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Relationship of ethnicity, age, education, and reading level to speed and executive function among HIV+ and HIV– women: The Women’s Interagency HIV Study (WIHS) Neurocognitive Substudy

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Use of neuropsychological tests to identify HIV-associated neurocognitive dysfunction must involve normative standards that are well suited to the population of interest. Norms should be based on a population of HIV-uninfected individuals as closely matched to the HIV-infected group as possible and must include examination of the potential effects of demographic factors on test performance. This is the first study to determine the normal range of scores on measures of psychomotor speed and executive function among a large group of ethnically and educationally diverse HIV-uninfected, high-risk women, as well as their HIV-infected counterparts. Participants (n = 1,653) were administered the Trail Making Test Parts A and B (Trails A and Trails B), the Symbol Digit Modalities Test (SDMT), and the Wide Range Achievement Test–3 (WRAT–3). Among HIV-uninfected women, race/ethnicity accounted for almost 5% of the variance in cognitive test performance. The proportions of...
variance in cognitive test performance accounted for by age (13.8%), years of school (4.1%), and WRAT–3 score (11.5%) were each significant, but did not completely account for the effect of race (3%). HIV-infected women obtained lower scores than HIV-uninfected women on time to complete Trails A and B, SDMT total correct, and SDMT incidental recall score, but after adjustment for age, years of education, racial/ethnic classification, and reading level, only the difference on SDMT total correct remained significant. Results highlight the need to adjust for demographic variables when diagnosing cognitive impairment in HIV-infected women. Advantages of demographically adjusted regression equations developed using data from HIV-uninfected women are discussed.

Keywords: HIV; Normative study; Race; Ethnicity; Reading level; Psychomotor speed.

INTRODUCTION

HIV infection is associated with increased risks for impairment in neurocognitive function (Grant & Martin, 1994; Heaton et al., 1995). Impairment in speed of information processing is a cardinal feature of HIV-associated brain dysfunction (Heaton et al., 1995). The pattern of cognitive deficits found in HIV-infected individuals can be broadly described as a “subcortical” pattern of cognitive dysfunction. Like other patients with neurological conditions that primarily affect the functions of the basal ganglia and their cortical connections, HIV+ individuals have slowed mentation, increased choice reaction times, and memory loss more characteristic of a retrieval deficit than of a storage loss (Becker et al., 1995; Martin, Sorensen, Edelson, & Robertson, 1992). Slowed mentation is common even in the early stages of infection (Villa et al., 1996) and is a predictor of subsequent cognitive and physical decline (Sacktor et al., 1996). According to the Northeastern AIDS Dementia Cohort and the AIDS Clinical Trials Group (ACTG), the prevalence of minor cognitive motor disorder (MCMD) is approximately 30%, whereas other data from recent cohort studies of persons with advanced HIV/AIDS put the prevalence at 37% (Sacktor et al., 2002).

Although accurate assessment of cognitive function among people with HIV is critical for determining the effects of the virus on the brain (Butters et al., 1990; Carey et al., 2004; Heaton et al., 1995; E. N. Miller, 1990), everyday function, and health variables such as medication adherence, validation of neuropsychological instruments for use among ethnic minorities with HIV has only recently begun (Heaton, Miller, Taylor, & Grant, 2004; Heaton, Taylor, & Manly, 2001). There is increasing interest in collecting comprehensive normative information on neuropsychological test performance of ethnic minorities (Heaton et al., 2004; Lucas et al., 2005; Ponton et al., 1996). However, the use of these norms to detect cognitive impairment that is related specifically to HIV infection has been questioned (Heaton et al., 1995; Levine et al., 2007), since these normative samples exclude many seronegative people at high risk for HIV infection. Since history of intravenous drug use, alcohol and drug dependence, and psychiatric disorders are typical exclusion criteria for normative studies of neuropsychological test performance, the use of these norms to identify HIV-specific cognitive dysfunction is problematic. For example, cognitive impairment is prevalent in substance abusers who are HIV negative (Martin, Pittrak, Pursell, Mullane, & Novak, 1995), and there is evidence of decreases in overall brain volume among high-risk group controls as compared to low-risk controls (Jernigan et al., 1993). Highlighting the importance of these high-risk behaviors in HIV research, when HIV seropositive and seronegative women were matched on demographics and substance use history, there were no significant differences in cognitive test performance between the groups (Stern et al., 1998).

