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ORIGINAL ARTICLE

The Revised National Alzheimer's Coordinating Center's Neuropathology Form—Available Data and New Analyses

Lilah M. Besser, PhD, Walter A. Kukull, PhD, Merilee A. Teylan, MPH, Eileen H. Bigio, MD, Nigel J. Cairns, PhD, Julia K. Kofler, MD, Thomas J. Montine, MD, PhD, Julie A. Schneider, MD, and Peter T. Nelson, MD, PhD

Abstract

Neuropathologic evaluation remains the gold standard for determining the presence and severity of aging-related neurodegenerative diseases. Researchers at U.S. Alzheimer's Disease Centers (ADCs) have worked for >30 years studying human brains, with the goals of achieving new research breakthroughs. Harmonization and sharing among the 39 current and past ADCs is promoted by the National Alzheimer's Coordinating Center (NACC), which collects, audits, and disburses ADC-derived data to investigators on request. The past decades have witnessed revised disease definitions paired with dramatic expansion in the granularity and multimodality of the collected data. The NACC database now includes cognitive test scores, comorbidities, drug history, neuroimaging, and links to genomics. Relatively, recent advances in the neuropathologic diagnoses of Alzheimer's disease, frontotemporal lobar degeneration (FTLD), and vascular contributions to cognitive impairment and dementia catalyzed a 2014 update to the NACC Neuropathology Form completed by all ADCs. New focal points include cerebrovascular disease (including arteriolosclerosis, microbleeds, and microinfarcts), hippocampal sclerosis, TDP-43, and FTLD. Here, we provide summary data and analyses to illustrate the potential for both hypothesis-testing and also generating new hypotheses using the NACC Neuropathology data set, which represents one of the largest multi-center databases of carefully curated neuropathologic information that is freely available to researchers worldwide.

Key Words: Lewy, MRI, Primary age-related tauopathy (PART), Stroke, Subjective memory complaint (SMC), Tauopathy.

INTRODUCTION

There is increasing appreciation of the heterogeneity and complexity of the brain diseases that are observed at autopsy among older individuals (1–5). Although the study of brain lesions after death is intrinsically cross-sectional, data from postmortem studies of lesion density and distribution have produced an understanding of the probable progression of various diseases over time and space in the brain. This understanding has been codified in the neuropathology (NP) staging systems that exist for some of the known brain lesions associated with cognitive impairment. Some of these staging systems are now being confirmed in longitudinal studies with positron emission tomography tracers and/or cerebrospinal fluid (CSF) analytes. Further, neuropathologic data may provide the basis for scientific advances related to both hypothesis testing and to the generation of new hypotheses that can be studied in other experimental and epidemiologic contexts. In order to characterize the neuropathologic phenotypes (individually, and the myriad combinations of diseases) in a comprehensive way, large data sets that derive from multiple state-of-the-art research centers are an important asset. Here, we describe how data from National Institute of Aging ([NIA], of the National Institutes of Health) funded Alzheimer's Disease Center (ADC) program, which has been gathered over decades, can be useful as a resource for investigators, and can also provide insights into how diagnostic practices that characterize state-of-the-art research centers have changed over time.

In 1984, the NIA established the ADC program (6), which evolved to include >30 different ADCs geographically dispersed across the US. It was tasked initially with collecting and maintaining a Minimum Data Set (MDS) (7). The MDS was a cross-sectional, primarily abstracted data set consisting of limited demographics and clinical information from

From the Department of Epidemiology, National Alzheimer's Coordinating Center, University of Washington, Seattle, Washington (LMB, WAK, MAT); Institute for Healthy Aging and Lifespan Studies and School of Urban and Regional Planning, Florida Atlantic University, Boca Raton, Florida (LMB); Feinberg School of Medicine, Northwestern University, Chicago, Illinois (EHB); Department of Neurology, Washington University in St Louis, St. Louis, Missouri (NJC); Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania (JKK); Department of Pathology, Stanford University, Stanford, California (TJM); Department of Pathology, Rush University, Chicago, Illinois (JAS); and Sanders-Brown Center on Aging, Division of Neuropathology, Department of Pathology, University of Kentucky, Lexington, Kentucky (PTN)

Send correspondence to: Lilah M. Besser, PhD, School of Urban and Regional Planning, Florida Atlantic University, 777 Glades Rd, SO-44 Room 371, Boca Raton, FL 33431; E-mail: lbesser@fau.edu

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Supplementary Data can be found at http://www.jnen.oxfordjournals.org.

participants' most recent evaluations at each ADC. The MDS included limited neuropathologic data by modern standards.

The National Alzheimer's Coordinating Center (NACC) was funded in 1999 in order to oversee data collection by the ADCs. A more comprehensive NP form was implemented by the ADCs in December 2001. With the 2001 NP form, the consensus-based NIA/Reagan neuropathologic criteria (8) became the rubric for operationalizing AD neuropathologic diagnoses among participants from the ADCs. Further, data were archived and disbursed so that researchers could analyze associations between clinical parameters (including rudimentary neurocognitive test scores) and AD-related neuropathologic changes (e.g. CERAD neuritic plaque densities (9) and Braak neurofibrillary tangle [NFT] stages (10)). The form also provided more detailed information on the presence of neuropathologic features including cerebrovascular disease (e.g. hemorrhages, microinfarcts), Lewy body disease, some types of frontotemporal lobar degeneration ([FTLD], e.g. Pick disease), prion disease, and medial temporal lobe sclerosis (including hippocampal sclerosis [HS]).

