Title

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Journal

Neurology, 97(13)

ISSN

0028-3878

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Publication Date

2021-09-28

DOI

10.1212/wnl.0000000000012600

Peer reviewed

RESEARCH ARTICLE

Data-Driven vs Consensus Diagnosis of MCI

Enhanced Sensitivity for Detection of Clinical, Biomarker, and Neuropathologic Outcomes

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Neurology® 2021;97:e1288-e1299. doi:10.1212/WNL.0000000000012600

Abstract

Background and Objectives

Given prior work demonstrating that mild cognitive impairment (MCI) can be empirically differentiated into meaningful cognitive subtypes, we applied actuarial methods to comprehensive neuropsychological data from the University of California San Diego Alzheimer's Disease Research Center (ADRC) in order to identify cognitive subgroups within ADRC participants without dementia and to examine cognitive, biomarker, and neuropathologic trajectories.

Methods

Cluster analysis was performed on baseline neuropsychological data (n = 738; mean age 71.8). Survival analysis examined progression to dementia (mean follow-up 5.9 years). CSF Alzheimer disease (AD) biomarker status and neuropathologic findings at follow-up were examined in a subset with available data.

Results

Five clusters were identified: optimal cognitively normal (CN; n = 130) with above-average cognition, typical CN (n = 204) with average cognition, nonamnestic MCI (naMCI; n = 104), amnestic MCI (aMCI; n = 216), and mixed MCI (mMCI; n = 84). Progression to dementia differed across MCI subtypes (mMCI > aMCI > naMCI), with the mMCI group demonstrating the highest rate of CSF biomarker positivity and AD pathology at autopsy. Actuarial methods classified 29.5% more of the sample with MCI and outperformed consensus diagnoses in capturing those who had abnormal biomarkers, progressed to dementia, or had AD pathology at autopsy.

Discussion

We identified subtypes of MCI and CN with differing cognitive profiles, clinical outcomes, CSF AD biomarkers, and neuropathologic findings over more than 10 years of follow-up. Results demonstrate that actuarial methods produce reliable cognitive phenotypes, with data from a subset suggesting unique biological and neuropathologic signatures. Findings indicate that data-driven algorithms enhance diagnostic sensitivity relative to consensus diagnosis for identifying older adults at risk for cognitive decline.

MORE ONLINE

Podcast
Dr. Gregg Day discusses the paper "Data-Driven vs Consensus Diagnosis of MCI: Enhanced Sensitivity for Detection of Clinical, Biomarker, and Neuropathologic Outcomes" with Dr. Emily Edmonds.
NPub.org/8r0hcr

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

$A\beta_{1-42}$ = β-amyloid peptide 1–42; **AD** = Alzheimer disease; **ADRC** = Alzheimer's Disease Research Center; **aMCI** = amnestic mild cognitive impairment; **ANOVA** = analysis of variance; **CDR** = clinical dementia rating; **CN** = cognitively normal; **DLB** = dementia with lewy bodies; **FDR** = false discovery rate; **FTLD** = frontotemporal lobal degeneration; **HR** = hazard ratio; **HSD** = honestly significant difference; **MCI** = mild cognitive impairment; **mMCI** = mixed mild cognitive impairment; **MMSE** = mini-mental state examination; **NACC** = National Alzheimer's Coordinating Center; **naMCI** = nonamnestic mild cognitive impairment; **NIA** = National Institute on Aging; **NINCDS-ADRDA** = National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; **oCN** = optimal cognitively normal; **PDD** = Parkinson disease dementia; **UCSD** = University of California San Diego; **tCN** = typical cognitively normal.

Mild cognitive impairment (MCI) is typically diagnosed based on a largely subjective interpretation of an individual's cognitive symptoms and test performance. In the context of research studies and clinical trials, the diagnosis is frequently based on the Petersen/Winblad criteria,[1,2] or on a consensus diagnosis in which a team of experts use subjective and objective assessment to varying degrees to arrive at a diagnostic impression.[3] A potential limitation of these diagnostic strategies is that they rely heavily upon subjective report and clinical judgment, which could lead to diagnostic errors[4-8] and limit standardization within and across research laboratories and clinics.

