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HIV/AIDS and an overweight body mass are associated with excessive intra-individual variability in response preparation

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Abstract

Factors other than HIV/AIDS may influence the cognitive function of patients living with this disease. The present study tested the influence of a common comorbid problem—an overweight body mass. It also examined intra-task variabilities in performance and brain activation as potentially more sensitive indicators of dysfunction than their mean levels. One-hundred seventy-eight participants were recruited and categorized by HIV-1 serostatus (−/+) and body mass (BMI < 26/≥ 26 kg/m^2). They performed a simple time estimation task during which response time accuracy and electroencephalographic readiness potentials were recorded. A few hours later, they completed a battery of tests measuring balance and gait. The analyses revealed an advantage of variability over the mean in differentiating groups: the presence of HIV-1 and an overweight body mass were independently and additively associated with greater variability across trials in readiness potential amplitude and response accuracy. The analysis also showed that intra-task variability in the readiness potential, but not in response accuracy, was predictive of decrements in single and tandem leg balance and gait velocity. The present findings suggest that an elevated body mass is associated with, and may contribute to, problems in brain function and motor behavior experienced by patients in the current era. The findings recommend a careful consideration of the manner in which these problems are measured. When the problems are episodic and subtle, measures of central tendency may be less than ideal.

Keywords HIV-1 · Intra-individual variability · Cognitive · Obesity · Balance · Gait · EEG · Readiness potential

Introduction

It has been suggested that the neuroAIDS research community should adjust its conceptualization of the causes of impaired neurocognitive function among patients living with human immunodeficiency virus (HIV) infection (Gelman, 2015). A shift in perspective is needed because the severity and nature of the impairment has changed. Indeed, with the introduction of effective antiretroviral treatment (ART), the prevalence of HIV-1-associated dementia has declined precipitously (Watkins and Treisman, 2015). It also appears that the prevalence of moderate and minimal cognitive impairment has declined (Crum-Cianflone et al., 2013; McDonnell et al., 2014). But, there is disagreement on this point (Heaton et al., 2011). The likely source of the disagreement is the inadequate control employed in some studies over the influence of other contributors, including substance abuse (Archibald et al., 2012; Bauer, 1998; Bauer and Shanley, 2006; Gongvatana et al., 2014; Morgan et al., 2012), familial/genetic risk (Bauer, 2008a; Bauer, 2008b; Bauer, 2013), and comorbid medical disorders (Dufouil et al., 2015; McCutchan et al., 2012; Rodriguez-Penney et al., 2013; Vance et al., 2016). As a result, the literature is clouded with higher-than-expected rates of impairment.

One contributor that has rarely been examined in studies of neurocognitive problems accompanying HIV-1 disease is an elevated body mass, which is rising in prevalence (Amorosa et al., 2005; Koethe et al., 2016; Tate et al., 2012). Among overweight study participants without HIV-1 infection, researchers have detected subtle cognitive impairments, principally in the domain of response inhibition (Bauer, 2014; Bauer et al., 2010b; Bauer and Shanley, 2006; Nederkoorn et al., 2007; Reinert et al., 2013), but also in other domains (Bauer et al., 2010a; Bauer, 2015; Bauer and Houston, 2017; Bauer and Manning, 2016; Liang et al., 2014). Among patients with HIV-1, there is evidence that an elevated body mass is associated with an amplification of impairment.

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One example of amplification was reported by our group (Bauer, 2011) from a study that examined P300 electroencephalographic potentials during a simple selective attention task. The results revealed a statistically significant delay in P300 latency over the frontal brain among HIV-1 seropositive versus seronegative participants. The latency delay was markedly greater among seropositive patients with a body mass index (BMI) greater than 25 kg/m^2.

Another example is a finding from our previous study (Bauer et al., 2011) of various measures of balance and gait (Berner et al., 2017). The study similarly showed that participants with HIV-1 infection and an overweight body mass were more impaired than would be expected from the sum of the independent effects of these attributes. Patients with both attributes were markedly impaired in fast gait initiation time and cadence, non-preferred leg stance time, 360-degree turn time, and body sway strategy scores.