In 2005, the Uniform Data Set (UDS) was implemented by NACC to replace the MDS (11). The UDS provided researchers with longitudinal clinical data that could be linked to the NP data set, including detailed participant and coparticipant demographics, family history, health history, current medications, physical exam data (blood pressure, weight), neurological exam findings, Clinical Dementia Rating, behavioral and functional assessments, and a multidomain neuropsychological battery, all of which factor into criteria-based clinical diagnoses. Because of the standardization of the UDS, the possible research topics were expanded dramatically when considered together with the NP data.

The latest NP Form update was in 2014 (version 10 [v10]), catalyzed by the 2012 NIA-AA consensus-based updated guidelines for the evaluation of AD neuropathologic change (ADNC) (12) and updated FTLD classification. The v10 form incorporated the NIA-AA ADNC criteria and sampling recommendations, as well as additional advances to the neuropathologic classification and nomenclature of FTLD (13) and vascular contributions to cognitive impairment and dementia (VCID) (3, 14–18). With NACC's NP Form v10 (19), neuropathologic data include information on Thal phase for Aβ amyloid plaques (20); burden and location of infarcts, microinfarcts, hemorrhages, and microbleeds; newly defined and categorized FTLD neuropathologic changes such as FTLD-tau with subtypes of 3R and 4R tauopathies and separate FTLD-TDP-43; amyotrophic lateral sclerosis/motor neuron disease (ALS/MND); and HS of the CA1 and/or subiculum.

Although numerous prior studies have used NACC NP data, the newly revised NP Form has been described incompletely to date (6, 21). This paper aims to describe the data set and changes over time in the characteristics of participants and in the types of NP data collected. Additionally, this paper will highlight some examples of the types of research aims that can be addressed using the new NP Form data. Evolving concepts and brain lesions that are increasingly appreciated to be clinically meaningful can be studied, including primary age-related tauopathy (PART), HS, TDP-43 inclusions, microinfarcts, and many other subtypes of lesions that occur in aging brains.

MATERIALS AND METHODS

Participants

Participant data came from the MDS, UDS, and NP data set, collected through September 2017, from 38 past and present ADCs. The MDS consists of primarily cross-sectional data based on the last available clinical evaluation and NP data from autopsy. MDS participants were included in the present work if they either had a nonmissing primary neuropathologic diagnosis from the MDS form or had nonmissing data on CERAD neuritic plaque burden and Braak NFT stage from the NP Form. UDS participants were restricted to those who were not missing CERAD neuritic plaque burden or Braak NFT stage. MDS participants with NP data who were later followed in the UDS were only reported in the UDS group.

Research using the NACC database was approved by the University of Washington Institutional Review Board. Informed consent was obtained from all participants at the individual ADCs. The NACC data were de-identified.

Descriptive statistics (sample size and percentage, mean and standard deviation) were calculated for the sample's demographics, apolipoprotein E (*APOE*) genotype, cognitive status, and neuropathologic features according to the following time periods of the neuropathologic exam: 1984–1996, 1997–2001, 2002–2011, 2012–2013, and 2014–2017. These time periods were chosen to distinguish important dates of change to diagnostic criteria or new NP Form implementation. These specific periods are 1) data collected on the MDS form before 1997, prior to the NIA/Reagan AD neuropathologic criteria; 2) data collected on the MDS form from 1997 to 2001, once the NIA/Reagan AD criteria were implemented; 3) data collected on the NP Form from 2002 to 2011, prior to the NIA-AA ADNC criteria; 4) data collected on the NP Form from 2012 to 2013, once the NIA-AA ADNC criteria were implemented; and 5) data collected on the NP Form from 2014 to 2017, once v10 was implemented. The most recent NP Form (v10) additions are highlighted by providing the sample size and percentage of ADNC scores according to each "A" (Thal phase), "B" (Braak NFT stage), and "C" (neuritic amyloid plaque densities according to CERAD criteria) score, and the sample size and percentage by region of "old" microinfarcts and microbleeds.

Additional descriptive analyses to highlight the newest features also were performed. Supplementary Data Table S1 shows the frequency and percentage of each FTLD neuropathologic change and regional distribution of TDP-43-immunoreactive inclusions. Supplementary Data Table S2 provides the frequency of availability of other data sources/specimens for individuals with NP Form data, such as brain or postmortem CSF/blood specimens available at an ADC (NACC helps initially coordinate for investigators requesting specimens at ADCs (22)). Also shown are magnetic resonance imaging (MRI) available for download at NACC, and genetic data available at the Alzheimer's Disease Genetics Consortium (ADGC), as described in the NACC's web portal (https://www.alz.washington.edu/).

Three exploratory analyses were conducted which help demonstrate some of the available NP data and possible approaches. The first exploratory analysis investigated which brain lesions were associated with subjective memory complaint (SMC). SMC was defined as having a clinical diagnosis of normal cognition (not mild cognitive impairment [MCI] or demented) at the last UDS visit before death, but a participant-reported memory complaint was documented. Unadjusted associations between the lesions of interest and SMC were examined using chi-square tests, and adjusted associations were obtained using multivariable logistic regression adjusted for age at death and the lesions of interest.

