DOI: 10.1111/j.1468-1293.2010.00910.x
HIV Medicine (2011), **12**, 472–480

ORIGINAL RESEARCH

Computerized testing augments pencil-and-paper tasks in measuring HIV-associated mild cognitive impairment*

L Koski,[1,2] M-J Brouillette,[3,4] R Lalonde,[1,4] B Hello,[2] E Wong,[2] A Tsuchida[2] and LK Fellows[1,2,5]

[1]*The Research Institute of the McGill University Health Centre, Montreal, Quebec,* [2]*Department of Neurology and Neurosurgery, Faculty of Medicine, McGill University, Montreal, Quebec,* [3]*Department of Psychiatry, Faculty of Medicine, McGill University, Montreal, Quebec,* [4]*Immunodeficiency Clinic, McGill University Health Centre, Montreal, Quebec and* [5]*Montreal Neurological Institute, Neurology and Neurosurgery, Montreal, Quebec, Canada*

Background

Existing tools for rapid cognitive assessment in HIV-positive individuals with mild cognitive deficits lack sensitivity or do not meet psychometric requirements for tracking changes in cognitive ability over time.

Methods

Seventy-five nondemented HIV-positive patients were evaluated with the Montreal Cognitive Assessment (MoCA), a brief battery of standardized neuropsychological tests, and computerized tasks evaluating frontal-executive function and processing speed. Rasch analyses were applied to the MoCA data set and subsequently to the full set of data from all tests.

Results

The MoCA was found to adequately measure cognitive ability as a single, global construct in this HIV-positive cohort, although it showed poorer precision for measuring patients of higher ability. Combining the additional tests with the MoCA resulted in a battery with better psychometric properties that also better targeted the range of abilities in this cohort.

Conclusion

This application of modern test development techniques shows a path towards a quick, quantitative, global approach to cognitive assessment with promise both for initial detection and for longitudinal follow-up of cognitive impairment in patients with HIV infection.

Keywords: executive function, HIV-associated neurocognitive disorder, Rasch analysis, test development

Accepted 16 November 2010

Introduction

Mild cognitive impairment has been increasingly recognized as a common feature of chronic HIV infection, even in patients with good viral control on highly active antiretroviral therapy (HAART) [1]. It occurs in 30–50% of patients, depending on both the cohort under study and how the impairment is identified [1–8]. The current diagnostic approach is descriptive: HIV-associated neurocognitive disorder (HAND) is termed 'asymptomatic neurocognitive impairment' when found on testing in the absence of symptoms, and 'mild neurocognitive disorder' when both signs and symptoms are present, but are not severe enough to constitute frank dementia [9]. The underlying pathophysiology remains poorly understood [10], posing challenges in the everyday management of these mildly affected patients.

How should cognitive impairment be detected in routine practice? Should those found to be affected have their HAART regimen changed, to emphasize antiretrovirals with better central nervous system penetration? Should additional therapies, such as anti-excitotoxic agents or drugs targeting neurodegenerative changes, be added to their treatment? If such changes are made, how should the effects be monitored? The answers to such questions require better tools to assess cognition in HIV-infected individuals. The ideal measure should not only establish the diagnosis, but also quantify the severity of impairment.

*Part of this work was presented at the American Academy of Neurology meeting: Wong E, Tsuchida A, Brouillette M-J, Lalonde R, Fellows LK. Preliminary evidence for selective orbitofrontal dysfunction in patients with HIV infection. *American Academy of Neurology Annual Meeting*, Toronto, April 2010.

Correspondence: Dr Lisa Koski, The Research Institute of the McGill University Health Centre, Royal Victoria Hospital, R4.74, 687 Pine Avenue West, Montreal QC H3A 1A1, Canada. Tel: + 1 514 934 1934, 34420; fax: + 1 514 843 1734; e-mail: lisa.koski@mcgill.ca

It should also be free, brief, easy to administer with minimal training by any health professional, and available to clinics where HIV-infected patients receive their care. The present study describes the initial steps in the development of such a method to measure cognition across the intact to mildly impaired range in HIV-positive patients.

Current approaches have limitations [11]. The clinical history alone is inadequate, as self-reported cognitive symptoms may not be predictive of objective performance [12–14]. Full neuropsychological assessment is the gold standard for the diagnosis of HAND, and consensus recommendations on appropriate tests exist. However, such tests require highly trained personnel and so are available only in specialized centres [9]. They may be replaced with briefer neuropsychological screening batteries [15], but this reduces precision, and in any case still requires a neuropsychologist, limiting feasibility in most settings. Resource limitations aside, existing cognitive assessment tools have focused on diagnosis, and may not be optimal for the *measurement* of cognition. Measurement of cognitive impairment is related to, but not synonymous with, diagnosis, and has distinct clinical goals. Cognitive measurement refers to the quantification of a person's performance with reference to a continuous unit of measurement along a scale representing the full spectrum of cognitive ability. Precise quantification of cognitive ability is required for comparing different treatment groups or for tracking changes in cognition in an individual patient, both goals of obvious clinical relevance in this population.

