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Utility of a brief computerized battery to assess HIV-associated neurocognitive impairment in a resource-limited setting

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Abstract

Despite the persistently high prevalence of neurocognitive impairment in HIV-positive patients, routine HIV care in many resource-limited settings does not include neuropsychological assessment. The objective of this study was to examine the utility of a brief computerized battery for identifying neurocognitive impairment in a busy HIV clinic in Uganda. Specifically, we compared performance on a gold standard neuropsychological exam to that on the CogState Brief Battery. In this cross-sectional study, 181 HIV-positive patients completed both assessment batteries in a randomized order. The primary outcome measures were neurocognitive impairment on the standard exam defined by the global deficit score and cumulative performance on the CogState Brief Battery. Sixty-nine participants (38%) were classified as impaired on the standard neuropsychological exam, and participants who were classified as impaired performed significantly worse on CogState compared to those who were unimpaired ($p < 0.001$). CogState had adequate specificity but low sensitivity, suggesting that it may not be a clinically useful screening tool to identify patients who likely have neurocognitive impairment in Uganda. This study supports the feasibility of using a computerized battery for assessing neurocognitive impairment in HIV-positive patients in resource-limited settings, but additional research is needed to identify screening tools with higher sensitivity for use in HIV clinics.

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AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: NY NN KRR CSM. Performed patient evaluations: NY. Analyzed the data: NY ST under the close guidance of DW CSM. Wrote the paper: NY ST DW NN KRR CSM.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

Keywords

HIV/AIDS; neuroAIDS; neurocognitive impairment; Africa; computerized assessment

INTRODUCTION

Despite major advances in antiretroviral treatment for HIV infection, neurocognitive impairment (NCI) in persons living with HIV remains a common clinical challenge (Volberding and Deeks, 2010). Prevalence estimates from large cohort studies conducted in high-income countries have found that approximately half of HIV-infected individuals experience NCI (Cysique *et al*, 2014; Heaton *et al*, 2010; Robertson *et al*, 2014), suggesting that NCI persists even in the era of combination antiretroviral therapy. Studies conducted in Africa also find high prevalence of HIV-associated NCI (Habib *et al*, 2013; Robertson *et al*, 2015). The manifestation of HIV-associated NCI can affect multiple cognitive domains, including learning, memory, attention, executive function, speed of information processing, and sensory-perceptual motor skills (Antinori *et al*, 2007; Heaton *et al*, 2010; Heaton *et al*, 2011), and thus can have a wide range of behavioral and health consequences.

HIV-associated NCI can affect many aspects of patients' lives, including medication adherence, daily activities such as cooking and cleaning, and the ability to hold a steady job (Benedict *et al*, 2000; Heaton *et al*, 2004; Lovejoy and Suhr, 2009; Rabkin *et al*, 2004; Volberding and Deeks, 2010). Therefore, it is important to identify and treat NCI as part of routine HIV care (Cysique *et al*, 2012). The gold standard assessment for HIV-associated NCI involves a comprehensive neuropsychological battery that assesses multiple domains by using standardized tests with published normative data (Antinori *et al*, 2007; Maj *et al*, 1993; Miller *et al*, 1990; Robertson *et al*, 2007). Such neuropsychological testing is not feasible to integrate into routine HIV care in resource-limited settings because of high patient-provider ratios and lack of trained professionals. In Uganda, for example, HIV clinics may have upwards of 300 patient visits a day (Castellnuovo *et al*, 2009).

Routine administration of standard neuropsychological testing in HIV clinics in resource-limited settings is challenging for several reasons (Robertson *et al*, 2009). First, the battery requires at least 1 hour to complete, which is prohibitively time-consuming in busy clinics. Second, the battery includes extensive testing forms, many of which must be purchased per administration. Third, it must be administered by a licensed clinician or a psychometrist under the supervision of a licensed clinician. HIV clinics often have few neurologists or psychologists on staff to administer or supervise the administration of neuropsychological tests. Due to these practical barriers of conducting comprehensive neuropsychological testing, screening for HIV-associated NCI has not been integrated into routine HIV care in many resource-limited settings, including Uganda (Robertson *et al*, 2009).