The second analysis examined if the severity of arteriolosclerosis pathology at autopsy was associated with presence of comorbid medial temporal lobe/HS. Individuals who were <80 years at death were excluded since both HS and arteriolosclerosis are increasingly prevalent in advanced old age (23, 24). Also excluded from this analysis were participants with FTLD-tau, FTLD-TDP, multiple system atrophy (MSA), or prion disease. An adjusted analysis was conducted using logistic regression to control for age of death.

The third analysis examined the clinical status of individuals with PART, defined as having no neuritic amyloid plaques (according to the CERAD criteria) but Braak NFT stage > 0 (25), and that analysis stratified by Braak NFT stages. The percentages of participants with a given cognitive status (normal cognition, SMC, and MCI) were calculated for each Braak NFT stage. The trends by cognitive status observed in Braak stages II and IV were compared with all other Braak stages to test for statistical significance, using the Cochran-Armitage test for trend.

TABLE 1. Number of Neuropathologic Parameters Collected Over Time

Data Collection Instrument	Year of Implementation	Neuropathology Parameters Assessed
Minimum Data Set	1984	2
Neuropathology Form, version 1	2001	33
Neuropathology Form, version 9	2008	43
Neuropathology Form, version 10	2014	91

RESULTS

NP Form Features That Have Changed over Time

Ninety-one different parameters are collected in NP Form v10, compared with only 2 on the MDS form, 33 on the NP Form v1, and 43 on NP Form v9 (Table 1). The new v10 parameters include TDP-43 evaluation, FTLD subtypes, Thal Aβ stages (20), and increased emphasis on subtypes of cerebrovascular disease, particularly small vessel disease.

Cohort Characteristics and Features That Have Changed over Time

The sample consisted of 15,862 NACC participants with NP Form data, 11,129 of which came from the MDS, and 4,733 from the UDS (Supplementary Data Fig. S1). NP Form v10 was used for 1,570 of the neuropathologic exams (Table 2), and 3,519 of the autopsied participants had longitudinal UDS data.

The mean age at death among autopsied participants in the NACC data set increased from 77 years for those who had a neuropathologic exam prior to 1997, to 81 years among those with autopsies from 2014 to 2017 (Table 2). The mean years of education among participants also increased, from 13.3 years to 15.6 years, respectively. A small increase in the number of neuropathologic exams among Hispanics was

TABLE 2. Characteristics of Participants by Year of Neuropathological Exam

Characteristic	Year of Neuropathological Exam				
	1984–1996	1997–2001	2002–2011	2012–2013	2014–present
Sample size, n	3357	3275	6389	1271	1570
Age at death (years), mean (SD)	76.9 (10.7)	79.2 (10.1)	80.4 (11.4)	80.7 (11.7)	81.0 (11.5)
Male, n (%)	1706 (50.8%)	1535 (46.9%)	3204 (50.2%)	652 (51.3%)	823 (52.4%)
Education, mean (SD)	13.3 (3.7)	13.9 (3.5)	14.8 (3.4)	15.2 (3.3)	15.6 (3.2)
Race, n (%)					
White	3137 (93.5%)	3133 (95.7%)	6015 (94.2%)	1173 (92.3%)	1462 (93.1%)
Black/African American	104 (3.1%)	79 (2.4%)	189 (3.0%)	50 (3.9%)	57 (3.6%)
American Indian/Alaskan Native	6 (0.2%)	8 (0.2%)	8 (0.1%)	1 (0.1%)	1 (0.1%)
Asian/Native Hawaiian/Pacific Islander	10 (0.3%)	11 (0.3%)	47 (0.7%)	9 (0.7%)	14 (0.9%)
Other/multiracial/unknown	100 (3.0%)	44 (1.3%)	130 (2.0%)	38 (3.0%)	36 (2.3%)
Hispanic ethnicity, n (%)	38 (1.2%)	46 (1.4%)	166 (2.6%)	57 (4.5%)	57 (3.7%)
≥1 *APOE* ϵ4 allele, n (%)	1257 (56.8%)	1185 (52.9%)	2467 (47.2%)	473 (43.7%)	548 (44.3%)
Cognitive status, n (%)					
Not demented	583 (18.2%)	472 (14.5%)	1325 (20.9%)	302 (23.8%)	387 (24.7%)
Dementia	2619 (81.8%)	2787 (85.5%)	5021 (79.1%)	968 (76.2%)	1182 (75.3%)