In the study described presently, we retained this interest in examining the synergistic contributions of HIV and an overweight or obese body mass to impairments in brain function and motor behavior. The study examined 93 HIV-1 seropositive and 85 seronegative participants who were challenged with a time estimation task, similar to a task employed previously (Bauer, 2001). Across 50 trials of this task, the participants were asked to press a response key exactly 2 s after the onset of a visual cue. The latency of the key press response provided a behavioral measure of time estimation accuracy. Additionally, electroencephalographic activity was recorded throughout the time estimation interval to provide a measure of covert response preparation: a frontally dominant (Gomez et al., 2007; Rosahl and Knight, 1995) cortically negative readiness potential (RP). In previous studies, healthy participants with accurate time estimation ability have been found to exhibit RPs of a smaller amplitude and slower rise time than participants with either poor time estimation ability (Brown et al., 1989; Ladanyi and Dubrovsky, 1985) or an impulsive, risk-taking personality style (Bauer, 2001).

An innovative aspect of the present study was its examination of the relative value of measures of variability versus measures of central tendency. In prior studies of older (Graveson et al., 2016; Holtzer et al., 2014; Reelick et al., 2011) or overweight (Bauer and Houston, 2017; Bauer and Manning, 2016) participants, who were neurologically normal and lacked obvious deficits, intra-individual variability was more valuable than the mean for differentiating groups. We could locate only three studies that have examined it as a correlate of HIV/AIDS or factors related to it.

In 2010, Ettenhofer and colleagues (Ettenhofer et al., 2010) reported findings from a study of 46 HIV-positive adults. No HIV-negative participants were included. Various measures of variability in response time were extracted from version 2 of Conner's Continuous Performance Test. The list of measures included the standard error of response time across all trials as well as its standard error across blocks of the task. The analysis of these measures revealed a statistically significant and negative association of response time variability with global cognitive ability as well as medication adherence over a 6-month monitoring period. Variability in response time was positively correlated with peak viral load.

A different study by Levine and colleagues (Levine et al., 2008) also focused on an exclusively HIV-1 seropositive sample. Yet, it did not examine a pure measure of performance variability. Instead, performance variability was part of larger entity—a factor score—that also included omission errors. Levine and colleagues found that the factor was negatively correlated with verbal IQ and medication adherence.

The final example was a study reported by Morgan and colleagues (Morgan et al., 2014). Their analysis included 90 HIV-negative and HIV-positive participants stratified by the presence versus absence of methamphetamine dependence during the preceding 18 months. The major finding was an elevation in response time variability during the Continuous Performance Test among methamphetamine-dependent patients and particularly among patients who reported amphetamine use during the prior 30 days. The authors detected no significant differences between the HIV-1 seropositive and seronegative groups in response time variability.

In our study, we included a measure of neurophysiological variability as a complement to the simple measurement of behavior variability. We did so by applying an aggressive low pass filter as well as artifact reduction routines to event-related electroencephalographic potentials obtained on individual trials. In this manner, the variability in the cortical readiness potential could be measured across trials in a manner analogous to the process used for calculating response time variability. It was hypothesized that intra-individual variability in the readiness potential would be superior to the mean in differentiating groups with or without HIV-1 infection or an overweight body mass.

The last notable feature of the present study was its attempt to demonstrate the value of intra-task variability for predicting problems in complex motor behavior among seropositive patients. Previous studies of healthy older adults have demonstrated an association between reaction time variability and balance and gait problems (Graveson et al., 2016; Holtzer et al., 2014). We therefore hypothesized that excessive variability in readiness measured during our time estimation task would be associated with disruptions in balance and gait measured at another time.

Method

Participants

HIV-1 seronegative and seropositive participants were recruited from outpatient infectious disease and substance abuse

treatment clinics in the greater Hartford, CT region as well as the local community. A variety of methods were used to advertise the study to them. The principal methods included posters, newsletters, and educational lectures. Newspaper and radio advertisements were also used.

The advertisements invited interested prospects to telephone a member of the research staff for eligibility screening. The telephone interview included questions about demographic characteristics, general medical status, substance use, and psychiatric symptoms. Two-hundred forty-four prospects who passed this initial telephone screen were invited to visit the Health Center on a subsequent day, during which an IRB-approved consent form and a medical records release were signed. Additional eligibility screening and laboratory evaluations were performed on the same day.

Collection of medical and psychological history and clinical laboratory data

After completing the informed consent and medical release documents, all prospects were asked to provide a blood sample for laboratory confirmation of HIV serostatus. The clinical laboratory evaluation also included the following assays: CBC with differential, HIV RNA viral load, CD4 lymphocyte count and percent, VDRL, HBV screen, HCV, toxoplasmosis and cytomegalovirus antibody titers, renal and liver function, serum protein, albumin, and G-6-PD. Additional tests included urine toxicological assays for evidence of recent cocaine, opiates, amphetamine, or marijuana use (Ontrak™, Varian Inc., Palo Alto, CA) as well as a breathalyzer test to detect recent alcohol use. The weights and heights of all participants were measured with a Health-o-Meter (McCook, IL) stadiometer and converted to a body mass index.

