urine test for methamphetamine obtained prior to experiments, and one participant was excluded due to being severely cognitively impaired despite a negative HIV status. All but one HIV positive participant were on anti-retroviral medications, and their CD4 cell count (number of T-lymphocytes cells in a cubic millimeter of blood) was in the range 256–1712 and with historical minimum level (nadir CD4) in the range 4–700. Table 1 shows demographic information and medication history of participants. Study protocols were approved by UCSD IRB and Sharp IRB (IRBANA).

2.2. Tasks

Three cognitive tasks were employed to assess the behavioral and neurophysiological effects associated with HIV: the three-choice vigilance task (3CVT), and two variants of the 1-back task designed to measure focused (FA) and divided attention (DA). The 3-Choice Vigilance Task (3CVT) has been designed to evaluate sustained attention (Berka et al., 2007; Stikic et al., 2011), and two variants of the n-back task to assess focused attention (FA), and divided attention (DA) capabilities (Nebel et al., 2005).

EEG and behavioral performance metrics derived from 3CVT has been previously shown to be sensitive to sustained attention in individuals with mild cognitive impairments (Waninger et al., 2018) as well as in healthy participants after full and partial sleep deprivation (Berka et al 2005), administration of stimulants and hypnotic drugs (Stone et al 2015) or using cannabis (Smith et al 2018). Furthermore, these neurobehavioral measures were successful in monitoring and quantifying deficits in patients with sleep disorders, mood disorders and neurodegenerative diseases (Levendowski et al., 2001; Riccio et al., 2001; Sateia, 2003; Berka et al., 2007; Johnson et al., 2011, 2014; Stikic et al., 2011; Correa et al., 2015; Stone et al., 2015).

Tests were conducted in the same order for all participants: 3CVT, FA, and DA. All tasks were conducted in a quiet, closed room to minimize any non-experimental sources of distraction. During testing, participants sat at a desk approximately 60–70 cm from a 44 cm (diagonal length) computer screen. All tasks were conducted using B-Alert Live commercial software (Advanced Brain Monitoring, Carlsbad, CA) while the collected data were analyzed in MATLAB. Prior to the start of each task, participants were given instructions on how to take the test that were followed by a training period to minimize practice effects.

2.2.1. Three-choice vigilance task (3CVT)

The 3CVT is a continuous performance task that probes sustained and selective attention (Riccio et al., 2001; Sateia, 2003;

Berka et al., 2007; Johnson et al., 2011). It instructs participants to discriminate frequent stimuli (Target, triangle shape pointing up ▲, 70% of trials) from infrequent stimuli (NonTarget, triangle shape pointing down: ▼, 15% of trials) as depicted in Fig. 1. On the remaining 15% of the trials, diamond shape stimuli (◆) were used as Distractors. All stimuli were presented at random location on the screen. The participants were instructed to press the left arrow key in response to Target (Frequent) trials (▲) and the right arrow key in response to all other stimuli (▼ or ◆).

A total of 376 trials comprised 264 Target (Frequent), 55 NonTarget (Infrequent), and 57 Distractors stimuli. The stimuli were presented for 200 ms with increasing lengths of stimulus onset asynchrony (SOA) across four 5-minute quartiles. During the first quartile, the SOA ranges from 1.5 to 3 seconds interstimulus interval, increasing up to 6 seconds during the second quartile, and up to 10 seconds during the third and fourth quartiles. Standard 3CVT measurements of sustained attention include accurate detection of the Frequent and Infrequent stimuli and the associated response times.

2.2.2. Focused Attention (FA) and Divided Attention (DA) tasks

The Focused Attention (FA) and Divided Attention (DA) tasks are variants of the n-back test in which a participant must maintain a stimulus presented on the previous trial (1-back) in working memory until the subsequent trial. The tasks are designed to assess behavioral and neurophysiological indices of attention when it is focused on one side of the screen (left), or divided between two stimulus streams that appear on both the left and right side of the screen (Nebel et al. 2005). Participants are asked to keep their gaze on a fixation cross centered on a grey background while a series of letters and symbols (stimuli) are presented individually on the left and right sides of the computer screen respectively (Fig. 2a). Every 2 seconds, a letter appears on the left side of the screen and remains visible for one second. Concurrently, a symbol is shown on the right side of the screen every 3 seconds and

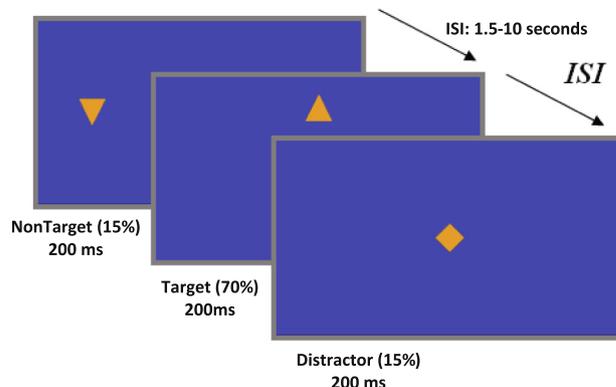


Fig. 1. Three-choice vigilance task (3CVT) paradigm. In this task, three different geometrical shapes (including NonTarget (Infrequent), Target (Frequent), and Distractor) appear individually at random locations on the screen in a randomized order and with widely ranging inter-stimulus intervals (ISI).

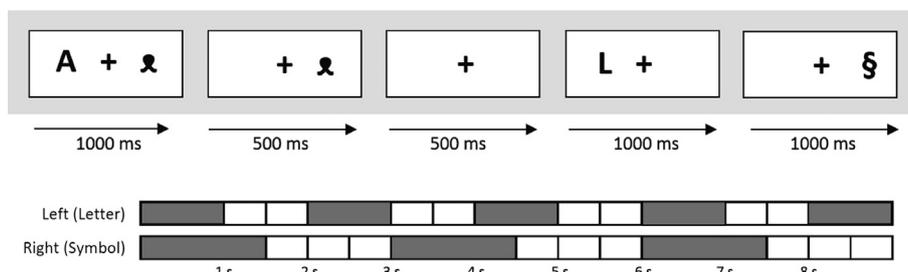


Fig. 2. Focused Attention (FA) and Divided Attention (DA) paradigms. Stimulus presentation (a) and timing of stimuli (b) in both tasks are shown. Inter-stimulus interval for letters (on left) and symbols (on right) are 2 and 3 seconds, respectively. Each white rectangle in (b) represent 0.5 seconds. Duration of presentation for letters and symbols are 1 second and 1.5 seconds, respectively.

Table 2
Median HIV and HC group reaction times and accuracy in 3CVT task.

	N(subjects, trials)	Median, 3CVT	
		RT (ms)	ACC (% Correct)
HC	59, 18,050	632	97.1
HIV	35, 10,599	671	97.1
$\Delta = HC - HIV$		-39	0.0
Wilcoxon Rank Sum		Z = 22.1 ($p = 1 \times 10^{-107}$), r = 0.13	Z = -0.52 ($p = 0.6$), r = -0.05

Significant results are in grey cells with bolded text. Effect size $r = Z\text{-statistic}/\sqrt{N}$, where $N = \text{total number of trials}$.

remains there for 1.5 seconds (Fig. 2b). In the FA task 200 stimuli are presented in total (120 stimuli are letters on the left side and 80 stimuli are symbols on the right). Of the 120 relevant stimuli on the left, there are 24 Target (Infrequent) and 96 NonTarget (Fre-

quent) stimuli. The participants are instructed to focus their attention to the letters that are presented on left side only and to respond when they detect two identical letters in succession which happens on 20% of trials (Target, Infrequent stimuli). They were also asked to ignore the nonrepeated letters presented on the left side of the screen (NonTarget, Frequent stimuli), as well as the symbols on the right side. In the DA task, participants engage in two 1-back tasks concurrently as they are asked to respond to both letters, presented on the left, and symbols that are presented on the right side of the screen. The left and right target stimuli never appear simultaneously in the DA task (Fig. 2b). There are 200 stimuli in total with 120 stimuli (letters) on the left and 80 stimuli (symbols) on the right. There is a total of 40 targets (24 letters and 16 symbols) and 160 NonTarget stimuli.