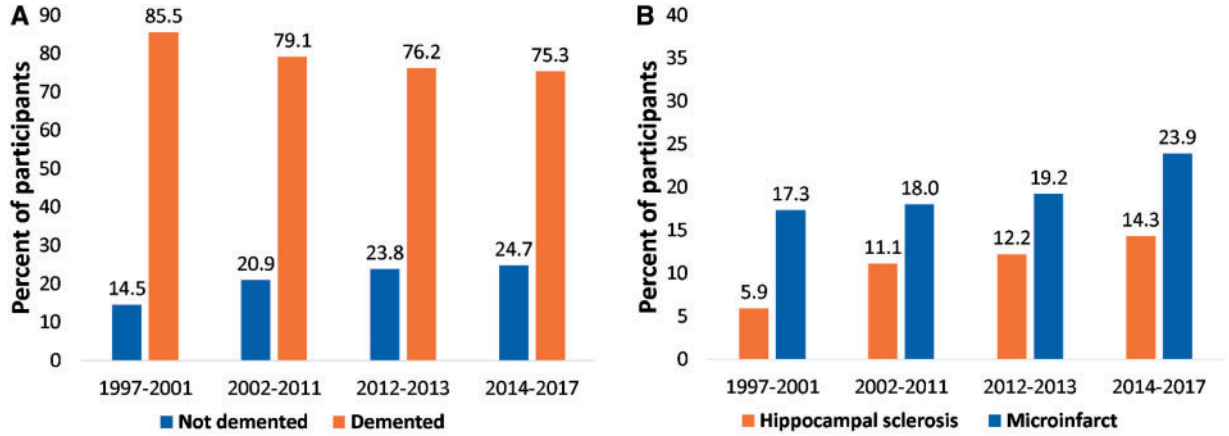

FIGURE 1. (A) Temporal change in cognitive status (from most recent evaluation) of autopsied participants in the National Alzheimer's Coordinating Center's data set. Note the trend for increased proportion of nondemented participants. **(B)** A sample of temporal change in underlying neuropathologies reported. Two pathologies that have tended to become more commonly diagnosed in recent years are microinfarcts and hippocampal sclerosis.

observed over time (1.2% prior to 1997 to 3.7% in 2014–2017), with little change observed for African Americans (3.1% prior to 1997 to 3.6% in 2014–2017). The percent of participants with at least one *APOE* ϵ4 allele decreased from 57% among exams prior to 1997 to 44% among exams conducted in 2014–2017. An increase over time was observed in the number of autopsied participants who were not diagnosed with dementia before death (15% in 1997–2001 to 25% in 2014–2017) (Fig. 1A).

From the standpoint of neuropathologic features, there was an increase in the number of participants who were indicated as having HS (6% in 1997–2001 to 14% in 2014–2017) or microinfarcts (17% in 1997–2001 to 23% in 2014–2017) (Fig. 1B). Reporting of no arteriolosclerosis decreased over time (27% in 2002–2011 to 19% in 2014–2017), whereas mild or moderate arteriolosclerosis increased slightly. FTLD with tau inclusions (e.g. corticobasal degeneration, progressive supranuclear palsy, and Pick disease) increased from 10% in 2002–2011 to 15% in 2014–2017, and FTLD with TDP-43 inclusions (ascertained in participants assessed using NP Form v10 only) was reported in 9% of participants from 2012 to 2017 (Table 3).

The percent of participants with a given neuritic plaque score or Braak NFT stage remained relatively consistent over time, from 2002 to 2017 (Table 3). ADNC scores were available from 1,727 participants who were assessed using NP Form v10 (Table 4). Approximately 50% of participants had a high level of ADNC, 20% had a moderate level of ADNC, 16% had a low level of ADNC, and 13% had no ADNC.

Certain neuropathologic features of small blood vessel disease were introduced in the NP Form v10. At least one "old" (i.e. not acute) microinfarct was observed in the cerebral cortex in 13% of participants, in the subcortical cerebral/periventricular white matter in 4% of participants, in the subcortical grey matter in 10% of participants, and in the brainstem and cerebellum in 4% of participants (Table 5). Microbleeds were noted less frequently, with at least one "old microbleed" observed in the cerebral cortex in 3% of participants, in the subcortical cerebral/periventricular white matter in 3% of participants, in the subcortical grey matter in 3% of participants, and in the brainstem and cerebellum in 0.5% of participants.

Association Between Brain Lesions and SMC

Among participants with clinical diagnoses of normal cognition, 93 had SMC and 388 had no SMC at their final UDS visit before neuropathological exam (Table 6). In unadjusted analyses, presence of frequent neuritic amyloid plaques and presence of Braak NFT stages V–VI were borderline associated with SMC, but these associations weakened further in the adjusted analysis. It must be noted that among those with frequent neuritic plaques, a small percentage (2.7%) had normal cognition (with or without SMC). Similarly, among those with Braak NFT stages V–VI, a small percentage had normal cognition (1.4%). As can be observed in Table 6 by summing the SMC and No SMC groups, the percentage of those with normal cognition prior to death who had frequent neuritic plaques or Braak NFT stage V–VI was also rare. Lewy body disease (any vs none), medial temporal lobe/HS, and severity of arteriolosclerosis were not associated with SMC in unadjusted or adjusted analyses. However, at least one microinfarct was noted more frequently in those with SMC (33%) than those without SMC (22%), and this difference was statistically significant in unadjusted and adjusted analyses (adjusted odds ration [OR]: 2.24; 95% confidence interval (CI): 1.24–4.06).

Association Between Severity of Arteriolosclerosis and Presence of HS

In v1-9 of the NP Form, HS was considered together with medial temporal lobe sclerosis. Therefore, our analysis was conducted separately for participants assessed with NP Form v1-9 and for those assessed with v10, which collected HS alone. After controlling for age of death, moderate arteriolosclerosis was associated with the presence of medial temporal lobe/HS in participants assessed with NP Form v1-9 (adjusted OR: 1.62; 95% CI: 1.28–2.05) and with HS in those