Prospective participants were subsequently brought to a private office where they completed a structured, computer-driven psychiatric interview, viz., the CDIS-IV (American, 1994; Robins, 2002), designed for detecting selected DSM-IV Axis I and II disorders. The interview was directed by a research assistant formally trained in its administration and with 11 years of relevant experience. Prospects also completed questionnaires or brief interviews assessing medical history, medication use, demographics, psychiatric symptoms, alcohol and drug use, and cognitive status. The assessments included the Addiction Severity Index [ASI (McLellan et al., 1980)], Michigan Alcoholism Screening Test [MAST (Selzer, 1971)], Drug Abuse Screening Test [DAST-10 (Skinner, 1982)], and Beck Depression Inventory version II [BDI-II (Beck, 1996)]. In addition, they completed the Kaufman Brief Intelligence Test [KBIT (Kaufman, 1990)] which provides an estimate of IQ.

Study volunteers were excluded from the analysis for evidence of recent (past year) pregnancy, seizures, myocardial infarction, stroke, mental retardation, dementia, neurosurgery, a BMI < 19, or a history of head injury with loss of consciousness for greater than 10 min. In addition, participants were required to have no acute illness, an IQ score greater than 70, and no major neurological or medical diseases such as chronic obstructive pulmonary disease, type 1 or type 2 diabetes, cirrhosis, hepatic encephalopathy, or cardiovascular disease. Positive urine toxicology tests indicating recent alcohol, cocaine, or opiates were also exclusions. However, current use of methadone was not. Volunteers were likewise excluded for a lifetime DSM-IV diagnosis of psychosis. Major depressive disorder was not an exclusion.

The application of these criteria to the 244 volunteers reduced the number of eligible participants to a total of 178 of whom 93 were HIV-1 seropositive and 85 were seronegative. The number of members within each serostatus group with a BMI ≥ 26 kg/m^2 versus a BM < 26 kg/m^2 were 41/52 and 51/34, respectively.

Collection of time estimation task data

For the collection of electroencephalographic readiness potentials during the time estimation task, tin electrodes were applied to 31 scalp sites positioned by an electrode cap (ElectroCap International, Eaton, Ohio). A reference electrode was taped over the bridge of the nose. The ground electrode was applied to the middle of the forehead. Interelectrode impedance was maintained below 5 Kilohms.

After the electrodes were applied, the participant was seated in a comfortable chair. The chair faced a 14-in computer monitor used for the presentation of visual stimuli. A response key was incorporated in a plastic box which the participant held in his/her lap. The participant was then provided with instructions about the task.

The instruction was to press a response key to designate the passage of a 2-s interval following the onsets of each of 50 cue stimuli. The cue stimulus was the letter "X" presented in the middle of a computer display for 50 ms. A small fixation spot was presented in the center of the monitor at all other times. Accuracy in task performance was summarized by the calculation of the absolute difference, in milliseconds, between the time estimation target of 2 s and the response time.

Feedback was provided to guide task performance. The computer was programmed to present either a 500 or 2000 Hz tone 3 s after response execution. The 500 Hz tone was presented if response latency was within a ± 250 ms window of the designated 2 s target. A 2000 Hz tone was presented if the response latency was outside of this range. The next trial commenced 5–10 s later.

The electroencephalogram was recorded throughout the task. Eyeblinks and eye movements were also recorded with a pair of electrodes placed diagonally above and below the left eye. The 31 channels of the EEG and 1 channel of eye movement (EOG) activity were appropriately amplified (EEG

gain = 20 K, EOG gain = 2 K) using a SA Instruments, Inc. (San Diego, CA) amplification system. Along with markers indicating stimulus and response onsets, the EEG and EOG channels were routed to an A/D converter and sampled at a rate of 200 Hz for 50 ms preceding and 1950 ms following the onset of each stimulus. During off-line computations, single-trial EEG epochs were sorted by electrode and digitally filtered (low-pass cutoff = 6 Hz, 48 db/octave roll-off). Epochs containing an eye movement deviation greater than 50 μV were deleted. Epochs with A/D converter overflow and omitted responses were also deleted. Voltage offsets were removed by subtracting the average voltage during the 50 ms pre-stimulus period from the voltages at each post-stimulus sampling point.

Readiness potentials (Figs.1 and 2) were derived from a minimum of 20 epochs recorded at the vertex (Cz) electrode. The means and standard deviations in RP amplitude were not calculated over the entire 2000 ms window. Doing so would invite contamination by premature button press responses occurring from 1710 to 1950 ms as well as exogenous evoked potential components occurring before 350 ms. Instead, on each trial, amplitude was averaged across a post-stimulus onset interval of 350–1710 ms. The average and standard deviation of this amplitude value were then computed over trials.