An alternative to these conventional methods is to assign diagnostic classifications using an actuarial, or data-driven, approach. Through application of statistical techniques such as cluster analysis or latent profile analysis to neuropsychological test scores, studies from our group and others have identified unique MCI subtypes in community-based,[4,9-12] clinic-based,[13-15] and clinical trial[16] samples. Our empirically derived MCI subtypes are tightly associated with CSF[4,9] and neuroimaging[17-19] biomarkers of Alzheimer disease (AD), as well as risk of functional decline[20] and dementia.[4,9] Generalizability of these actuarial methods has been demonstrated in non-AD populations such as HIV[21,22] and epilepsy.[23]

Given that much of our previous work has been limited by brief cognitive batteries administered in the context of large epidemiologic studies (e.g., Alzheimer's Disease Neuroimaging Initiative[24]), we applied actuarial methods to comprehensive neuropsychological data in a large, well-characterized sample from the University of California San Diego (UCSD) Shiley-Marcos Alzheimer's Disease Research Center (ADRC). We hypothesized that cluster-derived cognitive subgroups would be associated with differing rates of progression to dementia, CSF biomarkers, and neuropathologic findings.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The research protocol was reviewed and approved by the UCSD institutional review board. Written informed consent to participate in the study was obtained from all participants or their caregivers. Informed consent for autopsy was obtained at the time of death from the next of kin.

Participants

Participants were 738 individuals without dementia, age 50 or older (mean age 71.8 years [SD 7.7]; mean education 14.5 years [SD 4.0]; 54.2% female; 90.2% White), participating in the UCSD ADRC longitudinal study. Inclusion criteria included stable health status, availability of a study partner, and no history of major stroke, neurologic disorders, severe psychiatric illness, substance abuse, or learning disability. Participants diagnosed with dementia at baseline, as determined by consensus diagnosis and National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria,[25,26] were excluded from this study.

Diagnostic and Neuropsychological Procedures

Participants completed annual clinical, neurologic, and neuropsychological evaluations as part of the ADRC research protocol.[27,28] A diagnosis of cognitively normal (CN), impaired–not MCI (i.e., impaired performance judged to be related to other factors in a participant's history such as low premorbid functioning), MCI, or dementia was determined at each visit by the consensus of a multidisciplinary team (2 senior neurologists and a neuropsychologist).

A battery of neuropsychological tests was administered at baseline and each subsequent follow-up evaluation. For the current study, raw scores were converted into demographically adjusted (age, education, sex) *z* scores based on regression coefficients derived from performance of a subset of the sample identified as robust CN participants (n = 355). Participants in the robust CN sample were all ADRC participants who had at least 1 year of follow-up data available and remained classified as cognitively normal based on the consensus diagnosis for the duration of their participation in the ADRC longitudinal study (mean follow-up 6.6 years [SD 5.6]). The robust CN sample was well-matched at baseline (mean age 71.6 years [SD 8.5]; mean education 14.9 years [SD 3.7]; 59.4% female; 92.1% White) with the overall study sample.

Composite *z* scores were created in order to capture performance across 5 cognitive domains based on up to 19 test

scores (Table 1). The learning and memory domain was overrepresented for the detection of early AD. The cluster analysis included all participants without dementia with sufficient neuropsychological data (309 of the robust CNs were included; the remaining 46 were missing all scores from one or more of the cognitive domains, most commonly the visuospatial domain).

CSF Biomarkers

CSF data were available for 197 (26.9%) participants (mean age 72.6 years [SD 5.6]; mean education 16.3 years [SD 2.7]; 54.3% female; 95.4% White). Each participant received a lumbar puncture with standardization of procedures as previously described[29] and in accordance with recommended best practices[30] (see eMethods, available from Dryad [doi.org/10.6076/D1F300]). CSF AD biomarkers examined were β-amyloid ($A\beta_{1-42}$), total tau, and the ratio of tau over Aβ ($tau/A\beta_{1-42}$), which has been shown to provide a better subdivision of individuals into those with and without preclinical AD.[31] A cut point for biomarker positivity ($tau/A\beta_{1-42} > 0.52$) was derived from a larger cohort of 462 CSF samples from ADRC participants (see eMethods); the cut point is highly consistent with a previously published cut point.[32]

