# Motor based assessment of neurocognitive functioning in resource-limited linternational settings

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This study compared variance accounted for by neuropsychological tests in both a brief motor battery and in a comprehensive neuropsychological battery. 327 HIV+ subjects received a comprehensive cognitive battery and a shorter battery (Timed Gait, Grooved Pegboard, and Fingertapping). A significant correlation existed between the motor component tests and the more comprehensive battery (52% of variance). Adding Digit symbol and Trailmaking increased the amount of variance accounted for (73%). Motor battery sensitivity to impairment diagnosis was 0.79 and specificity was 0.76. A motor battery may have broader utility to diagnose and monitor HIV related neurocognitive disorders in international settings.

## INTRODUCTION

For individuals diagnosed with AIDS dementia complex (ADC), the deficits in neuropsychological and cognitive functioning often represent a pervasive and debilitating source of difficulty that interfere with their functional abilities and quality of life. This has made it increasingly important to include neuropsychological measures in assessments that diagnose and monitor the course of ADC. Unfortunately, many neuropsychological batteries either sacrifice brevity and facility for comprehensiveness, or are language-dependent tests that require English as a first language or an appropriate translation supported by normative data. The demands of more complicated neuropsychological measures may also fail to match the resources of the assessing provider, especially in international settings where services are limited. The objective of this study was to therefore determine the utility of a brief, motor-based battery, particularly when compared with a larger, comprehensive neuropsychological battery.

# AIDS DEMENTIA COMPLEX (ADC)

AIDS dementia complex (ADC) is an HIV-associated chronic, neurodegenerative syndrome that usually occurs at the later stages of HIV infection when severe immunodeficiency has developed. It affects 15–20 percent of patients with AIDS and carries a prognosis of two to 12 months, with an average sixmonth survival rate (Adams & Ferraro, 1997; Patel et al., 2002; Rausch & Stover, 2001). As this suggests, it represents one of the final phases of central nervous system dysfunction, with corresponding cognitive, motor, and behavioral disturbances (Adams & Ferraro, 1997; Rausch & Stover, 2001).

To meet criteria for ADC, there must be an acquired abnormality in motor functioning, as well as deficits in at least two cognitive domains

Supported by RO1NSMH34243, RO1MH62690, RR00046.

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(Working Group, 1991). The exact type of cognitive deficit may depend on the stage of illness, with memory, concentration, and motor functioning showing some declines in the early stages (Lopez-Villegas, Leinski, & Frank, 1997). As the disease progresses, however, the greatest declines appear in motor functioning, executive skills, verbal free recall, and information processing speed (Baldewicz et al., 2004; Reger, Welsh, Razani, Martin, & Boone, 2002; Suarez et al., 2000).

Of these, motor functioning and psychomotor slowing have emerged as one of the most sensitive indicators of ADC (Koutsilieri, Sopper, Scheller, ter Meulen, & Riederer, 2002; Rausch & Stover, 2001). Not only is reduced motor functioning a uniform feature across the stages of HIV and AIDS infection, but it also has direct implications for individuals' mood and functional independence, including mobility, employment, and driving (Sacktor et al., 1996). For this reason, some research has suggested that cognitive and functional assessments should be heavily weighted toward timed motor tasks as strong indicators of cognitive performance during ADC (Clifford, 2002), particularly considering their convenience, facility, and lack of sensitivity to cross-cultural context. Motor functioning may therefore provide a sensitive estimate of the general neurocognitive functioning of individuals with AIDS dementia complex (Robertson et al., in press). In fact, one study found that the combined performance on a measure of graphomotor speed (WAIS-III Digit Symbol) and a test of fine motor control (Grooved Pegboard) had a sensitivity of .60, specificity of .90, and overall predictive power of .81 (Carey et al., 2004). Motor functioning may therefore represent a sensitive estimate of the general cognitive functioning of individuals with AIDS dementia complex.

