

Evaluation of Two New Neuropsychological Tests Designed to Minimize Cultural Bias in the Assessment of HIV-1 Seropositive Persons: A WHO Study

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In the course of the preparatory work for the WHO cross-cultural study on the neuropsychiatric aspects of HIV-1 infection, two new neuropsychological tests (the WHO/UCLA Auditory Verbal Learning Test and the Color Trails 1 & 2) were developed. The evaluation of these tests was performed at four sites, two in developed and two in developing countries. The data obtained suggest that the tests are more culture fair than others currently used to assess the same functional domains, that they are sensitive to HIV-1-associated cognitive impairment, and that this sensitivity "holds" across different cultures.

The World Health Organization (WHO) has launched a multicenter longitudinal study to explore the nature and prevalence of HIV-1-associated neurological and psychiatric disorders in persons living in different geographic and sociocultural contexts. The study is being performed in Bangkok (Thailand);

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Kinshasa (Zaire); Los Angeles, CA (United States); Munich (Germany); Nairobi (Kenya); and Sao Paulo (Brazil) (Maj et al., 1991).

A major component of this investigation is the assessment of cognitive functions in physically asymptomatic HIV-1 seropositive persons (groups II and III according to the Centers for Disease Control [CDC], 1986). This is at present a controversial research topic; in fact, although many studies (e.g., Goethe et al., 1989; Janssen et al., 1989; Korallnik et al., 1990; Miller et al., 1990; Tross et al., 1988) did not find any significant difference in the performance on neuropsychological tests among HIV-1 seropositive asymptomatic persons compared to HIV-1 seronegative controls, several others (e.g., Grant et al., 1987; McKegney et al., 1990; Perry, Belsky-Barr, Barr, & Jacobsberg, 1989; Wilkie, Eisdorfer, Morgan, Loewenstein, & Szapocznik, 1990) observed significant differences on measures of attention, concentration, information processing speed, and verbal memory.

Almost all the above-mentioned studies have been conducted in samples of well-educated, mostly white, homosexual or bisexual men in Europe and in North America. However, the need for cross-cultural investigations in this area has been repeatedly emphasized (Janssen et al., 1989; Miller et al., 1990; Perry et al., 1989; World Health Organization [WHO], 1990). It has been argued, in fact, that subtle cognitive deficits may appear earlier and progress more rapidly in HIV-1 infected subjects with fewer compensatory resources, such as those living in countries where the cerebral "reserve" is likely to be reduced in most of the population (due to the high frequency of infectious diseases and obstetric traumas, and to malnutrition, poor education, and inadequate health care) (Satz, 1991).

Indirect support for this hypothesis has been recently provided by some preliminary data from the Multicenter AIDS Cohort Study (MACS), showing a significant impairment of neuropsychological performance in a subsample of physically asymptomatic HIV-1 seropositive persons with a low educational level, whereas no deficit was observed in the overall sample of asymptomatic seropositives (Visscher et al., 1991).

Also beyond HIV-1-related research, the question of mild cognitive impairment occurring in the absence of any psychiatric diagnosis is currently attracting the interest of several investigators. Such an impairment has been found to be present in over 2% of the general population, and to be related to education, geographical background, race, and neurological status (Bassett & Folstein, 1991). No cross-cultural study has approached this research area until now, and the main reason for this has been the availability of only a few neuropsychological tests which are both culture fair and sensitive to subtle cognitive deficits.

Therefore, a crucial step in the development of the data collection instrument for the WHO study has been the construction of a battery of neuropsychological tests designed to be a) able to tap the primary functional domains known to be affected in symptomatic HIV-1 cases; b) sensitive to milder degrees of cognitive and motor dysfunction; c) brief enough to permit large-

scale administration; and d) suitable for use in a cross-cultural context. In order to develop such a battery, the WHO entrusted a committee of experts with the following tasks: a) to identify the functional domains which are most sensitive to HIV-1-induced brain damage; b) to list the available neuropsychological tests covering such domains, with special regard to those allowing the quantification of minor cognitive and motor deficits; c) to estimate the time needed for the administration of each of these tests; and d) to review the evidence (if any) of the suitability of each test for cross-cultural use.