In both FA and DA tasks, participants respond to stimulus repetitions (Target Infrequent) by pressing the left-arrow key and ignore nonrepeated stimuli (NonTarget Frequent). A total of 200 stimuli are presented in a randomized order.

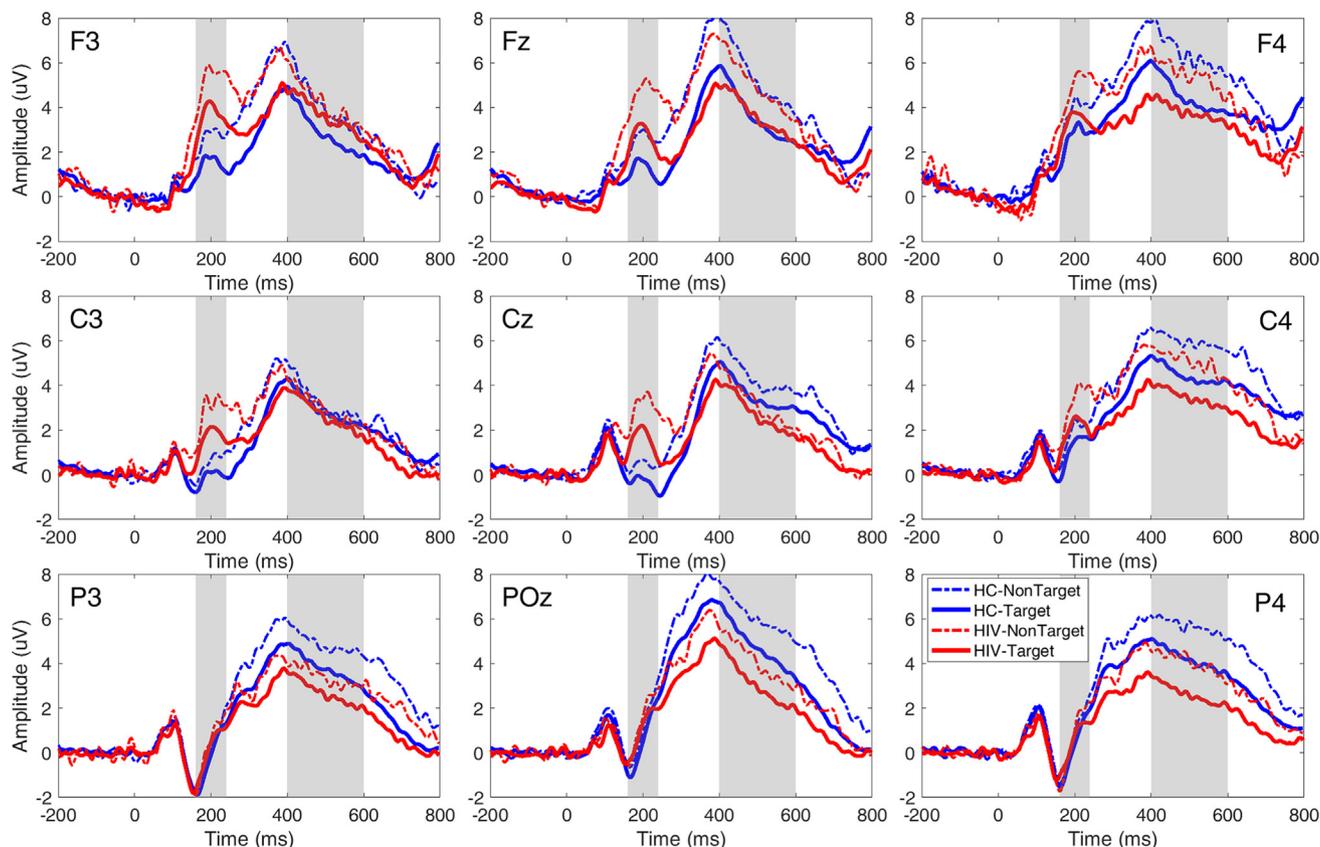


Fig. 3. Grand average ERPs in 3CVT task. Grand averages for Target (Frequent) and NonTarget (Infrequent) trials during 3CVT task plotted for both HC and HIV group. Target trials are indicated by solid lines, NonTarget trials by dotted lines. HC and HIV groups are shown with blue and red colors, respectively. The grey boxes mark the time ranges used to determine P200 and LPP boundaries in this study.

2.3. Materials and equipment

EEG signals were recorded using the Stat X10 EEG headset (Advanced Brain Monitoring Inc., Carlsbad, CA). The X10 is a battery-powered, lightweight, wireless EEG system that acquires data from nine EEG channels (Fz, F3, F4, Cz, C3, C4, P3, P4, POz) organized according to a standard 10–20 montage with reference electrodes linked to mastoids, and one ECG channel. The headset uses passive Ag/AgCl electrodes with flexible flat cables printed on polyester strips. The amplifier’s low and high cut-off frequencies are 0.1 Hz and 100 Hz, respectively. Sampling rate of the X10 system is 256 Hz. Data are amplified and digitized using a 16-bit analog-to-digital converter by the onboard processing unit built into the headset and transmitted wirelessly via Bluetooth to a host computer. The system has an external syncing unit (ESU) that produces synchronized time stamps marking stimulus onset and response events on the concurrently recorded EEG data stream.

2.4. Signal processing

For all tasks, raw EEG signals were filtered between 0.1 and 50 Hz with a 0.1 Hz transition band at the cutoff frequency. EEG data were epoched from 1.0 second before to 2.0 seconds after onset of each stimulus and were baseline normalized using a 100 ms pre-stimulus interval. Trials were rejected if the absolute value of the EEG amplitude in any channel was larger than 100 μ V within a time window of –50 ms to 750 ms relative to

stimulus onset. EEGLAB software (Delorme and Makeig 2004) was used to further reject trials as follows: trials with high kurtosis or low probability of occurrence were excluded using a threshold of 6 z-score (with respect to channel activity) and 5 z-score (with respect to global activity, all channels). EEG trials with power spectra 35 dB higher or lower than the baseline in the frequency range of 20–30 Hz were also excluded to remove interfering muscle artifacts (Goncharova et al., 2003; Delorme et al., 2007). Only trials with correct responses were included in the analysis.

Average ERPs for each stimulus type were computed for each participant and were additionally visually inspected for artifact contamination. Measurement windows for the P200 and LPP (Late Positive Potential) ERP components were selected based on visual inspection of the grand means. For each participant, P200 and LPP amplitudes were computed as the average voltage in a measurement window from 160–240 ms and 400–600 ms post-stimulus onset, respectively. Grand average ERPs across all participants in each group were computed using a weighted average with respect to the number of trials. Average ERP waveforms with less than 15 trials were automatically excluded from the analysis.

2.5. Statistical analysis

Wilcoxon rank sum test was used to determine whether reaction times (RT) or accuracy (ACC) differed between the HC and HIV groups in the 3CVT, FA, and DA tasks. Histograms for both RT and accuracy were skewed, deviating sufficiently from normal-

