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Effort and Neuropsychological Performance in HIV-Infected Individuals on Stable Combination Antiretroviral Therapy

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Abstract

The expression of cognitive symptoms associated with HIV varies over time and across individuals. This pattern may reflect transient contextual factors, including the degree of effort exerted by individuals undergoing cognitive testing. The present study examined whether effort corresponds to the expression of persistent HIV-related cognitive impairment among individuals receiving combination antiretroviral therapy (cART). HIV+ individuals (n = 111) averaged 48.2 (14.9) years of age 13.0 (2.7) years of education and HIV− individuals (n = 92) averaged 34.9 (17.2) years of age and 13.5 (1.9) years of education. Participants completed a neuropsychological battery and a clinically validated measure of effort (Test of Memory Malingering, Trial 1). Results revealed that the vast majority of HIV+ (85%) and HIV− (89%) individuals performed above published guidelines for adequate effort. Furthermore, the expression of cognitive impairment in HIV was not related to effort performance. The results were unchanged when examining HIV+ individuals with and without viral suppression. Finally, disability and disability-seeking status, and a proxy measure of apathy did not correspond to effort levels in HIV+ individuals. These findings suggest that variability in the expression of cognitive impairment in the cART era is unlikely to represent overt effort failures or other confounds unrelated to the disease. Persistent cognitive impairment in HIV likely represents historical and/or ongoing disease mechanisms despite otherwise successful treatment.

Keywords

Test of Memory Malingering (TOMM); effort; HIV; neuropsychological performance; cognition

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Introduction

Individuals infected with human immunodeficiency virus (HIV) continue to exhibit cognitive impairment despite suppressive combination antiretroviral therapy (cART; Antinori et al., 2007; Clifford & Ances, 2013; Zhou & Saksena, 2013). The frequency and severity of cognitive impairment related to HIV varies across individuals (Saylor et al., 2016), cohorts (De Francesco et al., 2016; Nightingale et al., 2014), and time (Heaton et al., 2015; Marcotte et al., 2003) among those on stable cART. Variable cognitive performance in HIV-infected (HIV+) individuals is consistent with the pattern of cognitive impairment associated with other chronic immunoregulatory diseases, such as multiple sclerosis (Amato et al., 2001; Lovera & Kovner, 2002; Rao et al., 1991) and systemic lupus erythematosus (Carbotte et al., 1986; Maneeton et al., 2010). However, individual and contextual factors, such as secondary gain, reduced drive, or engagement during completion of challenging cognitive tasks undermine the validity and reliability of testing. This may result in high variability in performance during formal cognitive assessments (Bush et al., 2005; Green et al., 2007; Vickery et al., 2001).

The potential for suboptimal effort to confound cognitive testing is particularly relevant in the assessment of HIV-related cognitive status. HIV+ individuals report reduced motivation to engage in goal-directed activities (Castellon et al., 1998; Hinkin et al., 2001; McIntosh et al., 2015; Kamat et al., 2012; Paul et al., 2005a; Paul et al., 2005b) and high rates of psychiatric comorbidities that could interfere with validity of cognitive assessment (Bing et al., 2001; Chander et al., 2006; Klinkenberg & Sacks, 2004). Early work by Slick and colleagues (2001) reported a correlation between feigned effort and memory impairment in HIV+ individuals with immune suppression (mean CD4 T-cell count = 259). However, the degree of feigned effort was derived from secondary measures intended to identify intentional cognitive failures due to secondary gain. Furthermore, only 60% of the sample was on treatment (zidovudine monotherapy) and 30% were diagnosed with acquired immunodeficiency syndrome (AIDS). Woods et al. (2003) reported adequate performance on an abbreviated measure of effort in mildly impaired HIV+ individuals (70% with AIDS), though the authors cautioned that the abbreviated measure may have lacked the requisite sensitivity to detect suboptimal effort. Further, the study focused on HIV+ individuals with defined cognitive impairment and the results may not generalize to the larger HIV+ population, in which cognitive impairment is not universal (De Francesco et al., 2016; Nightingale et al., 2014).