The functional domains identified by the committee were motor speed, fine motor control, sustained attention, selective attention, cognitive flexibility, perceptual-motor analysis, verbal memory, visual memory, and verbal fluency. The neuropsychological tests tapping these domains, sufficiently sensitive to minor degrees of dysfunction, and brief enough to be considered for inclusion in the battery, were subdivided into three groups. The first group included those tests whose suitability for use in a cross-cultural context was regarded as obvious, since they do not include any task or item which may put a person from a non-Western culture at a significant disadvantage (e.g., the Timed Gait Test for motor speed; the Grooved Pegboard [Matthews & Klove, 1964] for fine motor control; the Word List Generation Test, animals and first names [Benton & Hamsher, 1977] for verbal fluency). The second group comprised those tests whose suitability for cross-cultural use was supported by available literature, such as the Block Design subtest from the EIWA, Spanish version of the Wechsler Adult Intelligence Scale (Wechsler, 1968), for perceptual-motor analysis; and the Digit Symbol subtest from the same scale, for fine motor control, selective attention, and cognitive flexibility (cross-cultural data provided by Fletcher, Satz, & Carter, 1978, and Satz, Krauskopf, & Fletcher, 1980). The third group included those tests whose suitability for cross-cultural use was questionable, such as the Rey Auditory Verbal Learning Test (Rey AVLT) (Rey, 1964) for verbal memory, and the Trail Making A and B (Reitan & Wolfson, 1985) for fine motor control, sustained and selective attention, and cognitive flexibility. For tests in Group 3, it was decided to develop more culture fair counterparts.

The present paper reports on the evaluation of two of these new neuropsychological tests, that is the WHO/UCLA Auditory Verbal Learning Test (WHO/UCLA AVLT) and the Color Trails 1 and 2.

METHOD

Brief Description of the New Neuropsychological Tests:

WHO/UCLA Auditory Verbal Learning Test (WHO/UCLA AVLT)

The Rey AVLT enjoys widespread application. However, its usefulness in cross-cultural contexts is weakened by inclusion of item content (e.g., turkey,

ranger, curtain) which is unfamiliar to individuals in different cultures. A second potential problem with the test is the fact that the items are not selected to represent different conceptual categories (e.g., animals, food), which would facilitate organizational recall strategies known to be affected by HIV-1 (van Gorp, Miller, Satz, & Visscher, 1989).

The WHO/UCLA AVLT is similar to the Rey AVLT in that it is a supra-span list learning task. However, all the test items have been carefully selected (from five categories, including parts of the body, animals, tools, household objects, and transportation vehicles) to have universal familiarity, and can be grouped into cross-culturally relevant categories to facilitate organizational recall. There are three exemplars from each category, and the list is presented in fixed random format. The WHO/UCLA AVLT is based on the use of auditory verbal stimuli selected with reference to a standardized lexicon of 250 universally familiar concepts (Snodgrass & Vanderwart, 1980), thereby ensuring item content translation into most languages. Similar to the Rey AVLT, the subject is verbally presented with the 15-item list of words, which are to be learned over five trials. The sixth trial is an interference list, which the subject is also asked to recall immediately. Following the interference list, the subject is asked to recall the original list which was repeated five times. Delayed recall is obtained, without prior warning, after 30 min, and a verbally presented recognition trial is administered immediately thereafter. All responses are sequentially marked by the examiner on the test protocol which contains all word lists.