Use of appropriate normative data for detection of HIV-related neurocognitive impairment also involves proper adjustment for educational experience. Prior studies, primarily among older adults, have shown that years of school is an inadequate measure of educational experience among ethnically diverse adults, and that quality of education must also be taken into account (Manly, Byrd, Touradji, & Stern, 2004; Manly, Jacobs, Touradji, Small, & Stern, 2002; Manly, Touradji, Tang, & Stern, 2003), but thus far, limited research has been conducted examining the role of reading level (as an estimate of quality of education) in cognitive test performance among HIV-infected individuals. Research conducted among 200 participants in the Manhattan HIV Brain Bank (Ryan et al., 2005) found that African Americans and Hispanics had lower overall reading levels than non-Hispanic Whites, African Americans were more likely to have reading levels significantly discrepant from their reported years of school, and discrepancies between years of school and education had a stronger relationship to neuropsychological test performance than racial/ethnic classification. A study of 113 HIV-infected participants of the National Neurological AIDS Bank (Rohit et al., 2007) found that when cognitive test scores adjusted for reading level were used, they had increased specificity for detection of physician-diagnosed possible or probable MCMD or HIV-associated dementia by over 20% above that of scores corrected for years of education among African Americans. This increase in specificity of reading-level-adjusted scores was accompanied by a decrease in sensitivity as compared to education-adjusted scores (48.4% vs. 61.3%). Among Whites, reading level adjustment did not improve sensitivity or specificity of the measures. Neither of these studies examined the relationship of reading level to test scores among HIV-seronegative individuals.

The primary goal of this study was to determine the normal range of scores on measures of psychomotor...
speed and executive function among ethnically and educationally diverse HIV-uninfected, high-risk women, as well as their HIV-infected counterparts. We sought to compare test performance between HIV-infected and HIV-uninfected women and to determine whether adjustment for age, years of education, racial/ethnic classification, and reading level altered differences between HIV-infected and HIV-uninfected women. This study also describes the methodology used to determine cutoffs that define neurocognitive dysfunction after examining the role of cultural, linguistic, and educational experience on test performance.

METHOD

Population and study design

The Women’s Interagency HIV Study (WIHS) is a multicenter prospective cohort study of the natural history of HIV Type I infection in women who were recruited and evaluated at any of six research sites in New York (Bronx and Brooklyn), California (Los Angeles and San Francisco), Washington DC, and Chicago. In 1994/1995, 2,623 women (2,054 HIV+ and 569 HIV–) were enrolled. In 2001/2002, an additional 1,143 women (737 HIV+ and 406 HIV–) were enrolled into the WIHS. Methods for recruitment and the characteristics of the baseline cohort are described elsewhere (Barkan et al., 1998). The recruitment of the HIV-uninfected women is of particular relevance to the current analyses. HIV-negative women were enrolled if they reported one or more of the following behaviors within the past year: injection drug use; having a sexually transmitted disease; having unprotected sex with three or more men or protected sex with more than five men; or having exchanged sex for drugs, money, or shelter. Participants returned every 6 months for an interview, which included questions about sociodemographic, medical, obstetric, gynecological, and contraceptive history, as well as alcohol, tobacco, and other drug use and sexual behaviors. Plasma, serum, lymphocyte, tissue, genital secretion, and urine samples were collected and stored. The institutional review boards (IRBs) of each of the participating centers approved the protocol, and informed consent was obtained from every participant. The Neurocognition Substudy was initiated in October 2004. Participants who were interviewed in English and provided complete data on the neurocognitive measures, the reading-level measure, and the educational history assessment were eligible for inclusion in the current study.

Measures

Racial/ethnic group

Ethnic group was determined by self-report using the format of the 2000 US Census (United States Office of Management and Budget, 1997). All individuals were first asked to report their race (i.e., American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black or African American, White, or “other race”) and then, in a second question, were asked whether or not they were Hispanic. From this, four racial/ethnic groups were derived: non-Hispanic White, non-Hispanic Black, Hispanic, and “other race.” Women in the “other race” category stated that they were not Hispanic but did not feel that the racial categories listed represented their racial self-identification.

The Wide Range Achievement Test—Version 3 (WRAT–3; Wilkinson, 1993)

English reading level was measured using the Reading Recognition subtest from the WRAT–3. On this test, participants are asked to name letters and pronounce words out of context. A detailed assessment of educational experience was administered, which provides information about educational attainment and clarification of the setting in which education was completed. The following variables were assessed separately for elementary, high-school, and post-high-school phases of education: years completed, age or date of first year attended, location (country, state, rural vs. urban), setting (public vs. private), class size (one-room school or multiroom school), and estimated ethnic composition of student body and teachers. Total years of education is the sum of years completed in elementary, high-school, and post-high-school phases of education, with a minimum of 0 and a maximum of 20. In addition, participants were asked whether they were ever “left back or had to repeat a grade.” Those who did not attain a high-school degree were asked why they left school. As is standard in many normative samples (Heaton et al., 2004; Strauss, Sherman, & Spreen, 2006), women who obtained a GED (general education degree) as a terminal degree were assigned the number of actual years of formal schooling (as opposed to 12 years).