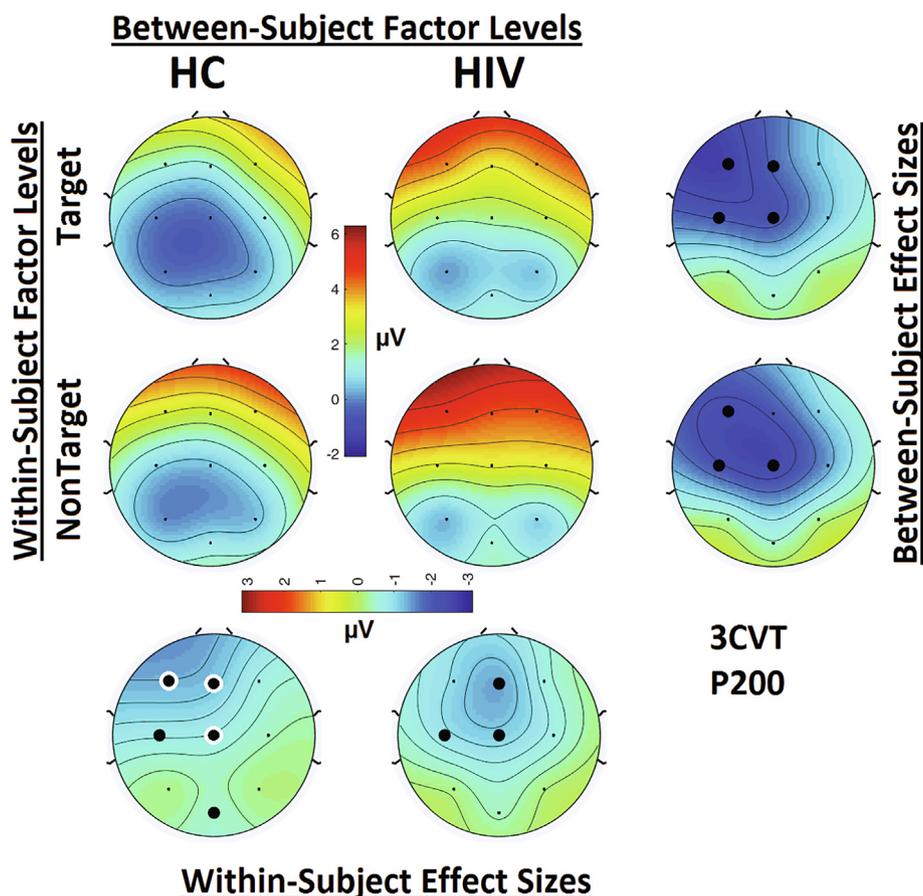


Fig. 4. Topographical maps of P200 during 3CVT. Group average topographical maps of P200 amplitude and effect sizes (all in μ V) by seropositivity and stimulus types (Target, Frequent and NonTarget, Infrequent). Effect sizes represent differences between seropositivity groups ($ES_{BS} = HC - HIV$), or stimulus types ($ES_{WS} = Target - NonTarget$). Channels with significant differences are marked with black circle (●) with or without white border; former marker type indicates significance after Benjamini-Hochberg correction. Within-subject HC ($df = 50$): Fz, $p = 0.012$, $t = -2.6$; Fz, $p = 0.002$, $t = -3.23$; C3, $p = 0.031$, $t = -2.22$; Cz, $p = 0.012$, $t = -2.62$; POz, $p = 0.032$, $t = -2.2$; Within-subject HIV ($df = 21$): Fz, $p = 0.017$, $t = -2.58$; C3, $p = 0.04$, $t = -2.2$; Cz, $p = 0.017$, $t = -2.6$; Between-subject Target: Fz, $p = 0.04$, $t = -2.13$, $df = 36.8$; F3, $p = 0.011$, $t = -2.73$, $df = 29.5$; Cz, $p = 0.035$, $t = -2.19$, $df = 38.1$; C3, $p = 0.026$, $t = -2.34$, $df = 32.8$; Between-subject NonTarget: F3, $p = 0.049$, $t = -2.03$, $df = 36.3$; C3, $p = 0.03$, $t = -2.24$, $df = 39.2$; Cz, $p = 0.022$, $t = -2.38$, $df = 43.8$; $N_{HC} = 51$, $N_{HIV} = 22$.

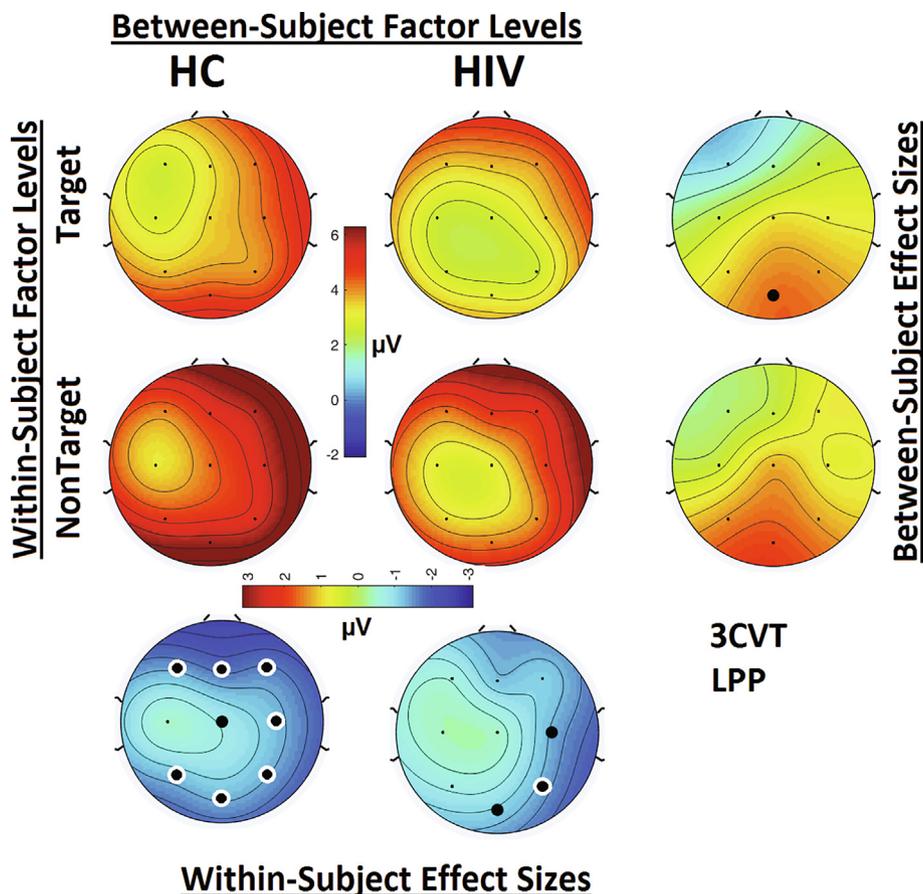


Fig. 5. Topographical maps of LPP during 3CVT. Group average topographical maps of LPP amplitude and effect sizes (all in uV) by seropositivity and stimulus types (Target, Frequent and NonTarget, Infrequent). Effect sizes represent differences between seropositivity groups ($ES_{BS} = HC - HIV$), or stimulus types ($ES_{WS} = Target - NonTarget$). Topographical maps are color coded using vertical color bar (factor levels), or horizontal color bar (effect sizes). Channels with significant differences are marked with black circle (●) with or without white border; former marker type indicates significance after Benjamini-Hochberg correction. Within-subject HC ($df = 50$): F3, $p = 0.019$, $t = -2.42$; Fz, $p = 0.0007$, $t = -3.64$; F4, $p = 0.001$, $t = -3.5$; Cz, $p = 0.049$, $t = -2.01$; C4, $p = 0.002$, $t = -3.28$; P3, $p = 0.02$, $t = -2.42$; POz, $p = 0.0003$, $t = -3.93$; P4, $p = 0.0005$, $t = -3.69$; Within-subject HIV ($df = 21$): C4, $p = 0.039$, $t = -2.2$; P4, $p = 0.002$, $t = -3.48$; POz, $p = 0.019$, $t = -2.53$; Between-subject Target: POz, $p = 0.028$, $t = 2.25$, $df = 65.7$; $N_{HC} = 51$, $N_{HIV} = 22$.

Table 3
Group averages and differences between HIV and HC groups in FA and DA task performance.

	N(subject, trials)	Median Focused Attention (FA)	
		RT (ms)	ACC (% Correct)
HC	55, 1204	578	99.0
HIV	35, 766	603	99.0
$\Delta = HC - HIV$		-25	0.0
Wilcoxon Rank Sum		Z = 2.3 (p = 0.02) r = 0.05	Z = -0.63 (p = 0.53) r = -0.07
	N(subjects, trials)	Median Divided Attention (DA)	
		RT (ms)	ACC (% Correct)
HC	46, 1372	734	93.0
HIV	31, 862	707	92.5
$\Delta = HC - HIV$		+27	+0.5
Wilcoxon Rank Sum		Z = -1.59 (p = 0.11) r = 0.03	Z = 0.0 (p = 1.0) r = 0.0

Significant results are in grey cells with bolded text. Effect size $r = Z\text{-statistic}/\sqrt{N}$ (N), where N = total number of trials

ity to justify a non-parametric analytic approach. RT histograms for each task were generated using all target trials with correct responses. Effect size r was derived by the formula, $r = Z/\sqrt{n}$ where Z is the z-statistic and n = total number of trials. Only reac-

tion times that fell within the 300 ms to 1500 ms post-stimulus onset range were used in the RT and ACC analyses. This range was selected given the physiological limitations in how short choice reaction times can be, particularly in older adults (Woods et al. 2015a, 2015b), the increased likelihood that very short reaction times represent accidental responses, and the paucity of reaction times that were less than 300 ms after stimulus onset.