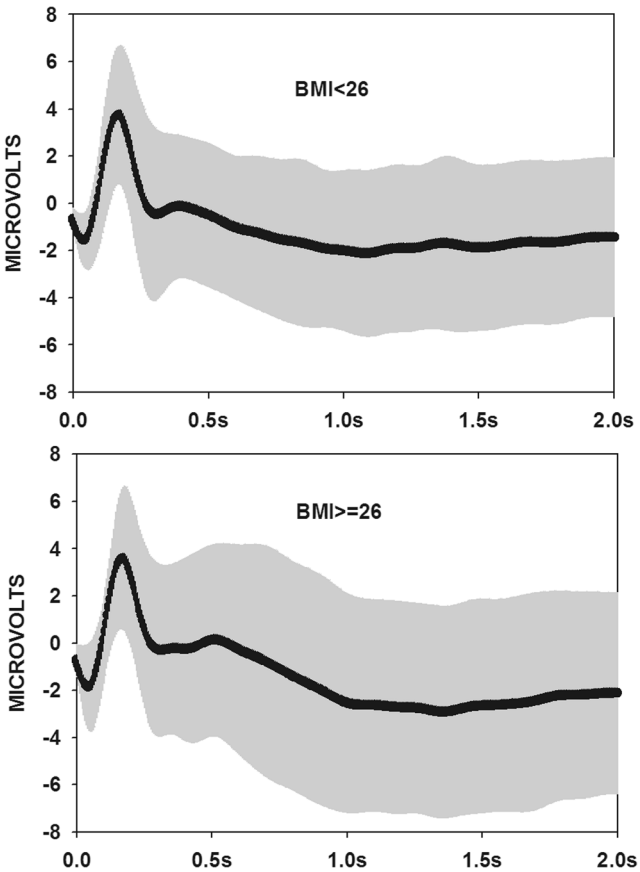

Fig. 1 Group-averaged readiness potential waveforms spanning the 2000 ms time estimation interval. The average voltage across trials is shown with a bold line. The standard deviation around the average is shown in gray. Note the large difference between BMI ≥ 26 and BMI < 26 groups in RP amplitude variability. No group differences were detected in analyses of the average voltage

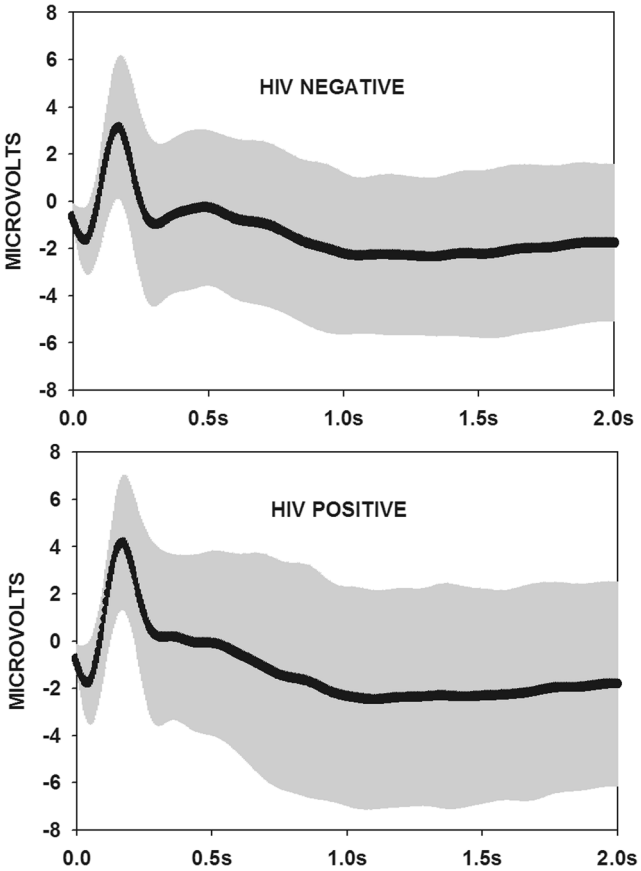

Fig. 2 Group-averaged readiness potential waveforms spanning the 2000 ms time estimation interval. The average voltage across trials is shown with a bold line. The standard deviation around the average is shown in gray. Note the large difference between HIV-1 seronegative and seropositive groups in RP amplitude variability. No group differences were detected in analyses of the average voltage

Collection of balance and gait data

Balance and gait data were obtained during the afternoon following the administration of the time estimation task and other cognitive tasks that have been described in other publications. These data were collected in a separate laboratory, the Balance and Gait Enhancement Laboratory (BAGEL), which was also located on the Health Center campus. A research assistant with 8 years of relevant experience administered the following tests to all participants.