In contrast to the findings above, Levine et al. (2017) reported a strong link between subjective ratings of effort and neuropsychological performance in HIV+ individuals. In this study, effort was self-rated by HIV+ participants on an analogue scale, and the relationship between self-ratings and severity of neuropsychological impairment was defined using Frascati criteria (Antinori et al., 2007). Consistent with Woods et al. (2003), the vast majority of HIV+ individuals rated themselves as providing adequate effort when completing a demanding neuropsychological battery. However, HIV+ individuals with cognitive impairment were more likely to rate themselves as providing suboptimal effort. A change in HIV-Associated Neurocognitive Disorder (HAND) status correlated with a change in self-defined effort levels. These results suggest that while most HIV+ individuals endorse

optimal effort during testing, those with cognitive impairment perceive themselves as less engaged in the testing process. The study did not include a validated measure of effort as a cross reference, and therefore, it is unclear whether HIV+ cognitively impaired individuals exhibited objective evidence of suboptimal effort.

The purpose of the present study was to examine effort and cognitive performance in a large sample of HIV+ individuals (n =111) on stable cART using a common, standardized measure of effort (Test of Memory Malingering Trial 1; Tombaugh, 1996). Effort was compared between HIV+ individuals (n=111) and a sample of community-based HIV− individuals (n = 92). All participants completed cognitive testing to determine whether frequencies of adequate versus suboptimal effort corresponded to cognitive status. We also examined whether effort performance was associated with predictors of secondary gain (e.g., disability-seeking status) or lack of interest in goal-oriented behavior (e.g., apathy).

Methods

Participants

HIV+ participants were recruited from the Washington University School of Medicine (WUSM) Infectious Disease Clinic in Saint Louis, the WUSM AIDS Clinical Trial Group (ACTG), and the Supporting Positive Opportunities with Teens (SPOT). HIV− controls were selected from a community sample that lived within the same general vicinity but were not at increased risk of acquiring HIV. HIV− individuals did not report high frequency of HIV-related risk behaviors (e.g., unprotected anal sex, injection drug use, etc.). Recent use of marijuana, opiates, stimulants (e.g., methamphetamine, cocaine) barbiturates, benzodiazepines, hallucinogens, and alcohol was recorded for all participants. HIV− controls were administered a rapid oral HIV buccal test to confirm seronegative status at the time of neuropsychological testing. Inclusion criteria were as follows: ≥ 18 years of age, ≥ 8 years of education, ability to read/write in English, and ability to provide informed written consent. Exclusionary criteria for all participants included: history of loss of consciousness > 30 min, seizures, developmental delay, severe psychiatric conditions, or significant depression defined by a score of ≥ 29 on the Beck Depression Inventory-II (BDI-II; Beck et al., 1996).

All HIV+ participants were infected for ≥ 3 months (M = 13.7 years; SD = 8.6 years). Lab values including current plasma CD4 T-cell count and plasma HIV RNA levels were collected within 3 months of evaluation. Nadir CD4 T-cell count was recorded as the lowest value from either self-report or review of medical records. All HIV+ individuals were on stable cART and most had an undetectable (≤ 20 copies/mL) plasma viral load (77%; Table 1). All individuals provided informed consent and were financially compensated for participation. The WUSM Institutional Review Board approved the study. Overall demographics are presented in Table 1.

The Test of Memory Malingering

The Test of Memory Malingering (TOMM; Tombaugh, 1996) is a forced-choice symptom validity measure utilized frequently in clinical practice (Ashendorf et al., 2004; Batt et al.,

2008; Merten et al., 2007; O'Bryant et al., 2007; Sharland & Gfeller, 2007; Teichner & Wagner, 2004; Tombaugh, 1997; Yanez et al., 2006). The test requires participants to discriminate between 50 visual targets from paired foils following two separate learning trials. After a 10-minute delay, participants are administered the recognition trial. Published guidelines identify a score of ≥ 45/50 correct on either the first or second learning trial as consistent with adequate effort (Gavett et al., 2005; Hilsabeck et al., 2011; O'Bryant et al., 2008), while a score < 45/50 is defined as suboptimal effort on the TOMM. Prior work suggests similar sensitivity between performance on Trial 1 alone or Trial 1 and Trial 2 (Bauer et al., 2007; Hilsabeck et al., 2011). For the present study, we administered only Trial 1 (T1) of the TOMM to reduce participant burden.