Neuropsychological measures

All participants received neuropsychological tests administered by trained psychometrists using standardized procedures. The Trail Making Test (Parts A and B; Heaton, Grant, & Matthews, 1991; Reitan, 1978) was administered to assess processing speed and cognitive flexibility. Participants were allowed 5 min to complete Trails A and 5 minutes to complete Trails B before the tasks were discontinued. Total time to complete the tests, as well as number of errors, was recorded. If either test was discontinued at 5 min, the correct number of connections made was recorded. The Symbol Digit Modalities Test (SDMT; Smith, 1968) was administered to assess speed of information processing and perceptual motor ability. Score was the total number of boxes that were correctly filled within the time limit of 90 s. An incidental recall condition was added, in which the code table and previous answers were hidden, the nine symbols were shown, and participants were asked to recall the digits that matched the symbols (Demakis, Sawyer, Fritz, & Sweet, 2001;

Data analyses

The distributions of time to complete Parts A and B of the Trail Making Test were somewhat skewed to the right and were therefore log transformed. Errors on Part A of the Trail Making task were quite rare, and presence of errors had no relationship with age or other demographic variables. Because of the extremely skewed distribution of Trails A errors, this variable was dropped from further analyses. Pearson correlation coefficients were calculated for all continuous variables (Spearman’s rho was used to examine Trail Making Test Part B error totals) in the entire sample and then separately among HIV-negative women and among HIV-positive women. The relationships of other demographic variables and cognitive test scores were compared across the four ethnic groups in the entire sample and two serostatus groups using analyses of variance (ANOVAs), and post hoc Tukey’s tests were used to follow up significant overall findings. Trails B errors were compared across all four ethnic groups using a Kruskal–Wallis one-way ANOVA, and Mann–Whitney U tests were used to compare individual ethnic groups in the case of a significant overall test.

A multivariate analysis of variance (MANOVA) was performed in which the normally distributed, raw cognitive test scores (time to complete Trails A and Trails B, log transformed; total correct on the SDMT; and incidental recall score) were dependent variables, and race/ethnicity (non-Hispanic White, non-Hispanic Black, and Hispanic) was the independent variable. We then repeated this analysis in a multivariate analysis of covariance (MANCOVA) controlling for age, years of school, and WRAT–3 score. We compared the F value and significance of the overall effect of race/ethnicity between these two analyses. Logistic regression models were conducted to test the effect of demographic predictors on presence or absence of errors on Trails B.

A MANCOVA was performed to test the effect of serostatus on the four normally distributed test scores after controlling for age, years of school, reading level, and racial/ethnic group (non-Hispanic White, non-Hispanic Black, and Hispanic). In the case of a significant overall effect, post hoc univariate F tests were used to determine which group means differed. Logistic regression models were constructed to determine whether HIV-uninfected and HIV-infected women differed on the presence or absence of errors on Trails B after accounting for age, years of school, WRAT–3 scores, and reference code race/ethnicity.

Finally, we describe the development of normative standards for these cognitive measures in this cohort. All HIV-negative participants were included in the normative sample. Demographically corrected T-scores were developed based on the Heaton et al. (1991) regression method. We developed the norms using two approaches, both using multiple linear regression analyses to obtain normative values. In the first method, we adjusted scores for the influences of age, years of education, reading level, and ethnicity. We designed this first approach to take advantage of all of the measured background variables that may assist in determining “premorbid” level of function. The four cognitive test variables were included as dependent variables in a regression, with age, years of education, WRAT–3 reading subtest total, and ethnicity as predictors. For each of the four regression analyses, we initially included all four predictors in the model, but the final model retained only those variables that significantly contributed to prediction of cognitive test score. The unstandardized beta weights of each of the predictors in the final model, the constant, as well as the standard error, were used to calculate predicted scores on each test. These predicted scores were subtracted from each participant’s actual composite score to calculate residual scores, and z scores were derived according to the formulas:

\[
\text{Predicted score} = \text{Constant} + (\text{Age} \times \beta_{\text{age}}) + (\text{WRAT} \times \beta_{\text{WRAT}}) + (\text{Years of education} \times \beta_{\text{yeduc}}) + (\text{African American status} \times \beta_{\text{AA}}) + (\text{Hispanic status} \times \beta_{\text{Hispanic}})
\]

\[
z \text{ score} = \frac{\text{Predicted score} - \text{Actual score}}{\text{Standard error of the estimate}}
\]

The signs of the z scores for time to complete Trails A and Trails B were reversed, since higher values on these tasks reflect worse performance.