P200 and LPP amplitudes at each EEG channel were analyzed using a 2x2 mixed factorial design with HIV seropositivity as the between-group factor (HC, HIV), and stimulus type (Target, NonTarget) as the within-subject factor. The main effects of HIV seropositivity, stimulus type, and their interaction on ERP components were examined at each of the nine EEG channels. Brown-Forsythe test for homogeneity of variance was applied to every channel under each of the three behavioral tasks (3CVT, FA, and DA). Independent two-sample t-tests with Satterthwaite approximation (Welch's test) were used to examine between-group differences at each EEG channel while controlling for unequal variances. Paired t-tests were used to compare within-subject differences between target and nontarget trials by channel. Significance was reported for these channelwise tests from p-values before and after Benjamini-Hochberg correction (Benjamini and Hochberg, 1995) as a protection against false discoveries.

Linear regression models were employed to determine whether, and to what degree, the estimated duration of HIV infection predicted P200 or LPP amplitudes in any of the three behavioral tasks.

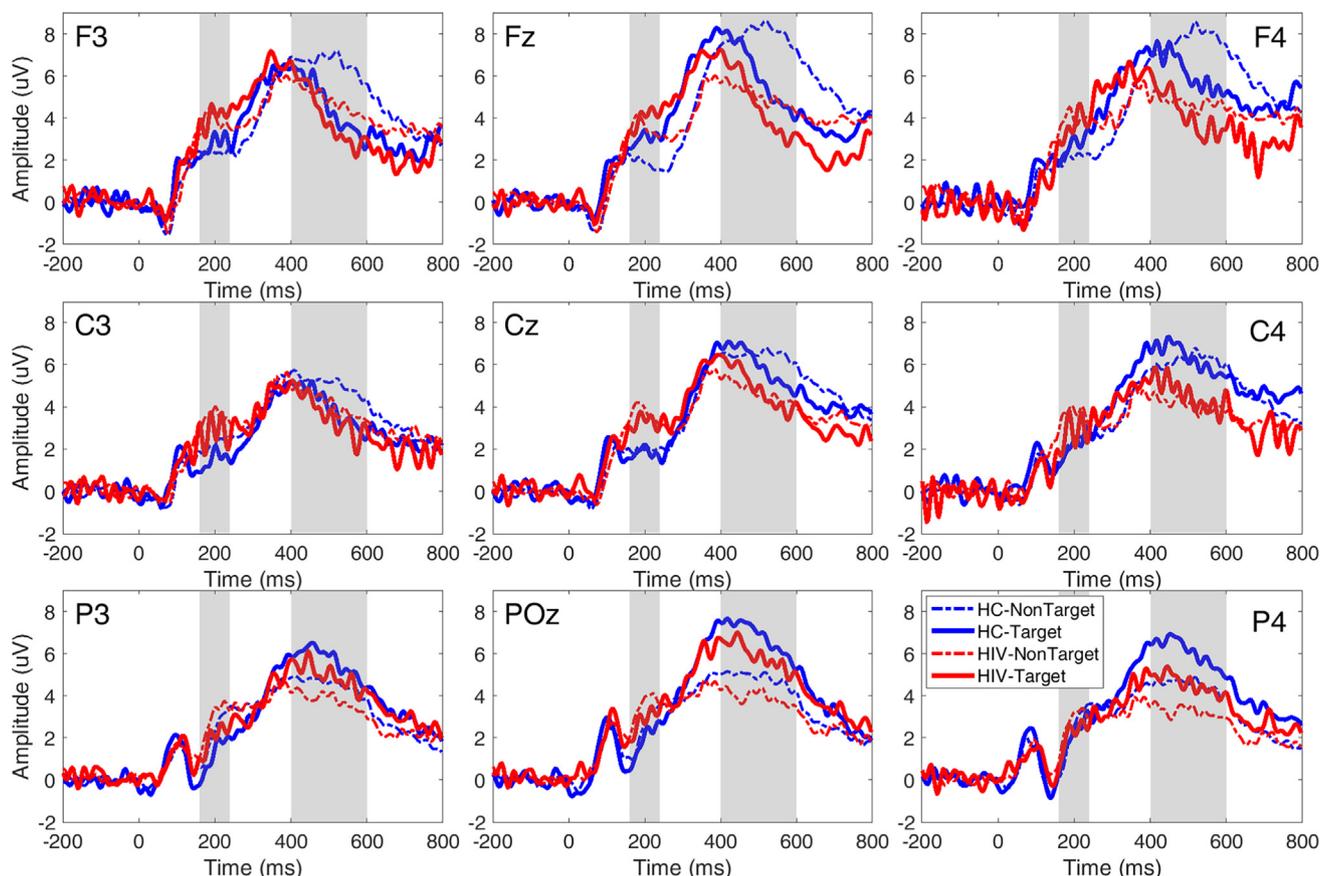


Fig. 6. Grand average ERPs in FA task. Grand averages for Target (Infrequent) and NonTarget (Frequent) trials during Focused Attention task (FA) plotted for both HC and HIV group. Target trials are indicated by solid lines, NonTarget trials by dotted lines. HC and HIV groups are shown with blue and red colors, respectively. The grey boxes mark the time ranges used to determine P200 and LPP boundaries in this study.

Given the possible confounding effect of age on duration estimates, the same testing was undertaken using age as the predictor variable. Residuals from each model were checked for gross deviations from normality, and heteroscedasticity was assessed from observed vs. fitted residual plots. Model assumptions were satisfied in almost all conditions, but in the few cases where violations were discovered, they have been explicitly outlined in the results. All hypothesis tests used two-tailed statistics. The α criterion for significance was set to 0.05. Statistical analyses were conducted using MATLAB.

3. Results

3.1. Sustained attention task (3CVT): Behavioral performance

The HC group on average exhibited significantly faster reaction time compared to healthy controls (Supplementary Figure 1; $Z = 22.1, p = 1 \times 10^{-107}$). However, the two groups did not significantly differ in terms of accuracy (ACC) measured by percentage of correct responses ($Z = -0.52, p = 0.6$). Table 2 shows median group differences and results of hypothesis testing for RT and accuracy in the 3CVT task.

3.2. Sustained attention task (3CVT): ERPs

ERP waveforms averaged across all correct trials for all conditions are plotted for both groups (HC, HIV) (Fig. 3) Group-average ERP waveforms showed significant differences between HC and HIV groups with respect to (1) the average voltage of the P200 component (Fig. 4, Supplementary Figure 2 and Supplementary

Table 1) which was maximal over EEG channels recording from the left and midline frontal (Fz, F3) and central regions (Cz, C3), and (2) the Late Positive Potential (LPP) where the largest significant group differences were from the midline parietal-occipital electrode, POz (Fig. 5, Supplementary Table 2).

The HIV group exhibited larger average P200 amplitudes than the HC group at Fz, F3, Cz, and C3. No significant interactions were found between HIV seropositivity and stimulus type for either P200 or LPP amplitudes at any EEG channel. Fig. 4 shows topographical maps of P200 amplitudes at each channel averaged by seropositivity group and stimulus type with accompanying maps showing the differences between the groups. The HIV group had significantly higher P200 amplitudes than HCs at left frontal channels, Fz and F3, and left central channels, Cz and C3.