Neuropsychological Battery

A standardized neuropsychological battery was administered to all participants. The tests and the representative cognitive domains were as follows: Learning and Memory: Hopkins Verbal Learning Test-Revised-immediate and delayed recall (HVLT-R; Benedict et al., 1998; Brandt & Benedict, 2001). Psychomotor/Processing Speed: Grooved Pegboard dominant and non-dominant hand (Klove, 1963), Digit Symbol (DSMT; Wechsler, 1997), and Trail Making Test A (Reitan & Davison, 1974). Executive Function: Letter Number Sequencing (LNS; Wechsler, 1997), Trail Making Test B (Reitan & Davison, 1974), verb fluency (Piatt et al., 1999), and letter fluency (FAS; Borkowski et al., 1967). Raw scores were converted to standardized z-scores using published normative standards with adjustments for demographics where applicable (Supplemental Table 1; Benedict et al., 1998, Friedman et al., 2002; Gladsjo et al., 1999; Heaton et al., 2004; Lucas et al., 2005; Norman et al., 2011; Piatt et al., 2004; Wechsler, 1997; Woods et al., 2005; see Supplemental Table 1). Performances were aggregated by domain to create domain-specific Z-scores (Learning and Memory; Psychomotor/Processing Speed; Executive Function). A global measure of cognitive function (NPZ-Global) was determined by averaging the individual domain Z scores. Individuals were classified as cognitively impaired if they had a Z-score of < −1.0 in two or more cognitive domains or a Z-score of < −2.0 in at least one cognitive domain.

Beck Depression Inventory II

The BDI-II (Beck et al., 1996) is a 21-item self-report instrument of depression, The scale is generally consistent with symptoms of depression defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychological Association, 2000). A total score of 0–13 is considered minimal depression, 14–19 is mild, 20–28 is moderate, and 29–63 is severe (Beck et al., 1996). A proxy measure for apathy was determined based on three items from the BDI-II that reflect loss of interest in rewarding/motivated behavior: loss of pleasure, loss of interest, indecisiveness, and loss of interest in sex.

Disability and Disability-Seeking Status

Employment status (i.e., employed, unemployed, retired, or on disability) was collected via self-report for all participants. Disability-seeking status was operationalized as being under the age of 62 and self-reported unemployment in the absence of current disability benefits.

Statistical Analyses

Statistical analyses were conducted using IBM SPSS Statistics software (version 24). Each continuous variable was examined for normality using a Shapiro-Wilk test. TOMM T1 scores significantly deviated from normality (p's < 0.001). Therefore, TOMM T1 variables were log-transformed for subsequent analyses. Differences in demographic variables (age, sex, education, and race) and BDI-II scores were examined between HIV+ and HIV− individuals using independent samples t tests for continuous variables and chi-square analyses for categorical variables. The duration of infection and immunological factors (nadir and recent CD4 T-cell count) were compared between cognitively impaired and cognitively normal HIV+ participants. These same variables were contrasted between individuals that performed below versus above the recommended cutoff for adequate effort. Variables that significantly differed between groups served as covariates in subsequent analyses.

An independent samples t test (or analysis of covariance [ANCOVA]) was used to determine differences in TOMM T1 scores between the HIV+ and HIV− groups. Differences in frequencies of individuals exhibiting adequate or suboptimal effort on the TOMM T1 were also examined between HIV serostatus groups using a chi-square analysis. Furthermore, differences in mean TOMM T1 as a function of cognitive status were assessed for the HIV+ group using an independent samples t test (or ANCOVA). Relationships between TOMM T1 scores and cognitive performance (NPZ-Global, Learning and Memory, Psychomotor/Processing Speed, and Executive Function) in HIV+ individuals were assessed using Pearson's correlation coefficients.

Additional analyses were conducted to determine whether disability/disability-seeking status or estimated apathy corresponded to suboptimal effort in HIV+ individuals. Differences in apathy scores were examined between groups using an independent samples t test (or ANCOVA). Lastly, a chi-square analysis examined employment status (currently employed [n = 48)], disability [n = 23], or disability-seeking [n = 22]) and TOMM T1 performance.