Sensory organization test

The sensory organization test (SOT) is a standardized balance assessment protocol that employs a force-sensitive platform,

A/D converter, and computer (Equi-Test™ System, NeuroCom International, Inc., Clackamas, OR). Three conditions were examined within the protocol. All of the conditions provided inaccurate somatosensory information by moving the support platform to track changes in the center of gravity (i.e., sway-referenced). The differences across conditions related to the amount of visual information available to the participant regarding posture and sway. In the first condition (SOT 4), visual input was normal and, in the second condition (SOT 5), eyes were closed, i.e., visual input was absent. In the third condition (SOT 6), eyes were open but the visual horizon was sway-referenced, i.e., visual input was inaccurate. For each condition, three 20-s trials were presented.

Performance during each condition of the SOT was summarized by calculating the equilibrium quotient (EQ) and the number of falls. The equilibrium quotient was calculated from an algorithm owned by the manufacturer of the Equi-Test™ System. The algorithm defines perfect postural stability, without sway, with a score of 100 (range = 0–100). Our analysis retained the EQ score for a condition if the participant completed at least one of its three trials without experiencing a fall. If he/she fell during a trial, then the EQ data for that trial were deleted and the EQ score was the average of the remaining trials. Falls were defined as loss of balance maneuvers, including shifts in foot position, compensatory hand movements, or flexions of the trunk.

Functional base of support

While standing on the Equi-Test™ platform without shoes, the participant was instructed to lean as far forward as possible without losing balance. In the next condition, he/she was instructed to lean as far backward as possible without losing balance. Each condition was composed of two trials. An index of lean performance was calculated by adding the larger of the two forward lean distances in centimeters to the larger of the two backward lean distances. This value represents the range over which the base of support remains functional. The lean performance index was then divided by foot length in centimeters. This ratio served as an estimate of the functional base of support.

Single leg and tandem stance time

The participant was instructed to stand for as long as possible on the preferred leg, non-preferred leg, and both legs. The instruction also stated that arms should be crossed over the chest. Two trials were conducted for each stance. Rest breaks were permitted between trials. The dependent variable was the length of time that an immobile stance was maintained (maximum = 30 s). The single best score was retained.

Gait velocity

During a "normal" gait speed condition, the participant was asked to walk 8 m at a typical pace. During a second condition, estimating "fast" gait speed, he/she was asked to walk 8 m as quickly as possible without running. Times were recorded serially at distances of 0.5, 1, 2, 4, and 8 m. Gait velocity, in m/s, was calculated as 7.5 m divided by the time to walk between the 0.5 and 8 m markers. Two trials were conducted per condition and averaged.

Data analysis plan

The data analysis was divided into four phases. The first phase was designed to describe the demographic, medical, and psychiatric characteristics of four groups defined by the crossing of HIV-1 serostatus with weight status—a BMI < 26 versus ≥ 26 kg/m^2. Differences across the groups were tested with serostatus × weight status ANOVAs for continuous variables and Pearson's X^2 statistic for categorical variables.

The next phase was designed to more thoroughly interrogate the medical and psychiatric backgrounds of the participants. There was a concern that a simple description of the background would not adequately reveal confounds complicating the interpretation of group differences in the variables of primary interest: response time and RP amplitude. Accordingly, correlations were computed between selected background variables and these time-estimation task variables. Significant associations revealed by this approach were used to guide the selection of covariates in the next analysis phase.

The third phase of the plan focused on the analyses of intratask variabilities and mean levels of both response time and readiness potential amplitude. An obvious challenge in preparing the data for analysis is the fact that standard deviations and means are related. Often, the relationship is nonlinear and cannot be removed with the simple calculation of a coefficient of variation. Following the recommendations of Schmiedek and colleagues (Schmiedek et al., 2009), we did not make assumptions about the nature of the relationship. Instead, curve-fitting tests were used to suggest an appropriate transform that could be applied to the standard deviations. Findings suggested that an inverse quadratic transform was most effective. Therefore, it was applied.

The transformed standard deviations and untransformed means were then submitted to analyses of variance tests with serostatus, weight status, and sex as grouping factors. For ease of interpretation, untransformed SD values are reported in the tables. The ANOVAs of means and standard deviations included a statistical correction for the probable influence of substance dependence and childhood psychopathology. To this end, an addiction severity factor score, created from MAST and DAST scores as well as urine toxicology results,

and the number of childhood Conduct Disorder diagnostic criteria were entered as covariates.

