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Estimating premorbid IQ in the prodromal phase of a neurodegenerative disease

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Abstract

Estimates of premorbid intellect are often used in neuropsychological assessment to make inferences about cognitive decline. To optimize the method of controlling for premorbid intellect in assessments of prodromal neurodegenerative disease, we examined performance on the American National Adult Reading Test (ANART; administered during Years 1 and 3) and the two-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI; administered in Years 2 and 4) in an ongoing prospective longitudinal study of 371 participants with prodromal Huntington disease and 51 participants with normal CAG repeats. Although both measures performed similarly, the ANART demonstrated slightly lower variability in performance over a two-year period and had slightly higher test-retest reliability than the WASI.

Keywords

premorbid IQ; intelligence; neuropsychological assessment; assessment; Huntington disease; prodromal neurodegenerative disease

Neuropsychological test performance is known to be associated with intellectual ability (Diaz-Asper, Schretlen, & Pearlson, 2004). In persons with disease or brain injury, assessment of cognition typically considers a person's original intellectual endowment, or their premorbid intellect (e.g., Watt & O'Carroll, 1999). Specifically, this original intellectual endowment, or premorbid intellect, is not impacted by age, education, or gender and provides an estimation for premorbid level of functioning (for a review see Kleges,

Wilkening, & Golden, 1981). Therefore, estimations of premorbid intellect/premorbid functioning are essential to neuropsychological test interpretation in order to determine the extent of intellectual changes due to neurological insult.

In this manner, clinically significant changes due to neurological damage can be determined by examining current test performance relative to estimations based on premorbid intellect (e.g., O'Carroll, 1995). Many clinicians utilize tests thought to be resilient to changes associated with a neurological insult (a.k.a., "hold measures") in order to estimate premorbid intellect (e.g., word pronunciation measures or brief measures of IQ; Wechsler, 1958). Although this approach is appropriate for estimating intellectual functioning in normal individuals over the life span, the fact that many of these measures are not necessarily "resilient" to neurological insult challenges their applicability in individuals with neurological disturbance (for review, see Franzen, Burgess, & Smith-Seemiller, 1997).

The most common methods of premorbid function estimation include demographic based approaches (e.g., Barona, Reynolds, & Chastin, 1984), best current performance (e.g., Lezak et al., 2004), reading ability (Willshire, Kinsella, & Prior, 1991), achievement measures (e.g., Baade & Schoenberg, 2004), or a combination of these approaches to create algorithms that estimate premorbid functioning (e.g., Lange, Schoenberg, Chelune, Scott, & Adams, 2005; Schoenberg, Scott, Duff, & Adams, 2002). Regardless of the number of different approaches, clinicians and researchers still grapple with the difficulties associated with estimating premorbid intellectual assessment. For researchers, questions regarding measurement and covariate selection are often central to study design and data analysis. For example, in studies of persons with brain damage or disease, covarying for premorbid intellect (i.e., using IQ scores as an estimate for "g") may also remove variance associated with the disease process itself, making it more difficult to detect disease-related differences in cognitive performances. This is a particularly difficult problem when studying conditions with relatively subtle cognitive changes, such as early neurodegenerative disease (i.e., mild cognitive impairment or cognitive declines prior to clinical diagnosis in people with the Huntington disease CAG expansion; Duff et al., 2010). To our knowledge, the question of whether estimates of premorbid functioning (such as premorbid IQ measures) are affected when individuals are in the prodromal phases of neurological diseases—prior to disease—diagnosis has not been addressed.

Huntington disease (HD) is an autosomal dominant disease which typically manifests in middle adulthood. Individuals with the CAG expansion that causes HD typically appear neurologically normal throughout adolescence and early adulthood but gradually develop motor, cognitive, and psychiatric disturbances, often leading to diagnosis during their early 40s, with higher CAG numbers conferring earlier onset. Common cognitive difficulties in HD include difficulties in attention, fluid intelligence, verbal fluency, learning and memory, visuospatial function, and executive function (for review see Paulsen & Conybeare, 2005). Premorbid IQ estimates using word pronunciation or brief traditional measures of IQ have both been shown to be affected in diagnosed HD (Crawford, Parker, & Besson, 1988; O'Rourke et al., 2011), thus making it complicated to disentangle the effects of original intellectual endowment and ongoing disease processes in cognitive performance. It is unclear whether these findings generalize to the prodromal phase of HD (i.e., individuals that have the HD CAG expansion, but who do not yet meet criteria for diagnosis; Paulsen et al., 2008).