RESULTS

Sample characteristics

A total of 613 HIV-uninfected women and 1,497 HIV-infected women completed at least one cognitive test from the Neurocognitive Substudy. Of these, 172 were evaluated in Spanish and were excluded from the current sample. Among the remaining English-speaking women, 285 were excluded from the current sample because information about educational experience was not collected. The primary reason for missing educational data for most participants (88%) was that they were not seen for the Neurocognitive Substudy during Visit 21, when the one-time educational history questionnaire was introduced. Appendix Table A1 shows that the 285 English speaking women excluded from the study due to missing educational data did not differ from the women included in the analyses with respect to age, HIV status, Trails A and B time, incidental recall, and Trails A errors. There were some small but statistically significant differences between those included and excluded, in that the women who were excluded were more likely to be White (and
less likely to be Hispanic), obtained lower scores on the Symbol Digit task, and were less likely to make errors on the Trails B task. The final sample of 1,653 participants included 511 HIV-negative women and 1,142 HIV+ women. Although most of the women completed the initial evaluation in Visit 21 of the WIHS study (n = 1,282, 77%), because the IRB at two sites did not approve the protocol before the beginning of Visit 21, 363 (22%) did not enter until Visit 22 (04/01/05 to 09/30/05).

An additional 6 (<1%) participants did not enter until Visit 23 (10/30/05 to 3/31/06), and 2 (<1%) entered in Visit 24 (4/1/06 to 9/30/06). Among the women in the final sample, 72 were not administered the English reading-level measure; they were not excluded from the sample but their data could not contribute to our planned analyses involving reading level.

The mean age of final sample was 41.0 years (SD = 9.2 years), and they had an average of 12.0 (SD = 3.0) years of education. The cohort was 63.1% non-Hispanic Black, 21.5% Hispanic, 11.9% non-Hispanic White, and 3.5% “other race.” Table 1 details the demographic characteristics of the sample by HIV status.

Educational experience

All but 4 women (99.8%) reported completing at least one year of school. Of these participants, 88% attended elementary school in the United States. The other 12% of the cohort reported attending elementary school in primarily Caribbean countries (such as Puerto Rico, Jamaica, Trinidad, and Guyana), Mexico and Central America, and Canada, and some in African and European nations.

The most common reasons for discontinuing school reported by women who did not attain a high-school degree were “not liking school,” “had children,” “difficulty learning in school,” and “family problems.” Of the women who attended any school, 17.7% reported that they were left back or failed a grade at least once. Women who reported failing a grade attained approximately one less year of school than women who reported that they never failed a grade (11.0 years vs. 12.3 years), t(1610) = 7.1, p < .001. A total of 21% of the participants reported that they had attained a GED.

Relationship of demographics to raw cognitive test scores

Among the entire sample (HIV-positive and HIV-negative women), the demographic variables had strong relationships with most of the cognitive test scores. Overall, the cognitive test scores were significantly correlated with each other. Women who described themselves as White or “other race” obtained higher scores on the WRAT-3 and the cognitive measures than did African Americans and Hispanics. African Americans and Hispanics rarely differed from each other, with the exception of the SDMT total, where Hispanics obtained higher scores than African Americans. These relationships in the entire group were also present in the HIV-infected subgroup; Whites and “other race” obtained higher scores on the cognitive measures than did African Americans and Hispanics.

The relationships between demographics to raw test scores among HIV-negative women are detailed in Tables 2 and 3, since these relationships serve as the basis of the normative standards for this study. Table 2 shows that, as expected, older women completed the Trail Making task slower and made more errors on the Trails B, and got fewer items correct on the SDMT and the incidental recall task than did younger women. Women with more education and with higher reading level obtained better scores on the cognitive measures than women with lower education and reading level. White and “other race” participants had more years of school, higher WRAT-3 scores, faster performance on the Trail Making tasks with fewer errors, and more correct items on the SDMT than did African American and Hispanic women. Finally, Whites recalled more items on the incidental recall task than did African Americans and Hispanics (who did not differ from each other). The small size of the “other race” group (n = 20) precluded inclusion of these women in the MANCOVAs and regression-based norms, described below.