Fig. 5 shows the topographical maps of the within- and between-subject differences for the LPP component. Average LPP amplitudes were larger for NonTarget (Infrequent) trials in both groups. This target effect was significant over left central and frontal regions for P200 in both groups. Significant differences in LPP amplitudes between trials of the two stimulus types were widespread for HC group, but restricted to right central and parietal regions for the HIV group. The HIV group had significantly lower LPP amplitude than the HC group at channel POz.

3.3. Focused attention and divided attention tasks: Behavioral performance

Wilcoxon rank sum test revealed the only significant difference between HIV and HC groups was in FA reaction time (Table 3). In the FA task (Supplementary Figure 3), the median reaction time

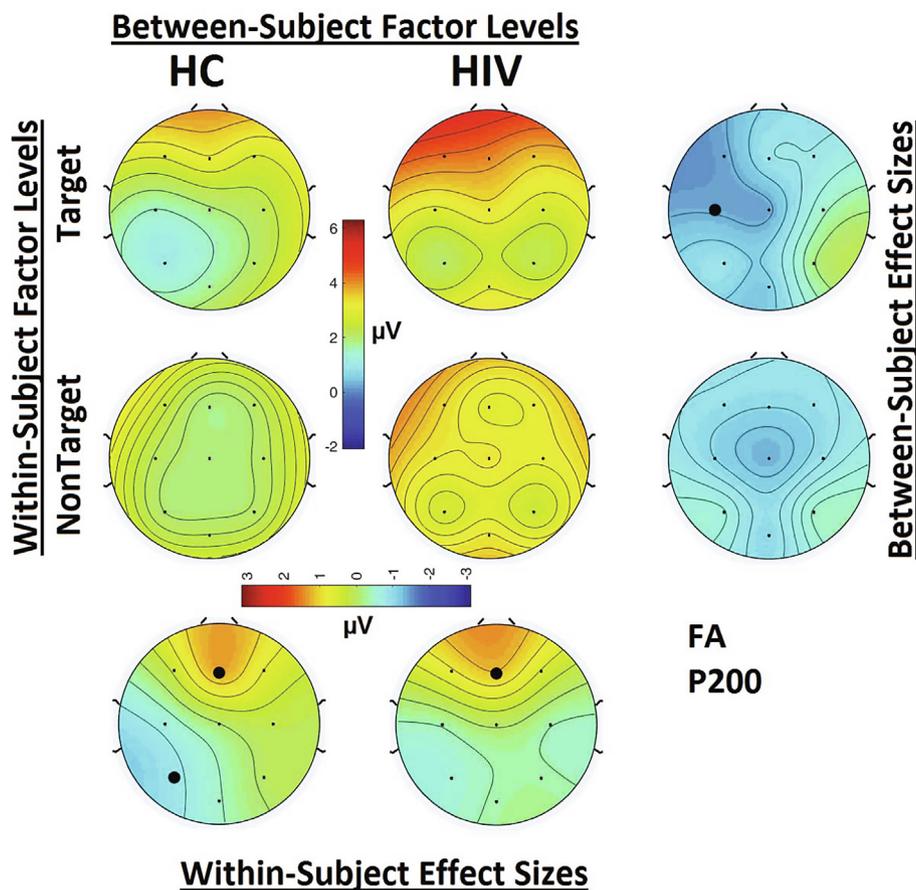


Fig. 7. Topographical maps of P200 during FA task. Group average topographical maps of LPP amplitude and effect sizes (all in μV) by seropositivity and stimulus types (Target, Infrequent and NonTarget, Frequent). Effect sizes represent differences between seropositivity groups ($ES_{BS} = \text{HC} - \text{HIV}$), or stimulus types ($ES_{WS} = \text{Target} - \text{NonTarget}$). Topographical maps are color coded using vertical color bar (factor levels), or horizontal color bar (effect sizes). Channels with significant differences are marked with black circle (●) with or without white border; former marker type indicates significance after Benjamini-Hochberg correction. Within-subject HC ($df = 44$): Fz, $p = 0.018$, $t = -2.45$; P3, $p = 0.01$, $t = -2.67$; Within-subject HIV ($df = 32$): Fz, $p = 0.029$, $t = 2.28$; Between-subject Target: C3, $p = 0.037$, $t = -2.13$, $df = 73.74$; $N_{HC} = 45$, $N_{HIV} = 33$.

for the HIV group was 25 ms slower RT than HC group ($Z = 2.33$, $p = 0.0198$). In the DA task (Supplementary Figure 4), the difference between medians for the two groups revealed a +27 ms faster RT in the HIV group ($Z = -1.588$, $p = 0.11$), and 0.5% decrease in ACC in HIV compared to HC group ($Z = 0.0$, $p = 1.0$).

3.4. Focused attention task: ERPs

In the FA task, average ERPs were computed for Target (Infrequent, 20% trials) and NonTarget (Frequent, 80% trials) stimuli. Like the 3CVT task, the HIV and HC groups differed in both the P200 and LPP components. Fig. 6 shows the grand average of ERPs across all participants in each seropositivity group plotted for Target (Infrequent) trials and NonTarget (Frequent) trials.

Results of the 2×2 mixed factorial model employed to investigate the main effects of HIV seropositivity (HC or HIV), stimulus type (Target-Infrequent or NonTarget-Frequent), and their interaction on ERP components are summarized in Supplementary Table 3 and Supplementary Table 4 for average P200 and LPP amplitudes, respectively. HIV seropositivity had a significant main effect on P200 amplitude at channel C3 (Supplementary Figure 5), however variances were also significantly different with greater variance in the HC than in HIV group (Brown-Forsythe $F_{1,76} = 5.28$, $p = 0.02$). The main effect of stimulus type on P200 was significant at Fz and P3. Supplementary Figure 6 shows boxplots for EEG channels found significant in the mixed model results for LPP. Significant differences between HC and HIV groups (reported in Supplementary Table 4)

were found at right frontal and central EEG channels (Fz, F4, C4), with significant main effects of stimulus type at all three posterior channels (P3, POz, P4). There were no significant interactions between seropositivity and stimulus type in either ERP component.

Group differences were also evaluated at each channel location using Welch's two-sample t-tests. Fig. 7 and Fig. 8 show topographical maps of the P200 and LPP amplitudes by HIV seropositivity groups, HC and HIV. P200 amplitudes at the central left channel, C3, were on average 1–2 μV higher in the HIV group. Average P200 amplitudes were like those obtained for the 3CVT task in that the HIV group had higher P200 amplitude and reduced LPP amplitude when compared to HCs.

Average amplitudes of both LPP and P200 components are generally larger for infrequent (Target) than the frequent (NonTarget) stimulus. The within-subject effect is maximal over the frontal region for P200 (Fig. 7), and over the parietal region for LPP (Fig. 8). The difference between P200 amplitudes elicited from Target (Infrequent) versus NonTarget (Frequent) was greatest at channel Fz in both HC and HIV groups. LPP amplitude differences between the two stimuli were concordant in both HC and HIV groups with significance at all three posterior EEG channels even after Benjamini-Hochberg correction.

