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The Alzheimer's Disease Centers' Uniform Data Set (UDS): The Neuropsychological Test Battery

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Abstract

The neuropsychological test battery from the Uniform Data Set (UDS) of the Alzheimer's Disease Centers (ADC) program of the National Institute on Aging (NIA) consists of brief measures of attention, processing speed, executive function, episodic memory and language. This paper describes development of the battery and preliminary data from the initial UDS evaluation of 3,268 clinically cognitively normal men and women collected over the first 24 months of utilization. The subjects represent a sample of community-dwelling, individuals who volunteer for studies of cognitive aging. Subjects were considered "clinically cognitively normal" based on clinical assessment, including the Clinical Dementia Rating scale and the Functional Assessment Questionnaire. The results demonstrate performance on tests sensitive to cognitive aging and to the early stages of Alzheimer disease (AD) in a relatively well-educated sample. Regression models investigating the impact of age, education, and gender on test scores indicate that these variables will need to be incorporated in subsequent normative studies. Future plans include: 1) determining the psychometric properties of the battery; 2) establishing normative data, including norms for different ethnic minority groups;

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and 3) conducting longitudinal studies on cognitively normal subjects, individuals with mild cognitive impairment, and individuals with AD and other forms of dementia.

INTRODUCTION

Neuropsychological evaluation has played a central role in the clinical characterization of Alzheimer's disease (AD), its differentiation from "normal aging" and other forms of dementia, its staging over the course of illness, and its response to cholinergic and other pharmacologic treatments. Neuropsychological measures have been validated against AD pathology [1–12] and have been correlated with genetic risk factors and biomarkers of disease [1,2]. The Alzheimer's Disease Centers (ADC) program of the National Institute on Aging (NIA) recently designed a neuropsychological test battery as a component of the Uniform Data Set (UDS), a systematic and centralized method of assessing patients and cognitively intact participants at all contributing ADCs (N=29) [13–15].

In existence since 1984, the ADC program has been highly successful in promoting research on AD, other dementias, and cognitive aging [16]. In 1999, the first step was taken to standardize data collection across all ADCs by the establishment of the National Alzheimer's Coordinating Center (NACC) and the development of the Minimum Data Set (MDS). The MDS consisted of a centralized catalogue of clinical and demographic information on participants (about 60 data elements), retrospectively collected in the ADCs since their inception in 1984. It largely served a registry function but, in combination with the companion Neuropathology Data Set, could generate and test clinico-pathologic correlation hypotheses. In 2002 the ADC Clinical Task Force (CTF) was established by NIA with the mission of developing a set of standardized evaluation and data collection procedures for all ADCs. The standardization of data collection and its annual schedule of follow-up were intended to provide a solid platform for multi-center collaboration, enabling research on relatively large numbers of subjects, documenting change over time, and helping to develop new research hypotheses.

The UDS gathers data annually from research participants on a total of 918 variables (20 administrative) relevant to the study of aging and dementia. These include demographics, features of symptom onset and course, personal medical history, concurrent medications (363 variables), family history of dementia, and performance measures from neurological and neuropsychological examinations [13]. Data are collected from the participants and from their designated study partners by trained clinicians using structured interviews and objective test measures. Study partners provide subjective observations regarding participants' cognitive function, behavior, and level of functional ability in activities of daily living, providing evidence for decline in these areas.

Although ADCs also follow patients with non-AD forms of dementia, the initial intent was to create a data set focusing on the continuum from aging in cognitively normal controls, to mild cognitive impairment (MCI), to early stages of AD. Subsequent expansions of the UDS are planned to also sample symptoms of vascular dementia, dementia with Lewy bodies, behavioral variant frontotemporal dementia and primary progressive aphasia. The purpose of the present paper is to describe the development of the neuropsychological test battery component of the UDS and to present initial descriptive data from 3,268 participants determined to be "clinically cognitively normal", collected in the first 24 months following implementation of the UDS in September 2005.

METHODS

1. Rationale and Procedures For Selection Of Cognitive Domains

Cognitive domain and test selection were based on a combination of methods evolving from regular meetings of the CTF. A subcommittee was formed to specifically undertake the design of the neuropsychological test battery, to bring essential issues to the larger group and to interface with the ADCs. Three overriding criteria governed decisions for selecting domains and tests. The first was the mandate for the UDS to initially focus on cognitive markers of aging and of dementia associated with AD, the second was to minimize burden on the ADCs and their subjects, and the third was to accommodate the continuity of measures that ADCs have previously collected. A fourth principle that emerged after an initial set of domains and tests was identified was the need to overlap with other ADC initiatives such as the Late Onset Alzheimer's Disease (LOAD) Genetics study and the Alzheimer's Disease Neuroimaging Initiative (ADNI). Because of the need to focus on the cognitive continuum from aging without dementia, to MCI, to AD, cognitive domains were selected for their sensitivity to age-related change in cognition [17–29] sensitivity to the demonstrated primary cognitive impairments in AD [30–36], ability to measure change over time and to stage AD [37], and ability to predict progression from MCI to AD [38–41]. Additional criteria for test selection included applicability of the measures to different educational levels, to diverse racial/ethnic minority groups and to Spanish-speaking populations. A Spanish translation of the UDS has been completed and is available on the NACC website (https://www.alz.washington.edu).