Neuropathology

Neuropathologic data were available for 157 (21.3%) participants (mean age at death 86.3 years [SD 7.3]; mean education 15.3 years [SD 3.0]; 47.8% female; 98.1% White). Autopsy procedures were followed as previously described.[27] Brains were staged for degree of neurofibrillary tangle pathology using the Braak staging scheme.[33] Estimates of neuritic plaque density were calculated using methods recommended by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD).[34] AD was operationalized using the National Institute on Aging (NIA)–Reagan consensus criteria for the postmortem diagnosis of AD, resulting in classification as low, intermediate, or high likelihood that cognitive impairment was due to the observed AD neuropathology.[35]

Dementia with Lewy bodies (DLB) and Parkinson disease dementia (PDD) pathology fell into either the limbic (transitional) or neocortical subtypes proposed in the 1996 consensus guidelines for the pathologic diagnosis of DLB.[36] Cases were considered to have significant vascular pathology if there were apparent macroscopic infarcts, microinfarcts, or hemorrhages. Other pathologies were rare and grouped together for analysis. These included hippocampal sclerosis (n = 17), frontotemporal lobal degeneration (FTLD, n = 3), Hallervorden-Spatz disease (n = 1), primary age-related tauopathy (n = 6), and multiple sclerosis (n = 1).

Statistical Analysis

Cluster analysis was performed on baseline neuropsychological data for all participants. Composite cognitive domain *z* scores were entered into a hierarchical cluster analysis, consistent with our previous work.[4,9,10,13] To examine the ability of the neuropsychological scores to discriminate between cluster-derived groups, a discriminant function analysis was conducted using the composite *z* scores to predict group membership.

Analysis of variance (ANOVA) and χ^2 tests compared cluster-derived groups on demographic characteristics, *APOE* ε4 status, and duration of follow-up. Cox regression adjusting for demographics determined the risk of dementia by group classification. Kaplan-Meier curves were used to depict the rate of progression to dementia over time in the cluster groups and survival curves were compared using a log-rank test. In these analyses, follow-up time was the number of years from baseline to dementia diagnosis; participants who did not progress to dementia during their follow-up period were censored at their last visit.

χ^2 analyses examined dementia type (probable AD, non-AD, mixed AD) in those who had progressed. CSF biomarkers and neuropathologic findings were analyzed using ANOVA and χ^2 tests. All *p* values were false discovery rate (FDR)–adjusted at $p < 0.05$ using the Benjamini-Hochberg method to account for multiple comparisons.

Table 1 Neuropsychological Measures Included in the Composite Domain z-Scores

Cognitive domain	Neuropsychological measures
Learning/memory	CVLT or CVLT-II Learning Trials 1–5; CVLT or CVLT-II Long Delay Free Recall; CVLT or CVLT-II Recognition Discriminability; WMS-R Logical Memory Immediate; WMS-R Logical Memory Delay; WMS-R Visual Reproduction Immediate; WMS-R Visual Reproduction Delay
Attention	Trail-Making Test Part A; WAIS-R Digit Symbol; WAIS-R Digit Span
Executive functioning	Trail-Making Test Part B; WCST Categories Completed; WCST Perseverative Errors
Language	BNT or MINT; Letter Fluency (F, A, S); Category Fluency (Animals, Fruits, Vegetables)
Visuospatial	WISC-R Block Design; WMS-R Visual Reproduction Copy; Cube Copy

Abbreviations: BNT = Boston Naming Test; CVLT = California Verbal Learning Test; MINT = Multilingual Naming Test; WAIS-R = Wechsler Adult Intelligence Scale–Revised; WCST = Wisconsin Card Sorting Test; WISC-R = Wechsler Intelligence Scales for Children–Revised (administered rather than WAIS-R Block Design to avoid floor effects); WMS-R = Wechsler Memory Scale–Revised.

Data Availability

Anonymized data are available by request to any qualified investigator.

Results

Neuropsychological Cluster-Derived Groups

Cluster analysis resulted in 5 cognitive groups: (1) optimal CN (oCN; n = 130), with above-average cognition in all domains; (2) typical CN (tCN; n = 204), with average cognition in all domains; (3) nonamnestic MCI (naMCI; n = 104), with impaired performance (defined as >1 SD below the demographically corrected normative mean) in the domains of executive function and visuospatial abilities; (4) amnestic MCI (aMCI; n = 216), with impaired memory and language; and (5) mixed MCI (mMCI; n = 84), with impairment in all 5 domains (see Figure 1; see also eFigure 1, available from Dryad [doi.org/10.6076/D1F300], for dendogram). A discriminant function analysis using the neuropsychological measures to predict group membership into these 5 clusters correctly classified 81.4% of the participants.