Results

Relationship between effort and HIV serostatus

Results revealed significant differences in age, sex, and race between HIV serostatus groups (p's < 0.05), therefore these variables were used as covariates in subsequent analyses examining differences between the HIV+ and HIV− groups. There were no significant differences in recent substance misuse according to serostatus (all p's > 0.05; Table 1). The HIV+ and HIV− groups did not differ significantly on TOMM T1 scores ($F(1, 201) = 0.08$, $p = 0.78$; *Cohen's d* = −0.04; raw mean difference = 0.15, 95% confidence interval (CI) [−0.94, 1.24]) after controlling for age, sex, and race. Additionally, there were no significant differences in the proportion of individuals who performed above the recommended cutoff for adequate performance between serostatus groups ($X^2(1, n = 203) = 0.86$, $p = 0.35$; HIV+ = 85%, HIV− = 89%; Table 1).

Relationships between effort and cognitive performance

Results comparing the HIV+ individuals that met criteria for cognitive impairment and HIV + participants without cognitive impairment indicated no significant differences on demographic factors, BDI-II scores, duration of infection, immunological factors, or percent of individuals with undetectable plasma viral load (p's > 0.05). The subset of HIV+ individuals who met criteria for cognitive impairment (n = 31) did not perform significantly worse on the TOMM T1 than HIV+ individuals without cognitive impairment (n = 80) ($t(109) = 1.73$, $p = 0.09$; *Cohen's d* = 0.32; Figure 1). Additionally, TOMM T1 scores did not correlate with the NPZ-Global ($r = 0.15$, 95% CI [−0.04, 0.33]; $R^2 = 0.02$; $p = 0.12$; Figure 2), or performance in the Learning and Memory ($r = 0.10$, 95% CI [−0.09, 0.28]; $R^2 = 0.01$; $p = 0.29$), Executive Function ($r = 0.12$, 95% CI [−0.07, 0.30]; $R^2 = 0.01$; $p = 0.20$) or Psychomotor/Processing Speed ($r = 0.10$, 95% CI [−0.09, 0.28]; $R^2 = 0.01$; $p = 0.28$) domains. Half of the HIV− controls who met criteria for suboptimal effort were cognitively impaired. However, only 5% of the HIV− cohort was cognitively impaired.

Relationships between effort, apathy, disability, disability-seeking status, and substance use

Results comparing HIV+ individuals who exhibited adequate performance on the TOMM T1 and HIV+ individuals exhibiting suboptimal performance indicated no significant differences on demographic factors, BDI-II scores, duration of infection, immunological factors, or percent of individuals with an undetectable plasma viral load (p's > 0.05; Table 2). There were no significant differences in apathy scores in HIV+ individuals with adequate and suboptimal effort ($t(109) = -0.55$, $p = 0.58$, *Cohen's d* = −0.15; Table 2). The frequency of suboptimal effort on the TOMM T1 did not significantly differ between HIV+ individuals who were currently employed, on disability, or disability-seeking ($X^2(2, 93) = 0.51$, $p = 0.77$, *Cramer's V* = 0.07; Table 2).

Discussion

Results of the present study indicate that HIV+ individuals and HIV− controls provide adequate effort on neuropsychological assessment based on TOMM T1 performance. In both HIV+ and HIV− participants, the vast majority of individuals (85–89%, respectively) exhibited adequate performance on a common clinical measure of effort. The pattern of results did not change based on the severity of cognitive impairment, viral suppression, disability/disability-seeking status, history of substance use, or score on an estimated measure of apathy derived from the BDI-II scale. Considering that most of the HIV+ individuals had an undetectable viral load, the findings suggest that objectively poor effort is an unlikely explanation for persistent cognitive impairment in the cART era.

Our outcomes bolster results reported by Woods et al. (2003) describing a low frequency of poor effort in HIV when examined using an abbreviated effort measure. Importantly, Woods et al. (2003) focused on individuals with at least some degree of cognitive impairment, many of whom were immunosuppressed. The current results provide compelling new data that HIV+ individuals receiving cART exhibit adequate effort on the TOMM T1 during demanding neuropsychological testing, independent of cognitive status, prior or current level

of immunosuppression, or AIDS diagnosis. It is important to note that these results may not generalize to a clinical setting. As such, clinicians are encouraged to consider effort testing, particularly when concerns of secondary gain exist.