One alternative to standard neuropsychological testing is the CogState Brief Battery, a computerized exam that has been developed to screen and monitor NCI in patient populations, including persons living with HIV (Cysique *et al*, 2006; Maruff *et al*, 2009; Overton *et al*, 2011). This battery is much shorter than standard neuropsychological testing, taking less than 15 minutes to administer, and therefore can be implemented more efficiently

with fewer clinic resources. Since the battery is fully computerized, administration does not require specialized training, and the software program also scores the tests. Given its brevity and ease of administration, the CogState Brief Battery has potential as a neurocognitive screen that could be integrated into standard HIV care in high volume, busy clinic settings. Furthermore, the CogState Brief Battery is language independent, and was designed to ensure validity in culturally diverse populations (Cairney and Maruff, 2007; Lewis *et al*, 2010). As computers become increasingly available even in resource-limited HIV treatment centers, CogState may be a useful tool to assess cognitive functioning in HIV-positive patients in such settings.

The CogState Brief Battery has been validated in HIV-positive adult patients in high-income countries, with reported sensitivities ranging from 80–90% (Cysique *et al*, 2006; Maruff *et al*, 2009; Overton *et al*, 2011). However, the CogState Brief Battery has not yet been evaluated as a screening tool for HIV-associated NCI in sub-Saharan Africa. The purpose of this study was to determine if the CogState Brief Battery is an acceptable alternative to standard neuropsychological testing by comparing performance on a gold standard neuropsychological battery with performance on the CogState Brief Battery in HIV-positive patients receiving HIV care in Uganda.

METHODS

Procedures

This study was conducted between August and October 2011 in Mulago Hospital of Makerere University in Kampala, Uganda. We recruited 181 HIV-positive subjects from the Infectious Disease Clinic. Each morning as general announcements were made, the staff alerted patients to a flyer describing the current study, and interested participants volunteered. On average, six participants were recruited each day, comprising a convenience sample from the clinic. Eligibility criteria were: 18–50 years of age, ability to read English, and no history of neurological or psychiatric illness unrelated to HIV. Ethical approval was obtained from Duke University School of Medicine, the Infectious Disease Clinic at Mulago Hospital, and Makerere University. Participants provided written informed consent in English prior to any study-related activities.

Participants first completed a demographics and medical history questionnaire. Participants then completed the two batteries sequentially, with the administration order randomized such that half the sample completed the standard exam first and the other half completed the CogState Brief Battery first. To obtain objective data on HIV treatment and history, clinical variables were abstracted from participants' medical records.

Measures

Standard exam—A trained research assistant administered a standard neuropsychological test battery in a private clinic room. The 8 individual tests in the battery assessed function in 6 cognitive ability domains:

1. Verbal Learning: WHO/UCLA Auditory Verbal Learning Test – total number of words recalled on trials 1–5 (Maj *et al*, 1993).

2. Verbal Memory: WHO/UCLA Auditory Verbal Learning Test – total number of words recalled after 30 minute delay (Maj *et al*, 1993).
3. Attention: Digit Span Forwards and Backwards – total number correct (Wechsler, 1945).
4. Speed of Information Processing: Color Trails 1 – number of seconds to completion (D'Elia *et al*, 1996).
5. Executive Functioning: Color Trails 2 – number of seconds to completion (D'Elia *et al*, 1996).
6. Sensory-perceptual motor skills: Grooved Pegboard Test dominant and non-dominant hand – number of seconds to completion (Matthews and Klove, 1964).

This battery has been successfully administered in Uganda to identify HIV-associated neurocognitive impairment (Maj *et al*, 1994; Robertson *et al*, 2007). As in that study, participants had the option to complete the standard exam in English or Luganda (Robertson *et al*, 2007). The standard exam took approximately 60 minutes to administer.

CogState Brief Battery—The CogState Brief Battery was administered on a laptop computer and took approximately 25 minutes to administer. This battery consists of 4 tasks using playing cards. Directions for each CogState task were provided in English. For each task, the participant focused on a playing card in the center of the screen, and then pressed one of two keys on the keyboard to respond either “yes” or “no”. The first task, Detection, is a simple reaction-time test in which the participant must follow the rule “Has the card turned face up?” The second task, Identification, is another reaction-time test in which the participant must follow the rule “Is the face-up card red?” The third task, One Card Learning, requires the participant to follow the rule “Have you seen this card before in this task?” The final task, One Back, requires the participant to follow the rule “Is this card the same as the previous card?” Detection and Identification are scored based on speed and the primary outcome measure for these tests is the mean of the log10 transformed reaction times for correct responses, with lower scores indicating better performance. The primary outcome measure for the One Card Learning and One Back tests, which are scored based on accuracy, is the arcsine transformation of the square root of the proportion of correct responses, with higher scores indicating better performance. Raw scores for each task were transformed automatically by the CogState program (<http://cogstate.com/computerized-tests/featured-batteries/cogstate-brief-battery/>).