The minimization of burden, an issue of feasibility, had to figure centrally in test selection. Many ADCs have been conducting research for over 20 years. Well-established protocols and longitudinal research projects could be disrupted by the need to significantly alter assessment and enrollment methods, notwithstanding the added time burden for subjects and their study partners. Thus, with input from the ADCs, the CTF concluded that the neuropsychological battery should not add more than 30 minutes to existing protocols at each Center. One implication of this principle was that tests already in use by all or most ADCs would be high on the list of candidates for inclusion.

The CTF conducted several surveys of the ADCs to gather data about their ongoing assessment practices including, among other variables: 1) cognitive domains tested; 2) specific instruments and versions, for tests with multiple forms; 3) populations of subjects followed (i.e., disease and control groups; clinic and/or community samples); 4) frequency of subject visits. Once these data were acquired, the most commonly tested domains and the most commonly used specific measures were identified and comments and approval were solicited from the ADCs.

2. Methods For Standardizing Administration And Scoring

Individuals who conduct the cognitive battery differ across ADCs and may include physicians, neuropsychologists, neuropsychology technicians, research coordinators, and nurses. A number of steps were taken in order to assure standardization of test administration and scoring. First, a detailed manual of administration and scoring instructions was designed (UDS Guidebook and Appendix, the latter replaced in Version 2.0 with the Neuropsychological Test Instructions), distributed to the ADCs for comments, revised on the basis of feedback, and disseminated. A meeting was held in November 2005, after several months of pilot testing, to train individuals who administer and score the tests at each ADC. At the meeting, each item of the testing was reviewed and questions and answers about the instructions were discussed. Based on this meeting, possible revisions to the UDS neuropsychological battery and manual were considered for future updates of the UDS. A web-based data entry system has been established and data are either entered directly or downloaded regularly. Error checks have been built into the system to minimize entry error [15]. The NACC also conducts separate

quality assurance/control procedures to review standardized reports in order to identify and verify any data anomalies. Future plans include creation of a videotape to demonstrate administration procedures and for training and certification purposes and to support maintaining inter-tester reliability at each site.

3. Types of Data, Summaries and Analyses

The data submitted to NACC from each center using Versions 1.1 and 1.2 of the UDS between September 2005 and September 2007 were analyzed for this report. The differences between the two versions consisted largely of clarification of instructions for administration and scoring, and a modification in the instructions for delayed story recall (Logical Memory A Delayed). In Version 1.1, delayed story recall is tested after 30 minutes without cueing; in Version 1.2, it is tested after a 20-minute delay and there is cueing with one detail from the story. However, it also was permitted to record the actual delay time if the recommended time could not be accommodated due to individual constraints. We were unable to separate the data reported here based on the version number but were able to conduct an analysis of the impact of the delayed recall interval on performance (see below). Version 2.0 has been released and maintains all of the characteristics of Version 1.2 with the addition of scores for numbers of errors of commission and correct lines on the Trail Making Tests and a score for the overlapping pentagons on the MMSE.

Due to the exploratory nature of this review, only basic tabular summaries and regression methods are presented on the neuropsychological data from subjects with no clinical evidence of cognitive abnormality. The primary covariates of interest in these analyses, along with their method of coding, include age (continuous), gender (indicator: reference group = female) and education (continuous). We also investigated the effect of interval of delayed recall on Logical Memory Delayed scores. All summaries and analyses were performed using R Version 2.6.1 [42] and STATA Version 9 [43].

RESULTS

1) Domain and Test Selection

Based on a review of the literature on neuropsychological features of aging and AD, the domains that have shown the greatest applicability, and that were the focus of the initial battery, were: 1) attention [44]; 2) speed of processing [45]; 3) executive function [46–50]; 4) episodic memory [51,52]; and 5) language [6,53]. The visual-spatial domain was not included in the initial versions of the battery as explained below. Aging itself is associated with a reduction in the immediate span of attention [54], slowed processing speed [55,56], and a reduction in the amount of information that can be learned and retrieved over time [17,57–59]. Each of these cognitive functions is excessively affected by AD, with a decline in episodic memory considered a hallmark of early AD [60]. An isolated decline in scores on memory tests beyond that expected with normal aging, in the presence of normal scores in other domains and no observable impairment in activities of daily living (ADLs) has been cited as a key feature for characterizing the condition of MCI [61–64]. This “amnestic profile” of MCI has high predictive validity for subsequent decline to a state of early AD [40,41,61,62,65,66] and, in fact, several investigators propose that amnestic MCI is prodromal AD [67–69]. Executive function deficits have also been cited as a predictor of progression from MCI to Alzheimer’s disease [40]. Memory tests can differentiate between normal aging and AD, however, they lose discriminant power for staging AD because of their early decline to floor levels. Tests of attention, executive function, word fluency and naming can be used for this purpose [37].

The Clinical Core leaders of the ADCs in discussion with their neuropsychologists and data managers completed surveys about which tests they used and their administration and scoring

practices. A poll of the ADCs showed that the domains outlined above were universally tested, with at least one measure for each, and that all ADCs used a performance measure of global dementia severity. With the exception of tests of constructional ability, visuospatial functions were not commonly tested. Table 1 shows the frequency with which ADCs used different measures. The most widely used test of dementia severity was the Mini Mental State Examination (MMSE) [70]. The Trail Making Tests [71], tapping executive functions, were used with similar frequency. For the language domain, the Boston Naming Test (BNT) [72, 73] and animal list generation were the most common measures. Digit Span and Digit Symbol subtests of a version of the Wechsler Adult Intelligence Scale (WAIS) were used to measure attention and processing speed by more than 72% and 55%, respectively, of ADCs. Finally, all ADCs used both word list and story recall tests of episodic memory while a smaller number also tested nonverbal memory. Story recall was most often tested with a version of the Wechsler Memory Scale (WMS) [74] (i.e., original, WMS-R or WMS-III).