3.5. Divided attention task (DA): ERPs

In the DA task, participants were asked to attend to two stimuli streams, one on each side of the screen, and to appropriately

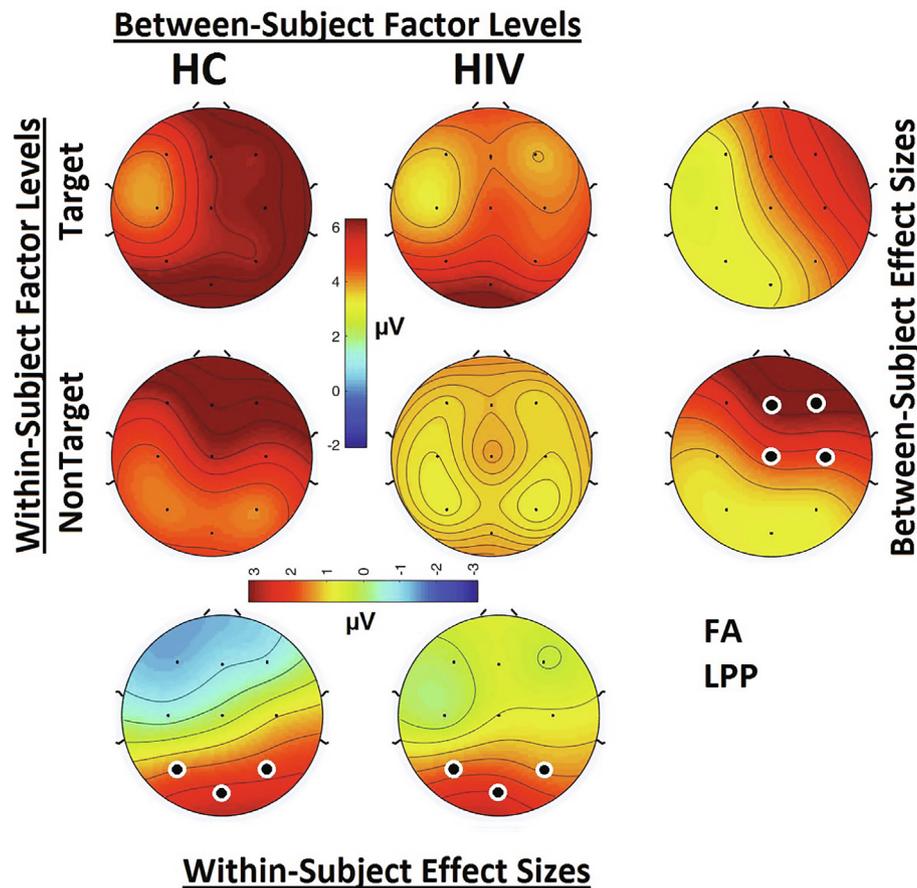


Fig. 8. Topographical maps of LPP during FA task. Group average topographical maps of LPP amplitude and effect sizes (all in μV) by seropositivity and stimulus types (Target, Infrequent and NonTarget, Frequent). Effect sizes represent differences between seropositivity groups ($ES_{BS} = \text{HC} - \text{HIV}$), or stimulus types ($ES_{WS} = \text{Target} - \text{NonTarget}$). Topographical maps are color coded using vertical color bar (factor levels), or horizontal color bar (effect sizes). Channels with significant differences are marked with black circle (●) with or without white border; former marker type indicates significance after Benjamini-Hochberg correction. Within-subject HC ($df = 44$): P3, $p = 0.005$, $t = 2.95$; POz, $p = 0.0006$, $t = 3.68$; P4, $p = 0.001$, $t = 3.44$; Within-subject HIV ($df = 32$): P3, $p = 0.006$, $t = 2.94$; POz, $p = 0.0009$, $t = 3.65$; P4, $p = 0.007$, $t = 2.89$; Between-subject NonTarget: Fz, $p = 0.012$, $t = 2.59$, $df = 67.9$; F4, $p = 0.009$, $t = 2.68$, $df = 73.8$; Cz, $p = 0.019$, $t = 2.4$, $df = 66.3$; C4, $p = 0.01$, $t = 2.65$, $df = 76.0$; $N_{\text{HC}} = 46$, $N_{\text{HIV}} = 33$.

respond at the presentation of either letters (on the left) or symbols (on the right). The ERP responses to trials on both left and right side were combined for analysis. Fig. 9 shows the grand average ERPs in response to Target (Infrequent) trials and NonTarget (Frequent) trials.

Results from the 2x2 mixed factorial models indicate that HIV seropositivity and stimulus type did not show any significant effect on P200 amplitude (Supplementary Table 5). Null hypotheses could not be rejected for either main effect of HIV seropositivity or stimulus type, nor were any significant differences seen for interaction between the two factors. Mixed model results for LPP (Supplementary Table 6) revealed a significant main effect of HIV seropositivity at right posterior channel P4 (Supplementary Figure 7), and a significant main effect of stimulus type across all channels except for C3 and F4.

Fig. 10 shows topographical maps of LPP during the Divided Attention task illustrating between- and within-subject differences for HC and HIV groups, and Target (Infrequent) and NonTarget (Frequent) trials, respectively. Results from Welch's test corroborated the significant difference between HC and HIV found at channel P4 in the mixed factorial model, with greater average LPP in healthy controls compared to HIV group. Topographical maps from the divided attention task reveal that, on average, the HIV group exhibited 1.25 μV lower LPP component at P4 than HCs during Target (Infrequent) trials. In both seropositivity groups, LPP amplitudes were greatest during Target (Infrequent) trials, particularly

in posterior EEG channels (P3, POz, P4). The significant differences in posterior LPP amplitude between the two stimulus types extended to C4 in the HIV group. The LPP amplitude increases at frontal channel Fz were unique to the HIV group. There were no EEG channels at which average P200 amplitudes significantly differed between the HIV and HC groups, nor by stimulus type.

3.6. Correlations across tasks

In order to assess the reliability and specificity of ERP measures, P200 and LPP were compared for all participants that had available data in all 3 tasks. The correlation coefficient between ERP measures across tasks are listed in Supplementary Table 7 and Supplementary Table 8. The most significant P200 correlation was between 3CVT and FA at channel Cz for Infrequent stimuli ($r = 0.67$, $p = 1.4 \times 10^{-8}$, $df = 54$). The least significant correlation was between 3CVT and DA at channel F3 for Infrequent stimuli ($r = 0.3$, $p = 0.025$, $df = 54$). The correlation coefficients for all stimulus types and channels are listed in Supplementary Table 7. The average correlation coefficients across all channels was highest for FA vs. DA both for Frequent stimuli ($r = 0.57$, $df = 62$) and Infrequent stimuli ($r = 0.53$, $df = 54$).

Similarly, correlations between LPP amplitudes across tasks are listed in Supplementary Table 8. Overall, correlations for LPP measures were significant only for a subset of channels as marked in Supplementary Table 8. The most significant correlation was

