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Neuropsychological Equivalence of the Clinical Diagnosis of Mild Cognitive Impairment in the National Alzheimer's Coordinating Center Uniform Data Set and Alzheimer's Disease Neuroimaging Initiative

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Abstract

Introduction: Our understanding of Alzheimer's disease may be improved by harmonizing data from large cohort studies of older adults. Differences in the way clinical conditions, like mild cognitive impairment (MCI), are diagnosed may lead to variability among participants that share the same diagnostic label. This variability presents a challenge for cohort harmonization and may lead to inconsistency in research findings. Little research to date has explored the equivalence of the diagnostic label of MCI across 2 of the largest and most influential cohort studies in the USA: the National Alzheimer's Coordinating Center (NACC) and the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Methods: Participants with MCI due to presumed Alzheimer's disease from the NACC Uniform Data Set ($n = 789$) and ADNI ($n = 131$) were compared on demographic, psychological, and functional variables, as well as on an abbreviated neuropsychological battery common to the 2 data sets.

Results: Though similar in terms of age, education, and functional status, the NACC sample was more diverse (17.4% non-White participants vs. 7.6% in ADNI; $\chi^2 = 7.923$, $p = 0.005$) and tended to perform worse on some cognitive tests. In particular, participants diagnosed with MCI in NACC were more likely to have clinically significant impairments on language measures (26.36–31.18%) than MCI participants in ADNI (16.03–19.85%).

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Author Contributions

The authors collaborated to develop the manuscript idea. Dr. Kiselica wrote the introduction and discussion sections and provided revision of the methods and results sections. Dr. Benge led analyses, wrote the methods and results sections, and provided revision of the introduction and discussion sections.

Statement of Ethics

This research was determined to have exempt status by the University of Missouri Institutional Review Board.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Discussion: The current findings suggest important differences in cognitive performances between 2 large MCI cohorts, likely reflective of differences in diagnostic criteria used in these 2 studies, as well as differences in sample compositions. Such diagnostic heterogeneity may make harmonizing data across these cohorts challenging. However, application of shared psychometric criteria across studies may lead to closer equivalence of MCI groups. Such approaches could pave the way for cohort harmonization and enable "big data" analytic approaches to understanding Alzheimer's to be developed.

Keywords

Alzheimer's disease neuropsychological test; Aging research; Clinical assessment of Alzheimer's disease; Cognitive tests; Mild cognitive impairment; Neuropsychological Alzheimer's disease and mild cognitive impairment; Psychometrics

Introduction

Some have argued that the so-called "big data approaches" are necessary to advance the science of aging and jump-start precision medicine development in response to expected growth in numbers of individuals living with Alzheimer's disease and related dementias [1]. Research groups have begun the process of harmonizing data across large cohorts of older adults to create the critical mass of clinical, biomarker, and imaging data necessary to yield major breakthroughs in understanding and treatment of AD [2].

Central to such efforts is the assumption that diagnostic classifications across databases are uniform, meaning that an individual in one cohort with a diagnosis can be assumed to be similar in important characteristics to an individual in the other cohort. Consensus criteria are important to this end. For example, consensus criteria for the diagnosis of mild cognitive impairment (MCI) and dementia due to AD outline ranges of cognitive and behavioral impairments and their impacts on functioning in activities of daily living [3, 4] that are needed to qualify for a diagnosis. However, such consensus criteria lack specific empirical operational definitions [5]. For instance, they tend to provide a range of scores that might reflect evidence of cognitive impairment and differentiate individuals with MCI from those with more benign subjective cognitive concerns [6]. Similarly, there is no guidance provided in the consensus criteria about the number of low test scores across a battery that must be observed to qualify for MCI or dementia diagnoses (though research groups have offered evidence for empirical MCI criteria [7], none has emerged as a gold standard). This lack of specification recognizes that clinical practice and research studies may use a variety of instruments to reach a diagnosis. Current criteria also account for the fact that persons with cognitive impairment may have other relevant factors that influence interpretation of psychometric scores.