This study used two possible "hold" measures used to estimate premorbid intellect: a word pronunciation test and an abbreviated IQ measure. Word pronunciation lists, such as the American National Adult Reading Test (ANART; Grober & Sliwinski, 1991) and the Test of Premorbid Functioning (Wechsler, 2009), are thought to provide an estimate of

vocabulary set size (Nelson & O'Connell, 1978) and appear to be relatively immune to neurological decline (Willshire, Kinsella, & Prior, 1991). Abbreviated IQ measures, or shortened versions of more "standard" IQ tests, include the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) and the Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman, 1990). Although these abbreviated IQ measures (relative to word pronunciation estimates) were not specifically designed to be immune to neurological disease (or to be used as "hold" measures), they may yield a better estimate of what an individual would have obtained on a full IQ test if there has been no significant change from premorbid functioning.

Direct comparisons between tests of word pronunciation and abbreviated IQ measures suggest that pronunciation-based instruments may be more resilient to the effects of the disease process than abbreviated IQ tests (Crawford et al., 1988; Hart et al., 1986). In particular, there are a number of studies that have found word pronunciation-based measures to be more resilient to the effects of dementia than abbreviated IQ tests (e.g., Bright, Jaldow, & Kopelman, 2002). While these findings suggest that word pronunciation measures may provide a better estimate of premorbid intellect than abbreviated measures for individuals with neurological insult, these word pronunciation estimates are not resilient to neurological insult. Specifically, studies have suggested that word pronunciation measures are affected in individuals with dementia (including in HD-related dementia; Crawford et al., 1988) relative to controls (e.g., Taylor et al., 1996). As further evidence that these measures are not entirely robust in dementia, longitudinal studies in dementia indicate that word pronunciation-based estimates decline over time (e.g., Cockburn, Keene, Hope, & Smith, 2000).

Brief IQ estimates (such as the WASI) rely on both expressive vocabulary and visuospatial functioning. Expressive vocabulary is more likely to be resistant to neurological declines and the negative effects often found on cognitive performance with aging (e.g., Heaton, Taylor, & Manly, 2003; Schroeder & Salthouse, 2004). Therefore, measures that rely on expressive vocabulary are strong candidates for use as a hold measures in populations with known cognitive declines. On the other hand, the inclusion of a visuospatial-based estimate of performance may be less appropriate as a hold measure because of the known declines in visuospatial performance in neurological disease (e.g., Levin et al., 1991) and normal aging (e.g., Heaton et al., 2003; Schroeder & Salthouse, 2004). Therefore, brief IQ estimates are most appropriate as hold measures when visuospatial decline is not yet present (or expected). To summarize, both brief and word pronunciation-based IQ estimates appear to be useful as hold measures, although neither is resilient to the effects of neurological insult. Regardless, word pronunciation-based estimates may be a better alternative (than brief estimates) for estimating premorbid IQ in neurodegenerative disease (e.g., Paque & Warrington, 1995).

For this project, we examined a word pronunciation-based measure (the ANART) and an abbreviated IQ measure (the two-subtest version of the WASI) for their suitability as "hold" measures in a large sample of individuals with prodromal HD (from individuals with the dominant gene mutation for HD but without clinically significant symptoms) from PREDICT-HD, a 32-site longitudinal study (Paulsen et al., 2006). Initially, only the ANART was included in the PREDICT-HD test battery as an estimate of premorbid functioning due to its brevity (Visit 1). After data collection began, concerns were raised regarding the small normative base for the ANART. Therefore the team decided to implement a multimodal approach for premorbid functioning estimation and added a second measure that provided much more extensive normative data, the two-subtest WASI (Visit 2). To determine suitability of two candidate tests as "hold" measures, we examined data longitudinally to determine whether either or both of the tests showed evidence of stability, which is a key

characteristic of a good “hold” measure. To do so, we examined test stability over time, including relationships between test performance and disease progression, test-retest reliability and standard error of performance. Secondly, we examined how performance on these candidate tests related to other factors with known relationships to cognitive test performance, including age, education, gender, and test site location. We also examined performance at baseline to determine if there were differences in estimates for prodromal HD groups that were identified as nearer to clinical diagnosis than those who were farther from clinical diagnosis. We hypothesized that our word pronunciation-based estimate, the ANART, would provide a more robust estimate of premorbid intellect because it is less demanding in terms of visuospatial and executive functions, better test stability, and weaker relationships with factors known to influence test performance (i.e., age, education, gender, and test site location), than our abbreviated IQ measure, the two-subtest WASI.

Method

Participants

We included all PREDICT-HD study participants who had completed both the ANART and the two-subtest WASI at the time of data analysis for this paper. The sample included a total of 422 participants: 371 participants with the HD CAG expansion who were not diagnosed with HD (prodromal HD) and 51 with normal CAG repeat length but a family history of HD (“at risk” control group). Participants were tested annually, and all participants completed a two-year follow-up; participants completed the ANART at Visits 1 and 3, and the two-subtest WASI at Visits 2 and 4. Inclusion criteria required participants to have undergone previous voluntary genetic testing for the presence of the CAG expansion in the HD gene. Exclusion criteria included: clinical evidence of unstable medical or psychiatric illness (participants with stabilized conditions were able to be included in this study); alcohol or drug abuse within the previous year; learning disability or mental retardation requiring special education; history of other central nervous system disease or event, such as seizures or head trauma; pacemaker or metallic implants; age less than 18 years; prescribed antipsychotic medications within the past six months; and use of phenothiazine-derivative anti-emetic medications for at least three months (these medications could subdue motor abnormalities which is the method used to diagnose HD). Other prescribed, over-the-counter and natural remedies were not restricted.