Other questionnaires—Demographic variables included age, sex, main language, income, and education. The medical history items asked about HIV disease characteristics, medications, and other medical conditions (e.g., syphilis, tuberculosis).

HIV clinical variables—WHO stage, antiretroviral regimen, current CD4 count, and history of neurotoxic drug use (specifically, isoniazid, dapsone, and metronidazole) were abstracted from the electronic medical records for each participant.

Data Treatment—Standardized scores for each test in the standard exam were obtained using normative data from a published study of HIV-seronegative patients in Uganda (Robertson *et al*, 2007). Raw scores for each test were normalized to produce z-scores by subtracting the mean (M) test score from the HIV-seronegative referent population, and then dividing by the referent standard deviation (SD). For tests based on reaction time (Grooved Pegboard dominant and non-dominant, Color Trails 1 and 2), z-scores were multiplied by -1 so that for all tests positive z-scores indicated above average performance and negative z-scores indicated below average performance.

To quantify overall performance and severity of impairment on the standard exam, the global deficit score (GDS) was computed for each participant (Carey *et al*, 2004). First, z-scores for each of the 8 tasks were converted to T-scores ($M = 50$, $SD = 10$). T-scores were then converted to the deficit score, a numerical scale ranging from 0 (normal functioning) to 5 (severe impairment), as follows: 0 = 40, 1 = 35–39, 2 = 30–34, 3 = 25–29, 4 = 20–24, 5 < 20. Because Digit Span and Grooved Pegboard each contain two tasks that assess the same domain, the deficit scores for these two tasks were averaged. Next, the 6 domain deficit scores were averaged to obtain the GDS (Carey *et al*, 2004). Impairment on the GDS was classified as scoring ≥ 0.5 (Carey *et al*, 2004). Previous findings show high agreement between clinical ratings and the GDS classification (Blackstone *et al*, 2012; Carey *et al*, 2004; McCutchan *et al*, 2012).

For CogState, raw scores for individual tasks were normalized to produce sample z-scores by subtracting the mean test scores from the overall mean for the task, and then dividing by the sample SD. For tasks based on reaction time (Detection and Identification), z-scores were again multiplied by -1 . The z-scores were averaged to obtain the CogState QNPZ-score reflecting cumulative performance on the CogState battery (Jawaid *et al*, 2011).

Data Analysis

We used chi-square tests, student t-tests, and Wilcoxon rank sum tests to compare demographic and clinical characteristics between those who were classified as impaired versus those who were not on the standard exam. A t-test was used to compare performance on CogState between participants who were impaired versus not impaired on the standard exam, and a Pearson's correlation was used to examine the correlation between performance on CogState and GDS on the standard exam. In addition, a multivariate logistic regression analysis predicting impairment was conducted, with age (in years) and education (full secondary vs. anything less) entered in a first step. Level of agreement between CogState and the standard exam were assessed using the c-statistic. Sensitivities and specificities for various cutoffs for performance on CogState relative to impairment on the standard exam were determined.

RESULTS

Sample Characteristics

Of the 181 patients, 58% were female. The median age was 37 (interquartile range: 31 – 43), and most (92%) had at least some secondary education. Nearly half (48%) reported that their

main language was Luganda, although English was also commonly identified as a main language (38%). The majority (80%) were being treated with antiretroviral therapy, and the median CD4 count was 405 (269–586).

Impairment on the Standard Neuropsychological Exam

Based on the GDS from the standard exam, 38% of participants were classified as impaired. Table 1 compares participants who were impaired versus unimpaired on demographic and clinical variables. Participants who were impaired were significantly older, had less education, and were more likely to report neuropathy (Table 1). They were also significantly more likely to be taking antiretroviral therapy, but regimen type was unrelated to impairment status.

Comparison of the CogState Brief Battery to the Standard Exam

Participants who were classified as impaired on the standard neuropsychological exam had significantly lower z-scores on CogState ($M = -0.32$, $SD = 0.70$) than those who were unimpaired ($M = 0.20$, $SD = 0.59$) [$t(179) = 5.301$, $p < 0.001$] (Figure 1). Cumulative CogState scores were significantly correlated with the GDS from the standard exam ($r = -0.463$, $p = 0.01$). After controlling for age and education, CogState performance was still significantly associated with impairment status [AOR = 2.93 (1.69–5.09), $p < .001$].