TABLE 3. Neuropathological Features at Autopsy by Year of Death

Neuropathology	2002–2011	2012–2013	2014–Present
Sample size, n	6389	1271	1570
NP Form Version			
Versions 1–9	6387 (100.0%)	1091 (85.8%)	6 (0.4%)
Version 10	2 (0.0%)	180 (14.2%)	1564 (99.6%)
Neuritic plaques, n (%)			
None (C0)	1223 (19.1%)	258 (20.3%)	356 (22.7%)
Sparse (C1)	816 (12.8%)	162 (12.8%)	135 (8.6%)
Moderate (C2)	1179 (18.5%)	239 (18.8%)	332 (21.2%)
Frequent (C3)	3171 (49.6%)	612 (48.2%)	747 (47.6%)
Braak stage for neurofibrillary degeneration, n (%)			
0 (B0)	455 (7.1%)	85 (6.7%)	88 (5.6%)
I–II (B1)	1093 (17.1%)	234 (18.4%)	260 (16.6%)
III–IV (B2)	1532 (24.0%)	278 (21.9%)	349 (22.2%)
V–VI (B3)	3309 (51.8%)	674 (53.0%)	873 (55.6%)
Lewy body pathology, n (%)			
None	4353 (69.2%)	860 (68.2%)	1002 (64.1%)
Brainstem predominant	224 (3.6%)	52 (4.1%)	58 (3.7%)
Limbic	498 (7.9%)	119 (9.4%)	294 (18.8%)
Neocortical	820 (13.0%)	159 (12.6%)	191 (12.2%)
Present, other region/unspecified	392 (6.2%)	71 (5.6%)	18 (1.2%)
Medial temporal lobe/hippocampal sclerosis, n (%)	657 (11.1%)	143 (12.2%)	222 (14.3%)
Microinfarcts, n (%)	1123 (18.0%)	244 (19.2%)	375 (23.9%)
Arteriolosclerosis, n (%)			
None	1508 (26.8%)	224 (19.7%)	275 (18.9%)
Mild	2003 (35.6%)	421 (37.1%)	559 (38.3%)
Moderate	1489 (26.5%)	325 (28.6%)	457 (31.3%)
Severe	622 (11.1%)	165 (14.5%)	168 (11.5%)
FTLD-tau (CBD, PSP, Pick disease, other)	616 (9.6%)	169 (13.3%)	229 (14.6%)
FTLD-TDP-43 (v10)	NC	13 (9.4%)	104 (9.0%)

Abbreviations: NC, not collected; FTLD, frontotemporal lobar degeneration; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; TDP, transactive response DNA binding protein.

TABLE 4. Distribution of Alzheimer Disease Neuropathologic Change (ABC) Score among 1727 Participants With Neuropathology Form Version 10

AD Neuropathologic Change		B (Braak/Neurofibrillary Score)		
A (Thal Phase)	C (CERAD)	0 or 1 n (%)	2 n (%)	3 n (%)
0	0	168 (9.7%)	55 (3.2%)	3 (0.2%)
1	0 or 1	101 (5.9%)	73 (4.2%)	5 (0.3%)
	2 or 3	17 (1.0%)	32 (1.9%)	22 (1.3%)
2	Any C	54 (3.1%)	93 (5.4%)	61 (3.5%)
3	0 or 1	29 (1.7%)	30 (1.7%)	14 (0.8%)
	2 or 3	20 (1.2%)	91 (5.3%)	859 (49.7%)

Abbreviations: AD, Alzheimer disease; CERAD, Consortium to Establish a Registry for Alzheimer's Disease.

assessed with NP Form v10 (adjusted OR: 1.88; 95% CI: 1.03–3.41) (Table 7). The association between severe arteriosclerosis and HS was suggestive but not statistically significant among NP Form v10 participants (adjusted OR: 1.91; 95% CI: 0.94–3.88). The refinement in the definition of HS for NP Form v10 may help to explain the stronger association between arteriolosclerosis severity and HS using v10 versus v1-9.

Although data on TDP-43 inclusions by region is limited to date (collected only in v10), posthoc analyses were conducted to examine associations between arteriolosclerosis severity and presence of TDP-43 pathology in the hippocampus, since many of those with HS are expected to be TDP-43-positive. Seventy-eight percent of the v10 participants with HS had TDP-43 in the hippocampus (104 with HS had non-missing data on TDP-43). In this relatively small subsample, the association between arteriolosclerosis and TDP-43 pathology in the hippocampus was not statistically significant after controlling for age of death, although the association with severe arteriolosclerosis was suggestive (adjusted OR: 1.45; 95% CI: 0.77–2.75) (Supplementary Data Table S3).

Braak NFT Stage in PART by Cognitive Status

To assess the association between PART and cognitive status, we stratified by severity of PART (operationalized

TABLE 5. Number and Region of Old Microinfarcts and Microbleeds Collected on Neuropathology Form Version 10

Region	"Old" Microinfarcts, n (%)				"Old" Microbleeds, n (%)			
	None	1	2	≥3	None	1	2	≥3
Cerebral cortex	1519 (87.3%)	120 (6.9%)	39 (2.2%)	62 (3.6%)	1586 (97.2%)	18 (1.1%)	16 (1.0%)	11 (0.7%)
Subcortical cerebral/periventricular WM	1666 (95.8%)	33 (1.9%)	10 (0.6%)	31 (1.8%)	1580 (96.9%)	2 (0.1%)	9 (0.6%)	40 (2.5%)
Subcortical grey matter	1556 (89.5%)	88 (5.1%)	35 (2.0%)	59 (3.4%)	1575 (96.6%)	15 (0.9%)	20 (1.2%)	21 (1.3%)
Brainstem and cerebellum	1661 (95.7%)	43 (2.5%)	11 (0.6%)	21 (1.2%)	1621 (99.5%)	5 (0.3%)	0 (0.0%)	4 (0.3%)

Abbreviations: WM, white matter.