Based on the responses and further discussions among the CTF, the final recommendation to the ADCs were the tests and associated scores summarized in Table 2. Most of these tests are well-known and will not be described in detail here. Instead, only UDS adaptations will be described.

The MMSE [70], not very sensitive for detecting early dementia in individuals with above average (or beyond) cognitive abilities [75] or for distinguishing steps within severe stages of dementia [76], was chosen because it is useful in tagging clinical milestones once dementia is diagnosed [77]. An adaptation of the MMSE for the UDS was to create a separate score for the Orientation items in addition to the standard Total score.

The Digit Span test from the WMS-R [74] is administered in its standard format, with two scores derived, namely total trials and the longest digit sequence (i.e., span) correctly reproduced. Parts A and B of the Trail Making Test [71] are administered according to standard rules but time limits were set, up to a maximum of 150 seconds for Part A and 300 for part B. If the subject cannot complete the sample item for each part or exceeds the time limits, a maximum time score is assigned. Digit Symbol Coding from the WAIS-R [78] is administered in the standard way, with the total number of items completed correctly in 90 seconds as the total score.

Decisions about which form of a particular test to recommend, for example the WMS, WMS-R or WMS-III, were based on frequency of current use at ADCs and the methods of the LOAD and ADNI studies. LOAD employs Digit Span and Logical Memory from the WMS-R and so those forms were recommended for the UDS. Furthermore, the decision was made to use only the first story (A) from Logical Memory to be comparable to the LOAD study and to reduce testing time. The LOAD method consistently provides a cue for delayed story recall to all subjects, not just to those who need one, which was incorporated into Version 1.2 of the UDS.

Because of different demands at each center, testers were instructed to attempt to maintain at least a 20 minute delay between immediate and delayed story recall but in the event that this was not possible, they were asked to note the number of minutes elapsed between these to two test points. A potential confounder, the time interval between immediate and delayed recall was analyzed to determine its effect on performance (see below). Chapman and colleagues have shown that the duration of the delay interval may not affect the ability to differentiate between Alzheimer's disease and aging on story recall and that even immediate recall can be used for this purpose [79].

Due to the amount of time required to test word list memory and to the fact that there was great variability among the ADCs with respect to the word list measures used, it was decided to exclude this measure from the UDS and to encourage the centers to study the relationship

between their preferred word list measures and Story A of Logical Memory in ancillary investigations.

To test naming, a short version of the BNT [72,73], (the 30-odd numbered items) was constructed. The administration of each item adheres to the standard for the full BNT with the exception that testing is discontinued after 6 consecutive failures. The score consists of the total number of items named correctly within the 20-second limit plus the number of items named correctly with a semantic cue. Finally, vegetable list generation was added as a second measure of word fluency to parallel methods of the LOAD study.

Of the measures in the battery, only the Trail Making and animal and vegetable list generation tests are in the public domain. The remaining measures are copyrighted and arrangements were made with the relevant publishers to use portions of tests and incorporate them into the UDS battery with appropriate licenses and agreements. All of the tests are fully structured instruments that directly assess performance. The full UDS evaluation includes additional instruments to assess daily living activities [i.e., Functional Assessment Questionnaire (FAQ)] [80] and behavioral symptoms [Neuropsychiatric Inventory, short form (NPI-Q)] [81,82], and these are completed in interviews with study partners. The Geriatric Depression Scale (15-item version, [83]) is administered as a measure of depression. These three measures are included in the Clinical Assessment portion of the UDS, as described elsewhere [13].

In order to account for the inability to perform specific test items, the scoring protocol for the UDS provides codes that signal unwillingness to respond, the presence of physical barriers, such as decreased vision, hearing, or motor deficits, and severe cognitive incapacity that attends later stages of dementia.

The UDS cognitive test battery can be administered in approximately 30 to 40 minutes by a trained psychometrist or other clinical professional under supervision of a clinical neuropsychologist. It is administered annually. The UDS test battery itself is not commercially available, but the individual materials and administration and scoring instructions for most of the individual tests have been published previously. The specific test administration and scoring procedures and data report forms used by the UDS (copyrighted by the University of Washington) are available from NACC (http://www.alz.washington.edu).

2) Initial Data

a) Subjects—Subjects were clinically cognitively normal older adults who were volunteers at the ADCs. Each Center utilizes its own recruitment strategy to identify potential participants. Based upon referral information within the UDS database, 36% of participants were referred by a relative or friend, 21% by a clinician or from a clinic sample (geriatrics, memory clinics and other medical specialties), 14% by ADC solicitation, 4% by non-ADC media appeal, and the remaining 25% from other or unknown sources. Written informed consent was obtained from all participants at each center and from the “study partners” that each participant was required to provide as an informant to corroborate information about daily functioning.