Pencil-and-paper tools for cognitive assessment are brief and easily administered, but fall short of the ideal in other respects. Tools such as the HIV Dementia Scale (HDS), the International HDS, and the Folstein Mini-Mental Status Examination (MMSE) are relatively insensitive to the milder cognitive signs that predominate in the HAART era [14,16]. Furthermore, such scales were designed to detect, but not to measure, cognitive impairment. A total score is derived from summing the scores for individual items but, because this score does not represent a continuous quantity of cognition, it is unsuitable for monitoring change over time [17].

The Montreal Cognitive Assessment (MoCA) is a brief bedside test of cognition originally developed to screen for cognitive impairment in a geriatric population at risk for early dementia. It is sensitive to mild cognitive impairment in that population [18,19] and includes items testing a broad range of cognitive domains, including memory, attention and frontal-executive functions, that are commonly affected in patients with HIV infection. We hypothesized that it would be suitable for measuring cognition in HIV-infected individuals with mild cognitive deficits.

Computerized testing is another alternative. Responses can be collected with millisecond-level accuracy, potentially increasing sensitivity to subtler deficits. Further, such testing provides the advantages of standardized administration and scoring with minimal training of evaluators. Existing computerized batteries, such as the CANTAB and Cog-State, are useful for assessment of mild cognitive deficits and for tracking changes in cognition over time [20,21], but neither has been well validated in HIV-infected patients with mild cognitive deficits. In addition, these tests are expensive to purchase and maintain. Our group has extensive experience in the development of computerized measures of specific frontal-executive functions in basic neuroscience settings, and could make these tools freely available for public use. First, though, we needed to determine whether these tests improved measurement of the subtle deficits in cognitive ability that we expected in this population over and above what could be achieved with simpler pencil-and-paper measures.

Rasch analyses are statistical techniques for improving the reliability and validity of measurements based on responses to a multi-item test, such as responses to a questionnaire containing many questions probing the same general field of ability or competence. This analytical approach has been successfully applied to develop quantitative measures of cognition in other contexts, including a quantitative version of the MoCA for use in geriatric populations [22–27]. We thus applied Rasch analysis to evaluate the suitability of the MoCA alone, and in conjunction with computerized cognitive tests, as a method of measuring cognition in HIV-infected patients with mild neurocognitive deficits.

Methods

Participants

A convenience sample of patients with HIV infection without frank dementia was recruited from sequential patients attending the Immunodeficiency Clinic at the Montreal Chest Institute, McGill University Health Centre. Inclusion criteria were age between 18 and 70 years, HIV positive status, and the ability to communicate adequately in either French or English. Patients with dementia, identified either by their treating clinician or on the basis of an MMSE score <23 or an MoCA score <20, were excluded. Other exclusion criteria were a history of central nervous system (CNS) infection, stroke, serious head injury, or other neurologic event likely to affect cognition. Many patients were exposed to low doses of psychoactive drugs, either on a prescription or recreational basis. Given that this is a clinical reality in this population, we excluded only those in whom drug effects might be expected to substantially affect cognition. Of the patients originally referred for the study, only three met one of these exclusion

criteria (one with MoCA <20, one with a history of another CNS process, and one with intoxication at the time of testing). The protocol was approved by the ethics board of the McGill University Health Centre, and all participants provided informed consent.

Data collection

All tests were administered in the same session by a trained research technician, in a quiet room, in the patient's choice of either French or English. Clinical information was collected using a semi-structured interview at the time of testing, supplemented by clinic chart review.

Demographic and clinical variables

Patient age, sex, educational level, and mother tongue were recorded and evaluated for their impact on cognitive test performance. Age was coded into 5-year bins and educational level was coded as some *vs.* no education at the university level. Mother tongue was coded as English, French or other. Clinical characteristics deemed relevant to cognitive test performance and HIV-infection-related variables were also recorded, including the presence of self-reported cognitive complaints (no/yes), and the presence of depressive symptoms as evaluated with the Beck Depression Inventory II (BDI-II; minimal, mild, moderate or severe).

The MoCA test

The MoCA was administered and scored according to the published instructions for this test (www.mocatest.org). Individual items of the MoCA test were coded dichotomously as failed or passed for each patient, with the exception of Serial 7s subtraction. For this item we used a polytomous scoring system of 0 to 5 based on the sum of correct responses over five consecutive subtractions.

Additional computerized tests

Participants performed seven tasks examining different aspects of frontal lobe function.

Reversal learning. Participants learned to make response selections based on feedback. The score was the total number of correct selections [28].

Emotion recognition. Participants rated the degree of emotional expression in a series of faces and were scored based on the difference between ratings of emotional and neutral faces [29].

Letter 2-back task. In this working memory test, a series of letters was presented and participants were scored on their ability to detect letters matching the one presented two trials previously [30].

Stop-signal task. Participants were scored on their reaction times (RTs) to a speeded stimulus (go RT) and on their ability to inhibit this response on rare trials when an auditory tone was presented (stop-signal RT) [31].

Flanker task. Participants were scored for their RTs to a visual stimulus in the presence and absence of conflicting information, as well as the difference between these two conditions [32].