The final phase of the analysis was an attempt to demonstrate the predictive validity of the major findings from the second analysis phase. It used correlational methods to test the associations of variability in readiness potential amplitude and response accuracy with the balance and gait data. The correlations were adjusted for the background variance associated with addiction severity and childhood conduct problems.

Results

Background characteristics

Analyses of the statistical effects of HIV-1 serostatus and weight status revealed few significant findings. The main effect of HIV-1 was statistically significant in the analyses of four variables. Seropositive participants exhibited higher AST [$F(1, 168) = 19.3$, $p < 0.002$)] and, ALT [$F(1, 168) = 18.6$, $p < 0.004$)], and lower CD4+ [$F(1, 168) = 94.7$, $p < 0.001$)] levels and reported more depression symptoms on the BDI-II [$F(1, 168) = 6.2$, $p < 0.02$)], in comparison to seronegative participants. Also, a higher percentage of seropositive participants reported Caucasian ancestry (30.1%) in comparison to seronegative (15.3%) participants [$X^2(1\ df) = 5.5$, $p < 0.02$].

Weight status was associated with only one background difference. Among HIV-1 seropositive participants, an elevated BMI was associated with a lower viral load than a normal BMI [$F(1, 91) = 5.0$, $p < 0.03$]. Seropositive participants with an elevated BMI did not differ significantly from their normal BMI peers on CD4+ cell count [$F(1, 91) = 1.2$, $p = 0.27$].

Association of background characteristics with time estimation task data

Further analyses focused on evaluating the impact of the background characteristics listed in Table 1 on time estimation task data. The analyses revealed a few significant findings. The addiction severity factor score was significantly correlated with RP amplitude ($r = 0.24$, $p < 0.005$) and RP variability ($r = 0.21$, $p < 0.005$). Also, the number of conduct disorder problems during childhood was significantly correlated with RP variability ($r = 0.15$, $p < 0.05$) but not with RP amplitude or response time. There were no other significant correlations.

Time estimation task data

Analyses of estimates of the variability and central tendency in response time and readiness potential amplitude revealed an interesting pattern of findings (Table 2). Neither average response time nor average RP amplitude differed as a function of the main or interactive effects of serostatus or weight status. It was only the across-trial standard deviations that differentiated the groups.

In comparison to its absence, the presence of HIV-1 [$F(1,168) = 4.4, p < 0.05$] was associated with greater variability in response time ($SD_{HIV+} = 0.58$ vs. $SD_{HIV-} = 0.52$). HIV-1 was also associated [$F(1, 168) = 8.1$, $p < 0.01$] with greater variability in RP amplitude ($SD_{HIV+} = 12.5$ vs. $SD_{HIV-} = 10.7$) over trials. Similarly, in comparison to participants with a normal BMI, participants with an elevated BMI showed greater variability in both response time [$F(1, 168) = 4.9$, $p < 0.03$; $SD_{BMI \geq 26} = 0.57$ vs. $SD_{BMI < 26} = 0.53$] and readiness potential amplitude [$F(1, 168) = 4.7$, $p < 0.04$; $SD_{BMI \geq 26} = 12.3$ vs. $SD_{BMI < 26} = 10.9$].

These statistical effects of serostatus and weight status were independent and additive. Their main effects on the readiness potential are illustrated in the waveforms presented in Figs. 1 and 2, respectively.

Predictive validity of across-trial variability in response time and RP amplitude for motor function

The remaining analyses focused the two dependent measures from the time estimation task analysis that significantly differentiated the groups. These analyses tested the associations of variability in response time and readiness potential amplitude with various indices of balance and gait.

As shown in Table 3, the variability in response accuracy was an inconsistent and weak predictor of balance and gait problems. It was only associated with the sway equilibrium score on the most difficult of the three sensory organization tests (SOT6) and was in the unpredicted direction. Table 3 shows more compelling and consistent evidence of an association between variability in a covert measure of response preparation, i.e., readiness potential amplitude, and balance and gait. The within-person variability in RP amplitude was associated with shorter preferred leg, non-preferred leg, and tandem stance times as well as a smaller functional base of support (FBOS) and a lower EQ score on the SOT4 subtest. In addition, it was correlated with slower gait velocity when a fast pace was required.