The data set reported in this paper were obtained from a larger database of 11,287 participants that included patients with various forms of dementia, individuals with mild cognitive impairment, and cognitively healthy individuals. Only those who met the following clinical criteria were included: 1) CDR Global score of 0 (No Dementia and no Questionable Dementia). 2) No deficits in activities of daily living due to cognitive symptoms, as indicated by a score of 0 on the Functional Assessment Questionnaire (FAQ). 3) No evidence of cognitive decline or dementia based on other (clinician-administered) questionnaires. 4) Available data values for age, gender and education.

The total number of subjects who met these criteria is 3,268. Eighty-five percent are White, non-Hispanic and there is a female-to-male ratio of 2:1. The sample breakdown by age (5 groups), education (4 levels) and gender appears in Table 3. Due to the relatively low representation of minorities and those with less than high school education, the initial data presentation did not attempt to separate groups based on these variables. However, subsequent analyses will be conducted when there are sufficient numbers as data continue to be accumulated.

This initial report describes demographic variables of clinically cognitively normal subjects enrolled at ADCs. It presents some preliminary analyses to show that age, gender, and level of education each influences test scores, consistent with findings from many studies of cognitive aging. This implies that these variables will definitely need to be considered in creating norms. Although future work will establish psychometric properties and values that can be used as norms, raw test scores are also important in attempting to compare individuals to their own baseline over a longitudinal course of study. For example, Rentz and colleagues ([84,85] have shown that cognitive decline can be missed in elderly individuals with high peak levels of cognitive ability earlier in life, whose age-corrected scores continue to fall in the "normal" range despite significant decline from their own benchmarks. The raw test data are too extensive for inclusion in this report and will be posted on the NACC website for ADC personnel.

b) Summary Statistics—Table 4 presents summary statistics for each neuropsychological test including the mean, standard deviation, median, 25^{th} and 75^{th} quantiles, and range (minimum and maximum). Figure 1 contains histograms for each of the tests and graphically demonstrates the potential pitfalls of relying on mean/standard deviation combinations for norms. Tests with normally distributed scores included Logical Memory A Immediate and Delayed Recall, Digit Span Forward and Backward Total Trials, and WAIS-R Digit Symbol. Skewed distributions were observed on the remaining measures due to ceiling effects on Digit Span Forward and Backward Length (fixed not to exceed 8 and 7 digits, respectively), the Boston Naming Test, and the MMSE's Orientation score and Total score. Based on our sample population, namely, clinically cognitively normal subjects, and the relative ease of the MMSE, most subjects scored a perfect or near-perfect score.

Despite strict inclusion criteria, however, some values appeared to be well below the normal range based on commonly available normative data for the individual measures. Of the 3,268 subjects, 584 had 1 or 2 outlying scores and 61 had 3 or more. We examined some of the background characteristics of these subjects but did not find any systematic relationship between age, education, race, or status of hearing and vision, and outlying scores. We considered eliminating subjects with scores in the lowest 1 percent of the range on each measure from further analysis but because this report is descriptive and not intended to provide normative data, decided to retain them because they met criteria for clinical normalcy.

c) Effects of Age, Gender and Education—To estimate the effect of age, gender and education on each neuropsychological measure, a series of linear regression models were constructed that took into account the multiple sources of the data (e.g. ADC). For all instruments except Logical Memory A Delayed, a series of models were estimated, three looking at each demographic variable individually and the fourth that combined all into a single model. Included within all of the models summarizing Logical Memory A Delayed was the length of the time delay. The standard outputs of these models include estimates of coefficients and their 95% confidence intervals which are summarized in Table 5. Estimates that were found to be statistically significant ($p<0.01$) are noted in bold. Only one estimate related to gender differences using a univariate model was significant at the .05 level but not the .01 level.

From the first three columns of Table 5, it is observed that gender, age and education are statistically associated with many, if not all, tests. For nearly all tests, except Trail Making A and B, an increase in age is associated with lower test scores, that is poorer performance. This was expected for the Trail Making tests since a higher score signifies poorer (i.e., slower) performance. Education also was statistically associated with each test, although Digit Symbol score was the most affected by this variable. Finally, gender was statistically associated with all tests except Digit Span Forward and Backward and Category Fluency-Animals. Women tended to outperform men on 8 of the test scores but the magnitude of the coefficients are minimal for the most part. The may not likely have clinical relevance (e.g. women on average score 0.39 points higher than men on the MMSE), although statistical significance was reached because of the large sample size. Similar results were found when adjusting for all demographics simultaneously as illustrated in the last three columns of Table 5.

The time delay of Logical Memory A Delayed was included in all regression models of this test. Regardless of which demographic variable was included in the model, this delay was not statistically associated (coefficient: ≈−0.03, 95% CI: ≈(−0.09,0.03)) with the number of units accurately recalled. Additional analyses, such as the inclusion of an interaction term between gender and education, were performed but not reported here. Tests that exhibited a significant interaction effect include Category Fluency: Animals, Trail Making A and B, and Boston Naming Test. More sophisticated statistical methods may need to be applied in the future to verify this interaction and validate the above findings.

The UDS neuropsychological test measures differ in the extent to which they are influenced by age, but generally show declining scores over the age range. This is consistent with findings from numerous other studies of the effect of aging on cognition. These results also suggest, as others have shown repeatedly, that education has a very strong effect on performance. Furthermore, the education variable has several confounds, as has been suggested in studies demonstrating independent effects of literacy, education and acculturation, especially in minority populations and these can be explored in future research studies [86–89].