### TABLE 1

Sample demographics and reading test scores

<table>
<thead>
<tr>
<th></th>
<th>HIV– (N = 511)</th>
<th>HIV+ (N = 1,142)</th>
<th>T, χ², or U</th>
<th>p</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.7 9.9</td>
<td>42.4 8.5</td>
<td>&lt;.001</td>
<td>.020</td>
<td>21</td>
<td>66</td>
</tr>
<tr>
<td>Years of education</td>
<td>12.3 3.0</td>
<td>11.9 3.0</td>
<td>2.3</td>
<td>.035</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>62.6 24.1</td>
<td>63.3 20.4</td>
<td>ns</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Other race”</td>
<td>3.9</td>
<td>3.3</td>
<td>ns</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WRAT reading³</td>
<td>43.6 7.7</td>
<td>43.8 8.0</td>
<td>0.1</td>
<td>ns</td>
<td>15</td>
<td>57</td>
</tr>
</tbody>
</table>

*Note.* WRAT = Wide Range Achievement Test.

³The total N for analyses involving the WRAT was 495 HIV-uninfected and 1,086 HIV-infected participants.
The demographic variables were entered as covariates, age and WRAT–3 score were significant predictors of presence of Trails B errors. After adjusting for age, years of school, and WRAT–3, African Americans (OR = 3.05, 95% CI = [1.34, 6.93]) and Hispanics (OR = 2.46, 95% CI = [1.02, 5.92]) were still more likely to make Trails B errors.

**Effect of HIV serostatus on neuropsychological measures of speed and executive function**

A MANOVA revealed that, overall, HIV-infected women obtained worse scores than HIV-uninfected women on time to complete Trails A and Trails B (log transformed), total correct on the SDMT, and incidental recall score, without correcting for differences in background variables, Wilk's λ(4) = .981, p < .001. HIV status accounted for only 1.9% of the overall variance in overall cognitive test score. Table 4 shows the results of univariate ANOVAs, which revealed significant effects of HIV status on each of the individual cognitive tests. HIV status was unrelated to number of errors on Trails B.

### TABLE 2
Correlations between demographic variables and neuropsychological measures among HIV-negative women

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Years of education</th>
<th>WRAT reading</th>
<th>Trails A time</th>
<th>Trails B time</th>
<th>Trails B errors</th>
<th>SDMT correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of education</td>
<td>−.12**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WRAT–3 reading</td>
<td>−.13**</td>
<td>.37***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails A time</td>
<td>.20***</td>
<td>−.21***</td>
<td>−.22**</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails B time</td>
<td>.27***</td>
<td>−.29***</td>
<td>−.41***</td>
<td>57***</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails B errors</td>
<td>.16***</td>
<td>−.17***</td>
<td>−.28***</td>
<td>.21***</td>
<td>.55***</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>SDMT correct</td>
<td>−.38***</td>
<td>.33***</td>
<td>−.38***</td>
<td>−.49***</td>
<td>−.56***</td>
<td>−.28***</td>
<td>1</td>
</tr>
<tr>
<td>Incidental recall</td>
<td>−.31***</td>
<td>.16***</td>
<td>.19***</td>
<td>−.21***</td>
<td>−.31***</td>
<td>−.17***</td>
<td>.40***</td>
</tr>
</tbody>
</table>

*Note.* WRAT–3 = Wide Range Achievement Test–Third Edition. SDMT = Symbol Digit Modalities Test. Trails A and B times and errors are log transformed for this analysis. Spearman's rho correlations are used for Trail Making Part B errors.

*p < .01, ***p < .001.

### TABLE 3
Relationship of background variables and neuropsychological test scores to race/ethnicity in HIV-negative participants