Participant Characterization

CAG repeat numbers were validated using polymerase chain reaction (PCR). Based on these results, participants were designated as either prodromal HD (CAG length ≥ 36) or controls. We estimated the proximity to diagnosis of HD for each prodromal HD participant based on current age and CAG repeat length as per the formulas described by Langbehn, Brinkman, Falush, Paulsen, and Hayden (2004). This weighted formula is based on the inverse relationship between CAG repeat number and age of clinical symptom onset (CAG repeat number typically accounts for between 50 and 60% of the variance in this estimation). At baseline, 135 participants were classified as far from estimated clinical diagnosis (far; > 15 years), 138 as midway to estimated clinical diagnosis (mid; 9–15 years), and 98 near to estimated clinical diagnosis (near; < 9 years). At follow-up, participants were reclassified both using the formulas cited above, as well as using a standardized neurological examination (UHDRS; Huntington Study Group, 1996) to determine if motor abnormalities demonstrated unequivocal signs of HD ($\geq 99\%$ confidence) and thereby justified classifying the participant as having a clinical diagnosis of HD. A breakdown of participant group membership by study visit is included in Table 1.

Preliminary analyses did not indicate significant group differences for education, $F(3, 418) = 0.97, p = .40$, gender ($\chi^2 = 1.63, p = .65$), or region of testing (either USA, Australia, or Canada; $\chi^2 = 1.04, p = .98$; see Table 2). As expected, significant differences were seen for age (as age is used to calculate proximity to clinical diagnosis), with individuals who are far from diagnosis being younger than any of the other groups, $F(3, 418) = 15.18, p < .0001$. Further, previously published findings in this sample indicate that approximately 40% of our prodromal HD participants would meet criteria for mild cognitive impairment (i.e., performance on tests of episodic memory, processing speed, executive functioning was at least 1.5 standard deviations below the mean of the comparison group; Duff et al., 2010).

Measures

Word pronunciation based estimate of premorbid functioning—The ANART (Grober & Sliwinski, 1991) was administered at a two-year interval (visits 1 and 3) at our sites in Canada, Australia, and the United States. The ANART is a 50-word test that examines the pronunciation of phonetically-irregular words thought to provide an index of the size of a person's vocabulary (Lezak et al., 2004). Test administration time is generally less than 5 minutes. Due to the multi-site nature of our study and the subjectivity of evaluating pronunciation accuracy, all examiners were required to audiotape ANART administrations for central scoring. Once examiner's scores were within 2 points of our objective criteria on their last three assessments, their scores were accepted without review; however, in all cases, the summation of correct responses was double checked by a single person at central scoring (B.A. staff person supervised by a Ph.D. level neuropsychologist). For the purposes of this study, we examined the number correct on the ANART (note these raw scores were converted to standard scores using the control participants' normative data to enable cross test comparisons¹).

Brief Estimate of IQ—We administered the two-subtest version of the WASI (Wechsler, 1999) to all participants at a two-year interval (visits 2 and 4). The WASI Vocabulary subtest is a measure of expressive vocabulary, word knowledge, and fund of information that is similar to the WAIS-III Vocabulary subtest. To assure scoring consistency of items on the Vocabulary test, which has some subjective elements, examiners were asked both to record responses verbatim and to audiotape all responses. All responses and scores were double checked by a single person at central scoring (B.A. staff person supervised by a Ph.D. level neuropsychologist). The WASI Matrix Reasoning subtest requires the participant to complete 35 trials depicting a series of abstract gridded patterns by selecting the missing portion of the pattern from five possible response choices. This subtest is a measure of nonverbal fluid reasoning, problem solving ability and general intellectual ability that is similar to the WAIS-III Matrix Reasoning subtest. All responses were double checked by central scoring. For the purposes of this study, we examined raw scores on WASI Vocabulary and WASI Matrix Reasoning, as well as two-subtest WASI Combined subtest scores (note these raw scores were converted to standard scores using the control participants' normative data to enable cross test comparisons). Combined test administration time for WASI Vocabulary and Matrix Reasoning is approximately 15 minutes.