DISCUSSION

This paper describes the initial neuropsychological data set collected from clinically cognitively normal ADC subjects at their baseline UDS assessment. The subjects are not representative of the general population, but do constitute the demographic characteristics of individuals participating as cognitively healthy subjects in dementia research in the United States. They have substantially more education than the general population. Furthermore, they have had a careful medical examination and have relatively few medical and psychiatric illnesses. Summary statistics are provided for the entire sample for each UDS measure. Although not constituting a formal set of norms for these measures, this data set represents the largest compilation of such data on a relatively well-educated sample of individuals who participate in research at the ADCs across the country. While additional data and analyses will be needed to develop norms for the UDS neuropsychological test battery, these initial descriptive data and analyses are a first step in interpreting the cognitive performance of research participants at ADCs. Furthermore, this enterprise has been exceedingly valuable in bringing the ADCs together to adopt a uniform method of collecting data on the same set of neuropsychological instruments.

As anticipated, preliminary analyses have shown that factors such as gender, age and education all affect test scores. Males and females differed significantly on more than half of the measures. Consistent with the findings in many longitudinal cognitive aging studies, the older cohorts consistently scored more poorly than the younger age groups and individuals with more years of education had higher scores than those with fewer years.

The psychometric properties of the UDS cognitive test battery are not yet established. However, the reliability and validity of the original versions of the tests included in the battery are well known and have been described in detail in compendia of neuropsychological tests such as those published by Lezak, Howieson and Loring [90] and Strauss, Sherman and Spreen [91]. The utility of the original versions of the tests for detecting very early dementia of the Alzheimer type (or of MCI), tracking the progression of the disease, differentiating AD from other dementing disorders, and exploring the relationship between specific cognitive deficits and the pathology of AD has been described in numerous studies (for a review, see Salmon and Bondi [92]). These studies suggest that the UDS cognitive tests should be effective for the early detection and characterization of AD. A study that examined the diagnostic utility of many of the tests included in the UDS battery, for example, showed that similar versions of the Logical Memory Test (sensitivity (se)=87%; specificity (sp)=89%), Trail Making Test: Part B (se=85%; sp=83%), and Category Fluency Test (animals) (se=96%; sp=88%) were quite effective in differentiating between healthy elderly individuals and very mildly demented patients (MMSE scores ≥ 24) with AD that was subsequently verified by either autopsy or typical clinical course over the next three years [93]. Validation studies, and studies to develop normative data, are currently being conducted by the ADCs.

The UDS neuropsychological test battery assesses most of the major cognitive domains that are compromised in AD and some other neurodegenerative disorders and should be effective for evaluating cognitive status in patients with known or suspected dementia. Furthermore, the tests should be able to differentiate “average” aging from MCI and dementia. Although we found that some measures yielded ceiling effects in our cognitively normal cohort, most of them are anticipated to be sensitive to even the earliest stages of dementia. The ceiling effect is overcome over the course of AD and thus this neuropsychological test battery should also effectively track the progression of dementia throughout most of the course of the underlying neurodegenerative disease. However, it may not be effective in tracking severe dementia because of the difficulty of some of the tests for late stages of illness. Furthermore, our cohort was relatively highly educated so that ceiling effects may be less apparent in individuals with lower levels of education.

The pattern of performance produced across the tests included in the UDS cognitive battery has been used in the past to differentiate among etiologically and neuropathologically distinct disorders that result in dementia (for review, see [92].) Thus, the UDS battery might have the potential to aid in clinically distinguishing among AD, frontotemporal dementia, Huntington’s disease, Parkinson’s disease with dementia, vascular dementia, progressive supranuclear palsy and other neurodegenerative disorders. Some of the tests, for example, such as Trail Making, verbal fluency-animals, the Boston Naming Test, and Digit Symbol, overlap with those proposed in the recent recommendations from the Work Group on Vascular Cognitive Impairment [94].

Although future analyses may show differences in test performance among different forms of dementia, such as frontotemporal dementia and dementia with Lewy bodies (DLB), or distinctive “profiles,” the battery as it stands may *not* be broad enough to distinguish among these subgroups. None of the tests of the UDS neuropsychological battery were specifically chosen for their sensitivity to forms of dementia other than AD. Future versions of the UDS will attempt to add items sensitive to other forms of dementia. For example, in Version 2.0 of the UDS, additional quantitative scores have been added to capture errors of commission (incorrect lines) and number of correct lines, enhancing the types of available information to be gained from this test and perhaps discriminating those who are impulsive from those who are merely slow. A separate score is also provided for the overlapping pentagons item of the MMSE to provide a measure of visuospatial function that might discriminate DLB from other dementias.

Normative neuropsychological data have been collected on elderly cohorts in numerous studies. In many of these studies, it is highly probable that many of the participants developed cognitive decline which could influence the derived norms. Future analyses and longitudinal data will permit us to further separate individuals who maintain their cognitive functions from those whose functions decline over the same interval of time. One study suggests that socalled "robust norms" that exclude impaired individuals from the normative sample do not significantly alter the ability to detect cognitive impairment in pathological populations [95]. However, other studies suggest that norms should be corrected for an individual's *personal* prior peak cognitive level in order to detect change, even when scores decline but remain in the "normal-for-age" range [84,85].

Some of the limitations of this initial report include the fact that the population studied mainly consists of a highly educated volunteer group that is representative of the non-demented individuals who participate in research at NIA-supported Alzheimer's Disease Centers. Thus the participants are not representative of, and the findings may not apply to, the general population. Further, at this time, we do not have sufficient numbers to establish norms for minority and Spanish speaking populations. As we accumulate larger samples of ethnic-racial minorities and Spanish speaking individuals, it will be possible to apply this battery to community based samples.