A 4-cluster solution from the cluster analysis was also examined, in which the 2 CN groups were collapsed into 1 group (n = 304), while the 3 MCI groups were identical to the 5-cluster solution. A discriminant function analysis predicting group membership into the 4 clusters correctly classified 86.3% of the participants. Given the potential utility of identifying subgroups of CN individuals, including identifying factors that may allow one to age more "successfully" than others, we elected to focus on the 5-group solution for the remainder of the analysis.

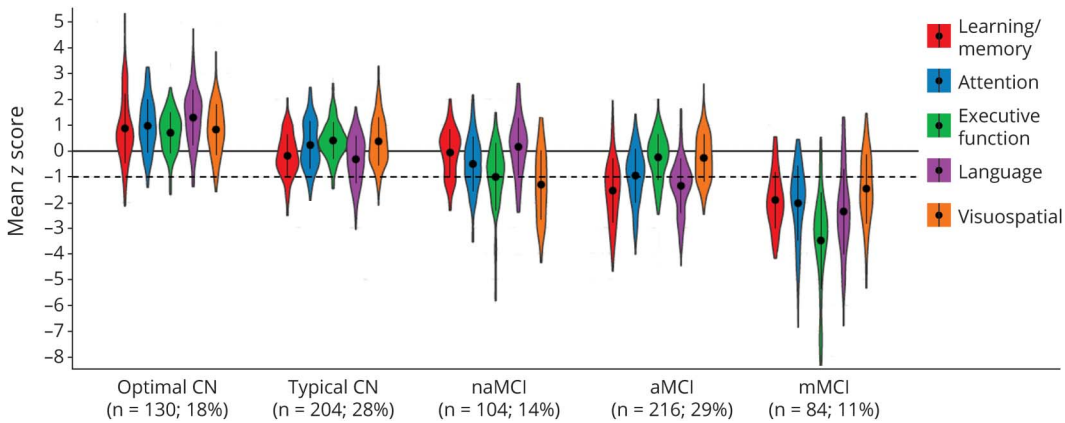
There were no significant differences in age or sex among the 5 cluster groups. The groups differed on education ($p < 0.002$), as the mMCI group had the lowest level of education (13 years vs 14–15 years in the other groups; see Table 2). The 3 MCI groups had a greater percentage of non-White participants relative to the 2 CN groups ($p < 0.001$), although racial/ethnic diversity was limited in this largely White sample. Scores on clinical (Mini-Mental State Examination [MMSE]) and functional (Pfeffer Outpatient Disability scale) measures were within the range of CN or MCI for all groups (see Table 2), consistent with all participants being classified as not having dementia by consensus criteria. *APOE* data were available for a subset of participants (n = 590); analyses showed no significant differences between groups.

Progression to Dementia

Of the 738 participants, 172 (23.3%) progressed to a diagnosis of dementia. Dementia diagnoses were made at an average of 6.3 years postbaseline (SD 5.4, range 2–30). Of those who progressed, there were no differences between the cluster groups with regard to demographic characteristics or *APOE* ε4 status. All 3 MCI groups had a shorter length of follow-up time relative to the oCN group ($p \leq 0.005$) and the mMCI group had a shorter follow-up relative to the tCN group ($p < 0.001$; see Table 2).

There were significant group differences in the overall rate of progression to dementia ($p < 0.001$; see Table 2). Cox regression adjusting for demographics showed a significantly increased risk of progression to dementia in the naMCI (hazard ratio [HR] 1.98; $p < 0.02$), aMCI (HR 3.56; $p < 0.001$), and mMCI (HR 5.76; $p < 0.001$) groups relative to the tCN reference group. Kaplan-Meier curves showing rate of progression to dementia over time are shown in Figure 2. A log-rank test revealed significant group differences in survival curves ($\chi^2[4] = 105.23$; $p < 0.001$). All groups differed significantly from one another, with the exception of the oCN and tCN groups. The mMCI group showed the steepest

Figure 1 Neuropsychological Performance of the Cluster-Derived Groups



Distribution of cognitive z-scores for each neuropsychological domain across cluster-derived groups. The points denote group mean and lines denote 1 SD. The dotted line represents impairment at 1 SD below the mean. aMCI = amnestic mild cognitive impairment; CN = cognitively normal; mMCI = mixed mild cognitive impairment; naMCI = nonamnestic mild cognitive impairment.