Corsi block test. This was a computerized version of a traditional neuropsychological test, in which patients repeated a spatial sequence backwards [33] and were scored on the maximum length of sequence that could be performed without error.

Self-ordered spatial working memory task. Participants had to maintain spatial location information in mind across delays and in the face of interfering inputs. The score was the number of errors [34].

Additional noncomputerized tests

Three additional conventional neuropsychological tests were administered. These were the digit spans forwards and backwards, the FAS test of phonetic verbal fluency, and the Grooved Pegboard test for dominant and nondominant hands [35–37].

Data analysis

Rasch analysis compares a set of test data against the Rasch model to determine whether the total score obtained by adding individual item scores actually represents the quantity of an attribute possessed by an individual [17,38]. In Rasch, both item difficulty and person ability are placed on the same scale. As a result, the difficulty of an item can be estimated from the performance on that item by a person with known ability. Similarly, an individual's ability level can be estimated from their performance on a set of items of known difficulty.

The MoCA test was Rasch analysed to evaluate its reliability and validity as a quantitative measure of cognitive ability in this sample. Analyses were performed in RUMM2020 software (RUMM Laboratory Pty Ltd, Duncraig, Australia) using the partial-credit model. The difficulty of individual items was quantified in terms of their fit to a normal distribution of cognitive ability and calibrated on an interval-like difficulty scale with a mean of zero. Goodness of fit to a unidimensional Rasch model was evaluated globally and for individual items with the standardized residuals (cut-off: ± 2.5) [39], χ^2 and *F*-statistics provided in RUMM2020 (cut-off: $P = 0.05$; Bonferroni-corrected). The dimensionality of the test was also examined with principal components analysis of the Rasch residuals, with cut-offs for significant eigenvalues specified through parallel analysis (MacParallel software, Parallels, Renton, WA, USA).

The cognitive ability of the patients was described relative to the scale described by the test items, at both the individual level and the group level (item-patient mapping). The effects of individual demographic and clinical variables on overall and individual item performance were evaluated using analyses of variance (ANOVAS) with a cut-off value of $P = 0.05$ (uncorrected).

In a second set of analyses, scores from the additional cognitive tests were added to the set of MoCA data. For analysis in RUMM2020 these additional scores were coded into two to three ordinal response categories based on the distribution of observed test scores in the sample; for example, low, medium or high. The digit spans forwards and backwards were left as raw spans. The full data set was subsequently subjected to the same Rasch analyses as described above.

Results

Demographic and clinical characteristics of the patient sample are shown in Table 1. The population we studied was similar to that in recent work on the mild cognitive impairment spectrum in HIV-infected patients from centres in North America. Patients were predominantly men (92%), were relatively well educated (with 44% having completed at least some university-level education), had a long history of HIV infection (mean disease duration 13.9 ± 6.7 years), and were treated with HAART. The majority had undetectable viral loads at the time of testing. Two patients were coinfected with hepatitis C virus. About a third of the sample reported current drug use, most commonly marijuana. About 10% reported consuming more than 7 units of alcohol per week. Over half the sample (55%) was taking one or more psychoactive medications. These were most commonly antidepressants or sedatives/hypnotics. Patients were tested in either English or French. For most, one of these was their native language, although for a minority (12%) neither was their mother tongue.

This was a clinic-based convenience sample. Cognitive impairment was not an inclusion criterion, but we suspect that both referring clinicians and patients were more likely to consider participation if there were pre-existing concerns about cognition. This sample is thus likely to be enriched with patients representative of those who are presenting with mild cognitive complaints. Consistent with this supposition, subjective cognitive complaints were present in 47% of the sample. Depressive symptoms ranging from mild to severe were also common, being present in 56% of the sample. Ten patients (13%) were classified as severely depressed (BDI >28). It is worth noting that other recruitment approaches, such as selecting patients with poor viral control, might yield different sample characteristics, but would be unlikely to substantially affect the goal of this study, which was to develop a method of measuring cognitive ability, rather than to categorize patients within the existing diagnostic framework for cognitive impairment.

Table 1 Characteristics of the patient sample ($n = 75$)

Characteristic	Value
Age (years) [mean (SD)]	47.3 (8.6)
Education (years) [mean (SD)]	15.5 (3.9)
Sex [*n* (%)]	69 (92) male, 6 (8) female
Currently employed [*n* (%)]	33 (44)
Mother tongue [*n* (%)]	23 (31) English, 43 (57) French, 9 (12) other
Time from diagnosis (years) [mean (SD)]	14 (7)
Time from beginning ART (years) [mean (SD)]	10.5 (6.0)
Currently on ART [*n* (%)]	71 (95)
Cognitive complaints [*n* (%)]	33 (47)
Psychoactive medication use [*n* (%)]	41 (55)
Current alcohol use (>7 units/week) [*n* (%)]	8 (11)
Current drug use [*n* (%)]	26 (35)
Current tobacco use [*n* (%)]	26 (35)
Current HIV viral load (log copies/mL) [mean (SD)]	1.9 (0.8)
Peak HIV viral load (log copies/mL) [mean (SD)]	3.8 (1.5)
Undetectable HIV viral load [*n* (%)]	55 (80)
Current CD4 count (cells/μL) [mean (SD)]	462 (257)
Nadir CD4 count (cells/μL) [mean (SD)]	201 (173)
BDI [mean (SD)]	15 (11)

ART, antiretroviral therapy; BDI, Beck Depression Inventory II; SD, standard deviation.