Discussion

The present study was designed to accomplish several goals. The first goal was to investigate the joint contribution of HIV/AIDS and an overweight body mass to brain dysfunction. It was inspired by studies demonstrating that overweight/obesity is an emerging and increasingly prevalent problem among HIV/AIDS patients receiving antiretroviral therapy (Amorosa et al., 2005; Hodgson et al., 2001; Jacobson et al., 2006; Shor-Posner et al., 2000). It was also inspired by

Table 1 Background characteristics of study participants

	HIV− BMI < 26 $N = 34$	HIV− BMI ≥ 26 $N = 51$	HIV+ BMI < 26 $N = 52$	HIV+ BMI ≥ 26 $N = 41$
Age in years (SD)	38.6 (7.1)	38.7 (6.8)	40.8 (5.3)	40.7 (7.2)
% Female	44.1	58.8	40.4	43.9
% Caucasian	14.7	15.7	23.1	39.0
Years of education	12.7 (2.2)	11.4 (3.5)	11.6 (2.0)	11.6 (1.8)
KBIT composite IQ	90.9 (19.1)	90.4 (11.9)	91.1 (11.3)	93.3 (13.1)
Beck Depression Score	11.0 (9.2)	12.1 (10.8)	16.4 (12.1)	14.4 (9.2)
Drug Abuse Screening Test Score	2.9 (3.1)	2.9 (3.1)	3.0 (2.9)	3.2 (3.2)
Michigan Alcohol Screening Test Score	2.6 (4.1)	4.6 (6.5)	4.5 (6.1)	4.4 (5.0)
AST (u/L)*	27.7 (17.8)	31.0 (17.6)	43.9 (29.8)	50.9 (41.3)
ALT (u/L)*	22.6 (13.3)	32.1 (32.3)	40.2 (43.7)	44.5 (35.1)
Current CD4+ (cells/mm^3)*	760.2 (1008)	832.7 (1064)	260.5 (430)	323.3 (506)
Current HIV RNA (log_{10} copies/mL)**	–	–	4.34 (0.9)	3.81 (0.9)

*$p < 0.05$, HIV+ vs. HIV−; **$p < 0.05$, BMI < 26 vs. BMI ≥ 26

demonstrations showing that the combination of HIV/AIDS and an overweight body mass is associated with poorer health outcomes than either factor alone.

The most obvious targets for the joint effects of HIV-1 and an elevated BMI on health are the heart and vasculature. Both factors are known to increase risk for atherosclerosis, diabetes, and myocardial infarction (Calza, 2016; Chow et al., 2017; Drozd et al., 2017). But, an additional and under-appreciated target could be the brain. HIV-1 disease has been shown to disrupt white matter tracts in autopsy studies (Solomon et al., 2017), increase the number of white matter abnormalities or hyperintensities in MRI studies (Pfefferbaum et al., 2007), and delay or dampen the neural processing of auditory, visual, or somatosensory information in evoked electroencephalographic potential studies (Chao et al., 2004; Harrison et al., 1998). Interestingly, within the brain, obesity is also—primarily—a white matter disease. An increased waist-to-hip ratio (Jagust et al., 2005) and an elevated BMI (Gazdzinski et al., 2008) are associated with an increase in the prevalence of white matter abnormalities in magnetic resonance images. The potential therefore exists for detrimental effects of HIV/AIDS and overweight/obesity on brain function that are either additive or synergistic.

The present analysis revealed additive effects. HIV/AIDS and overweight/obesity were independently associated with increased variability in both readiness potential amplitude and response time accuracy. We did not find evidence of the synergistic interaction previously found in analyses of P300 evoked potentials (Bauer, 2011) and motor function (Bauer et al., 2011). At the risk of accepting the null hypothesis, one could interpret the absence of the interaction as evidence that our time estimation task engages a different neural circuit than selective attention and motor tasks and this circuit is differently challenged by these two factors.

The second study goal was inspired by questions that have been raised about the importance of the typically subtle cognitive and neurophysiological differences associated with HIV-1 and an overweight or obese weight status. We tried to address the concern by identifying an alternative means of comparing groups in their function. It was expected that the alternative measurement method—intra-individual variability—would yield findings that are more conceptually and statistically compelling than we see in studies that focus on central tendency as the estimate.