TABLE 6. Neuropathology in Cognitively Normal Individuals With and Without Subjective Memory Complaint

Neuropathology	SMC at Last Visit n = 93 n (%)	No SMC at Last Visit n = 388 n (%)	Chi-square Test p value	Multivariable Model[d] OR (95% CI)
Neuritic plaques				1.37 (0.57–3.31)[a]
None or sparse	42 (45.2%)	184 (47.4%)	0.05[a]	
Sparse	23 (24.7%)	89 (22.9%)		
Moderate to frequent	13 (14.0%)	79 (20.4%)		
Frequent	15 (16.1%)	36 (9.3%)		
Braak stage for neurofibrillary degeneration				1.68 (0.66–4.26)[b]
Stage 0	6 (6.5%)	24 (6.2%)	0.08[a]	
Stage I–II	36 (38.7%)	182 (46.9%)		
Stage III–IV	41 (44.1%)	160 (41.2%)		
Stage V–VI	10 (10.8%)	22 (5.7%)		
Lewy body pathology, any	15 (16.1%)	58 (15.0%)	0.79	0.83 (0.38–1.84)
Arteriolosclerosis				0.74 (0.27–1.99)[c]
None	16 (23.2%)	89 (25.9%)	0.68[c]	
Mild	31 (44.9%)	154 (44.8%)		
Moderate	16 (23.2%)	76 (22.1%)		
Severe	6 (8.7%)	25 (7.3%)		
Medial temporal lobe sclerosis including HS	2 (2.2%)	5 (1.4%)	0.59	0.43 (0.04–4.18)
Microinfarcts	**31 (33.3%)**	**87 (22.4%)**	**0.03**	**2.24 (1.24–4.06)**

Abbreviations: SMC, subjective memory complaint; HS, hippocampal sclerosis; OR, odds ratio; CI, confidence interval.
[a]Comparing frequent neuritic plaques to all other neuritic plaque scores combined.
[b]Comparing Braak V–VI to all other Braak stages combined.
[c]Comparing severe arteriolosclerosis to all other severities combined.
[d]Additionally controlling for age at death.

using Braak NFT stages) according to the participant's final documented cognitive state (Fig. 2). We emphasize that PART is a tauopathy that is distinct from FTLD-tau as described previously (25). Among those with documented PART (which we defined here as participants with no neuritic plaques according to the CERAD criteria), several patterns emerged. The percentage of participants with Braak NFT stage II decreased with worsening cognitive status (normal cognition to SMC to MCI) (trend test, Braak stage II vs all other stages, $p = 0.03$) and the percentage with Braak NFT stage IV increased with worse cognitive status (trend test, Braak stage IV vs all other stages, $p = 0.007$). We highlight the apparent importance of the transition-point between Braak NFT stages III and IV. Additionally, while the large majority of PART participants with normal cognition or SMC had Braak stage II or lower, the large majority of those with MCI had Braak stage II–IV.

DISCUSSION

Here, we present data focusing on the newly revised NACC NP form (v10), in the context of the NACC database that has been actively expanding, with many updates and audits over the span of several decades. These data underscore that both cohort characteristics and neuropathologic diagnoses are "moving targets". The focus of prior scholarship has

TABLE 7. Hippocampal Sclerosis by Arteriolosclerosis Severity

Severity of Arteriolosclerosis	NP Form Versions 1–9[a]			NP Form Version 10		
	HS+, n (%)[b, c]	HS-, n (%)[b]	aOR (95% CI)[d]	HS+, n (%)[b, c]	HS-, n (%)[b]	aOR (95% CI)[d]
None	137 (26.5%)	1387 (32.9%)	Ref.	16 (11.8%)	132 (19.1%)	Ref.
Mild	124 (23.9%)	1229 (29.2%)	0.98 (0.76–1.26)	47 (34.6%)	242 (34.9%)	1.60 (0.88–2.94)
Moderate	189 (36.5%)	1120 (26.6%)	**1.62 (1.28–2.05)**	53 (39.0%)	233 (33.6%)	**1.88 (1.03–3.41)**
Severe	68 (13.3%)	478 (11.3%)	1.33 (0.97–1.81)	20 (14.7%)	86 (12.4%)	1.91 (0.94–3.88)

Abbreviations: HS, hippocampal sclerosis; FTLD, frontotemporal lobar degeneration; NP, neuropathology; TDP, transactive response DNA binding protein; aOR, adjusted odds ratio; CI, confidence interval; Ref, reference group.
[a]NP Form versions 1–9 assessed hippocampal sclerosis and medial temporal lobe sclerosis together.
[b]Mild, moderate, or severe HS.
[c]Excluding: FTLD-tau, multiple system atrophy, prion disease, FTLD-TDP, individuals who died younger than 80.
[d]Controlling for age at death in logistic regression.