Further, while our results appear on the surface to differ from the findings recently reported by Levine et al. (2017), it is important to point out that the overwhelming majority of HIV+ individuals in the latter study defined themselves as providing sufficient effort. It is noteworthy that change in HAND status corresponded to a different level of perceived effort as rated by the HIV+ individuals. The temporal correspondence between these outcomes implies that fluctuations in effort account for within person differences in cognitive impairment over time. However, perceived effort vs. true effort exerted during cognitive testing is difficult to differentiate. That individuals with the greatest degree of cognitive impairment rated themselves as having adequate effort suggests that the relationships between these constructs is complicated and not a linear function. Future studies are needed that examine both perceived and objectively defined effort to help disentangle these dimensions. Relatedly, it is possible that other symptom validity tests (e.g., The Word Memory Test; Green, 2005), use of both trials of the TOMM, and/or use of multiple symptom validity tests, would have greater sensitivity in identifying differences in effort between groups.

The rate of cognitive impairment in our HIV+ sample (28%) is generally consistent with other studies in the cART-era (Heaton et al., 2010; McCutchan et al., 2007; Sacktor et al., 2016). In our HIV− sample, the elevated rate of cognitive impairment (27%) likely reflects our recruitment strategy aimed at matching HIV+ and HIV− groups on demographic and historical factors that could impact cognition (e.g., recruiting from community samples within the same general vicinity). Our groups were well matched on most variables, and when present, differences in demographics were adjusted in the analyses and application of appropriate norms.

A few limitations warrant discussion. Relatively few HIV+ individuals exhibited major cognitive impairment and therefore, the opportunity to examine relationships between more severe cognitive impairment and effort was restricted. Since the introduction of cART, severe cognitive impairment (HIV associated dementia) is rare (Clifford & Ances, 2013; Heaton et al., 2010; Heaton et al., 2011; McArthur et al., 2010). As such, our HIV+ sample adequately reflects the cognitive phenotype in the cART era. Finally, the study was not designed to model an exhaustive list of predictors of poor effort (e.g., fatigue, pain) and the measure of apathy utilized in the current study was derived from a small subset of questions on the BDI-II. It is possible that a formal apathy measure would have detected more severe levels of apathy and a stronger link between apathy and effort. However, the low frequency of poor effort observed in the study suggests that the pattern of results would not have changed with the inclusion of these additional measures.

In summary, results of the present study suggest that the majority of HIV+ individuals provide adequate effort, as assessed by the TOMM T1. This finding is important, as it suggests that persistent cognitive difficulty in the modern era of HIV patient care does not reflect overt or clear alterations in motivated engagement during neuropsychological

assessment. However, vigilance to the integrity of the testing process remains a high priority. Management of internal distractors (e.g., nicotine withdrawal), external distractors (e.g., noises and interruptions), and drift from the test protocol are required to facilitate a valid assessment process. Results from the present study, combined with strong fidelity to the testing process, provides additional support for the application of neuropsychological assessment to delineate the historical and/or ongoing disease mechanisms and functional consequences of HIV-related neurocognitive disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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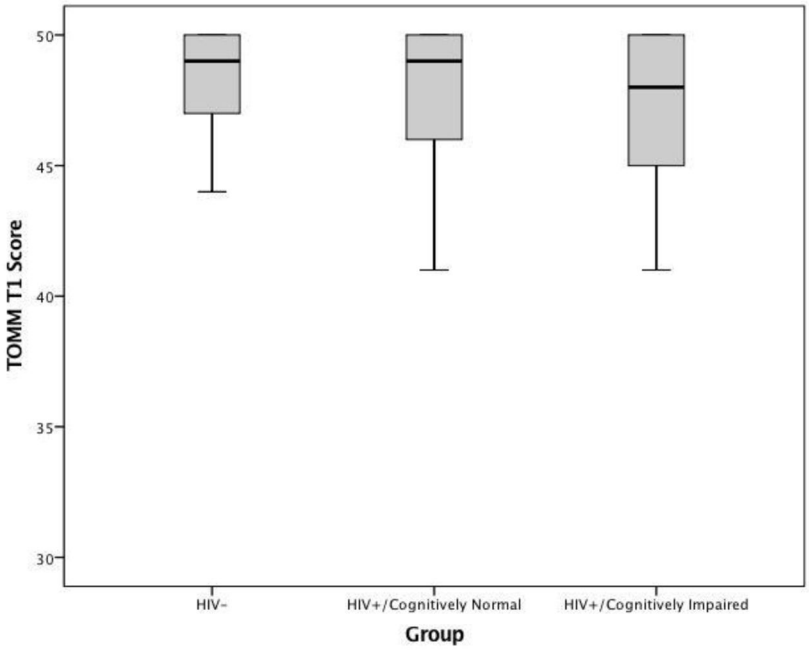

Figure 1.