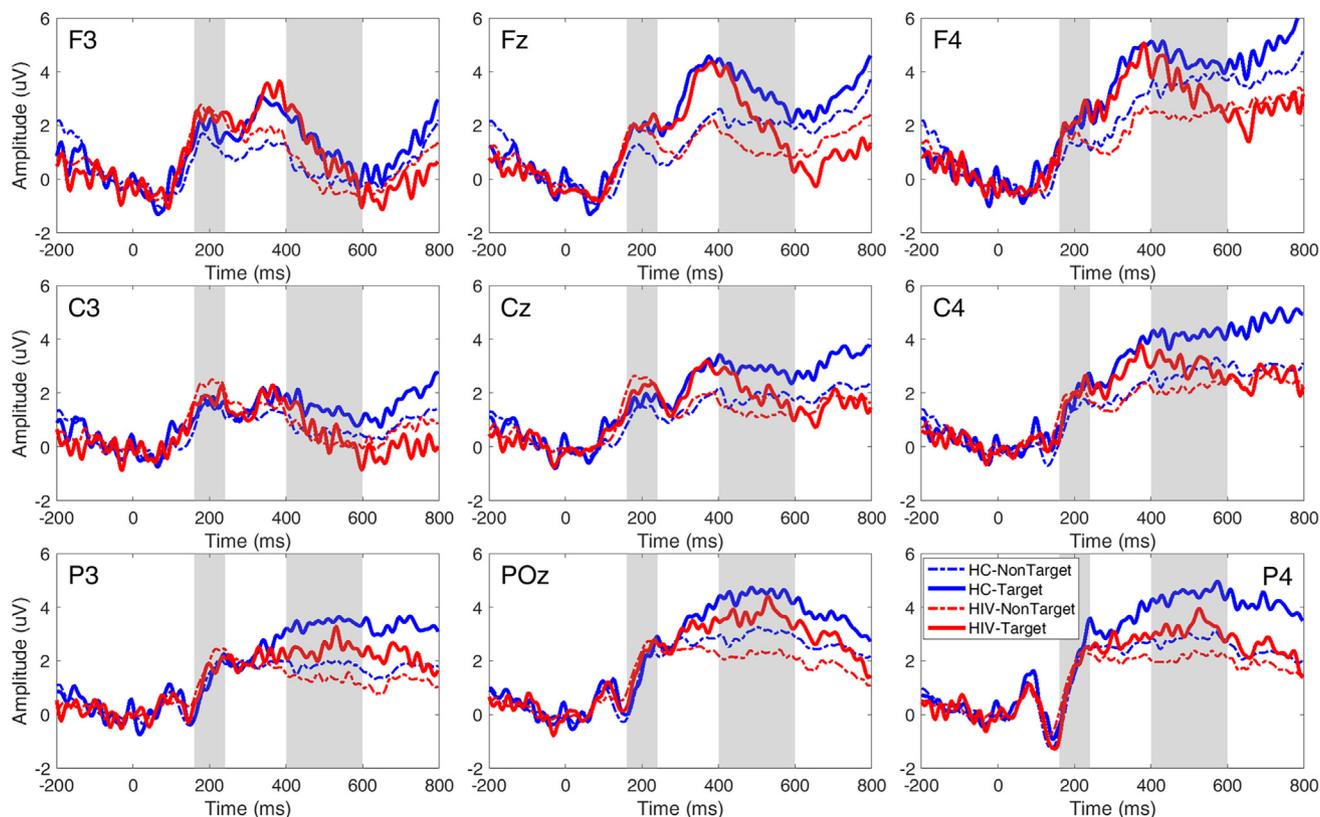


Fig. 9. Grand average ERPs in DA task. Grand averages for Target (Infrequent) and NonTarget (Frequent) trials during Divided Attention task (DA) plotted for both HC and HIV group. Target trials are indicated by solid lines, NonTarget trials by dotted lines. HC and HIV groups are shown with blue and red colors, respectively. The grey boxes mark the time ranges used to determine P200 and LPP boundaries in this study.

between 3CVT and FA at channel Cz for Infrequent stimuli ($r = 0.64$, $p = 8 \times 10^{-8}$).

3.7. P200 and duration of HIV infection

Correlation analysis was conducted for each EEG channel of average P200 amplitudes and the number of years since subjects in the HIV group received their first HIV positive test (estimated duration of infection). Significant correlations were found across all channels during the FA task with greater duration of HIV infection associated with increasing P200 amplitudes (Table 4). To address the possibility that age may explain this as a potential confound, the same analysis was done of P200 amplitudes versus subject age, and no significant correlations were found at any channel for either the HC or HIV groups.

4. Discussion and conclusions

Neural and behavioral correlates of sustained, focused and divided attention were recorded and analyzed from HIV and HC groups. The ERP measures showed an overall decrease in the LPP amplitude and an increase in the P200 amplitude in the HIV group compared to HC.

This reduction of the LPP is consistent with prior findings in HIV infection (Babiloni et al. 2015) and several other neurodegenerative diseases (Berka et al., 2018; Waninger et al., 2018). However, the observed increase in the P200 amplitude in the HIV group (consistent across all tasks) is a novel finding. To the best of the authors' knowledge, this P200 effect has not been previously reported for HIV patients, except in a limited study with a completely different protocol (emotion-eliciting stimuli) and population (all female, 25–40 years of age) (McIntosh et al. 2015).

Additionally, the authors have not observed any evidence of increased P200 amplitude during the same task (3CVT) in their prior work on neurodegenerative diseases (Berka et al., 2018; Waninger et al., 2018), sleep disorders and psychiatric conditions.

The P200 effect in the present work was similar across tasks suggesting that the P200 component may reflect a common construct across three unique attention tasks. Therefore, this effect does not seem to be specific to the tasks and rather reflect the common aspect of all these tasks.

Additionally, the correlation between P200 amplitude and estimated duration of HIV infection suggests a link between the progression of underlying neuropathological changes associated with the duration of HIV infection. The underlying mechanisms generating this P200 effect during sustained, divided and focused attention tasks require further exploration.

The P200 component in general is known to reflect early allocation of attention and awareness (Perrault and Picton, 1984; Näätänen, 1992; Singhal et al., 2002; Lijffijt et al., 2012). P200 and N100-P200 complex have been shown to index some aspects of selective attention through suppressing irrelevant stimuli or preferential processing of distinct types of stimuli. For example, a decreased amplitude of the P200 component is shown to reflect automatic auditory sensory gating that could reflect cognitive functions involved in behavioral and attentional inhibition (Singhal et al., 2002; Lijffijt et al., 2009, 2012). There has been supporting evidence that HIV seropositive individuals show deficient response inhibition and impulsivity (Hinkin et al. 1999; Martin et al. 2004). For example, (Minassian et al. 2013) reported that individuals with HAND showed impairment in sensory motor gating (Minassian et al. 2013) that could result in impulsivity. Some of the conditions that have been shown to increase P200 amplitude are: emotional valence of the stimuli (negative biases) (Carretié et al., 2001; McIntosh et al., 2015), increased anxiety and intoler-

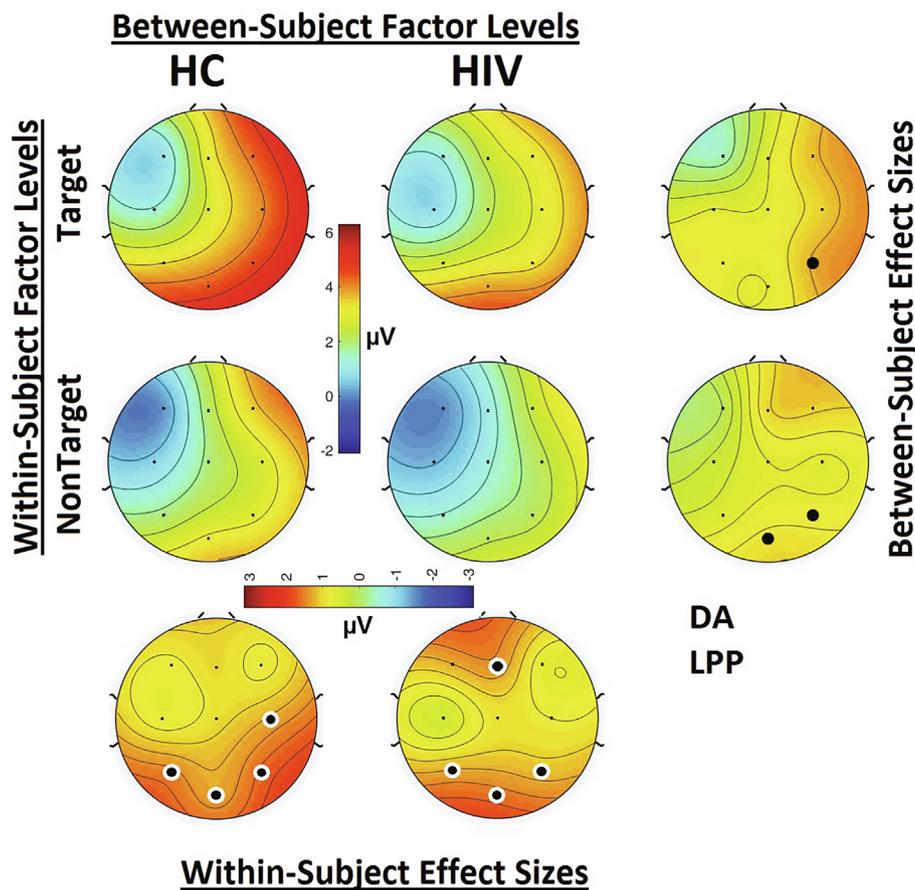


Fig. 10. Topographical maps of LPP during DA task. Group average topographical maps of LPP amplitude and effect sizes (all in μV) by seropositivity and stimulus types (Target, Infrequent and NonTarget, Frequent). Effect sizes represent differences between seropositivity groups ($ES_{BS} = \text{HC} - \text{HIV}$), or stimulus types ($ES_{WS} = \text{Target} - \text{NonTarget}$). Topographical maps are color coded using vertical color bar (factor levels), or horizontal color bar (effect sizes). Channels with significant differences are marked with black circle (●) with or without white border; former marker type indicates significance after Benjamini-Hochberg correction. Within-subject HC ($df = 44$): C4, $p = 0.005$, $t = 2.95$; P3, $p = 0.0002$, $t = 3.99$; POz, $p = 0.002$, $t = 3.29$; P4, $p = 0.00008$, $t = 4.34$; Within-subject HIV ($df = 29$): Fz, $p = 0.02$, $t = 2.45$; P3, $p = 0.002$, $t = 3.46$; POz, $p = 0.005$, $t = 3.06$; P4, $p = 0.005$, $t = 3.04$; Between-subject Target: P4, $p = 0.046$, $t = 2.03$, $df = 70.53$; Between-subject NonTarget: POz, $p = 0.026$, $t = 2.27$, $df = 72.9$; P4, $p = 0.036$, $t = 2.14$, $df = 66.8$; $N_{\text{HC}} = 45$, $N_{\text{HIV}} = 30$.

ance of uncertainty (Eldar et al., 2010; Gole et al., 2012) and some subtypes of Attention-Deficit Hyperactivity Disorder (ADHD) (Lazzaro et al., 2001; Barry et al., 2009).