<table>
<thead>
<tr>
<th></th>
<th>White (N = 48)</th>
<th>African American (N = 320)</th>
<th>Hispanic (N = 123)</th>
<th>Other race (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.0</td>
<td>9.2</td>
<td>10.2</td>
<td>34.0</td>
</tr>
<tr>
<td>Years of education</td>
<td>14.2</td>
<td>3.4</td>
<td>42.7***</td>
<td>43.8***</td>
</tr>
<tr>
<td>WRAT reading</td>
<td>49.0</td>
<td>5.5</td>
<td>7.4</td>
<td>43.5</td>
</tr>
<tr>
<td>Trails A time</td>
<td>3.4</td>
<td>0.3</td>
<td>0.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Trails B time</td>
<td>4.1</td>
<td>0.4</td>
<td>0.4</td>
<td>4.3**</td>
</tr>
<tr>
<td>Trails B errors</td>
<td>0.2</td>
<td>0.5</td>
<td>1.5</td>
<td>0.7**</td>
</tr>
<tr>
<td>Symbol Digit total</td>
<td>52.2</td>
<td>13.4</td>
<td>10.8</td>
<td>46.2**</td>
</tr>
<tr>
<td>Incidental total</td>
<td>6.2</td>
<td>2.5</td>
<td>4.4***</td>
<td>4.4**</td>
</tr>
</tbody>
</table>

*Note.* WRAT = Wide Range Achievement Test. Trails A and B times were log transformed for this analysis. Significance is marked when group mean differed from that of Whites using a Tukey's HSD (honestly significant difference) post hoc test, with the exception of Trails B errors where follow-up Mann–Whitney U tests were conducted.

*p < .05, **p < .01, ***p < .001.

As expected based on the individual mean comparisons, a MANOVA revealed a significant overall effect of race/ethnicity on performance on Trails A and B time, Symbol Digit total correct, and incidental recall among HIV-negative women, Wilk's λ(8) = .900, p < .001. Racial/ethnic group accounted for about 5% of the variance in cognitive test performance (η² = .051). Using a MANCOVA model and entering age, years of school, and WRAT–3 as covariates, the effect of race on cognitive test score was still significant, Wilk's λ(8) = .938, p < .001, although the effect size of race was reduced (η² = .032). The proportions of variance in cognitive test performance accounted for by age (15.0%), years of school (3.3%), and WRAT–3 score (11.6%) were each significant in this model.

The effect of race/ethnicity on presence of Trails B errors was examined separately using logistic regression models, since errors were not normally distributed. African Americans were 4.5 times as likely (odds ratio, OR = 4.5, 95% confidence interval, CI = [2.05, 9.93]) and Hispanics about 3.5 times as likely (OR = 3.59, 95% CI = [1.55, 8.32]) to make errors on the Trails B test than were women who identified as White. When
After age, years of school, WRAT–3 score, and race/ethnicity were accounted for in a MANCOVA model, the effect of HIV status on overall cognitive test performance remained significant, Wilk’s $\lambda(4) = .994$, $p < .05$, even though HIV status accounted for a very small amount (0.7%) of the overall variance. The relative contributions of the demographic variables was much higher than HIV serostatus in this overall model: Age accounted for 10.8% of the variance, while years of school (2.4%), reading level (12.2%), African American race (4.3%), and Hispanic origin (2.9%) all accounted for significant variance in cognitive test performance.

Table 4 shows the $F$ values and effect sizes of HIV status on the individual tests after accounting for the covariates. The effect of HIV infection on SDMT total score remained significant after adjusting for demographic factors. However, there was no effect of HIV infection on time to complete Trails A and Trails B (both log transformed), and incidental recall score was no longer significant after accounting for age, years of school, WRAT–3 score, and race/ethnicity.

### Development of normative data

Four regression models were performed using the four continuous neuropsychological variables as outcomes and the demographic predictors (age, years of education, WRAT–3 score, and reference-coded race/ethnicity among Whites, Blacks, and Hispanic) as predictors among the HIV-uninfected women. The Appendix Table A2 shows the regression coefficients and significance levels for each of the predictor variables when all of the demographic predictors were entered into the models. The final models used to develop normative data, however, retained only those predictors that significantly contributed to prediction of cognitive test score. The final models for Trail Making A and B times and SDMT score all included age, years of education, WRAT–3 score, and African American status as predictors. For SDMT incidental recall, years of education was not a significant predictor but Hispanic status entered into the model. Appendix Table A3 shows the regression coefficients (and significance of those coefficients), constants, and standard error of estimates for the regression equations using each of the cognitive variables as outcomes. These values were used to derive $z$ scores, also shown in Appendix Table A3. For example, using the formula described earlier in the “Data analyses” section and the regression coefficients in Table A3, a 43-year-old African American woman with 11 years of school and a WRAT performance of 39 would have a predicted log-transformed Trails B score of $\log((0.09 \times 43) - (0.018 \times 11) - (0.017 \times 39) + (0.09 \times 1) + 4.949)$, or 4.565. If her actual time to complete Trails B was 178 s (the natural log of 178 is 5.182), her Trails B time $z$ score would be $(-4.565 - 5.182)/3.62 = -1.714$.