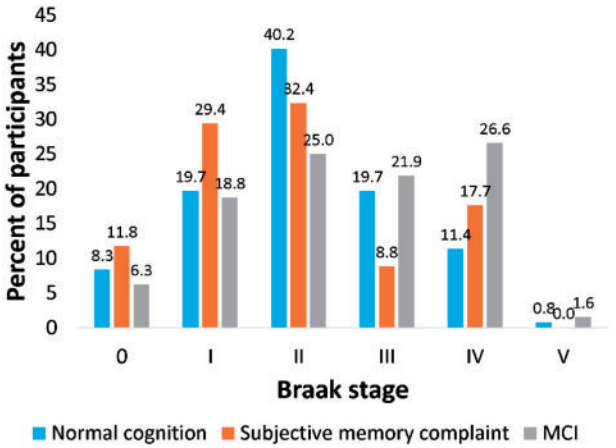

FIGURE 2. Individuals with primary age-related tauopathy ([PART]; no neuritic plaques), stratified by cognitive status at last visit. Excluded from this analysis were persons who died at <70 years of age or who had hippocampal sclerosis or Lewy body disease pathology. Sample sizes: n = 132 with normal cognition; n = 34 with subjective memory complaint; n = 64 with mild cognitive impairment. Cochran-Armitage test for trend: Braak neurofibrillary tangle (NFT) stage II versus all other Braak NFT stages, p = 0.03; Braak NFT stage IV versus all other Braak NFT stages, p = 0.007.

shifted to incorporate more emphasis on predementia states and a complex array of disease phenotypes. We highlighted some of the research topics that can be addressed using the new NP Form data. For example, we showed data and analyses that suggests microinfarcts may be a pathologic substrate related to SMC, and, arteriolosclerosis tends to be more severe in cases with comorbid HS, according to prior data with a trend in v10 data. Further, we provide analyses of clinical-pathological correlation in PART, which considered altogether help display some of the research questions that can be addressed with the NACC NP data set.

Since no extant data set with NP data is of truly epidemiologic scope (no diverse population has 100% autopsy rate with state-of-the-art NP diagnosis and rigorous data collection as far as we know), the characteristics of each data set are important to document in order to understand the types of research questions that can be addressed using that resource. There are important potential pitfalls that should be considered when using the NACC data set to study brain diseases. The data set's characteristics provide limits to the types of questions that can be asked and the generalizability of the results. Fundamentally, NACC data derive from ADCs, many of which are associated with dementia clinics. Dementia clinics can supply patient populations that are enriched for rare, genetic, early-onset, and "pure" subtypes of diseases that include AD but also FTLD, MSA, prion diseases and other conditions that are relatively rarely (<1%) seen in community-based cohorts (which, by contrast, tend to have more VCID, HS, and mixed pathologies). Indeed, clinic cohorts select for diseases more likely to bring a person to medical attention such as impairment at a younger age, hallucinations (e.g. dementia with Lewy bodies) or behavioral abnormalities (e.g. FTLD). These considerations need to be incorporated into study designs when analyzing NACC data—some studies should exclude rare diseases up-front, whereas there also are opportunities for other research projects that focus on rarer diseases themselves. Additionally, investigators using NACC data should carefully consider the differences in data collected over time, as well as changes in the demographics and clinical and neuropathologic characteristics of the sample over time. To assist with this, NACC developed a researcher's data dictionary for the NP data (RDD-NP (21)) to help tease apart major changes in the NP Form versions.

Another set of potential biases apply to parameters related to participant characteristics. The NACC-contributory ADCs tend to recruit, retain, and achieve autopsy consent for Caucasian/white individuals of relatively high socioeconomic status; thus, due to this "volunteer bias" there are relatively few non-Caucasian individuals or those lacking higher education. It is unsafe to assume that the individuals recruited from one ethnicity are truly comparable in every way with individuals that are recruited from a different ethnic group, since ADCs may be recruiting from completely different population pools. Further, ADCs apply exclusion criteria that can limit the number of autopsied participants with mental illness, substance abuse, physical disability, or other prevalent conditions. Collectively these problems are probably more impactful because of the "sameness" of the ADCs, rather than differences

between ADCs—the demographic and disease-related biases of the NACC data set need to be kept in mind.

When considering differences between ADCs, perhaps most important are the methods and practices of individual neuropathologists, although inter-ADC differences have been decreased substantially due to the relatively standardized sampling and staining suggestions of the 2012 NIA-AA recommendations (12). A recently published study provided some evidence that center-to-center practice differences may not make a substantial difference in ultimate determination of a pathologic diagnosis of AD (26). However, systematic studies of other pathologic lesions have not been conducted. Nonuniform data collection could potentially lead to erroneous conclusions or be a source of uninformative nulls. For these reasons, replication of these findings will be important. The heterogeneity of neuropathologist practices at ADCs can also be seen as a strength of the NACC data set. These ~30 research centers represent both the state-of-the-art and also the state-of-the-field. For example, one could argue that the results of cerebral amyloid angiopathy evaluation methods applied by the 30 different ADCs (using similar but nonidentical diagnostic approaches within the rubric of the NACC NP Form) could be more generalizable than the findings applied by a single neuropathologist using his or her own particular techniques given that no gold-standard method exists currently. It seems likely that some of the changes over time (e.g. increased rates of diagnoses of microinfarcts and HS pathologies) simply reflect the changing diagnostic tendencies of neuropathologists at ADCs. Since both clinical and pathological practices have rapidly evolved, revisions of the NACC NP form have necessarily required updating data fields; researchers should be careful when conducting studies involving data that spans NP versions. The NACC RDD-NP is a great help in negotiating this difficulty, and we emphasize that researchers should carefully review it and/or consult NACC personnel when planning their studies.