Statistical Analyses

We conducted a multivariate mixed model to examine the relationship between clinical group (control, near, mid, far) and premorbid functioning estimate change over time (standard score conversions for ANART total correct; standard score conversions for raw scores from WASI Vocabulary and WASI Matrix Reasoning subtests; standard score

¹Controls were selected as the normative sample because manualized norms for both the ANART and the WASI included different corrections. Specifically, the WASI controls for age, while the ANART controls for both age and education.

conversions for two-subtest WASI Combined scores) while controlling for age, gender, education, and testing region. This model evaluates both within group differences, as well as between group differences. For these analyses, we considered performance across groups defined by estimated time to diagnosis broken down into participants far from diagnosis (> 15 years), midway to diagnosis (9–15 years), near to diagnosis (< 9 years), and those who have received a formal HD research diagnosis by UHDRS diagnostic confidence rating of > 99%. The main variables of interest were the mean two-year change in IQ test performance (either ANART, WASI Matrix Reasoning, or WASI Vocabulary) between prodromal HD groups and control participants. Each IQ measure was administered every two years and sample sizes included all prodromal HD participants without baseline diagnosis who had at least one follow-up visit. For all measures, data from 371 prodromal HD (with a two-year follow-up) and 51 control participants were analyzed (of these participants 248 had a four-year follow-up). Because individuals' estimated time to clinical diagnosis is constantly changing² (see Table 1), any longitudinal analysis needs to take this change into account. In other words, HD group membership is time-dependent; for example, if a participant is classified in the “near” group at visit 2 and then received a research diagnosis of manifest HD at visit 4, this conversion would be reflected in the analyses, with the scores at visit 2 contributing to the “near” group estimates and those at visit 4 to the “diagnosed” group estimates. A Toeplitz covariance structure was used to model within subjects' dependencies of change scores. Satterthwaite approximation was used to estimate degrees of freedom in all F- and *t*-tests on the longitudinal analysis (Brown & Prescott, 1999)³. There was no evidence of a violation of the assumptions of linearity, constant variance, and normality.

We also conducted a series of analyses of covariance (ANCOVAs) to determine if baseline premorbid functioning estimates (standard score conversions for ANART total correct; standard score conversions for raw scores from WASI Vocabulary and WASI Matrix Reasoning subtests; standard score conversions for two-subtest WASI Combined scores) differed by clinical group status (control, near, mid, far) after controlling for age, gender, education, and testing region. For these analyses, we considered performance across groups defined by estimated time to diagnosis broken down into participants far from diagnosis (> 15 years), midway to diagnosis (9–15 years), near to diagnosis (< 9 years), and those who have received a formal HD research diagnosis by UHDRS diagnostic confidence rating of > 99%. The ANCOVA examining ANART IQ estimates included data from 371 prodromal HD and 51 control participants, whereas the ANCOVAs examining WASI estimates included data from 353 prodromal HD and 51 control participants.⁴ Examination of residual diagnostic plots for each measure showed that the assumptions of linearity, constant variance, and normality were satisfied.

Results

An examination of the interrelationships among measures of interest and demographic variables indicated that all measures of premorbid intellect were significantly related to education for prodromal HD participants (all Pearson correlation $ps < .0001$; see Table 2). In addition, for prodromal HD participants, all premorbid IQ measures, except two-subtest WASI Combined scores, were significantly related to age (all Pearson correlation $ps < .001$; see Table 2). Further, prodromal HD males had higher scores than females for WASI Matrix Reasoning, $t(369) = 1.836, p = .01$, and two-subtest WASI Combined scores, $t(369) = -2.51, p = .01$; no gender differences were seen for prodromal HD participants on either ANART or WASI Vocabulary scores. For controls, better WASI Matrix Reasoning

²This estimate is based on CAG repeats, which is stable, and age, which is constantly changing.

³Please note that these models account for varying sample sizes across covariates.

⁴Please note that these analyses account for varying sample sizes across covariates.

performance was significantly related to younger age and better two-subtest WASI Combined scores were significantly related to more education ($ps < .01$; see Table 2). No gender differences were seen for control participants on any of the premorbid functioning measures. Reliability coefficients between ANART and education ($z = 2.71, p = .003$), and WASI Vocabulary and education ($z = 1.7, p = .04$) indicated stronger relationships for prodromal HD than controls. This suggests that the relationship between greater education and better ANART or WASI Vocabulary performance is stronger for individuals with prodromal HD than it is for controls. Reliability coefficients between WASI Matrix Reasoning and age ($z = 2.05, p = .02$) indicated stronger relationships for controls than HD participants (note that the z score is a reflection of group differences in the strength of the correlation). This suggests that the relationship between greater education and better WASI Matrix Reasoning performance is stronger for controls than it is for individuals with prodromal HD.