Measurement properties of the MoCA test in HIV-positive patients

Response categories for serial 7s were rescored when some scores (e.g. 0/5) occurred with insufficient frequency to produce reliable estimates of their thresholds. Four other naming and orientation items were removed because they failed to contribute information to the measurement of cognition (correct in 100% of patients). The resulting set of 24 items showed good fit to a Rasch model of cognitive ability, including absence of an item–trait interaction ($\chi^2 = 48.92$; $P = 0.44$). The items ranged in difficulty, encompassing over 95% of the construct of cognitive ability, from -2.313 logits (easiest) for the clock contour to $+2.061$ logits for letter-*F* fluency (Fig. 1). Therefore, the test is able to measure cognition in groups of people with a wide range of cognitive ability. Analysis of the residual correlation matrix revealed little redundancy in the test items, meaning that most items targeted a unique level of cognitive ability. The component analysis of the residuals suggested only minor extradimensionality of the test (9% of the residual variance; eigenvalue >2.03), which was associated with items requiring abstract reasoning.

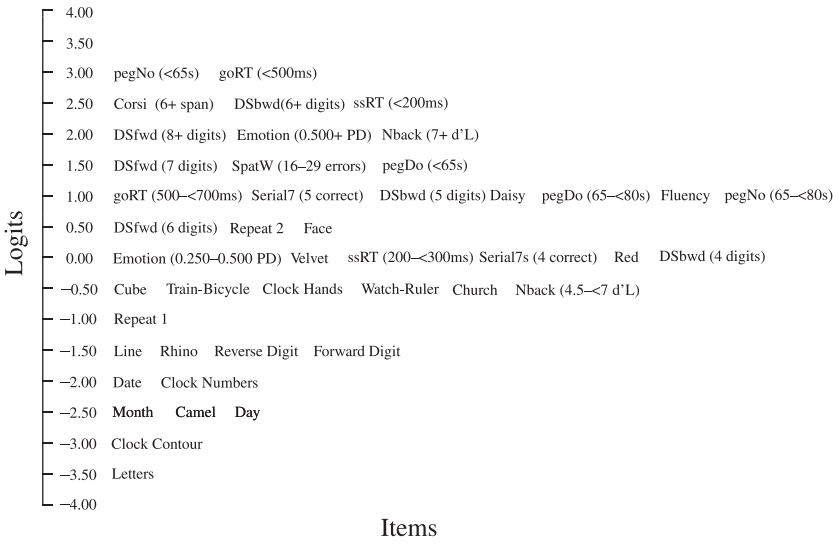

Fig. 1 Map illustrating the hierarchy of difficulty for each item administered. The scale on the left represents the ruler-like measurement tool for evaluation of cognition, with the units expressed in logits. A value of 0 on the logit scale anchors the middle of the scale. Positive values indicate increasing difficulty of the items as we move up the scale from 0. Negative values indicate decreasing difficulty of the items as we move down from 0. To the right are the locations of the items along the scale, with items from similar difficulty levels spreading horizontally to the right. The location of each item is the point at which a person would have a 50% chance of passing the item. For items from the MoCA, passing is defined by correct performance coded with a score of 1. For the other tests and for the polytomous serial 7s item from the MoCA, the criterion for moving from one scoring category to the next (e.g. from category 2 to category 3) is shown in parentheses beside each item.

The internal consistency of the test was only 0.52, probably because the variation in cognitive ability of this sample was limited. The bar graph in Fig. 2a shows the distribution of persons (upper bars) and items (lower bars). Many of the test items were too easy for the ability level of this patient sample. Three people could not be measured accurately because they obtained perfect scores. The ability of the remaining patients ranged from + 0.422 to + 3.456. The information function (plotted as a line over the person distribution) shows that measurement precision is greatest around the mid-range of difficulty (0 logits), which is below the range of cognitive ability in this patient sample.

Contribution of additional test scores to the measurement of cognition

In the iterative process of Rasch analysis, two test scores were removed because they showed a poor fit to the model (reversal learning score and flanker test) and one (FAS) because it yielded no additional information beyond that provided by the fluency item on the MoCA. Three items were rescored because the thresholds defining the ability to move from one level to the next were disordered or because of too few observations in a particular response category (digit spans and spatial working memory).

The resulting set of items showed good fit to a unidimensional Rasch model, including absence of an item–trait interaction ($\chi^2 = 67.062$; $P = 0.509$). As seen in the lower bars of Fig. 2b, the distribution of items spans the range of difficulty from −3.120 logits (easiest) for tapping to the letter A to + 3.321 logits for performance faster than 500 ms on the 'go' RT of the stop-signal test. In other words, the items are well spread out along the continuum of cognitive ability assessed by the items and span a greater range than the MoCA alone. Minimal extradimensionality was observed, with one additional component associated with orientation to time that accounted for just 7.6% of the residual variance.