This flexibility, however, comes at the cost of diagnostic precision and may introduce potentially problematic heterogeneity into clinical research. For example, in the National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS) 3.0, which gathers data on participants from Alzheimer's Disease Research Centers across the country, MCI is defined by the presence of (1) subjective cognitive concerns on the part of the participant, a coparticipant, or the assessing clinician; (2) impairment in one or more cognitive domains,

as defined by neuropsychological testing; and (3) preserved independence in day-to-day functioning [8]. In contrast, in another large cohort of older adults, the Alzheimer's Disease Neuroimaging Initiative (ADNI), MCI is defined by the presence of (1) subjective memory concerns reported by the participant, a coparticipant, or the assessing clinician; (2) impaired memory function documented by scoring below education adjusted cutoffs on the Logical Memory II subscale from the Wechsler Memory Scale – Revised [9]; (3) a Mini-Mental State Exam [10] score of 24 or higher; and (4) a Clinical Dementia Rating (CDR) Dementia Staging Instrument® [11] global score of 0.5 with a Memory Box score of at least 0.5 [12].

While conceptually overlapping, these operationalizations of MCI could obviously introduce heterogeneity of the MCI samples between the 2 cohorts. This heterogeneity may make it challenging to harmonize data from the cohorts, in addition to leading to inconsistent research findings. To date, there has been little work done to investigate equivalence of MCI participants across these highly important cohorts. Thus, the current study was intended to compare profiles of cognitive and functional performance for individuals classified as MCI in the ADNI and NACC databases.

Materials and Methods

This research included secondary analysis of deidentified data and was therefore given an exempt determination from our local institutional review board.

UDS Sample

The UDS includes data from participants involved in research at Alzheimer's Disease Research Centers across the country. We requested all available UDS information in the October of 2019 via the NACC online portal. These participants were recruited at 30 centers with data collected from March 16, 2015, to November 12, 2018. We restricted the data to individuals receiving the most recent version of the neuropsychological battery (version 3.0). The file included 6,657 individuals with baseline UDS 3.0 data available. Because a number of the cognitive measures required English language proficiency, we next restricted the analyses to individuals whose primary language was English (n = 6,042). Finally, due to our interest in examining individuals categorized as MCI, we further restricted the sample to only those with a diagnosis of MCI due to suspected Alzheimer's disease (n = 789).

ADNI Sample

ADNI is a public-private partnership with data collected at a number of participating sites across the country. Data were downloaded from the Laboratory of Neuro Imaging Data Archive in the January of 2020, focusing on the most recent iteration of ADNI, version 3 (ADNI3). The files included baseline ADNI3 data from 513 participants. Restricting the sample to primary English speakers left 502 cases. These participants were recruited at 56 ADNI sites with data collected from January 19, 2017, to January 13, 2020. After selecting only those individuals with a clinical diagnosis of MCI due to presumed Alzheimer's disease, 131 participants remained.

Measures

Both ADNI and NACC share some measures, which serve as the basis for the current comparisons across cohorts. Both projects include Trailmaking Test Parts A&B [13], the Multilingual Naming Test (MINT) [14, 15], the animal fluency test, and the Montreal Cognitive Assessment (MoCA) [16]. A critical difference between the 2 studies is the prose memory passage utilized in the respective batteries. Although ADNI utilizes units complete from the Wechsler Memory Scales Revised (WMS) Story A [9], NACC sites utilize immediate recall of the Craft Story [17]. However, a recent statistical crosswalk between these 2 measures has been published, and these procedures were utilized to allow for Craft Story scores to be converted into WMS scores [18]. With cognitive data thus compiled, cognitive test scores were transformed into age-, gender-, and education-corrected z-scores on the basis of published normative data from the NACC for the Montreal Cognitive Assessment, the Trailmaking Tests, the Multilingual Naming Test, and the animal fluency test [19]. Similar demographic corrections published from a prior version of the UDS were applied to the WMS immediate and delayed recall trials [20].