Word Pronunciation Based Premorbid Functioning Estimate

Longitudinal analysis—The analysis of the overall effect of groups yielded a significant result for longitudinal change in ANART scores, $F(4, 417) = 4.11, p = .0028$. Analyzing the trends within different groups, it was noted that although controls' task performance over time indicated a practice effect on the ANART (.09 z for the two-year period, $t = 4.34, p < .0001$), the prodromal HD groups' ANART performance did not indicate significant changes over time (far: $t = 0.68, p = .49$; mid: $t = 2.00, p = 0.047$; near: $t = 1.56, p = .12$; diagnosed: $t = 1.04, p = .30$; see Table 3 for estimates of two-year change). Analysis comparing groups revealed significant greater change over time for control participants compared to far ($p < .0001$), mid ($p = .014$), near ($p = .008$), and diagnosed groups ($p = .012$). Analysis of covariates (age, gender, education, and region of testing) did not show any significant effects.

Baseline analysis—The ANCOVA did not indicate baseline clinical group differences on ANART IQ estimates and clinical group status, $F(3, 421) = 1.76, p = .15$; partial $r^2 = .30$.

Brief IQ Based Estimates

Longitudinal analysis—Analysis over time did not yield significant results for WASI Matrix Reasoning, $F(4, 412) = 2.13, p = .08$, WASI Vocabulary test performance, $F(4, 412) = 0.73, p = .57$, or two-subtest WASI Combined scores, $F(4, 412) = 1.83, p = .12$ (see Table 3 for estimates of two-year change). Analysis of covariates (gender, education, and region of testing) showed regional differences for change scores for WASI Vocabulary test performance, $F(2, 412) = 6.08, p = .0025$, and for change scores for two-subtest WASI Combined scores, $F(2, 412) = 4.99, p = .007$. For WASI Vocabulary, there was no evidence for change over time in scores for participants in Australia, but there was evidence for decline for participants in Canada and the United States. For two-subtest WASI Combined scores there was no evidence for change over time in scores for participants in Australia or Canada, but there was evidence for decline for participants in the United States.

Baseline analysis—Our series of ANCOVAs identified significant relationships between WASI IQ estimates and clinical group status (WASI Vocabulary: $F(3, 403) = 7.98, p < .0001$; WASI Matrix Reasoning: $F(3, 403) = 2.84, p = .038$; two-subtest WASI Combined scores: $F(3, 403) = 8.61, p < .0001$). Specifically, individuals that were near to diagnosis had significantly lower WASI Vocabulary ($t = -4.25, p < .0001$; partial $r^2 = .37$), WASI Matrix Reasoning ($t = -2.19, p = .03$; partial $r^2 = .18$), and two-subtest WASI Combined estimates ($t = -4.26, p < .0001$; partial $r^2 = .34$) than controls.

Test-retest reliability was highest for the ANART (see Table 4). Statistical comparison of test-retest reliability coefficients between prodromal HD and control participants did not indicate differences for any of our premorbid intellect estimates (Fisher r -to- z transformation: $z = .52$, $p = .30$ for ANART; $z = .89$, $p = .19$ for WASI Vocabulary; $z = -.51$, $p = .31$ for WASI Matrix Reasoning; $z = .89$, $p = .19$, for two-subtest WASI Combined scores). In addition, statistical comparison of ANART test-retest reliability coefficients versus each WASI estimate reliability coefficient (WASI Vocabulary, WASI Matrix Reasoning, and two-subtest WASI Combined estimate test-retest reliability coefficient) indicated that ANART test-retest reliability was higher than any of the WASI estimates for both prodromal HD participants (Fisher r -to- z transformation: $z = 6.03$, $p < .0001$ for WASI Vocabulary and two-subtest WASI Combined scores; $z = 12.33$, $p < .0001$ for WASI Matrix Reasoning) and control participants (Fisher r -to- z transformation: $z = 2.46$, $p = .007$ for WASI Vocabulary and two-subtest WASI Combined scores; $z = 3.68$, $p = .0001$ for WASI Matrix Reasoning).

Discussion

Although all of our selected measures may be useful as ‘hold’ measures, the ANART offered advantages over the other estimates (see Table 5), particularly for individuals who are nearer to clinical HD diagnosis. Specifically, the ANART demonstrated smaller variability in performance over a two-year period (as evidenced by smaller SE estimates) and higher test-retest reliability than the other estimates (although reliability estimates were acceptable for all measures). Further, the ANART did not differ across groups at baseline and has a shorter test administration time than all of the other estimates.