# Motor functioning and subcortical processes

One of the potential reasons for the utility and relevance of these motor-based assessments may be their sensitivity to the subcortical and prefrontal-striatal processes underlying AIDS dementia complex. The profile of ADC has been likened to subcortical dementia, not only due to their similar neuropsychological manifestation, but also due to their similar histopathologies. By late disease stages, the neuropathologic findings of ADC is not restricted to frontal-striatal circuitry or deep white matter, but rather affects the entire brain parenchyma, as reflected by the significant negative relationship between brain parenchymal volume and level of impairment related to ADC (Patel et al., 2002). However, a significant part of the disease process involves the infection of subcortical brain structures, like the basal ganglia, globus pallidus, caudate nucleus, substantia nigra, and deep white matter. Neuroimaging consistently reveals that individuals with ADC demonstrate hypermetabolism and cerebral atrophy in subcortical structures, as well as diffuse and patchy white matter abnormalities (Kim et al., 1996; Paul, et al., 2002; Rao 1996). They also exhibit bilateral changes in alpha EEG activity that reflects functional deficits in subcortical regions (Baldeweg & Gruzelier, 1997). Moreover, neuropathological studies and autopsies on the brains of individuals with ADC reveal white matter atrophy and neuronal loss in the frontal cortex, as well as the highest concentrations of viral load in the basal ganglia, hippocampus, and deep white matter compared to other brain regions (Baldewicz et al., 2004; Lopez-Villegas et al., 1997; Rausch & Stover, 2001). Subcortical processes may therefore be particularly vulnerable to degeneration and atrophy in ADC.

Many of these subcortical areas are directly involved in motor functioning, such that the degree of neuronal loss or dysfunction in these regions may be directly related to degree of motor impairment (Kim, Tien, Byrum, & Krishnan, 1996; Suarez et al., 2000). The reduction of white matter volume and increased subcortical atrophy not only alters frontal-striatal circuitry, but it slows neural conduction and reduces the volume of myelin sheaths. These changes appear to directly contribute to the reduced psychomotor speed, mental slowing, and attenuated motor functioning that appear in ADC. These deficits in motor performance are also exacerbated by the finding that that neuronal degeneration occurring in the basal ganglia and nigrostriatal structures concomitantly alters the dopaminergic system, particularly reducing the amount of dopamine availability (Koutsilieri et al., 2002). Not only does this dopamine deficiency lead to motor difficulties, but it may also partially account for the Parkinsonian features that are frequently seen in ADC (Koutsilieri et al., 2002). This suggests that the pattern of motor deficits typically seen in ADC are a function of the disintegration of the subcortical systems. Considering the sensitivity of motor functioning to this degeneration, motorbased assessments may therefore be a necessary and vital part of cognitive and functional assessment in ADC.

#### **Resource-limited settings**

The efficacy of many traditional neuropsychological measures are often compromised by their length, language translations and cultural limitations when used in the developing world. Over 85 percent of those individuals with HIV infection and ADC live outside industrialized countries (Maj, 1994a), with sub-Saharan Africa accounting for over 70 percent of AIDS cases (Dal Pan & McArthur, 1996). Within the Unites States alone, HIV-infection and ADC are spreading at an alarming rate within ethnic and cultural minority populations, with the Latino community accounting for 19 percent of the AIDS cases reported to the Centers for Disease Control (Mindt et al., 2003).

Despite the prevalence of neuropsychological impairments associated with ADC in ethnic minorities, resource limited settings and non-western cultures, most of the studies assessing this impairment have been conducted on samples of well-educated, Caucasian, men in Europe or North America (Maj et al., 1993). Although research in these areas may be driven by convenience, this implicitly presupposes that the neuropsychological profiles of welleducated, Caucasian, men are representative of the larger population with ADC. According to Maj and colleagues (1994b), however, neither the pattern of neuropsychological impairment, nor the actual chance of developing ADC in the symptomatic stages, differs between cultures or geographical locations. Poor education and nutrition, inadequate health care, and high frequency of infectious diseases are factors in many individuals in resource-limited settings, leading to the possibility of fewer compensatory resources or a lower cerebral reserve. The compounded action of these factors may lower the threshold for developing neuropsychological deficits, which increases the need for timely, accurate, and culturally relevant neuropsychological assessment.