In summary, increased P200 amplitude in this study may indicate neurocognitive impairments manifested in attentional deficits such as impulsivity, inhibition deficiency and intolerance of uncertainty. These hypotheses are consistent with higher prevalence of psychiatric symptoms such as anxiety (Brandt et al. 2017) and ADHD (e.g. (Bakare, 2012; Shankar et al., 2014)) in HIV seropositive populations. In the present study, although self-reported ADHD diagnosis was an exclusion criterion, no clinical ADHD assessment was performed and thus participants with undiagnosed ADHD or individuals with subclinical symptoms may have been included (9 out of 39 HIV seropositive participants were taking anxiolytic medication for various reasons).

The neural generators of the visual P200 are not yet fully understood but some studies suggest multiple frontal and parietal sources may contribute to this component (Furutsuka, 1989; Luck and Hillyard, 1994; Freunberger et al., 2007). Further studies involving source localization or multimodal EEG/fMRI recording might better explain the neural sources of P200 that could help in identifying affected pathways in HIV related impairments and/or their relation to task difficulty. For example, in a previous fMRI study, it has been shown that untreated HIV patients compared to healthy controls demonstrated greater regional activation during attention and working memory tasks that depends on the task

and the level of difficulty (Chang et al., 2001). Additionally, structural MRI studies identify regional reductions in grey matter volumes and abnormalities in white matter (possibly linked to demyelination, neuroinflammation, microvascular or synaptic damage) as persistent features in HIV patients even when successfully treated with ART (O'Connor et al., 2018; Küper et al., 2011; Kallianpur et al., 2012). Specific findings suggested a relationship between impaired executive function and decreases in psychomotor processing speed were linked to grey matter atrophy in basal ganglia and overall cortical thinning. Additional exploration of these structural changes in the brain is required to determine whether there is a contribution to attentional circuits underlying the generation of the P200.

It is also possible that the attentional impairment reflected in the P200 are not a direct result of the HIV infection but rather a result of common co-morbidities such as illegal drug use, depression, anxiety or untreated hypertension. The ART medications may also have some deleterious effects on brain structure and function.

In summary, the finding of the present study may provide a biomarker for assessing the subtle neurocognitive impairments in HIV seropositive individuals. Whether these impairments are inherently caused by HIV infection or by subclinical comorbidities such as ADHD or anxiety, these biomarkers could help better characterize and quantify HIV related cognitive impairments. This is particularly important as performance scores from cognitive tests might

Table 4
Correlation coefficient between P200 amplitude in HIV group and estimated duration of infection. Significant correlations ($p < 0.05$) are in bolded text Lower and higher bounds of 95% confidence intervals in parenthesis.

P200 EEG channel	Frequent Stimulus			Infrequent Stimulus		
	3CVT	FA	DA	3CVT	FA	DA
P0z	$r = 0.16$ (-0.28,0.54) $p = 0.49$	$r = 0.26$ (-0.1,0.56) $p = 0.15$	$r = 0.07$ (-0.30,0.43) $p = 0.71$	$r = 0.17$ (-0.32,0.59) $p = 0.51$	$r = 0.47$ (0.12,0.71) $p = 0.01$	$r = 0.20$ (-0.2,0.54) $p = 0.32$
Fz	$r = 0.29$ (-0.15,0.64) $p = 0.19$	$r = 0.44$ (0.1,0.69) $p = 0.01$	$r = 0.42$ (0.07,0.68) $p = 0.02$	$r = 0.36$ (-0.12,0.71) $p = 0.14$	$r = 0.45$ (0.10,0.70) $p = 0.01$	$r = 0.43$ (0.06,0.69) $p = 0.03$
Cz	$r = 0.28$ (-0.16,0.63) $p = 0.21$	$r = 0.44$ (0.1,0.68) $p = 0.01$	$r = 0.47$ (0.13,0.71) $p = 0.01$	$r = 0.44$ (-0.03,0.75) $p = 0.07$	$r = 0.48$ (0.14,0.72) $p = 0.008$	$r = 0.40$ (0.02,0.68) $p = 0.04$
C3	$r = 0.33$ (-0.11,0.66) $p = 0.14$	$r = 0.29$ (-0.07,0.58) $p = 0.12$	$r = 0.41$ (0.06,0.68) $p = 0.03$	$r = 0.51$ (0.06,0.79) $p = 0.03$	$r = 0.49$ (0.16,0.73) $p = 0.006$	$r = 0.35$ (-0.04,0.64) $p = 0.08$
C4	$r = 0.29$ (-0.16,0.66) $p = 0.20$	$r = 0.28$ (-0.08,0.58) $p = 0.12$	$r = 0.43$ (0.07,0.69) $p = 0.02$	$r = 0.26$ (-0.24,0.65) $p = 0.30$	$r = 0.51$ (0.18,0.74) $p = 0.004$	$r = 0.31$ (-0.08,0.62) $p = 0.11$
F3	$r = 0.33$ (-0.11,0.66) $p = 0.13$	$r = 0.33$ (-0.03,0.61) $p = 0.07$	$r = 0.37$ (0.01,0.65) $p = 0.05$	$r = 0.46$ (-0.01,0.76) $p = 0.05$	$r = 0.49$ (0.15,0.73) $p = 0.007$	$r = 0.34$ (-0.04,0.64) $p = 0.08$
F4	$r = 0.27$ (-0.17,0.62) $p = 0.22$	$r = 0.28$ (-0.08,0.58) $p = 0.13$	$r = 0.39$ (0.03,0.66) $p = 0.04$	$r = 0.21$ (-0.29,0.62) $p = 0.41$	$r = 0.47$ (0.13,0.72) $p = 0.009$	$r = 0.35$ (-0.04,0.64) $p = 0.07$
P3	$r = 0.15$ (-0.29,0.54) $p = 0.51$	$r = 0.23$ (-0.14,0.54) $p = 0.22$	$r = 0.23$ (-0.15,0.55) $p = 0.24$	$r = 0.23$ (-0.27,0.63) $p = 0.37$	$r = 0.44$ (0.08,0.69) $p = 0.018$	$r = 0.22$ (-0.18,0.55) $p = 0.28$
P4	$r = 0.06$ (-0.37,0.47) $p = 0.77$	$r = 0.21$ (-0.15,0.53) $p = 0.25$	$r = 0.20$ (-0.18,0.53) $p = 0.30$	$r = 0.06$ (-0.42,0.51) $p = 0.82$	$r = 0.50$ (0.17,0.73) $p = 0.006$	$r = 0.22$ (-0.17,0.56) $p = 0.26$

not be sensitive to very subtle cognitive brain alterations in individuals with HIV and may depend on the task type and the level of difficulty. For example, the findings in the current paper demonstrated a slower response time for the HIV group in a simple sustained attention task and no significant difference in performance of focused and divided attention tasks. Further studies are needed to conclude possible impulsivity tendencies in more difficult tasks such as divided attention.

Declaration of Competing Interest

Amir H. Meghdadi, Chris Berka, Greg Rupp, Stephanie Smith, Marija Stevanović Karić, and Christian Richard are all employees of Advanced Brain Monitoring, Inc.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinph.2020.11.026>.

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