In addition to the above considerations, an investigator who is contemplating using the NACC data set to address research questions should also consider the many strengths of the NACC NP data set. Briefly mentioned above, the NP data set, with enriched sample sizes for rare or infrequently captured clinical symptoms and neuropathologic conditions, allows for research studies that are typically not possible using cohort or community-based studies (e.g. neuropathological observations in both African Americans and whites (27)), often providing sufficient statistical power to conduct multivariable analyses. Rarer diseases such as FTLD (Supplementary Data Table S1) and MSA, which are nearly impossible to study in community-based autopsy samples, can be examined using NACC's NP data set. There is a large and increasing pool of data from individuals followed longitudinally with yearly visits, and their cognitive trajectories and medical histories provide a rich potential for future studies. Additionally, many participants with NP data have supplemental data or specimens that are of great value and interest to researchers, including MRI and genotype data from the Alzheimer's Disease Genetics Consortium (ADGC) (Supplementary Data Table S2).

Further, NACC's data are extensively reviewed to ensure that the data values submitted by ADCs are within expected ranges and are scientifically sound. To date, NACC has programmed many thousands of data quality checks that require an ADC to either verify that an outlier value is valid or to correct it before it will be accepted by NACC. As an example, NACC programmed 15 data quality checks to verify that any submitted ADNC score on NP Form v10 corresponds to the correct combination of A (Thal Aβ phase), B (Braak NFT stage), and C scores (CERAD neuritic plaque score), based on the NIA-AA criteria guidelines (12). As the NP Form v10 was developed, new data quality checks were established to minimize erroneous data submission starting from the implementation of the form. In addition, data quality checks are revised continuously or created by NACC as new data quality issues come to light.

The research productivity using the NACC data continues to increase every year, which is a testament to the breadth of the data available and its ability to stay current with the most recent diagnostic criteria and the state of the science. As of October 2017, 462 manuscripts and 420 abstracts have been published using the NACC data (see "Publications and Productivity" link at http://www.alz.washington.edu). Since January 2017, published manuscripts using the NP data focused on a wide range of topics including the genetics of HS (28), factors associated with being symptomatic (29) and cognitive decline observed in PART (30), mixed pathologies and cognitive decline (2), pathologic correlates of Lewy body disease (31), the correlation between treated hypothyroidism and AD, cerebrovascular, and HS pathologies (32), and the association between Braak NFT stage and clinical progression in AD (33).

The exploratory analyses that are included in the present paper indicate two different critical contexts in which NACC NP data can be used: Relatively open-ended hypothesis generation analyses and relatively focused hypothesis testing (replication studies). An example of open-ended hypothesis generation is seen in our analyses of the neuropathologic features that are associated with SMC among ADC research participants. The NACC NP data set allowed us to test for associations between SMC status and more than a dozen different brain pathologies. These analyses would be quite challenging to achieve in any single-center study due to sample size restrictions. Prior scholarship has indicated the associative clinical-pathological impact of microinfarcts (34–38), but never specifically associated with SMC. The outcome of this exploratory analysis suggests that in addition to AD neuropathology, microinfarcts may be a candidate for an underlying substrate of SMC. Although not a hypothesis that was predicted a priori, this deserves more thorough investigation in other cohorts.

Examples of analyses that serve as more focused hypothesis-testing experiments using NACC NP data are shown in Table 7, related to the association between HS and comorbid arteriolosclerosis, and also Figure 2, related to the association between PART severity and antemortem cognitive status. Prior studies have indicated an association between HS and arteriolosclerosis (23, 39). The data shown in Table 7 demonstrate a statistically significant association between

moderate arteriolosclerosis and HS, and a suggestive association between severe arteriolosclerosis and HS after controlling for age at death. These findings are quite similar to prior results (23). Note that statistically, "two-tailed" tests were applied although it could be argued a "one-tailed" test may be more appropriate. HS pathology in the aged population, unlike that associated with anoxia or epilepsy, is in the large majority of cases comorbid with TDP-43 pathology (24, 40–42), but it is unknown whether TDP-43 pathology specifically is associated with arteriolosclerosis. An initial analysis of arteriolosclerosis severity and TDP-43 pathology in the hippocampus did not demonstrate a significant association (Supplementary Data Table S3). However, the sample size was limited since data collection on TDP-43 pathology by region started with NP Form v10 and not all ADCs report these data. While prior studies have generated recommendations for HS pathological evaluation (43), there still is a great need for additional study of HS and TDP-43 pathologies in advanced old age.

Another non-AD pathologic feature that we assessed was PART. Increasingly severe PART (operationalized using Braak NFT stages (25)) has previously been shown to be associated with impaired cognition (25) and with increased risk of being in SMC or MCI states (44, 45) versus intact cognition. The new data suggest that PART with Braak NFT stage IV in particular may be associated with an increased risk of experiencing SMC. This underscores that Braak NFT staging does not reflect a "linear" system to quantify disease burden; rather, the advanced stages of disease (VI > V > IV) reflect substantially greater disease burden than prior stages (46), which is consistent with the results of clinical-pathologic correlation studies (47–49).

We conclude by emphasizing that NP data are a key component of research in the field of neurodegenerative diseases, and, recent analyses of data from large autopsy series have enabled important conceptual breakthroughs. These studies have revealed rich complexity in the neuropathologic findings among aged brains and underscored that no other experimental system can fully recapitulate the unique environment of the aged human brain. As such, research focusing on the brain lesions of aged humans has suggested new opportunities and new challenges related to diagnostic and therapeutic strategies. The large amount of multimodal information in the NACC data set that can be integrated and analyzed collectively attest to the evolving nature of the field of neurodegenerative disease research, and to some of the roles that the NACC NP Form data can play in helping to move the field forward.

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