Table 2 Baseline Demographic, Clinical, Neuropsychological, and Biomarker Characteristics of the Cluster-Derived Groups

	Optimal CN (n = 130)	Typical CN (n = 204)	Nonamnestic MCI (n = 104)	Amnestic MCI (n = 216)	Mixed MCI (n = 84)	*F* or χ^2	Effect size	*p* Value
Demographics								
Age, y	71.32 (6.95)	71.77 (7.30)	71.25 (7.54)	71.53 (7.97)	74.08 (8.64)	$F = 2.21$	$\eta_p^2 = 0.01$	0.07
Education, y	14.42 (3.33)	14.87 (3.58)	14.68 (4.12)	14.82 (4.09)	12.90 (4.88)	$F = 4.31$	$\eta_p^2 = 0.02$	0.002
Female	60.0	53.9	48.1	50.0	64.3	$\chi^2 = 8.32$	$\varphi_c = 0.11$	0.08
White	97.7	95.1	84.6	88.4	78.6	$\chi^2 = 31.20$	$\varphi_c = 0.21$	<0.001
***APOE* ε4 carrier**	38.2 (39/102)	31.3 (52/166)	32.9 (27/82)	41.1 (74/180)	43.3 (26/60)	$\chi^2 = 5.28$	$\varphi_c = 0.10$	0.26
Clinical measures								
MMSE	29.23 (1.03)	29.06 (1.22)	28.86 (1.32)	28.24 (1.69)	27.47 (2.13)	$F = 26.74$	$\eta_p^2 = 0.13$	<0.001
POD	0.38 (1.06)	0.55 (1.59)	0.62 (1.71)	1.50 (2.68)	1.72 (3.15)	$F = 11.02$	$\eta_p^2 = 0.06$	<0.001
Neuropsychological domain *z* scores								
Learning/memory	0.88 (1.33)	−0.19 (0.83)	−0.06 (0.90)	−1.54 (1.23)	−1.91 (1.08)	$F = 143.14$	$\eta_p^2 = 0.44$	<0.001
Attention	0.97 (1.01)	0.23 (0.91)	−0.51 (1.06)	−0.96 (1.03)	−2.03 (1.45)	$F = 138.32$	$\eta_p^2 = 0.43$	<0.001
Executive function	0.70 (0.79)	0.40 (0.71)	−1.01 (1.30)	−0.25 (0.87)	−3.48 (1.86)	$F = 256.94$	$\eta_p^2 = 0.58$	<0.001
Language	1.29 (1.08)	−0.32 (0.91)	0.16 (1.10)	−1.36 (1.05)	−2.35 (1.65)	$F = 186.21$	$\eta_p^2 = 0.50$	<0.001
Visuospatial	0.83 (0.98)	0.37 (0.92)	−1.31 (1.33)	−0.27 (0.90)	−1.47 (1.34)	$F = 106.46$	$\eta_p^2 = 0.37$	<0.001
Clinical outcome								
Total years of follow-up	7.41 (6.88)	6.70 (6.47)	5.29 (5.26)	5.22 (4.85)	3.88 (3.84)	$F = 6.99$	$\eta_p^2 = 0.04$	<0.001
Progression to dementia, % (n)	9.2 (12)	13.2 (27)	18.3 (19)	36.1 (78)	42.9 (36)	$\chi^2 = 65.24$	$\varphi_c = 0.30$	<0.001
Year of dementia diagnosis	11.17 (6.99)	10.11 (6.31)	7.95 (6.38)	4.76 (3.90)	4.11 (3.44)	$F = 11.65$	$\eta_p^2 = 0.22$	<0.001
Type of dementia						$\chi^2 = 19.00$	$\varphi_c = 0.24$	0.02
Probable AD dementia, %	91.7 (11/12)	81.5 (22/27)	63.2 (12/19)	88.5 (69/78)	86.1 (31/36)			
Non-AD dementia, %	0.0 (0/12)	11.1 (3/27)	36.8 (7/19)	7.7 (6/78)	5.6 (2/36)			
Mixed AD dementia, %	8.3 (1/12)	7.4 (2/27)	0.0 (0/19)	3.8 (3/78)	8.3 (3/36)			
CSF biomarkers (n = 197)								
CSF data available	30.0 (39)	33.3 (68)	34.6 (36)	19.4 (42)	14.2 (12)			
Baseline to LP interval, y	0.27 (0.44)	0.17 (0.36)	0.26 (0.58)	0.28 (0.64)	0.39 (0.72)	$F = 0.76$	$\eta_p^2 = 0.02$	0.56
$A\beta_{1-42}$ concentration, pg/mL	750.92 (300.47)	764.53 (316.18)	771.23 (310.29)	718.19 (367.87)	505.79 (104.12)	$F = 1.90$	$\eta_p^2 = 0.04$	0.11
Tau concentration, pg/mL	322.90 (147.70)	385.41 (237.46)	325.42 (141.13)	442.54 (220.33)	645.55 (347.69)	$F = 6.83$	$\eta_p^2 = 0.12$	<0.001
Tau/$A\beta_{1-42}$ concentration	0.51 (0.36)	0.66 (0.65)	0.51 (0.39)	0.88 (0.75)	1.28 (0.57)	$F = 6.01$	$\eta_p^2 = 0.11$	<0.001
Positive for tau/AB1-42, % (n)	30.8 (12/39)	27.9 (19/68)	30.6 (11/36)	50.0 (21/42)	91.7 (11/12)	$\chi^2 = 19.59$	$\varphi_c = 0.32$	0.001
Neuropathology (n = 157)								
Neuropathologic data available	19.2 (25)	16.6 (34)	16.3 (17)	28.2 (61)	22.6 (19)			
Baseline to autopsy interval, y	14.87 (9.53)	14.79 (6.73)	12.46 (7.00)	8.69 (5.59)	7.33 (5.93)	$F = 8.07$	$\eta_p^2 = 0.18$	<0.001
Age at death, y	88.91 (7.17)	88.55 (6.43)	86.33 (6.61)	83.98 (7.99)	85.98 (4.97)	$F = 3.36$	$\eta_p^2 = 0.08$	0.01
Braak stage	2.92 (1.63)	3.28 (1.78)	2.94 (1.78)	3.84 (2.01)	4.37 (1.50)	$F = 2.72$	$\eta_p^2 = 0.07$	0.03