Unfortunately, many of the traditional neuropsychological tests are language dependent and lack normative data for international settings. The limited resources in these settings may also counterindicate full, comprehensive evaluations, particularly when individuals are impoverished and have limited access to health care. This has created a need for briefer measures that are less contingent upon language, but that retain sensitivity to the cognitive and functional impairments occurring in ADC. The objective of this study was to determine the utility of a brief, motor-based battery to fulfill this role and serve as a sensitive, but accurate measure of overall cognitive functioning in resource limited international settings.

#### METHODS

The University of North Carolina Institutional Review Board approved the study, and all participants gave informed consent for participation. The subjects for this study were enrolled in a prospective longitudinal study of the effects of HIV on the nervous system. Subjects underwent detailed neurological, psychological and neuropsychological examination, as well as HIV-RNA quantitative evaluation in plasma and cerebrospinal fluid (CSF).

The comprehensive neuropsychological evaluation and the neurological examination are structured to be particularly sensitive to the neurological effects of HIV. Subjects further undergo a psychological evaluation, which is sensitive to factors that may confound the results of the other studies (Wilkins et al., 1990) At each evaluation, subjects also undergo ultra-sensitive HIV RNA quantitative evaluation in both plasma and cerebrospinal fluid (CSF). The neurologist and neuropsychologist were blind to disease severity (CD4+, HIV RNA viral load), not to HIV status. Concensus ratings for Memorial Sloan Kettering Dementia Staging (Price and Sidtis, 1990) was not blind to CD4 or HIV RNA.

Inclusion/Exclusion Criteria: A participant was included in the study if they had the ability and willingness to provide informed consent, and completed HIV antibody testing, laboratory, neurological, and neuropsychological testing procedures. A participant was excluded from the study if they had any of the following: (1) Completion of treatment for any acute systemic infection (other than HIV) less than four weeks prior to study entry. Maintenance or prophylactic therapy was permitted for opportunistic infections; (2) Any active psychiatric illness including schizophrenia, severe depression, or severe bipolar affective disorder that, in the opinion of the investigator, could confound the analysis of the neurological examination or neuropsychological test results; (3) Active drug or alcohol abuse that, in the investigator's opinion, could prevent compliance with study procedures or confound the analysis of study endpoints; (4) less than a 9th grade education; Vocabulary score less than 7 on an Age Equivalent Scaled Score; prior history of head injury with loss of consciousness for more than 10 minutes and/or any cognitive sequelae (5) Active brain infection (except for HIV-1), brain neoplasm, space-occupying brain lesion requiring acute, or chronic therapy. Subjects with any fungal meningitis, toxoplasmosis, or CNS lymphoma were excluded from participation.

## Neuropsychological evaluation

neuropsychological evaluation included The assessment of the following domains: attention/ concentration (Ruff 2 and 7 test, Ruff, Evans, & Light, 1986; PASAT, Gronwall, 1977), speed of processing (computerized simple and choice reaction time tasks, Miller, Satz, & Visscher, 1991; digit symbol, Weschler, 1981; trailmaking A, Army Individual Test Battery, 1944; Stroop word, Comalli, Wapner & Werner, 1962), executive functioning (Trailmaking B, Army Individual Test Battery, 1944; Stroop color-word, Comalli et al., 1962; COWA, Benton & Hamsher, 1978), visuospatial (Rey complex figure copy, Rey, 1941, 1962), verbal memory (RAVLT), figural memory (Rey complex figure immediate, delay), gross motor (timed gait, Robertson et al., in press), fine motor (grooved pegboard, Lafayette Instrument Company, 1989; finger tapping, Reitan & Davidson, 1974), and language (WAIS-R Vocabulary, Weschler, 1981). The shorter neuropsychological battery is a subset of the comprehensive battery of tests: gross motor (timed gait), fine motor (grooved pegboard, finger tapping). When available, we used the Heaton, Miller, Taylor, and Grant's (2004) Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults. Sensitivity and specificity calculations were based on the comprehensive clinical diagnosis of AIDS dementia complex (ADC) stage. Sensitivity was calculated as the number of true positive cases divided by the sum of true positive and false negative cases. Specificity was calculated as the number of true negative cases divided by the sum of true negative and false positive cases.