Sensitivity and Specificity Analysis

Table 2 summarizes the results of the sensitivity and specificity analysis. Using the c-statistic, the optimal cut-off for performance on CogState in this sample was 1 SD below the mean on one or more tasks, which yielded sensitivity of 57% and specificity of 77%. At more stringent cut-offs, specificity improved. The highest specificity (97%) was obtained at a cut-off of 1 SD below the mean on three or more tasks, but the sensitivity at this cut-off was very low (13%).

DISCUSSION

This study provides initial feasibility for using the CogState Brief Battery to assess HIV-associated NCI in a resource-limited setting. In this sample of HIV-infected patients receiving care in Uganda, we found that 38% were classified as impaired based on the GDS, which is consistent with prevalence rates from other studies in Sub-Saharan Africa (Habib *et al*, 2013). As expected, participants who were impaired were more likely to report neuropathy and to be taking antiretroviral therapy, likely reflecting more advanced HIV disease. These results underscore the importance of monitoring HIV-associated NCI as part of routine HIV care, even after patients have initiated antiretroviral therapy.

While performance on CogState correlated adequately with performance on the standard neuropsychological exam, the sensitivity of the test was low at all cut-offs. Clinically, this low sensitivity would result in missed cases of NCI. On the other hand, CogState demonstrated high specificity when the cut-off was set at below average performance on two or more of the four tasks, though this was not the ideal cut-off identified by the c-statistic. These results are in contrast to prior evaluations of CogState in high-income countries,

which reported results that supported the utility of CogState as a brief screening tool for HIV-associated NCI (Cysique *et al*, 2006; Maruff *et al*, 2009; Overton *et al*, 2011). Though CogState was designed to be cross-culturally valid, there may have been unknown cultural factors within this population that affected task performance. While disappointing, our results are consistent with a systematic review of studies that have evaluated brief screening tools for HIV-associated NCI (Zipursky *et al*, 2013). In that review, the authors concluded that many of the available brief screening tools were not able to adequately identify NCI, and therefore were not recommended for broader use in clinical settings.

These disappointing results suggest that CogState may not be a useful tool to screen for HIV-associated NCI in Uganda, as many cases of NCI would be missed. Given the potential advantages of a brief computerized battery related to feasibility, including brief administration time, no need for specialized training, and minimal use of clinic resources, our results are disappointing. Additional research is needed to identify screening tools with both high sensitivity and specificity relative to the standard neuropsychological testing exam.

In addition to being more feasible to administer in high-volume clinics with low provider-to-patient ratios, the CogState Brief Battery may also avoid the problem of practice effects. Once the CogState rules are learned, every presentation is still a novel challenge that is cognitively demanding (Hammers *et al*, 2011). In contrast, performance on the standard exam is susceptible to practice effects (Bartels *et al*, 2010; Beglinger *et al*, 2005; Heilbronner *et al*, 2010), which may mask cognitive decline as increasing familiarity with the tasks leads to improved performance. The CogState Brief Battery may therefore have utility for tracking longitudinal changes in neurocognitive functioning, but this must be empirically evaluated in future studies.

While this study has multiple strengths, including a rigorous experimental design and large sample size, it also has limitations. First, there is no Ugandan normative database for CogState performance. Despite CogState's design for providing cross-cultural validity and language independence, a normative database needs to be established in Uganda before CogState and other tools can be further evaluated as brief screeners. Similarly, for the standard exam, demographically adjusted norms do not yet exist in the published literature. While we did utilize normative data from a sample of 100 HIV-negative individuals from Uganda to compute deficit scores, performance was not stratified by age or education. This could have led to misclassification of impairment status in the current sample. A second limitation is that CogState was not translated into Luganda or any other language commonly spoken in Kampala. However, English is the national language of Uganda, and ability to read English was an eligibility criterion. Patients who speak English (almost always as a secondary language in Uganda) may have systematically greater cognitive reserve than monolingual patients (Schweizer *et al*, 2011); however, language proficiency was not assessed in this study, and main language was unrelated to NCI. Finally, because these data are cross-sectional, future studies that focus on how individual performance on CogState changes over time are necessary.

In conclusion, while overall performance on CogState correlated moderately with performance on the gold standard neuropsychological exam, it was not sufficiently sensitive as a screening tool for HIV-associated NCI in Uganda. Additional research is needed to identify brief screening tools that are clinically useful for identifying HIV-associated NCI in resource-limited settings.

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Figure 1.

Mean z-scores of CogState performance for participants by impairment status based on the Global Deficit Score (GDS). Error bars show the 95% confidence interval.