Color Trails 1 & 2

Although Trail Making A & B is one of the most frequently administered neuropsychological tests in English speaking countries, its application in cross-cultural contexts is limited, due to its reliance on English alphabet stimuli in Part B. This feature of the test severely limits its application with individuals who are reading disabled, illiterate, poorly educated, and/or unfamiliar with the English alphabet. Furthermore, Trail Making A & B is probably the most widely photocopied test of the century. As a result, the test forms often vary in size and clarity. From a psychometric standpoint, these factors can introduce significant and uncontrolled error variance. On this basis, the sensitivity of Trail Making for cross-cultural application was questioned, and efforts were made to develop an equivalent form that corrected for the limitations, including potential flaws in copy reproduction.

The Color Trails 1 & 2 was developed following the idea of Trail Making A & B. However, in order to minimize cultural bias, no letters are used and all instructions are presented nonverbally with visual cues. Color Trails 1 & 2 is based on the use of numbered colored circles and universal sign language symbols, without any item or instruction requiring knowledge of any alphabet.

Parts 1 & 2 consist of several numbered circles colored in vivid pink or yellow (to control for color blindness). Color Trails 1 is similar to Trail Making A, with the exception that all odd numbered circles are printed with a pink background, and all even numbered circles are printed against a yellow background. In Color Trails 2 each number is printed twice, once in a pink and once in a yellow colored circle. In Color Trails 1, the subject is instructed to draw a line between the circles in consecutive order numbered 1 through 25. The incidental fact that color alternates with each succeeding number is not mentioned. The subject is told to perform the task as quickly as possible without making errors. He/she is informed that if errors are made the examiners will point them out, expecting him/her to correct them and proceed with the task. Up to 10 s are allowed for the subject to make a connection between one circle and the next. Following that 10-s period, the examiner provides a non-verbal prompt (points) indicating the position of the next appropriate circle. The number of errors and prompts are recorded, but the subject is not penalized for those, other than taking time to correct the error. Near-miss responses (initiation of an incorrect response that is self-corrected before the actual connection to a wrong circle) are also recorded. Before the actual administration of the test, a practice trial is given (See Figure 1).

In Color Trails 2, the subject is instructed to draw a line between numbered circles, maintaining the sequence of numbers but alternating between pink and yellow colors as they proceed. Therefore, the subject would draw a line from the Pink 1 to Yellow 2 (avoiding the Pink 2) and then to the Pink 3 (avoiding the Yellow 3) and so on through number 25. Timekeeping and treatment of errors and prompts are the same as in Color Trails 1. However, two types of errors are recorded: those pertaining to number sequence and those concerning

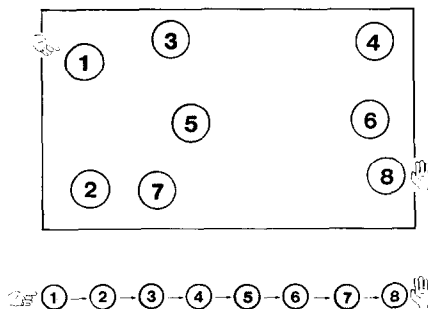


FIGURE 1. Color Trails 1, practice trial. What appears as gray in the noncolored picture is actually pink; what appears as white is actually yellow.

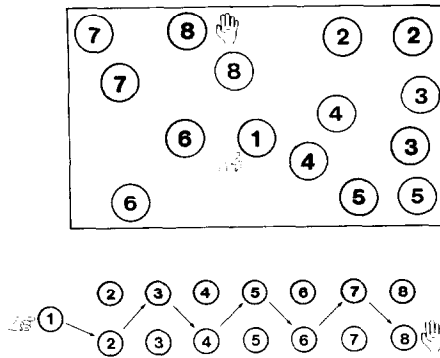


FIGURE 2. Color Trails 2, practice trial. What appears as gray in the noncolored picture is actually pink; what appears as white is actually yellow.

color sequence. A preliminary practice trial is given also in this case (See Figure 2).