#### Neurologic examination

The Price and Sidtis (1990) AIDS Clinical Trials Group full neurologic evaluation was used. The neurologic evaluation includes a global assessment of HAD (AIDS dementia complex stage), which varies from equivocal (0.5) to severe (3.0) dementia. To increase the sensitivity of the instrument and to provide domains of functioning, a quantitative scoring procedure for the neurologic evaluation was implemented, which provides a weighted scoring approach to the items of the neurologic examination and yields an overall neurologic total score as well as scores for cognitive, frontal, pyramidal, extrapyramidal, cranial nerve, cerebellar, spinal, autonomic, sensory, and peripheral domains.

#### **HIV RNA load**

Viral load assessment was performed through plasma and cerebrospinal fluid measurements. Within 8 hours of the neurologic evaluation, specimens for viral load and immune functioning were obtained. Blood and cerebrospinal fluid samples were obtained within 3 hours of each other. Cerebrospinal fluid samples were centrifuged to remove cells. The Roche Ultrasensitive assay was used to measure Quantitative HIV-1 RNA load. Prior to viral load analysis, neurologic and neuropsychological evaluations were completed in a blinded fashion.

#### Memorial sloan kettering dementia staging

Subsequent to each visit, the Memorial Sloan Kettering (MSK) dementia scale was determined for each participant at a consensus conference, utilizing the neurologic and neuropsychological evaluations, the psychiatric interview, and the quality of life scale. The MSK dementia scale is as follows: 0-Normal, 0.5-Equivocal/Subclinical (Either minimal or equivocal symptoms of cognitive or motor dysfunction that are characteristic of ADC, or mild signs (snout), but without impairment of work or ADL's), Stage 1- Mild dementia (unequivocal symptoms, signs, neuropsychological performance denoting functional intellectual or motor impairment but able to engage in all but the more demanding tasks of work or ADLs), Stage 2- Moderate (cannot work or maintain more demanding aspects of daily like, able to do self care and ambulatory), 3- Severe (Major intellectual incapacity or motor disability), Stage 4- End stage (Nearly vegetiative, rudimentary intellectual function, nearly mute or mute, paraplegic with double incontinence (Price and Sidtis, 1990).

## RESULTS

Three hundred sixty one subjects were recruited for participation in the study. The mean age was 24.24 years (SD = 17.91) and a mean educational level of 13.43 years (SD = 2.77 years). Sixty-six percent of the subjects were male and 34 percent were female. Fifty-two percent were black, 45 percent were white, and two percent Asian and one percent were Native American. Participant disease information included: mean CD4+ lymphocyte counts of 370 (SD = 342), and viral load assays (log mean = 3.83; SD = 1.69). Thirty-one percent of the group met CDC criteria for an AIDS diagnosis. Nineteen percent had CD+ cell counts <200 mm3 at the time of

	Beta	Std. Err.	В	Std.Err.	t(312)	p-level
Timed Gait	0.09	0.03	0.03	0.01	2.71	0.01
Digit Symbol	0.25	0.03	0.16	0.02	7.72	0.01
Trailmaking Test						
Part A	0.21	0.04	0.12	0.02	5.44	0.01
Part B	0.27	0.04	0.10	0.01	7.65	0.01
Grooved Pegboard						
Non-dominant	0.02	0.04	0.01	0.02	0.47	ns
Dominant	0.18	0.04	0.08	0.02	4.12	0.01
Finger Tapping						
Non-dominant	0.23	0.05	0.13	0.03	4.78	0.01
Dominant	0.01	0.05	0.01	0.02	0.29	ns

 TABLE 1

 Regression summary comparing motor component tests and the more comprehensive battery

Note: Overall analyses revealed R = .86;  $R^2 = .73$ ; Adjusted  $R^2 = .73$ ; F(8, 312) = 106.52 p < .0001; and Standard Error of estimate = .38.

 TABLE 2

 Regression summary between the international motor based neuropsychological tests and the individual functional domains

	Beta	Std. Err.	В	Std.Err.	t(312)	p-level
Attention	0.29	0.03	0.28	0.03	10.90	0.01
Executive	0.34	0.03	0.16	0.01	12.38	0.01
Figural memory	0.08	0.02	0.07	0.02	3.43	0.01
Verbal Memory	0.40	0.03	0.32	0.02	15.44	0.01
Language	0.17	0.03	0.14	0.02	6.40	0.01

Note: Overall analyses revealed R = .95;  $R^2 = .90$ ; Adjusted  $R^2 = .89$ ; F(5, 221) = 376.89 p < .0001; and Standard Error of estimate = .26.

the baseline evaluation. Approximately 38 percent of the sample was prescribed HAART.