Prodromal HD groups performed differently than controls. In particular, control participants had statistically, although not clinically, significant improvements over time while prodromal HD groups did not show any significant change over time. Group differences are consistent with Crawford and colleagues (1988) findings, but are not large enough to suggest that the ANART is not an adequate “hold” measure for either control (since the improvements in performance were not clinically significant) or prodromal HD participants (who did not exhibit declines in performance over our 2-year time frame). In addition, cross-sectional findings indicated that individuals with prodromal HD that are nearer to clinical diagnosis demonstrate lower performance on both WASI Vocabulary and WASI Matrix Reasoning than control participants, but these differences were small (those near to clinical diagnosis had approximately three more incorrect items on WASI Vocabulary and two more incorrect items on WASI Matrix Reasoning than controls). This finding is consistent with previous work indicating declines in premorbid estimates in mild and moderate HD (O’Rourke et al., 2011), as well as work that indicates that there are declines on “hold” measure performance in individuals with neurological insult (for review, see Franzen, Burgess, & Smith-Seemiller, 1997). Taken together, findings suggest that although the ANART might be a better choice among the four, any of these measures would be appropriate as a “hold” measure in individuals in the prodromal phase of a progressive neurological disease, but that NONE of these measures appear to “hold” once criteria for clinical diagnosis are met. Specifically, the ability to control for background variance in premorbid intellect outweighs the small amount of statistical bias that may be introduced by statistical control of premorbid IQ. Future research is warranted to determine the point during the disease process where the bias that is introduced by statistically controlling for premorbid IQ will outweigh the benefits of controlling for the background variance that is introduced in test performance.

Further, although our overall recommendation would be the ANART as a measure of premorbid intellect, it is also important to consider some additional factors that may

influence the generalizability of findings. It may be important to appreciate the relationships that each of these measures have with other factors that have known relationships with cognitive test performance. For example, the fact that higher levels of education were associated with better performance on all three premorbid IQ estimates is both consistent with previous research and will likely not influence test selection among these measures (for review, see Mayer, 2000). In contrast, there are gender effects (with men performing better than women) on both WASI Matrix Reasoning and two-subtest WASI Combined scores, but not on ANART and WASI Vocabulary. This is consistent with research that demonstrates that men often do better on nonverbal visuospatial tasks than women (Witelson & Swallow, 1988). If gender is a key measure of interest in a clinical study, then this factor should be considered when choosing an assessment measure. Finally, for studies spanning different regions of the world, it is also important to recognize that in this study, scores on WASI Vocabulary declined over time for individuals in the US and Canada, but not for people in Australia, and that two-subtest WASI Combined scores declined for participants in the United States but not for participants in Australia or Canada; whereas ANART performance didn't vary by testing region. These findings are not surprising given the complexities associated with regional differences in language (i.e., word pronunciation or usage) that may be influencing test performance (Lezak et al., 2004).

While findings highlight the relative strengths and weaknesses of using these “hold” measures in prodromal HD, it is unknown whether the findings reported here will generalize to groups with lower levels of education, as the PREDICT-HD cohort includes individuals with average to above average levels of education.⁵ Further, a methodological limitation of our study was that the ANART was administered about 12 months before the two WASI subtests. This occurred because our study was longitudinal, and we added the WASI for year two of the study. Thus, there may be bias for two-subtest WASI IQ estimates to be lower due to disease progression over this 12 month period. The absence of differences in our multivariate mixed model does not support this, however, so the difference in test administration does not explain our findings. Another limitation is that we based normative data on 51 controls, which is smaller than what is typically utilized to calculate normative data.

It is also important to recognize the weaknesses inherent in the premorbid IQ estimates themselves. In particular, the ANART is composed of words that rely on the pronunciation of irregular words that are dependent on reading, and are therefore less appropriate for use in individuals with low education (Johnstone, Slaughter, Schopp, McAllister, Schwake, & Luebbering, 1997). There is also some evidence to suggest that the two-subtest WASI may not always provide “desirable accuracy” (within a 6-point error margin) in predicting actual IQ scores (Axelrod, 2002). Further, both the ANART and the Vocabulary subtest of the WASI are in English, and are therefore not appropriate for use in countries where English is not the primary language.

It is frequently a limitation in premorbid assessment research that there is rarely a “true” premorbid measure of functioning (e.g., assessments of functioning that we can say with 100% certainty, precede the disease process). In addition, other studies have documented that most so-called “premorbid” measures are not truly “resilient” (e.g., Franzen, Burgess, & Smith-Seemiller, 1997). Future studies might also wish to consider the new Wechsler Test of Premorbid Functioning as an additional alternative for assessing premorbid function.

In conclusion, our findings suggest that while all four of our premorbid IQ estimates appear to perform similarly, the ANART is slightly more robust than the two-subtest WASI for

⁵In general, individuals choosing to undergo gene testing typically have average to above average education (Quaid & Morris, 1993).

assessing and controlling individual differences associated with IQ in prodromal HD. Importantly, however, the two-subtest WASI is also a reasonable method for doing so. Although all measures of IQ in this study had small relationships with demographic and regional variables, the bias induced by statistical control is preferable to not accounting for background variance in premorbid intellect.

More research is needed to confirm the reliability of these measures for assessing premorbid IQ in other populations. Given these findings in prodromal HD, other diseases with known prodromal phases, such as Alzheimer's disease and Parkinson's disease, may also benefit from using the ANART as a preferred method for estimating premorbid intellect. In addition, future work might examine the utility of using the two-subtest WASI and ANART to create an algorithm to predict premorbid IQ in prodromal HD; such work would build upon previous work using similar approaches in other neurological disorders (e.g., Lange et al., 2005; Schoenberg et al., 2002).