The Studies

Three studies were carried out, in order to verify 1) whether significant correlations could be obtained in a Western culture between the two newly developed tests and other tests currently used for the assessment of verbal memory (Rey AVLT), and fine motor control, rapid visual search, sustained and selective attention and cognitive flexibility (Trail Making A & B); 2) whether the new tests were less influenced by cultural factors than the above-mentioned reference ones; and 3) whether the new tests were sensitive to HIV-1-associated cognitive impairment across different cultures.

In each study, the administration of the new and reference tests was always performed by an experienced neuropsychologist previously trained on the tests at WHO Headquarters, Geneva. Test instructions for all tests were administered in the subject's native language. Translation of test materials into local languages, when required, was made under the supervision of WHO Headquarters.

Study 1 (Question: Do the new tests tap the same functional domains as the reference ones?) Study 1 was carried out at the Max Planck Institute for Psychiatry (Munich, Germany). The sample consisted of 30 healthy volunteers (15 men/15 women), all of whom were students, physicians, or nurses. The mean age was 27.4 (5.9) years. The first language of all subjects was German.

All subjects had at least 10 years of education [Mean = 16.0 (4.4) years]; had no formal neuropsychological training; had no previous history of a head injury that caused loss of consciousness or for which they sought medical advice; had no previous history of neurological or psychiatric disorders for which they sought medical advice; had no previous history of learning disabilities; were not currently taking any medication likely to affect the functioning of the central nervous system; did not drink more than two glasses of wine or beer during the 24 h preceding each study session, and did not consume any alcohol during the 6 h preceding each session.

Two test batteries (Battery A and Battery B) were individually administered to each subject in two sessions on consecutive days. Battery A included the Rey AVLT trials 1–7, the Trail Making A and B, and the Rey AVLT trials 8 and 9; Battery B included the WHO/UCLA AVLT trials 1–7, the Color Trails 1 and 2, and the WHO/UCLA AVLT trials 8 and 9. Odd numbered subjects received Battery A on day 1 and Battery B on day 2; even numbered subjects received Battery B on day 1 and Battery A on day 2. Administration time for each battery was approximately 45 min.

Pearson product moment correlations were used to compare the scores on the new tests to those on the corresponding old ones. The hypothesis was that if the correlations were significant the new tests were likely to tap the same domains as the old ones.

Study 2 (Question: Are the new tests more culture fair than the reference ones?) Study 2 was conducted at the following sites: Department of Psychiatry, Chulalongkorn University (Bangkok, Thailand); Mama Yemo Hospital (Kinshasa, Zaire); Max Planck Institute for Psychiatry (Munich, Germany); Department of Psychiatry, University of Naples (Italy). Subjects were 30 healthy volunteers (students, physicians, or nurses) per center, selected on the basis of the same criteria detailed for Study 1. The composition of the samples was the following: in Bangkok, 14 men and 16 women, mean age 27.0 (5.9) years, mean educational level 16.4 (2.0) years (first language Thai); in Kinshasa, 23 men and 7 women, mean age 29.3 (6.4) years, mean educational level 15.7 (2.7) years (first language Lingala); in Naples, 16 men and 14 women, mean age 29.0 (5.7) years, mean educational level 17.2 (4.4) years (first language Italian). In Munich, the sample was the same as in Study 1.

Subjects were tested in two sessions, following the same design described for Study 1. For each test, all the scores were pooled, and the means and standard deviations were calculated. Data were then transformed into standard deviation units (*z*-scores) and the variance of the corrected scores across the sites analyzed by the Kruskal-Wallis test. The hypothesis was that if the variance of the *z*-transformed scores was reduced for a new test as compared to the reference one, the former was likely to be more free from cultural influences. Moreover, a stepwise discriminant analysis was performed (Norusis,

1988), using the site membership as the grouping variable, and the z-scores on all tests as predictive variables.