Diagnosis

We described the differences in diagnosis of MCI across the ADNI and NACC cohorts in detail in the Introduction section. More info on diagnostic procedures in NACC and ADNI can be found in [8, 12].

Analyses

Given the unequal sample sizes and variances between the 2 groups, nonparametric median comparisons of demographic and cognitive scores were utilized (Mann-Whitney U). In addition, because group level statistics may obscure differences made in individual cases (i.e., one study allowing for a more permissive or restrictive score to be considered for an MCI diagnosis), we also evaluated the number of below average cognitive scores present in each case as defined by scores <9th percentile [21]. Then, we evaluated whether the proportions of below average scores between cohorts differed via χ^2 tests of independence. To help reduce the risk of false positives with this technique, given the number of comparisons, false discovery rate analyses were used [22].

Results

Descriptive statistics for age, education, and cognitive score variables are presented in Table 1. In terms of demographics, the ADNI and NACC samples were of similar age, education, and gender. χ^2 analyses revealed that the NACC sample had a higher proportion of non-White participants (17.4% non-White participants in NACC vs. 7.6% in ADNI; $\chi^2 = 7.923$, $p = 0.005$). Rates of depression and degree of reported difficulty with instrumental activities were similar across groups. Regarding cognitive performance, NACC MCI participants tended to have weaker Trailmaking Test Part B and language performances relative to their ADNI peers. Furthermore, NACC MCI participants had lower global cognitive screening scores on the MoCA. Recent research suggests that sociodemographic factors that differed between the cohorts, such as racial background, could explain additional variance in cognitive test scores [23]. However, the pattern of lower Trailmaking B, animals,

and naming scores remained when White participants in the 2 samples were compared alone. Comparisons within just the non-White participants were limited secondary to low representation in the ADNI sample (n = 10), but results suggested lower naming and MoCA scores in the NACC group for individuals of minority backgrounds as well.

At the level of individual participants, individuals with MCI in the ADNI sample had 1 (IQR = 2) impaired score on the 6 neuropsychological measures, while the NACC sample had on average 2 impaired scores (IQR = 2). This difference was statistically significant (Mann-Whitney U = 455,524, p = 0.025), though not significant after adjusting for the false discovery rate.

Rates of impaired scores by the cognitive variable are presented in Table 2. Low scores were most common on memory measures, present in about a third of individuals in both samples. Individuals from the 2 cohorts had similar rates of low scores on processing speed/executive functioning. However, there was a large difference in the likelihood of obtaining low scores on measures of language across cohorts. Individuals in NACC were more likely to have low scores on tasks involving confrontation naming and semantic fluency.

Discussion/Conclusion

There is increased interest in the harmonization of large cohorts of older adults with Alzheimer's disease and related conditions [1, 2]. Such harmonization requires homogeneity of clinical diagnoses across samples, a relatively unexplored topic in the literature. Our study addresses this gap by examining differences in the cognitive presentation of individuals with MCI due to suspected Alzheimer's disease across 2 large cohorts, NACC and ADNI.

We found evidence of differences in cognitive performance across the ADNI and NACC cohorts among individuals diagnosed with MCI. At the level of global cognitive status, median comparisons suggested that individuals in the NACC cohort demonstrated lower average scores on the MoCA than ADNI participants. This finding is unsurprising because a diagnosis of MCI in ADNI required a fairly high score (>24) on the Mini-Mental Status Exam [12], a similar cognitive screening test. This finding could imply that the ADNI MCI cohort has less overall cognitive impairment than the NACC cohort.

Consistently, individuals from ADNI also scored higher on some measures of language and executive functioning on average than participants in the NACC MCI cohort. Both clinical and demographic factors might contribute to these discrepancies. The NACC cohort had significantly more non-White participants than the ADNI cohort, and non-White participants often score lower on cognitive tests [24], especially on language tasks, where cultural biases in test construction and differences in access to educational resources have an influence on performance [25]. However, our finding of similar results when reanalyzing the data by racial/ethnic subgroups could indicate that this explanation for cohort differences in cognitive performance is incomplete.