A quantitative scoring procedure was utilized for the neurological exam, and summary z-scores were calculated for the neuropsychological battery.

A motor battery cutoff of -.42 carried a moderate value (0.79) for sensitivity of cognitive impairment diagnosis, but a lower value (0.76) for the specificity of neurocognitive impairment diagnosis. Although these sensitivity and specificity levels are moderate, it is important to note that the comprehensive battery was no better.

There was a significant correlation between the motor component tests and the more comprehensive battery [ $F(5, 321) = 72.03 \ p < .0001$ ] that accounted for 52 percent of the variance (adjusted  $R^2 = .52$ ) associated with the comprehensive battery (see Table 1 for a regression summary). As expected, the addition of Digit symbol [ $F(6, 319) = 86.938 \ p < .0001$ ; adjusted  $R^2 = .61$ ] and Trailmaking A and B [ $F(7, 314) = 96.455, \ p < .0001$ ; adjusted  $R^2 = .68$ ] led amount of variance accounted for to be improved. Adding both Digit Symbol and Trailmaking A and B [ $F(8, 312) = 106.52 \ p < .0001$ ; adjusted  $R^2 = .68$ ] accounted for almost 73 percent of the variance.

There were significant correlations between the international motor based neuropsychological tests and the individual functional domains of verbal memory, language, figural memory, executive functioning, and attention (p < .05; see Table 2 for a regression summary). The tests accounted for 58 percent of the variance in verbal memory [F (1, 364) = 515.42, p < .0001, 34 percent of language skills [F(1, 364) = 187.91, p < .0001], 52 percent of executive functioning [F(1, 364) = 398.83, p]< .0001], 28 percent of visuospatial skills [F(1, 361)] = 139.40, p < .0001 and 51 percent of attentional processes [F(1, 229) = 239.48, p < .0001]. Thus, there is overlap between the motor domains and the other functional domains. There were also significant relationships between the battery and Neurological Exam (p < .001) and Absolute CD4+ cells (p < .001).

#### DISCUSSION

This study attempted to determine the utility of a brief, motor-based battery for assessing the cognitive functioning of individuals with AIDS dementia complex in resource-limited, international settings. From the results, it appears that a group of fine and gross motor tests were significantly correlated with a larger, more comprehensive battery and accounted for a significant amount (52 percent) of the variance in this larger battery. The level of predicted variance increased to 73 percent when two additional measures of motor processing speed were added. Moreover, there were significant relationships between the set of international, motor-based measures and those tests comprising the functional domains of verbal memory, language, figural memory, executive functioning, and attention. These findings suggest that a brief assessment of motor functioning may represent a sensitive estimate of the general neurocognitive functioning of individuals with AIDS dementia complex. It also suggests that a motor-based battery may be administered as a strong indicator of neurocognitive performance without losing all of the explanatory power of larger batteries that cover multiple domains.

These findings are consistent with research suggesting that motor functioning and psychomotor slowing are one of the most accurate indicators of ADC and may capture a large portion of the variability in the cognitive functioning of individuals with ADC (Koutsilieri et al., 2002; Rausch & Stover, 2001). This study confirms Carey et al.'s (2004) findings that motor-based assessments have strong predictive power for detecting and capturing the cognitive deficits associated with HIV. It also contributes evidence that these motor-based measures detect cognitive impairment in the later stages of HIV, namely dementia, and retain the sensitivity and explanatory power of larger batteries.

The efficacy of these motor measures may be partially due to the sensitivity of motor-based assessments to the subcortical processes underlying ADC. Like most dementias, ADC affects the entire brain parenchyma, but it also reduces white matter volume, and increased atrophy in the frontal lobes, basal ganglia, and substantia nigra. These changes appear to alter frontal-striatal circuitry, slow neural conduction, reduce the volume of myelin sheaths, and change the dopaminergic system in a way that directly contributes to the reduced psychomotor speed, mental slowing, and attenuated motor functioning that appear in individuals with ADC (Kim, et al., 1996; Koutsilieri et al., 2002; Suarez et al., 2000). As a result, motor-based assessments may be particularly effective and accurate because they are sensitive to the neural degeneration seen in ADC and because they subserve many of the cognitive deficits seen in ADC.