### DISCUSSION

This is the first large-scale study to describe demographic influences on two widely used measures of psychomotor speed and executive function among HIV-infected and HIV-uninfected women. Similar to prior studies, we found that demographic factors account for a large amount of variance in cognitive test performance. This work joins the growing number of studies that have found influences of ethnic group (Adams, Boake, & Crain, 1982; Bohnstedt, Fox, & Kohatsu, 1994; Carlson, Brandt, Carson, & Kawas, 1998; Escobar et al., 1986; Fillenbaum, Heyman, Huber, Ganguli, & Unverzagt, 2001; Fillenbaum, Hughes, Heyman, George, & Blazer, 1988; Jacobs et al., 1997; Kuller et al., 1998; Manly et al., 1998a; Mast, Fitzgerald, Steinberg, MacNeill, & Lichtenberg, 2001; Overall & Levin, 1978; Roberts & Hamsher, 1984; Ross, Lichtenberg, & Christensen, 1995; Salmon et al., 1989; Teresi, Albert, Holmes, & Mayeux, 1999; Unverzagt, Hall, Torke, & Rediger, 1996; Welsh et al., 1995) and quality of education (Ardila, Rosselli, & Rosas, 1989; Lecours et al., 1987; Manly et al., 1999; Rosselli, Ardila, & Rosas, 1990; Weiss, Reed, Kligman, & Abyad, 1995) on cognitive test performance among ethnic minorities. The impact of cultural and educational background on neuropsychological test performance is
an important consideration in the diagnosis of disease-related cognitive impairment, where it has been shown that ethnic minorities are more likely to be misdiagnosed as impaired in studies of HIV-related cognitive impairment (Manly et al., 1998b; Miller, Heaton, Kirson, & Grant, 1997; Rohit et al., 2007) and dementia (Manly et al., 1998a). We found that the SDMT remained sensitive to HIV-related differences after adjusting for demographic variables; this is significant since the SDMT and other measures of psychomotor speed were shown to be very sensitive to HIV-related cognitive impairment (Carey et al., 2004; Durvasula, Miller, Myers, & Wyatt, 2001), are associated with poor cognitive outcomes and mortality among HIV-infected individuals (Sacktor et al., 1996), and are sensitive to age-related differences among HIV-infected participants (Sacktor et al., 2007). It is notable that after adjusting for demographic factors, there was no effect of HIV infection on performance on Parts A or B of the Trail Making Test, or the Symbol Digit Intercalated recall. This finding is in contrast to prior reports of the Trail Making Test as sensitive to HIV-related neurocognitive impairment (Applebaum, Otto, Richardson, & Safren, 1997; Selafani et al., 1997).

The results of this study suggest that assessment of cognition and determination of rates of cognitive impairment among HIV-infected and high-risk HIV-uninfected women require appreciation of the relationships between cognitive test performance and factors such as racial/ethnic identification, educational experience, and age. Reading level, as an estimate of quality of education, had the strongest relationship to cognitive test scores, accounting for more variance in cognitive test score than HIV status and years of education, and, in some cases, more than years of age. Although ethnic differences in test scores were not completely accounted for by measures of educational experience, adjustment for these factors did significantly reduce the effect size of race.

The current results regarding reading level are consistent with prior studies in other primarily male cohorts (Rohit et al., 2007; Ryan et al., 2005). The advantage of the current study over this prior work is the availability of a large, risk-factor-matched group of HIV-uninfected women in which to examine the relationships of demographic factors such as reading level to cognitive test performance in order to establish normative standards. One limitation of the current study is that unlike the National Neurological AIDS Bank study (Rohit et al., 2007), a physician-determined cognitive diagnosis independent of the neuropsychological evaluation was unavailable, and thus sensitivity and specificity of our measures could not be established.

Although there were very few neuropsychological measures administered in this introduction of cognitive measures to the WIHS project, these analyses highlight the clear need to correct for demographic variables when developing norms for cognitive impairment in HIV. In addition, if the focus of investigation is the influence of HIV infection on cognitive function, the current study demonstrates that the HIV-uninfected comparison group must be from the same risk group as HIV-infected individuals. Use of a normative group matched on ethnicity and education alone would not sufficiently isolate the effect of HIV on cognition due to other comorbidities that may accompany HIV infection among women (Durvasula et al., 2001; Richardson et al., 2005). A cohort of HIV-uninfected women within a risk group matched to the HIV-infected group is one of the major resources provided by the WIHS study. The norms that were developed in this study will allow for comparisons across time and allow for evaluation of additional risks for cognitive impairment associated with other HIV-related conditions.