Although the UDS battery marks progress in the ADC program with respect to standardization of methods and tests, there are a number of drawbacks. In the data reported, despite identifying subjects as clinically cognitively normal, several subjects obtained 1 or more abnormal scores. Follow up of these subjects will help us determine if low scores remain low or even decline over time or if they represent the intra-individual variability that is so common in cognitive performance of elderly subjects (see Hultsch and colleagues for a review [96]). Variability in performance may signal vulnerability to subsequent sustained cognitive decline or it may reflect the sensitivity of cognition to temporary perturbations in emotional or health states. Another issue has to do with the potential for practice effects on repeated testing. If, as we might expect, there are practice effects, then this may highlight the reliance on the stability or improvement in scores, or the *absence* of decline, as a measure of cognitive health.

The design of the UDS neuropsychological battery draws upon years of experience with these instruments in the evaluation of the elderly patient with cognitive decline. More sophisticated instruments that make use of available computer technologies, such as touch screens and interactive programs, offer an exciting opportunity to further improve our assessment methods. Computer adaptive testing and item response theory can be employed to create very brief and sensitive tests, especially for use with normal and very mildly impaired subjects. However, the development of such measures is costly and requires multiple specialists and resources but it might be an exciting direction for future expansion of this project.

The current UDS cognitive test battery will provide more than a simple assessment of mental status in patients with dementia, but it is an abbreviated battery and does not substitute for a comprehensive neuropsychological evaluation. Most cognitive domains are assessed by a single measure and some important cognitive domains, such as visual perceptual ability and reasoning, are not assessed. The UDS cognitive test battery will provide an excellent initial evaluation of the cognitive status of patients with suspected early dementia and will leverage efforts across all ADCs to enhance the yield of data with minimal subject and center burden.

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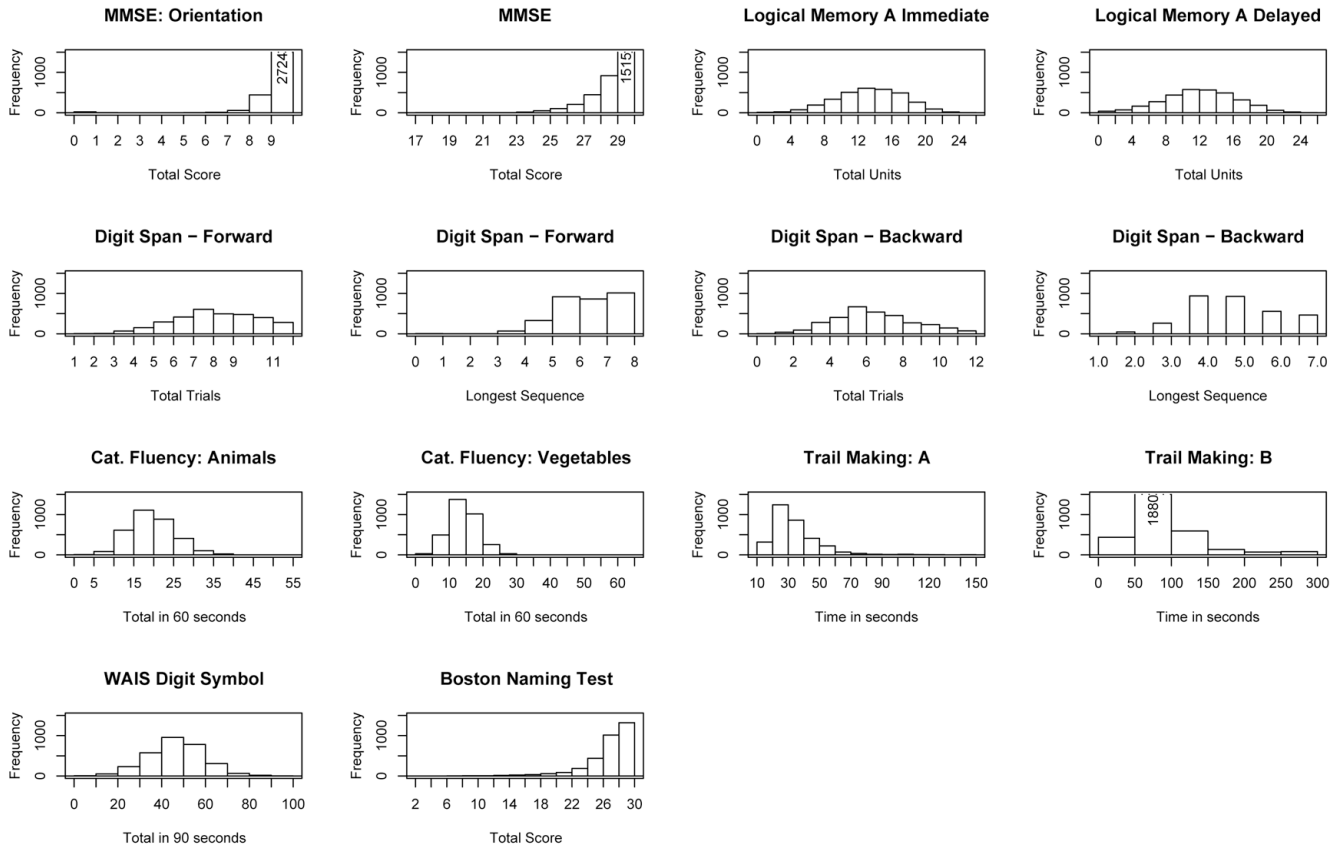

Figure 1.