In most situations, it may be preferable to administer a larger, more comprehensive battery of neuropsychological tests. However, many of these tests may be inadequate, irrelevant, and even culturallybiased in international and resource-limited settings (Maj et al., 1993). Due to poor educational opportunities and inadequate health care, many individuals in these settings may be unduly classified as impaired due to the poor specificity and high sensitivity of culturally-limited measures. Maj et al. (1993) determined that it is possible to develop variations of these tests that maintain relative freedom from cultural influence, while sustaining sensitivity to detecting and assessing neuropsychological symptoms of AIDS. Considering the impact of ADC on motor functioning, executive skills, verbal free recall, and information processing speed, the optimal battery would entail measures that that are sensitive to each of these cognitive domains. In the absence of resources to administer this battery, however, motor-based measures are brief, language-independent measures that are highly correlated with the larger batteries and retain sensitivity to the cognitive and functional impairments occurring in ADC. This suggests that they may have broad utility in the diagnosis and monitoring of HIV-related neurocognitive disorders, including the stage of ADC, the corresponding type of intervention, and the efficacy of treatment. They may also help determine an individual's functional abilities, including mobility, employment, and driving, which may directly inform the quality of life of those with ADC (Sacktor et al., 1996).

Further support for the use of a brief battery is based upon research into a common factor accounting for a wide degree of cognitive dysfunction in HIV. Becker and Salthouse (1999) found that neurocognitive variables shared a significant amount of variance related to HIV disease status. They concluded that HIV-related influences upon neurocognition reflect shared variance that should not be considered independent. Future studies should move beyond overreliance on a domain-based approach, which may be limited in that neuropsychological assessment is not categorically specifiable into welldelineated domains. According to Dodrill (1997), poor test specificity may be revealed in the median correlations for common neuropsychological tests. For example, Dodrill asserts that while the median correlation within domain groupings on a test was .52, the median correlation between groupings was .44. From this, Dodrill extrapolates that the tests are not unambiguously domain specific because the median correlations should be notably higher for the within groupings and lower for the between groupings. Consequently, the principal assessment measures used by practitioners may not be quantifying domains to a level of specificity that accounts for the covariance among the measures.

Modeling of cognitive domains among the HIV participants requires an analysis of possible covariance among the participants' item set. Covariance among cognitive measures indicates a common attribute. This common attribute among measures may obfuscate mean differences. If a cognitive domain does differ among HIV participants specific cognitive tests may not be equally good measures of this domain-some may be more sensitive than others in measuring the attribute, and may discriminate more clearly between levels of the attribute. Hence, while this study has made progress toward delineating neurocognitive performance using a brief, but specific battery, future studies are needed to determine if observed differences between symptomatics and asymptomatics are impacted by the covariance present between all cognitive tests.

Further work is required for establishing the validity and reliability of these measures in international settings, as well as gathering normative data across populations. It is also important to explore the influence of demographic differences, like age, gender, and education, on motor functioning and its interaction with ADC (Heaton et al., 2004; Selnes et al., 1991). However, it appears that motor-based tests may be a necessary and vital part of cognitive and functional assessment in ADC, with particular utility and relevance in settings where a comprehensive assessment may be limited.

In summary, AIDS related neurological disease has a very high cost in terms of loss of functional ability. The resultant loss of productivity has a broader impact on the family as the caregiver is no longer able to function and provide. AIDS Dementia has been associated with CNS white matter disease, and decreased speed of processing and reduced motor functioning. We assessed the relationship between a brief motor based neuropsychological battery widely implemented in NIH AIDS clinical trials for the assessment of neurocognitive functioning and improvement with treatment, and a more comprehensive battery. We found significant relationships between the shorter motor based battery, and the more comprehensive testing. While the briefer battery is appropriate for initial studies, further work is required on establishing validity and gathering normative data.

> Original manuscript received 8 June 2005 Revised manuscript accepted 22 November 2005 First published online 17 October 2006

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