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Table 1

Participant group membership by study visit

Study Visit	Controls	Prodromal HD			HD Clinical Diagnosis	
		Far	Mid	Near		
Year 1 (ANART Visit 1)	51	135	138	98		0
Year 2 (two-subtest WASI Visit 1)	51	122	122	109		18
Year 3 (ANART Visit 2)	51	109	114	105		42
Year 4 (two-subtest WASI Visit 2)	51	99	106	109		54

Note. HD = Huntington disease; Far = far from estimated clinical diagnosis (> 15 years); Mid = midway to estimated clinical diagnosis (9–15 years); Near = near to estimated clinical diagnosis (< 9 years); ANART = American National Adult Reading Test; WASI = Wechsler Abbreviated Scale of Intelligence.

Table 2

Baseline demographic information and summary information for performance on the American National Adult Reading Test (ANART; Visit 1) and the two-subtest Wechsler Abbreviated Scale of Intelligence (WASI; Visit 2).

Group	N	Control	Far	Mid	Near
Total Participants		51	135	138	98
<hr/>					
Age	<i>M</i>	42.9	37.6 [†]	43.3	45.9
	<i>SD</i>	9.9	8.1	10.2	10.9
	<i>range</i>	27.0–62.6	30.0–58.8	26.6–72.9	26.0–75.9
<hr/>					
Education	<i>M</i>	15.1	14.7	14.4	14.5
	<i>SD</i>	2.4	2.6	2.8	2.6
	<i>range</i>	9–20	9–20	8–20	8–20
<hr/>					
Gender	% female	62.8	65.4	62.9	57.1
<hr/>					
Region of Testing	USA	32	87	84	63
	Canada	9	24	25	19
	Australia	10	24	29	16
<hr/>					
ANART number correct	<i>M</i>	33.9	34.2	33.1	32.8
	<i>SD</i>	7.5	6.9	8.6	8.4
	<i>range</i>	18–47	15–48	10–48	9–49
	<i>d</i>	--	.22	.02	–.11
<hr/>					
WASI Vocabulary raw score	<i>M</i>	66.7	64.0	63.5	61.2 [*]
	<i>SD</i>	7.3	7.9	8.5	9.3
	<i>range</i>	47–80	36–76	32–80	31–76
	<i>d</i>	--	–.25	–.31	–.73
<hr/>					
WASI Matrix Reasoning raw score	<i>M</i>	26.8	27.3	25.7	24.7 [*]
	<i>SD</i>	3.6	4.4	5.1	5.6
	<i>range</i>	16–34	10–35	6–34	8–34
	<i>d</i>	--	–.05	–.12	–.39

Group	Control	Far	Mid	Near
two-subtest WASI Combined raw score	<i>M</i>	93.6	90.7	88.4
	<i>SD</i>	8.8	10.3	11.9
	<i>range</i>	67–109	50–109	48–113
	<i>d</i>	--	-.22	-.30
ANART Verbal IQ Estimate*	<i>M</i>	100	100	102
	<i>range</i>	99–124	96–125	91–125
WASI Verbal IQ Estimate*	<i>M</i>	114	109	109
	<i>range</i>	82–142	69–134	62–142
WASI Performance IQ Estimate*	<i>M</i>	109	109	106
	<i>range</i>	84–137	66–141	57–137
WASI Full Scale IQ Estimate*	<i>M</i>	113	110	109

Note. Far = far from estimated clinical diagnosis (> 15 years); Mid = midway to estimated clinical diagnosis (9–15 years); Near = near to estimated clinical diagnosis (< 9 years); IQ = intelligence quotient. Summary information for WASI scores is based on 404 participants (removing 18 participants who were diagnosed at visit 2). Cohen's *d* estimates compare the prodromal HD groups to the control group and are adjusted for age, gender, education, and testing region. IQ estimates (as indicated by *) are conversions of raw scores using the published ANART conversion equation for the ANART, or the conversion tables published in the WASI manual for the WASI estimates.¹

[†] indicates that the Far from diagnosis group is significantly younger than any of the other groups (including controls)

^{*} indicates a significant difference between the Near to diagnosis group and controls

Correlations for demographic variables and premorbid IQ estimates for prodromal Huntington disease (prHD) participants (N = 371) and controls (N = 51)

Table 3

	ANART		Matrix		Combined		Age		Education	
		Vocabulary		prHD (control)		prHD (control)		prHD (control)		prHD (control)
1. ANART number correct standard scores	—	.75 [†] (.71 [†])		.31 [†] (.07)		.70 [†] (.62 [†])		.14 ^{**} (.24)		.55 [†] (.20) [▲]
2. WASI Vocabulary standard scores		—		.36 [†] (.20)		.91 [†] (.91 [†])		.19 ^{***} (.23)		.54 [†] (.33 [*]) [▲]
3. WASI Matrix Reasoning standard scores				—		.71 [†] (.58 [†])		-.23 [†] (-.50 ^{***}) [▲]		.29 [†] (.23)
4. two-subtest WASI Combined standard scores						—		.04 (-.02)		.54 [†] (.37 ^{**})
5. Age								—		.09 (-.08)
6. Education										—

Note. ANART = American National Adult Reading Test; WASI = Wechsler Abbreviated Scale of Intelligence. Positive values indicate better performance.