Study 3 (Question: Are the new tests sensitive to HIV-1-associated cognitive impairment across different cultures?) Study 3 was carried out at two sites: Mama Yemo Hospital (Kinshasa, Zaire) and the Department of Psychiatry, University of Munich (Germany). At each site, 12 HIV-1 seropositive (determined by ELISA and Western blot) subjects who were symptomatic (CDC group IV) were randomly recruited from a general medicine outpatient unit, and compared with 12 HIV-1 seronegative controls, matched according to sex, age, education, and HIV-1 risk group, enrolled from the same outpatient unit.

In Kinshasa, the seropositive group consisted of 6 men and 6 women, with a mean age of 32.4 (5.5) years and mean educational level of 11.9 (2.7) years. The seronegative group consisted of 6 men and 6 women, with a mean age of 29.0 (4.3) years and mean educational level of 12.4 (4.4) years. Both groups were composed of heterosexuals with no history of drug abuse or blood transfusions, whose first language was Lingala. In Munich, the seropositive group consisted of 6 men and 6 women, with a mean age of 30.7 (4.4) years and mean educational level of 12.3 (3.8) years. The seronegative group consisted of 6 men and 6 women, with a mean age of 26.8 (3.4) years and a mean educational level of 14.2 (3.5) years. The Munich group included three drug addicts and nine heterosexuals with no history of drug abuse or blood transfusions, whose first language was German.

Each subject was administered in a single session the WHO/UCLA AVLT trials 1–7, the Color Trails 1 and 2, and the WHO/UCLA AVLT trials 8 and 9. The performance of each subject on each test was expressed as a z-score, calculated on the basis of the mean and standard deviation of the relevant seronegative group. Impairment on each test was defined as a z-score exceeding the mean of the relevant seronegative group by at least 1.5 standard deviations. Both in Kinshasa and in Munich, the percentages of impaired subjects on each test in the seropositive versus seronegative group were compared by the chi square test with Yates' correction. The hypothesis was that if the percentage of impaired subjects was significantly higher among the seropositives in both centers, the new tests were likely to be sensitive to HIV-1-associated cognitive impairment across different cultures.

RESULTS

Study 1 showed a significant correlation between the scores on each new test and those on the reference one (Table 1). Study 2 demonstrated that the variance of the z-transformed scores across the centers was reduced for the

TABLE 1
Correlations Between the Scores on the New and the Reference
Neuropsychological Tests in a Sample of Healthy Subjects from a
Western Culture

Tests	Product-moment coefficient
WHO/UCLA AVLT 1-5/Rey AVLT 1-5	.479** (.006)
WHO/UCLA AVLT 5/Rey AVLT 5	.474** (.006)
WHO/UCLA AVLT 8/Rey AVLT 8	.554** (.001)
Color Trails 1/Trail Making A	.408* (.017)
Color Trails 2/Trail Making B	.496** (.004)

$n = 30$; * $p < .05$; ** $p < .01$.

WHO/UCLA AVLT as compared to the Rey AVLT, and for the Color Trails 2 as compared to the Trail Making B, whereas it was almost the same for the Color Trails 1 and the Trail Making A (Table 2). On the stepwise discriminant function analysis, the only two variables predicting the site membership were the scores on Trail Making B (Wick's lambda = 0.61; equivalent $F = 13.60$, $r < 0.00001$) and on Rey AVLT (Wick's lambda = 0.51; equivalent $F = 14.60$, $r < 0.00001$).

Study 3 showed that the percentage of impaired subjects on each new test was significantly higher in the HIV-1 seropositive group compared with the seronegative one, both in Kinshasa and in Munich (Table 3).