The additional test items improved the internal consistency to 0.75. They also led to improved targeting of the range of ability in the patient sample (− 0.027 to + 4.608; Fig. 2b), and allowed for estimation of cognitive ability in the patients who scored at ceiling on the MoCA alone. The information function (Fig. 2b) shows that measurement precision was greatest in the range from + 1 to + 2 logits on the scale of cognitive ability.

Factors influencing cognitive ability

A university-level education was associated with higher estimates of cognitive ability for the MoCA items alone but did not reach significance for the combined data set (see Table 2). Lower estimates were obtained for patients who were not tested in their mother tongue, but French- and English-speaking patients performed similarly ($n = 75$; $P = 0.34$). Estimates of cognitive ability were not influenced significantly by sex, age, the presence of cognitive

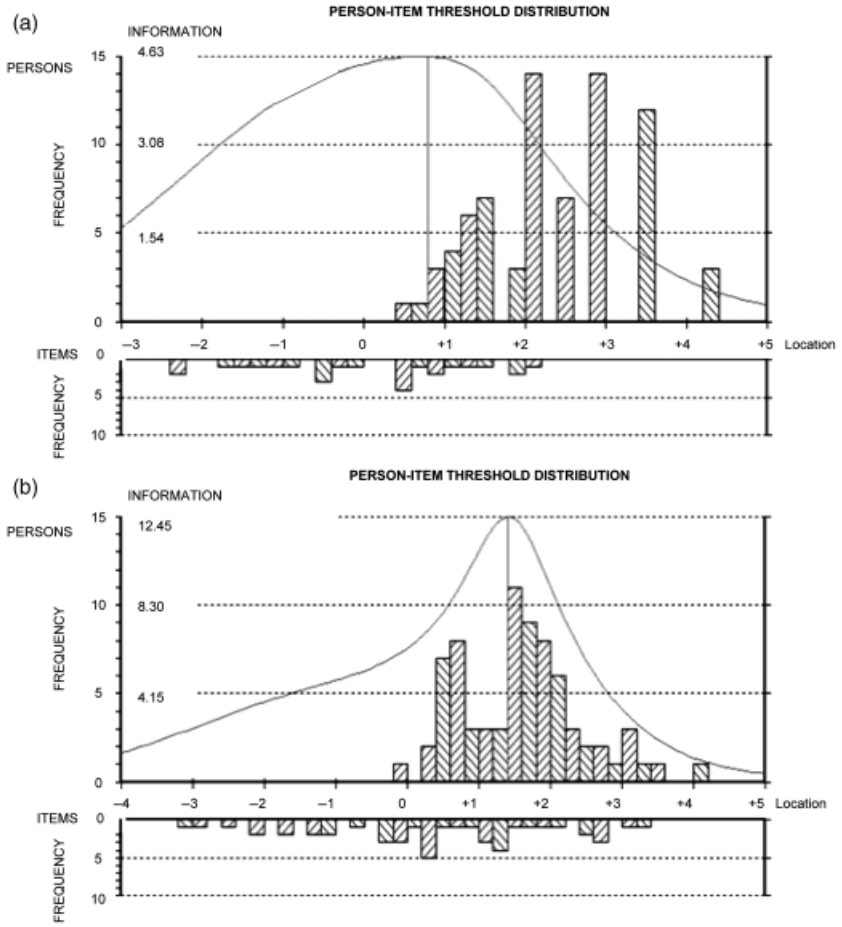

Fig. 2 Distribution of items and patients across the spectrum of global cognitive ability. The upper panel shows the distribution for the MoCA items alone. The lower panel shows the distribution for the combination of MoCA items with other cognitive tests. The hierarchy of cognitive ability is spread out along the *x*-axis, with 0 anchored to the test item of middle difficulty and easier and more difficult items spreading to the left and right, respectively. Bars ascending above the *x*-axis represent the frequency of patients at each level of cognitive ability. Bars descending below the *x*-axis show the number of items representing each level of cognitive ability. The line plotted above the *x*-axis is the information function, which reflects the precision of measurement that can be obtained at each point along the ability continuum. See text for interpretation. SD, standard deviation.

complaints, or the severity of depressive symptoms. The mean cognitive ability scores followed a predictable orderly decrease as depression symptom levels increased, suggesting that this effect might be significant in a larger sample size. The information about cognitive ability contributed by each individual MoCA item or additional test score was similar across sex, age, education, language, cognitive complaints, and severity of depressive symptoms.

Discussion

The present study represents the first application of Rasch analytic techniques to the development of a method for quantifying global cognitive ability in HIV-positive patients across a range from intact cognition to mild cognitive deficits. First, we have provided evidence that the MoCA, an existing brief screen for use in geriatric populations, could serve as a unidimensional measure of cognitive ability in a sample of nondemented HIV-positive patients, about half of whom had subjective cognitive complaints. Rasch analysis allowed us to characterize the relative level of difficulty of the individual items that make up this test, and to estimate the 'distance' between these items. After modifications to scoring based on Rasch analysis, the resulting modified MoCA total score was found to represent global cognitive ability as a numeric quantity in this population, as has been shown previously for geriatric patients evaluated for cognitive impairment [22].