Alternatively, it may be that the NACC MCI group is more enriched for the development of dementia. However, this finding is somewhat discrepant from studies on conversion from MCI to dementia, which tend to be higher in ADNI relative to NACC samples. To better

understand important clinical outcomes, such as the actual risk of conversion for those with MCI, clinical predictors of conversion, and to correct the issue of nonequivalence, researchers may need to rely on an empirical approach to diagnosing MCI that can be applied across both cohorts and ensure similarity of diagnostic groups. For example, we have previously put forth a multivariate base rate approach to diagnosing MCI in NACC that could be replicated in ADNI [26]. Alternatively, the Jak/Bondi empirical approach to diagnosing MCI in ADNI could be replicated in NACC [7, 27].

Of note, this study had certain limitations that impact interpretation of findings. First, comparisons across the ADNI and NACC samples focused on cognitive measures that the 2 databases held in common, such that other available tests were not included in analyses. In the future, one might use advanced linking and equating techniques to cross walk scores in the 2 databases [28], as we were able to for the prose memory measures [18]. Second, it was beyond the scope of the current paper to examine other variables important to the diagnosis of MCI, such as other neurobehavioral symptoms, like anxiety and apathy, which may be different across cohorts [29]. Finally, it must be noted that the 2 samples under study are weighted heavily with White, highly educated participants, and there is a need to expand data collection in large cohorts to more diverse groups.

These limitations notwithstanding, the current study offers important insights into the nature of MCI diagnosis across 2 important cohorts of older adults, ADNI and NACC. Results suggest that individuals in the ADNI cohort had less cognitive impairment than those in NACC, particularly on measures of language. This disparity might be resolved by applying similar empirical procedures for diagnosing MCI across the 2 samples. Once diagnostic groups are made equivalent across cohorts, seamless harmonization can occur, enabling big data analytic approaches to understanding Alzheimer's to be developed.

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Table 1.

Demographic, clinical, and demographically corrected cognitive scores by the study cohort

Variable	NACC		ADNI		Mann-Whitney U	*p* value
	Mdn	IQR	Mdn	IQR		
Age	73.00	11.00	72.10	10.83	49,563.00	0.54
Education	16.00	4.00	16.00	2.00	48,358.50	0.27
Montreal Cognitive Assessment (raw score)	22.00	5.00	24.00	3.00	41,345.00	0.00*
Functional Activities Questionnaire total score	1.00	4.00	1.00	5.00	48,516.00	0.95
Geriatric Depression Score	1.00	3.00	1.00	3.00	49,358.50	0.53
Naming	−0.43	1.72	0.09	1.47	41,338.00	0.00*
Animal fluency	−0.98	1.20	−0.63	1.12	38,884.00	0.00*
Trailmaking A	−0.39	1.61	−0.35	1.55	50,329.50	0.80
Trailmaking B	−0.59	1.74	−0.23	1.56	40,982.50	0.00*
Immediate story recall	−0.91	1.44	−0.91	1.14	50,492.00	0.85
Delayed story recall	−0.95	1.51	−1.01	1.03	49,787.50	0.66

NACC, National Alzheimer's Coordinating Center; ADNI, Alzheimer's Disease Neuroimaging Initiative; Mdn, median; IQR, interquartile range.

*Significant after false discovery rate analysis; all cognitive test scores except for the MoCA are presented in terms of demographically adjusted normative data.

Table 2.

Percentage of demographically corrected below average scores for each test by cognitive status in NACC and ADNI

Variable	NACC, %	ADNI, %	χ^2	*p* value
Naming	26.36	16.03	6.42	0.01
Animal fluency	31.18	19.85	6.93	0.01
Trailmaking A	24.46	31.00	0.04	0.84
Trailmaking B	29.78	20.61	4.64	0.03
Immediate story recall	34.09	33.59	0.01	0.91
Delayed story recall	35.74	36.64	0.04	0.84