Raw TOMM T1 score for HIV− individuals, cognitively normal HIV+ individuals, and cognitively impaired HIV+ individuals. Cognitive impairment was defined as a Z-score < −1.0 in two or more cognitive domains, or a Z-score of < −2.0 in at least cognitive domain. No significant differences existed between the three groups.

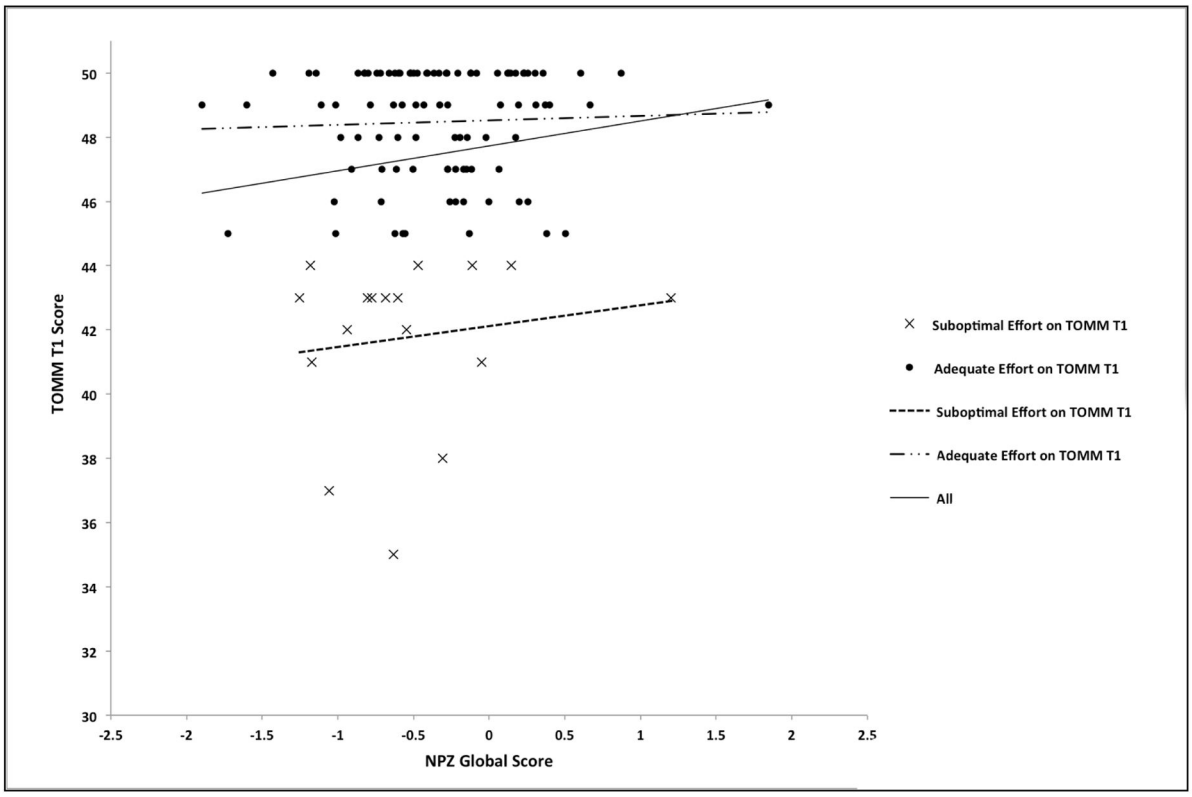

Figure 2.