Although the individual items that make up the MoCA provided an orderly measure of cognitive ability, the test

Table 2 Patient characteristics influencing measured cognitive ability

	Mean estimate of cognitive ability	
	MoCA	**MoCA + test battery**
Sex	$P = 0.72$	$P = 0.17$
Male	+ 2.311	+ 1.647
Female	+ 2.170	+ 1.155
Age	$P = 0.75$	$P = 0.22$
Up to 39 years	+ 2.118	+ 1.465
40–44 years	+ 2.519	+ 2.081
45–49 years	+ 2.173	+ 1.526
50–54 years	+ 2.441	+ 1.586
$\geq$ 55 years	+ 2.253	+ 1.413
Education	$P = 0.05$	$P = 0.14$
No university	+ 2.115	+ 1.479
University	+ 2.535	+ 1.772
Language	$P = 0.02$	$P = 0.004$
English	+ 2.152	+ 1.509
French	+ 2.516	+ 1.822
Other	+ 1.642	+ 0.837
Complaints	$P = 0.90$	$P = 0.80$
No	+ 2.313	+ 1.584
Yes	+ 2.285	+ 1.634
Depression	$P = 0.63$	$P = 0.70$
Minimal	+ 2.402	+ 1.715
Mild	+ 2.366	+ 1.620
Moderate	+ 2.207	+ 1.490
Severe	+ 1.997	+ 1.404

P-values are for the one-way analysis of variance (ANOVA).
MoCA, Montreal Cognitive Assessment.

was poorly targeted to this high-functioning sample, with half of the items being too easy and therefore contributing little to the measurement of cognition in this group. We conclude that the MoCA alone may serve as a convenient tool to evaluate cognition in routine clinical use but it is not well targeted to the ability level of the population we studied. The MoCA, with this modified scoring, would provide a quantitative estimate of the cognitive ability of those patients with more substantial cognitive impairment, including mild dementia. However, additional, more difficult test items were needed to measure cognition in patients of higher ability.

Accordingly, in a second step we demonstrated that additional computerized and noncomputerized tests of executive function can serve this purpose. We focused on cognitive capacities prominently affected in HIV-associated cognitive impairment: psychomotor speed and frontal-executive functions. The majority of these additional test items provided improved targeting of cognitive ability in this patient population when compared with the MoCA alone. Thus, the score obtained from this combined set of items can be considered as a ruler-like measure of a single construct of cognitive ability, much like the (modified) MoCA score alone, but with improved targeting of cognitive ability in this population. The combination of tests reported here, with the scoring provided by the Rasch analysis, provides a quantitative estimate of cognitive ability in the range from 'mild impairment' to normal in HIV-positive patients. The test battery could thus be applied to measure an individual's cognitive ability at a given point in time, and to measure the change in ability longitudinally.

A healthy population was not tested here, nor were the comprehensive neuropsychological data acquired that would be needed to determine the sensitivity and specificity of this set of tests as a diagnostic tool. Future work with this battery could certainly examine its validity and seek to determine cut-off scores if diagnosis is the goal. The results of our study do suggest that adjustment for second-language testing and educational level, at least for the MoCA, would be required in the development of diagnostic cut-off scores. Relating this novel measurement approach to the current diagnostic framework would be useful for several reasons, including potentially shedding light on the meaning of cognitive ability estimates in absolute terms. However, the clinical meaning of changes in cognitive ability is inherently individual, as it depends on both pre-morbid abilities and on current functional demands. The diagnostic classification of patients thus may be of less relevance to clinical decision-making than the precise tracking of an individual's cognitive ability over time. For example, cognitive deterioration in spite of an undetectable viral load raises the possibility of viral escape in the CNS, which would have important therapeutic implications [40]. Similarly, while the optimal management of individuals with cognitive impairment in the context of good viral control remains to be clarified, clinicians need to be able to track change over time when evaluating the response to treatment interventions. With this in mind, additional work along the lines shown here should aim to incorporate items that further improve the test–retest reliability of the cognitive ability score.

Implications of cognition as a global construct

The finding that cognitive ability in general can be measured with a single number advances our understanding of how cognitive impairment manifests in HIV-positive patients. In contrast to what might be expected in a heterogeneous sample of neurologically 'localized' conditions, the cognitive deficits associated with HIV infection seem to reflect diffuse brain dysfunction that varies in degree rather than in localization, at least across the cognitive domains and level of resolution assessed by this battery of tests. This interpretation may be relevant for understanding the pathophysiology of these deficits, arguing for causes that degrade brain function generally, rather than injuring some particular brain region or

network. More pragmatically, the results support a relatively straightforward approach to the measurement of cognition as a global construct, in which cognition is evaluated across an appropriate range of difficulty rather than across modular cognitive abilities.