Table 1

Sample characteristics by neurocognitive impairment status (N=181)

	Unimpaired (n=112)	Impaired (n=69)	Statistic	p-value
Age in years, Median (IQR)	36 (27–41)	40 (36–44)	U= 2533.50	0.000
Female sex, n (%)	69 (62%)	36 (52%)	$\chi^2(1)= 1.56$	0.212
Education, n (%)			$\chi^2(2)= 9.19$	0.010
Only Primary	5 (4%)	9 (13%)		
Some Secondary	58 (52%)	43 (62%)		
Full Secondary	49 (44%)	17 (25%)		
Monthly Income in 1,000 UGX, Median (IQR)	100 (0–300)	100 (20–300)	U= 3859.00	0.988
Main language spoken, n (%)			$\chi^2(3)= 1.95$	0.583
English	12 (11%)	5 (7%)		
English & Other	35 (31%)	17 (25%)		
Luganda	50 (45%)	37 (54%)		
Other	15 (13%)	10 (14%)		
Current WHO stage, n (%)			$\chi^2(3)= 1.12$	0.771
1	8 (7%)	3 (4%)		
2	32 (29%)	17 (25%)		
3	36 (33%)	25 (37%)		
4	34 (31%)	23 (34%)		
Currently on antiretroviral (ARV) therapy, n (%)	84 (75%)	61 (88%)	$\chi^2(1)= 4.82$	0.028
ARV regimen, n (%)				
Combivir & Nevirapine	37 (44%)	23 (38%)	$\chi^2(2)=0.928$	0.629
Combivir & Efavirenz	23 (27%)	21 (34%)		
Other	24 (29%)	17 (28%)		
Median current CD4 count, Median (IQR) ¹	392 (263–583)	413 (295–598)	U= 3467.50	0.415
History of syphilis, n (%)	33 (29%)	28 (41%)	$\chi^2(1)= 2.36$	0.124
History of tuberculosis, n (%)	37 (33%)	27 (39%)	$\chi^2(1)= 0.69$	0.405
Current neuropathy, n (%)	19 (17%)	24 (35%)	$\chi^2(1)= 7.48$	0.006
History of neurotoxic drugs, n (%) ²	96 (86%)	59 (86%)	$\chi^2(1)= 0.00$	0.969

¹Data missing for 3 participants (n=178)²Neurotoxic drugs included isoniazid, dapsone, and metronidazole

Table 2

Level of agreement between Cogstate performance and neurocognitive impairment based on the standard exam (N=181)

Cut-offs on CogState: Performance below the mean	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Predictive Value % (95% CI)	Negative Predictive Value % (95% CI)	c-Statistic (95% CI)
<u>Overall</u>					
-0.5 SD	45 (33–57)	88 (80–93)	69 (53–81)	72 (63–79)	0.662 (0.577–0.747)
-0.25 SD	51 (39–63)	79 (70–86)	59 (46–72)	72 (63–80)	0.646 (0.562–0.731)
0 SD	61 (48–72)	68 (58–76)	54 (42–65)	74 (64–82)	0.644 (0.560–0.727)
<u>On 1 or more tasks</u>					
-1 SD *	57 (44–68)	77 (68–84)	60 (47–72)	74 (65–82)	0.667 (0.583–0.750)
-0.75 SD	65 (53–76)	56 (47–66)	48 (38–58)	72 (62–81)	0.607 (0.523–0.692)
-0.5 SD	68 (56–79)	45 (35–54)	43 (34–53)	69 (57–79)	0.564 (0.478–0.649)
<u>On 2 or more tasks</u>					
-1 SD	29 (19–41)	92 (85–96)	69 (49–84)	68 (60–75)	0.605 (0.517–0.692)
-0.75 SD	45 (33–57)	85 (77–91)	65 (49–77)	71 (63–79)	0.649 (0.563–0.734)
-0.5 SD	54 (41–66)	76 (67–83)	58 (45–70)	73 (63–80)	0.648 (0.563–0.732)
<u>On 3 or more tasks</u>					
-1 SD	13 (7–24)	97 (92–99)	75 (43–93)	64 (57–72)	0.552 (0.464–0.640)
-0.75 SD	17 (10–29)	96 (91–99)	75 (47–92)	65 (58–73)	0.569 (0.481–0.657)
-0.5 SD	26 (17–38)	94 (87–97)	72 (50–87)	67 (59–74)	0.599 (0.511–0.687)

* Criterion with highest c-statistic

SD= Standard Deviation, CI = Confidence interval