▲ significant difference (using Fisher *r*-to-*z* transformation) between group correlation coefficients.

* < .05
** < .01
*** < .001
† < .0001

Table 4

Estimates of two-year change (change score estimates expressed as standard scores)

IQ Measure	Control		Far		Mid		Near		Diagnosed	
	Estimate (SE) d		Estimate (SE) d		Estimate (SE) d		Estimate (SE) d		Estimate (SE) d	
ANART number correct standard score	1.4 (0.3) .4 [▲]		-0.2 (0.2) -.04		0.4 (0.2) .1		0.4 (0.2) .1		0.3 (0.3) .1	
WASI Vocabulary standard score	-0.9 (0.6) -.2		-0.4 (0.5) -.1		-1.3 (0.4) -.3		-1.0 (0.4) -.3		-1.0 (0.6) -.2	
WASI Matrix Reasoning standard score	2.0 (1.1) .3		1.6 (0.9) .2		0.2 (0.8) .1		0.8 (0.8) .1		-1.9 (1.1) -.2	
two-subtest WASI Combined standard score	0.04 (0.7) .01		0.3 (0.5) .05		-1.2 (0.5) -.2		-0.6 (0.5) -.1		-1.6 (0.7) -.3	

Note. IQ = intelligence quotient; Far = far from estimated clinical diagnosis (> 15 years); Mid = midway to estimated clinical diagnosis (9–15 years); Near = near to estimated clinical diagnosis (< 9 years); ANART = American National Adult Reading Test; WASI = Wechsler Abbreviated Scale of Intelligence. All estimates are expressed as standard scores that have a $M = 100$ and $SD = 15$. Positive values indicate better performance over time.

[▲] significant within group change over a 2-year period, as well as significant group differences between the control groups and the other 4 groups (far, mid, near, and diagnosed). Cohen's d estimates compare the prodromal Huntington disease groups to the control group and are adjusted for age, gender, education, and testing region.

Table 5

Two-year test-retest reliability coefficients for IQ measures

	Two-Year Prodromal HD (N = 371)	Two-Year Controls (N = 51)
ANART number correct standard score	0.94	0.93
WASI Vocabulary standard score	0.86	0.82
WASI Matrix Reasoning standard score	0.68	0.72
two-subtest WASI Combined standard score	0.86	0.82

Note. IQ = intelligence quotient; HD = Huntington disease; ANART = American National Adult Reading Test; WASI = Wechsler Abbreviated Scale of Intelligence. All test-retest reliability coefficients (within group analysis) $p < .0001$.

Table 6
Summary of test evaluation criteria to compare/contrast to utility of the three premorbid functioning estimates

Test Evaluation Criteria	Supporting Analysis	ANART	WASI Vocab	WASI Matrix	two-subtest WASI Combined
1. Evidence for test stability	Multivariate regression baseline model	✓+	✓-	✓	✓-
	Multivariate mixed longitudinal model	✓	✓	✓	✓
	SE for estimated two-year change	✓+	✓	✓-	✓-
	Test-retest reliability	✓+	✓	✓-	✓
2. Test relationships with variables that have known relationships with cognitive functioning	Pearson correlation with age	✓	✓	✓	✓+
	Pearson correlation with education	✓	✓	✓	✓
	Spearman correlation with gender	✓	✓	✓+	✓
	Contrast by geographic region *	✓	✓-	✓	✓-
3. Administration time	N/A	✓+	✓	✓	✓-

Note. ANART = American National Adult Reading Test; WASI = Wechsler Abbreviated Scale of Intelligence; Vocab = Vocabulary subtest; Matrix = Matrix Reasoning subtest; Combined = Combined subtest scores. Evidence for test stability is demonstrated by no differences between Huntington disease groups and controls on IQ test performance, smaller relationships between test performance and indices of disease progression, smaller SE, and higher test-retest correlations. In addition, “hold” measures should also have little to no relationship with age, education, gender, and region of testing.

✓- = good; within range for standards generally accepted in the field, but lower/less strong relationships than the other premorbid functioning estimates
 ✓=very good; within range for standards generally accepted within the field
 ✓+= excellent; within range for standards generally accepted in the field, but higher/stronger relationships than the other premorbid functioning estimates
 * from multivariate mixed model