Extension to adaptive testing

An important implication of good fit to a Rasch model is the potential for developing adaptive tests. Subjects who pass a given item would not need to be tested on those items shown to measure lesser degrees of cognitive ability. Depending on the accuracy required and the ability of the subject, only a few items might need to be administered to measure cognitive ability. This item-bank approach reduces test burden without loss of information, even across a wider range of cognitive deficits. It also allows clinicians to continuously monitor the impact of therapies without the artificial interruption in scores introduced when having to switch from a 'hard' test to an 'easy' test if cognitive impairment worsens. The adaptive approach to cognitive measurement was recently validated for geriatric mild cognitive impairment in a study that combined test items from the MoCA and the MMSE (S. Konsztowicz *et al*., unpublished observations). The data we present here provide a basis for an adaptive approach to measuring cognition, but further work will be needed to implement and fully validate such a method.

Conclusion

Some limitations to this study must be considered. Firstly, the use of computerized measures adds inconvenience when compared with a brief pencil-and-paper test, although web-based testing software could be developed to minimize that inconvenience. A computerized approach has the additional advantage of greatly simplifying the process of administering a test in an adaptive format, automatically selecting the next items to be administered based on the pattern of previous responses and stopping once a criterion is reached for confidence in the accuracy of the resulting score. This approach has been used successfully to evaluate cognition in patients with cerebrovascular disease [41] and in a rehabilitation clinic population [42]. Secondly, the particular computer tests we used are drawn from the experimental cognitive neuroscience literature, and so have not undergone the extensive normative testing of more conventional measures. However, they are in the public domain and thus readily available for evaluation and development by others. At the very least, the present work illustrates a methodological path that could be profitably pursued as we seek to improve on current tools for the assessment of cognitive ability in people with HIV infection.

Acknowledgements

This work was supported by operating grants from CIHR and CECR to LKF, by salary support from the MUHC Research Institute (LK) and from CIHR and FRSQ (LKF), by a Canada Graduate Studentship (AT), and by a McGill Faculty of Medicine Research Bursary (EW). We thank the patients and family members who volunteered for this study, and the clinicians who provided referrals.

Conflicts of interest: The authors have no conflicts of interest to declare.

References

1 McCutchan JA, Wu JW, Robertson K *et al*. HIV suppression by HAART preserves cognitive function in advanced, immune-reconstituted AIDS patients. *AIDS* 2007; **21**: 1109–1117.
2 Cysique LA, Vaida F, Letendre S *et al*. Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy. *Neurology* 2009; **73**: 342–348.
3 Price RW, Spudich S. Antiretroviral therapy and central nervous system HIV type 1 infection. *J Infect Dis* 2008; **197**: S294–S306.
4 Robertson KR, Smurzynski M, Parsons TD *et al*. The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS* 2007; **21**: 1915–1921.
5 Valcour V, Shikuma C, Shiramizu B *et al*. Higher frequency of dementia in older HIV-1 individuals: the Hawaii aging with HIV-1 cohort. *Neurology* 2004; **63**: 822–827.
6 Hardy DJ, Vance DE. The neuropsychology of HIV/AIDS in older adults. *Neuropsychol Rev* 2009; **19**: 263–272.
7 Becker JT, Lopez OL, Dew MA *et al*. Prevalence of cognitive disorders differs as a function of age in HIV virus infection. *AIDS* 2004; **18**: S11–S18.
8 Cherner M, Ellis RJ, Lazzaretto D *et al*. Effects of HIV-1 infection and aging on neurobehavioral functioning: preliminary findings. *AIDS* 2004; **18**: S27–S34.
9 Antinori A, Arendt G, Becker JT *et al*. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 2007; **69**: 1789–1799.
10 Everall I, Vaida F, Khanlou N *et al*. Cliniconeuropathologic correlates of human immunodeficiency virus in the era of antiretroviral therapy. *J Neurovirol* 2009; **15**: 360–370.
11 Cherry CL, Affandi JS, Brew BJ *et al*. Hepatitis C seropositivity is not a risk factor for sensory neuropathy among patients with HIV. *Neurology* 2010; **74**: 1538–1542.
12 Garvey LJ, Yerrakalva D, Winston A. Correlations between computerized battery testing and a memory questionnaire for identification of neurocognitive impairment in HIV type 1-