We hypothesized that intra-individual variability would be of potential value and interest to the field because it is not

Table 2 F-ratios and p values for main and interactive effects of HIV-1 serostatus (−/+) and weight status (BMI < 26/≥ 26 kg/m^2). Covariates = substance use severity factor score, childhood conduct disorder problems

	HIV serostatus	Weight status	Serostatus × weight status
SD of response time accuracy[a]	$F = 4.4$ ($p = 0.04$)*	$F = 4.9$ ($p = 0.02$)*	$F = 0.9$ ($p = 0.33$)
Response time accuracy	$F = 2.8$ ($p = 0.09$)	$F = 0.1$ ($p = 0.93$)	$F = 0.3$ ($p = 0.58$)
SD of RP amplitude[a]	$F = 8.1$ ($p < 0.01$)*	$F = 4.7$ ($p = 0.03$)*	$F = 0.4$ ($p = 0.51$)
Average RP amplitude	$F = 0.0$ ($p = 0.97$)	$F = 0.1$ ($p = 0.82$)	$F = 0.0$ ($p = 0.98$)

*$p < 0.05$

[a] Corrected for the quadratic association of the SD with the average

Table 3 Partial correlations of RP amplitude and response time variability with balance and gait. Covariates = childhood conduct disorder problems, substance use severity factor score

	SD of RP amplitude	SD of response time accuracy
Single leg stance time—preferred leg	− 0.22 ($p < 0.01$)	+ 0.10 ($p = 0.19$)
Single leg stance time—non-preferred leg	− 0.23 ($p < 0.01$)	+ 0.15 ($p = 0.06$)
Full tandem stance time	− 0.18 ($p = 0.02$)	− 0.03 ($p = 0.64$)
Functional base of support	− 0.15 ($p = 0.05$)	+ 0.12 ($p = 0.11$)
SOT4	− 0.19 ($p = 0.01$)	+ 0.13 ($p = 0.09$)
SOT5	− 0.01 ($p = 0.90$)	+ 0.12 ($p = 0.13$)
SOT6	− 0.12 ($p = 0.12$)	+ 0.19 ($p = 0.01$)
No. of falls across SOT4, SOT5, SOT6	+ 0.11 ($p = 0.13$)	− 0.02 ($p = 0.83$)
Gait velocity—normal pace	− 0.08 ($p = 0.28$)	+ 0.04 ($p = 0.56$)
Gait velocity—fast pace	− 0.15 ($p = 0.04$)	+ 0.11 ($p = 0.18$)

simply an indicator of random noise in the generator or effector. It can also indicate a failure to learn or habituate (Ackerman and Cianciolo, 2000) and adopt a stable information processing scheme over trials (Bassano and van Geert, 2007). In addition, it demonstrates good-to-excellent test-retest reliability (MacDonald et al., 2009; Rabbitt et al., 2001). One could speculate that our demonstration of greater intra-individual variability in task performance and RP amplitude among HIV-1 seropositive or overweight participants indicates a failure by them to attend and learn from the feedback about performance that was presented on every trial.

The third study goal was to examine the association between variability in readiness—a covert process presumably related to compromised executive function (Chen et al., 2010; Scangos and Stuphorn, 2010) —and basic motor skills including single and tandem leg balance as well as gait speed. There are at least two likely explanations for our demonstration of a significant correlation between intra-individual variability in the readiness potential and diminished motor skills. One explanation hypothesizes the existence of a subtle decrement among individuals with HIV/AIDS or an overweight body mass that is neither neuroanatomically nor functionally specific. The other explanation hypothesizes the existence of a specific problem in executive cognitive function, involving either motor preparation or attentional processes. Through this mechanism, the excess variability in readiness indicated by RP variability may act downstream to disrupt both balance and gait. The present study does not contain data that can rule out either possibility.

Of course, the pursuit of these three study goals should be viewed in a larger context that considers alternative explanations for our findings. Indeed, although it is tempting to develop a theory that HIV-1 and an overweight body mass are causal factors that elicit changes in brain and motor function through mechanisms that have been discussed in the literature, e.g., white matter neuropathology, we cannot dismiss the possibility that these independent variables represent other background factors that are causal. One could argue, for example, that the group differences presently attributed to an elevated BMI are instead attributable to underlying and undetected problems with blood pressure regulation or sleep quality. Another alternative explanation could emphasize unmeasured differences between the groups in past medical problems or genetic predispositions. Finally, we should consider the possibility that there may be differences across groups in neurological or psychiatric histories that were not adequately captured and controlled by our intake assessments.

In summary, the present findings show that there is merit in exploring intra-individual variability in studies of the cognitive aspects of HIV/AIDS and obesity. When cognitive impairments are subtle, fleeting, and episodic, as we typically see in patients affected by these health problems, intra-individual variability can capture and detect the impairments. Rare failures are likely to be overwhelmed and missed when task performance or brain activity is summarized with an average over trials.

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Compliance with ethical standards

Conflict of interest The author declares that he/she has no conflict of interest.

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