Histograms illustrating the distribution of scores for each measure in the neuropsychological test battery. The y-axis represents numbers of subjects while the x-axis represents observed test scores. For comparisons across instruments, the y-axis is fixed at 1500. If any frequency exceeded this value, then the count is truncated at this value and the true value denoted within its bar.

Table 1

NACC Database search of test measures used by 29 ADC's

Used by ≥ 80% of centers (N) Category Fluency (Animals) (28) Boston Naming Test (20, 30, 60 items) (26) MMSE (Spell W-O-R-L-D backwards) (26) Trail Making Tests (Part A or B) (26)	**Used by < 40% of centers (N<12)** Blessed Information-Memory Concentration California Verbal Learning Test Mattis Dementia Rating Scale Global Deterioration Scale New Adult Reading Test Alzheimer's Disease Assessment Scale Lawton-Brody Activities of Daily Living Beck Depression Inventory Hopkins Verbal Learning Test Buschke Selective Reminding Test Rey Auditory Verbal Learning Test Telephone Interview of Cognitive State (TICS) Fuld Object Memory Test Modified Mini Mental State Examination (3MS) Center for Epidemiologic Studies-Depression Scale
Used by ≥ 60–79% of centers (N) CDR-Global Score (24) Letter Fluency Test (23) Digit Span (WAIS-R) (21) WMS (original, R or III) (21) Geriatric Depression Scale (19) Clock Drawing Test (19)	
Used by 40–59% of centers (N) CERAD Word List Learning (17) Blessed Dementia Scale (16) Block Designs (WAIS, WAIS-R, WAIS-III) (16) Digit Symbol (16)Neuropsychiatric Inventory (15) Visual Reproduction (WMS,WMS-R,WMS-III) (14) CERAD Neuropsychological Battery (13)	

Table 2

Uniform Data Set Neuropsychological Test Battery

DOMAIN/FUNCTION	Test/Measure	MAXIMUM SCORES
Dementia Severity	Mini Mental State Examination (MMSE) [70]	Total MMSE (30)
		Total Orientation items (10)
Attention	Digit Span Forward (Wechsler Memory	Longest Sequence (9)
	Scale-Revised) [74]	Total correct Trials (14)
	Digit Span Backward (WMS-R) (also,	Longest Sequence (8)
	working memory)	Total correct Trials (12)
Processing Speed	Digit Symbol (Wechsler Adult	Total number of items
	Intelligence Scale-Revised)[82]	completed in 90 seconds (99)
	Part A, Trail Making Test	Total time (150 seconds)
Executive Function	Part B, Trail Making Test [96–98]	Total time (300 seconds)
Memory	Logical Memory, Story A (WMS-R) [74]	
	Immediate Recall	Total items recalled (25)
	Delayed Recall	Total items recalled (25)
Language		
Verbal Fluency	Animal list generation [33]	Total items in 1 minute
	Vegetable list generation	Total items in 1 minute
Naming	Boston Naming Test (30 odd items) [72,73]	Total correct (30)

Table 3

Sample Distribution By Gender, Age and Education

Age	Education (Years)	Male	Female	N
< 60 years	**Total**	87	195	282
	≤12	12	26	38
	13–15	13	39	52
	16	31	51	82
	17 +	31	79	110
60–69 years	**Total**	252	584	836
	≤ 12	42	109	151
	13–15	45	148	193
	16	56	113	169
	17 +	109	214	323
70–79 years	**Total**	458	845	1303
	≤ 12	59	195	254
	13–15	69	208	277
	16	133	182	315
	17 +	197	260	457
80–89 years	**Total**	277	449	726
	≤ 12	66	119	185
	13–15	39	96	135
	16	82	108	190
	17 +	90	126	216
90 + years	**Total**	45	76	121
	≤ 12	12	27	39
	13–15	7	21	28
	16	15	12	27
	17 +	11	16	27
GRAND TOTAL		1119	2149	3268

Table 4

Summary Statistics For Clinically Cognitive Normal UDS Participants

	N	Mean (SD)	Q_{25}	Median	Q_{75}	Range
MMSE: Orientation Total Score	3258	9.7 (0.9)	10	10	10	(0,10)
MMSE Total Score	3257	29.0 (1.3)	28	29	30	(17, 30)
Logical Memory A Immediate Total Units	3181	13.9 (3.9)	11	14	17	(0, 25)
Logical Memory A Delayed Total Units	3181	12.6 (4.3)	10	13	16	(0, 25)
Digit Span – Forward Total Trials	3203	8.6 (2.1)	7	9	10	(1, 12)
Digit Span – Forward Longest Sequence	3201	6.7 (1.1)	6	7	8	(0, 8)
Digit Span – Backward Total Trials	3202	6.9 (2.2)	5	7	8	(0, 12)
Digit Span – Backward Longest Sequence	3202	5.0 (1.2)	4	5	6	(1, 7)
Cat. Fluency: Animals Total in 60 seconds	3232	20.0 (5.6)	16	20	24	(1, 54)
Cat. Fluency: Vegetables Total in 60 seconds	3201	14.7 (4.4)	12	15	17	(1, 63)
Trail Making: A Time in seconds	3216	34.6 (15.4)	25	31	40	(11, 150)
Trail Making: B Time in Seconds	3195	90.3 (50.0)	59	77	105	(10, 300)
WAIS Digit Symbol Total Items in 90 seconds	2995	47.0 (12.5)	39	47	55	(3, 93)
Boston Naming Test	3204	27.2 (3.2)	26	28	29	(2, 30)