infected subjects on stable antiretroviral therapy. *AIDS Res Hum Retroviruses* 2009; **25**: 765–769.
13 Millikin CP, Rourke SB, Halman MH, Power C. Fatigue in HIV/AIDS is associated with depression and subjective neurocognitive complaints but not neuropsychological functioning. *J Clin Exp Neuropsychol* 2003; **25**: 201–215.
14 Simioni S, Cavassini M, Annoni JM *et al.* Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS* 2010; **24**: 1243–1250.
15 Deutsch R, Mindt MR, Xu R, Cherner M, Grant I, Group TH. Quantifying relative superiority among many binary-valued diagnostic tests in the presence of a gold standard. *J Data Sci* 2009; **7**: 161–177.
16 Skinner S, Adewale AJ, DeBlock L, Gill MJ, Power C. Neurocognitive screening tools in HIV/AIDS: comparative performance among patients exposed to antiretroviral therapy. *HIV Med* 2009; **10**: 246–252.
17 Bond TG, Fox CM. *Applying the Rasch Model: Fundamental Measurement in the Human Sciences*, 2nd ed. Mahwah: Laurence Erlbaum Associates, 2007.
18 Nasreddine ZS, Phillips NA, Bedirian V *et al.* The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; **53**: 695–699.
19 Smith T, Gildeh N, Holmes C. The Montreal Cognitive Assessment: validity and utility in a memory clinic setting. *Can J Psychiatry* 2007; **52**: 329–332.
20 Gibbie T, Mijch A, Ellen S *et al.* Depression and neurocognitive performance in individuals with HIV/AIDS: 2-year follow-up. *HIV Med* 2006; **7**: 112–121.
21 Maruff P, Thomas E, Cysique L *et al.* Validity of the CogState Brief Battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and aids dementia complex. *Arch Clin Neuropsychol* 2009; **24**: 165–178.
22 Koski L, Xie H, Finch L. Measuring cognition in a geriatric outpatient clinic: Rasch analysis of the Montreal Cognitive Assessment. *J Geriatr Psychiatry Neurol* 2009; **22**: 151–160.
23 Jones RN, Gallo JJ. Dimensions of the Mini-Mental State Examination among community dwelling older adults. *Psychol Med* 2000; **30**: 605–618.
24 Schultz-Larsen K, Kreiner S, Lomholt RK. Mini-Mental Status Examination: mixed Rasch model item analysis derived two different cognitive dimensions of the MMSE. *J Clin Epidemiol* 2007a; **60**: 268–279.
25 Schultz-Larsen K, Lomholt RK, Kreiner S. Mini-Mental Status Examination: a short form of MMSE was as accurate as the original MMSE in predicting dementia. *J Clin Epidemiol* 2007b; **60**: 260–267.
26 Wouters H, Zwinderman AH, van Gool WA, Schmand B, Lindeboom R. Adaptive cognitive testing in dementia. *Int J Methods Psychiatr Res* 2009; **18**: 118–127.
27 Wouters H, van Gool WA, Schmand B, Lindeboom R. Revising the ADAS-cog for a more accurate assessment of cognitive impairment. *Alzheimer Disease Assoc Disorders* 2008; **22**: 236–244.
28 Tsuchida A, Doll BB, Fellows LK. Beyond reversal: a critical role for human orbitofrontal cortex in flexible learning from probabilistic feedback. *J Neurosci* 2010; **30**: 16868–16875.
29 Heberlein AS, Padon AA, Gillihan SJ, Farah MJ, Fellows LK. Ventromedial frontal lobe plays a critical role in facial emotion recognition. *J Cogn Neurosci* 2008; **20**: 721–733.
30 Tsuchida A, Fellows LK. Lesion evidence that two distinct regions within prefrontal cortex are critical for n-back performance in humans. *J Cogn Neurosci* 2009; **21**: 2263–2275.
31 Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nat Neurosci* 2003; **6**: 115–116.
32 Modirrousta M, Fellows LK. Dorsal medial prefrontal cortex plays a necessary role in rapid error prediction in humans. *J Neurosci* 2008; **28**: 14000–14005.
33 Robbins TW, James M, Owen AM *et al.* A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. *J Int Neuropsychol Soc* 1998; **4**: 474–490.
34 Owen AM, Roberts AC, Hodges JR, Summers BA, Polkey CE, Robbins TW. Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. *Brain* 1993; **116** (Pt 5): 1159–1175.
35 Spreen O, Benton AL. *Neurosensory Center Comprehensive Examination for Aphasia: Manual of instructions (NCCEA)*, rev. ed. Victoria: University of Victoria, 1977.
36 Wechsler D. *Wechsler Adult Intelligence Scale–Administration and Scoring Manual*, 3rd ed. San Antonio: The Psychological Corporation, 1997.
37 Matthews C, Klove K. *Instruction manual for the Adult Neuropsychology Test Battery.* Madison: University of Wisconsin Medical School, 1964.
38 Smith EV, Smith RM. *Introduction to Rasch Measurement: Theories, Models and Applications.* Maple Grove: Jam Press, 2004.
39 Wolfe EW, Smith EV Jr. Instrument development tools and activities for measure validation using Rasch models: part II–validation activities. *J Appl Meas* 2007; **8**: 204–234.
40 Clifford DB. Viral escape in cerebrospinal fluid-an achilles heel of HIV therapy? *J Infect Dis* 2010; **202**: 1768–1769.
41 Wouters H, de Koning I, Zwinderman AH *et al.* Adaptive cognitive testing in cerebrovascular disease and vascular dementia. *Dement Geriatr Cogn Disord* 2009; **28**: 486–492.
42 Haley SM, Coster WJ, Andres PL, Kosinski M, Ni P. Score comparability of short forms and computerized adaptive testing: simulation study with the activity measure for post-acute care. *Arch Phys Med Rehabil* 2004; **85**: 661–666.