Relationship between TOMM T1 and NPZ-Global in HIV+ Individuals. A majority of HIV+ participants provided optimal effort. No significant relationship was seen between cognition and effort for HIV+ individual

Table 1

HIV+ and HIV− Group Characteristics

	HIV+ (*n* = 111)	HIV− (*n* = 92)	*p value*
Mean age (years) (SD) **	48.15 (14.87)	34.87 (17.20)	0.00
Male sex, n (%) **	80 (72%)	43 (47%)	0.00
African American race, n (%) *	79 (71%)	52 (57%)	0.03
Mean education [a] (years) (SD)	13.00 (2.71)	13.50 (1.87)	0.12
Mean BDI-II (SD) (n = 201)	8.61 (6.74)	7.48 (6.77)	0.27
Mean duration of infection (years) (SD)	13.68 (8.64)		
Median CD4-T cell count (cells/μl) (IQR)	602 (424–884)	-	-
Median nadir CD4 T-cell count (cells/μl) (IQR)	188 (59–322)	-	-
Undetectable plasma viral load, n (%)	85 (77%)	-	-
Mean NPZ-Global score (SD)	−0.36 (0.58)	−0.40 (0.63)	0.65
Mean Psychomotor/Processing Speed Z score (SD)	−0.11 (0.76)	−0.28 (0.79)	0.12
Mean Executive Function Z score (SD)	−0.30 (0.69)	−0.14 (0.77)	0.12
Mean Learning and Memory Z score (SD)	−0.98 (1.01)	−1.16 (0.99)	0.21
Raw Mean TOMM T1 score (SD)	47.4 (3.1)	47.4 (3.9)	0.91
TOMM T1 score <45, n (%)	17 (15%)	10 (11%)	0.35
Substance use past six months, n (%)			
Marijuana	36 (32%)	38 (41%)	0.19
Cocaine	6 (5%)	9 (10%)	0.24
Methamphetamine	4 (4%)	2 (2%)	0.55
Barbiturates	2 (2%)	0 (0%)	0.20
Opiates	3 (3%)	6 (7%)	0.19
Benzodiazepines	6 (5%)	4 (4%)	0.73
Alcohol	64 (58%)	50 (54%)	0.64
Hallucinogens	2 (2%)	0 (0%)	0.20
Cognitively Normal	80 (72%)	67 (73%)	
Cognitively Impaired	31 (28%)	25 (27%)	

* $p < 0.05$;

** $p < 0.01$

SD = Standard Deviation; IQR = Interquartile Range; NPZ-Global= composite neuropsychological summary Z-score; BDI-II = Beck Depression Inventory-II

Table 2

Characteristics of Individuals Based on TOMM T1 Performance

	HIV+			HIV− controls		
	Adequate Effort (n = 94, 85%)	**Suboptimal Effort (n = 17, 15%)**	***p value***	**Adequate Effort (n = 82, 89%)**	**Suboptimal Effort (n = 10, 11%)**	***p value***
Age; mean (SD)	48.40 (14.88)	46.76 (15.21)	0.68	35.24 (17.63)	31.80 (13.32)	0.55
Male sex (%)	67 (71%)	13 (76%)	0.66	38 (46%)	5 (50%)	0.88
African American (%)	65 (69%)	14 (82%)	0.27	44 (54%)	8 (80%)	0.11
Education; mean (SD)	13.12 (2.83)	12.28 (1.80)	0.25	13.56 (1.91)	12.90 (1.37)	0.29
BDI-II (n =201)	8.70 (6.69)	8.12 (7.18)	0.74	7.31 (6.56)	8.80 (8.52)	0.52
Duration of infection	14.14 (8.70)	11.09 (8.10)	0.18	-	-	-
CD4-T cell count (cells/μl); median (IQR)	635 (459, 896)	438 (331, 745)	0.21	-	-	-
Nadir CD4 (cells/μl); median (IQR)	193 66, 333)	112 (28, 245)	0.30	-	-	-
Undetectable plasma viral load (%)	73 (80)	12 (71)	0.70	-	-	-
BDI-II apathy score	1.91 (1.86)	1.65 (1.69)	0.58	1.44 (1.67)	1.40 (1.26)	0.95
NPZ-Global score	−0.33 (0.57)	−0.54 (0.61)	0.16	−0.35 (0.63)	−0.71 (0.45)	0.12
Employed (%)	42 (44.7)	6 (35.3)		55 (67.1%)	6 (60.0%)	
On disability (%)	19 (20.2)	4 (23.5)		2 (2.4%)	0 (0.0%)	
Disability seeking (%)	18 (19.1)	4 (23.5)		16 (19.5%)	4 (40.0%)	
Cognitively Normal (%)	69 (73)	11 (65)		69 (84%)	5 (50%)	
Cognitively Impaired (%)	25 (27)	6 (35)		13 (16%)	5 (50%)	