	N	Mean (SD)	Q_{25}	Median	Q_{75}	Range
Total Score						

N= Number of subjects with data; SD=standard deviation; Q_i=i^{th} quantile; Range = minimum and maximum score

Table 5

Regression coefficients and 95% confidence intervals. Coefficients significant at the 0.01 level are bolded. Only one (underlined) was significant at the .05 but not the .01 level.

	Univariate Models			Multivariate Model		
	Gender	**Age**	**Education**	**Gender**	**Age**	**Education**
MMSE: Orientation Total Score	**<u>−0.12</u>** (−0.23, −0.02)	−0.01 (−0.01, 0.00)	**0.02** (0.01, 0.04)	**−0.14** (−0.24, −0.04)	−0.01 (−0.01, 0.00)	**0.03** (0.01, 0.04)
MMSE Total Score	**−0.39** (−0.50, −0.29)	**−0.03** (−0.04, −0.01)	**0.14** (0.07, 0.21)	**−0.48** (−0.59, −0.37)	**−0.02** (−0.03, −0.01)	**0.14** (0.07, 0.21)
Logical Memory A Immediate Total Units	**−0.95** (−1.31, −0.59)	**−0.04** (−0.05, −0.02)	**0.35** (0.27, 0.43)	**−1.21** (−1.53, −0.89)	**−0.02** (−0.04, −0.01)	**0.37** (0.30,0.45)
Logical Memory A Delayed* Total Units	**−1.10** (−1.49, −0.71)	**−0.04** (−0.05, −0.02)	**0.39** (0.30, 0.47)	**−1.39** (−1.76, −1.02)	**−0.03** (−0.04, −0.01)	**0.41** (0.33, 0.49)
Digit Span - Forward Total Trials	0.20 (−0.03, 0.42)	**−0.02** (−0.04, −0.01)	**0.18** (0.14, 0.21)	0.09 (−0.14, 0.33)	**−0.02** (−0.03, −0.01)	**0.17** (0.13, 0.20)
Digit Span - Forward Longest Sequence	0.11 (−0.01, 0.22)	**−0.01** (−0.02, −0.01)	**0.08** (0.07, 0.10)	0.05 (−0.07, 0.18)	**−0.01** (−0.01, −0.01)	**0.08** (0.06, 0.10)
Digit Span - Backward Total Trials	−0.09 (−0.36, 0.19)	**−0.03** (−0.04, −0.02)	**0.21** (0.16, 0.25)	−0.22 (−0.48, 0.05)	**−0.02** (−0.03, −0.01)	**0.20** (0.17, 0.24)
Digit Span - Backward Longest Sequence	−0.03 (−0.19, 0.12)	**−0.02** (−0.02, −0.01)	**0.11** (0.09, 0.13)	−0.10 (−0.25, 0.05)	**−0.01** (−0.02, −0.01)	**0.11** (0.09, 0.13)
Cat. Fluency: Animals Total in 60 seconds	0.29 (−0.37, 0.95)	**−0.14** (−0.17, −0.12)	**0.60** (0.48, 0.73)	0.01 (−0.62, 0.63)	**−0.13** (−0.15, −0.11)	**0.57** (0.44, 0.69)

	Univariate Models			Multivariate Model		
	Gender	**Age**	**Education**	**Gender**	**Age**	**Education**
Cat. Fluency: Vegetables	**−2.83**	**−0.10**	**0.25**	**−2.95**	**−0.09**	**0.28**
Total in 60 seconds	(−3.19, −2.48)	(−0.13, −0.08)	(0.16, 0.33)	(−3.23, −2.67)	(−0.11, −0.07)	(0.20, 0.36)
Trail Making: A**	0.99	**1.02**	**0.97**	0.99	**1.02**	**0.98**
Time in seconds	(0.95, 1.03)	(1.01, 1.02)	(0.96, 0.99)	(0.95, 1.02)	(1.01, 1.02)	(0.97, 0.99)
Trail Making: B**	0.96	**1.02**	**0.95**	0.97	**1.02**	**0.96**
Time in Seconds	(0.91, 1.02)	(1.01, 1.02)	(0.94, 0.97)	(0.94, 1.07)	(1.01, 1.02)	(0.94, 0.97)
WAIS Digit Symbol	**−3.00**	**−0.60**	**1.24**	**−3.15**	**−0.56**	**1.12**
Total Items in 90 seconds	(−4.09, −1.91)	(−0.67, −0.53)	(0.81, 1.68)	(−4.01, −2.29)	(−0.62, −0.50)	(0.73, 1.52)
Boston Naming Test	**0.82**	**−0.06**	**0.36**	**0.62**	**−0.05**	**0.34**
Total Score	(0.30, 1.34)	(−0.08, −0.03)	(0.20, 0.53)	(0.21, 1.03)	(−0.07, −0.03)	(0.19, 0.49)

* These models also adjusted for the delay interval;

** Log transformed / retransformed.