DISCUSSION

The Rey AVLT and the Trail Making A & B are tests of demonstrated sensitivity and specificity in symptomatic cases of HIV-1 infection (Miller et al., 1990; van Gorp et al., 1989). They present, however, some characteristics that put an individual from a non-Western culture at a distinct disadvantage. The

TABLE 2
Cross-Cultural Variance of the Z-Transformed Scores on
the New and the Reference Neuropsychological Tests in
Healthy Subjects

Tests	H values (Kruskal-Wallis statistics)
WHO/UCLA AVLT 1-5	3.47
Rey AVLT 1-5	27.53
Color Trails 1	21.46
Trail Making A	22.76
Color Trails 2	26.78
Trail Making B	47.68

$n = 120$.

TABLE 3
Percentages of Subjects Impaired on the New Neuropsychological Tests in the HIV-1 Seropositive Versus Seronegative Groups in Kinshasa and Munich

Tests	Kinshasa		Munich	
	HIV+ (n = 12)	HIV- (n = 12)	HIV+ (n = 12)	HIV- (n = 12)
WHO/UCLA AVLT 1-5	50.0*	8.3	50.0*	8.3
Color Trails 1	41.6*	8.3	33.3*	8.3
Color Trails 2	33.3*	8.3	33.3*	8.3

* $p < .001$.

main problem with the Rey AVLT is that some of the words it uses (e.g., curtain, turkey, ranger) identify objects that are rarely found in certain cultures, making these items of varying difficulty depending on the culture. The main difficulty with the Part B of Trail Making is that it incorporates the English alphabet in the design, thus being not culture fair to anyone who is not an English speaker, and unsuitable for use in subjects who are illiterate, or have limited educational experience, or are reading or learning disabled.

On this basis, the Rey AVLT and the Trail Making A & B tests were regarded as less appropriate for inclusion in the neuropsychological battery for the WHO cross-cultural multicenter study, and an attempt was made to develop new, more culture fair tests tapping the same functional domains. The WHO/UCLA AVLT and the Color Trails 1 & 2 are the products of this effort.

The purpose of the present study was to evaluate these two new tests, by a) comparing them to the above mentioned reference tests in a sample of healthy subjects from a Western culture, in order to explore whether they cover the same functional domains; b) comparing them to the reference ones in healthy subjects from different cultures, in order to confirm whether they are more culture fair; and c) applying them in HIV-1 seropositive and seronegative persons from different cultures, in order to verify if they are sensitive to the cognitive deficits produced by HIV-1 infection, and if this sensitivity "holds" across cultures.

The results of this evaluation have been positive on the whole. The pattern of the correlations of the new tests with the reference ones in a culture similar to the one where the tests were developed suggests that they do assess similar domains. The lower variability across cultures of the corrected scores on the WHO/UCLA AVLT and the Color Trails 2 as compared to corresponding traditional tests suggests that the former are more free from cultural influences, whereas no significant difference in this respect seems to exist between the Color Trails 1 and the Trail Making A. Data obtained in HIV-1 seropositive symptomatic persons support the sensitivity of the new measures to HIV-1-

related cognitive impairment in different cultures. The results of stepwise discriminant function analysis (using site membership as the grouping variable and test scores as predictive variables) point in the same direction. The inclusion of the two new tests in the WHO battery seems, therefore, justified, whereas there seems to be no reason to exclude from this battery the Trail Making A.

Besides the specific objectives of the WHO cross-cultural HIV-1 study, the WHO/UCLA AVLT and the Color Trails 1 and 2 appear to be suitable for use in the assessment of cognitive functions in other infectious or noninfectious diseases which affect the central nervous system and are highly prevalent in developing countries. These tests are likely to be particularly sensitive to mild cognitive impairment; in fact, the grouping of WHO/UCLA AVLT items into semantically related categories permits the use of organizational strategies that are known to be compromised after early frontal lobe injury, and the near-miss scores of the Color Trails allow quantification of subtle slippage in frontal functioning. This is of interest because current approaches in assessing performance on frontal tasks usually allow only for the quantification of gross errors.

Sensitivity to mild cognitive impairment and suitability for cross-cultural use should encourage a wide application of these tests in different geographic and sociocultural contexts and for various purposes.

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