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REFERENCES


APPENDIX

### TABLE A1
Comparison of demographics and neuropsychological test scores between English-speaking study participants and women excluded from study due to missing educational experience data

<table>
<thead>
<tr>
<th></th>
<th>Excluded (n = 285)</th>
<th></th>
<th>Included (n = 1,653)</th>
<th></th>
<th>χ²</th>
<th></th>
<th>F</th>
<th></th>
<th>Mann–Whitney U</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>M</td>
<td>SD</td>
<td>%</td>
<td>M</td>
<td>SD</td>
<td></td>
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<tr>
<td>Race/Ethnicity</td>
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<td></td>
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<tr>
<td>White</td>
<td>16.8</td>
<td>11.9</td>
<td>5.117*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>African American</td>
<td>63.5</td>
<td>63.1</td>
<td>0.018</td>
<td></td>
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<td>Hispanic</td>
<td>15.1</td>
<td>21.5</td>
<td>6.582*</td>
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<td></td>
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<tr>
<td>Other</td>
<td>4.6</td>
<td>3.5</td>
<td>0.719</td>
<td></td>
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<tr>
<td>HIV seropositive</td>
<td>68.8</td>
<td>69.1</td>
<td>0.011</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Seen at Visit 21</td>
<td>11.2</td>
<td>77.6</td>
<td>474.935***</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age (years)</td>
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<tr>
<td></td>
<td>41.9</td>
<td>9.0</td>
<td>2.291</td>
<td></td>
<td></td>
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<tr>
<td>Trails A timea</td>
<td>39.2</td>
<td>17.8</td>
<td>0.096</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Trails B timea</td>
<td>92.2</td>
<td>43.9</td>
<td>0.742</td>
<td></td>
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<tr>
<td>Symbol Digit total</td>
<td>40.3</td>
<td>14.4</td>
<td>8.321*</td>
<td></td>
<td></td>
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<tr>
<td>Incidental recall</td>
<td>4.36</td>
<td>2.777</td>
<td>0.257</td>
<td></td>
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<td>Trails A errors</td>
<td>0.21</td>
<td>0.55</td>
<td>229,233.0</td>
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<tr>
<td>Trails B errors</td>
<td>0.72</td>
<td>1.32</td>
<td>193,923.5*</td>
<td></td>
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</tr>
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</table>

a Unadjusted means are displayed, but log-transformed scores were used in the statistical comparisons.
*p < .05.  **p < .01.  ***p < .001.

### TABLE A2
Regression coefficients for the initial regression models among the normative sample of HIV-uninfected women

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Years of education</th>
<th>WRAT–3</th>
<th>African American</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trails A timea</td>
<td>0.006***</td>
<td>-0.012*</td>
<td>-0.005*</td>
<td>0.161*</td>
<td>0.096</td>
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<tr>
<td>Trails B timea</td>
<td>0.009***</td>
<td>-0.016*</td>
<td>-0.017***</td>
<td>0.175*</td>
<td>0.117</td>
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<tr>
<td>Symbol Digit total</td>
<td>-0.361***</td>
<td>0.643***</td>
<td>0.360***</td>
<td>-4.192**</td>
<td>-1.792</td>
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<tr>
<td>Incidental recall</td>
<td>-0.088***</td>
<td>0.043</td>
<td>0.045*</td>
<td>-1.114*</td>
<td>-1.439*</td>
</tr>
</tbody>
</table>

a Log-transformed scores were used.
*p < .05.  **p < .01.  ***p < .001.

### TABLE A3
Regression coefficients, constants, and standard errors for the final, pared-down regression models and z scores for the normative sample of HIV-uninfected women

<table>
<thead>
<tr>
<th></th>
<th>Regression coefficient</th>
<th>z score</th>
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<tbody>
<tr>
<td></td>
<td>Age</td>
<td>Years of education</td>
</tr>
<tr>
<td>Trails A timea</td>
<td>0.006***</td>
<td>-0.014*</td>
</tr>
<tr>
<td>Trails B timea</td>
<td>0.009***</td>
<td>-0.018*</td>
</tr>
<tr>
<td>Symbol Digit total</td>
<td>-0.360***</td>
<td>0.678***</td>
</tr>
<tr>
<td>Incidental recall</td>
<td>-0.089***</td>
<td>0</td>
</tr>
</tbody>
</table>

a Log-transformed scores were used.
*p < .05.  **p < .01.  ***p < .001.