Continued

Table 2 Baseline Demographic, Clinical, Neuropsychological, and Biomarker Characteristics of the Cluster-Derived Groups *(continued)*

	Optimal CN (n = 130)	Typical CN (n = 204)	Nonamnestic MCI (n = 104)	Amnestic MCI (n = 216)	Mixed MCI (n = 84)	*F* or χ^2	Effect size	*p* Value
Neuritic plaque score	1.36 (1.08)	1.47 (1.05)	1.53 (1.07)	1.64 (1.27)	2.10 (1.07)	$F = 1.36$	$\eta_p^2 = 0.04$	0.25
Severity of AD pathology, % (n)								
High	16.0 (4)	35.3 (12)	17.6 (3)	44.3 (27)	60.0 (12)	$\chi^2 = 13.43$	$\varphi_c = 0.29$	0.01
Intermediate	20.0 (5)	17.6 (6)	29.4 (5)	13.1 (8)	15.0 (3)			
Low	64.0 (16)	47.1 (16)	52.9 (9)	42.6 (26)	25.0 (5)			
Lewy body pathology	8.0 (2)	20.6 (7)	29.4 (5)	14.8 (9)	15.0 (3)	$\chi^2 = 3.94$	$\varphi_c = 0.16$	0.42
Vascular pathology	44.0 (11)	29.4 (10)	11.8 (2)	31.1 (19)	30.0 (6)	$\chi^2 = 4.99$	$\varphi_c = 0.18$	0.29
Other pathology	4.0 (1)	11.8 (4)	23.5 (4)	19.7 (12)	35.0 (7)	$\chi^2 = 8.66$	$\varphi_c = 0.24$	0.07

Abbreviations: $A\beta_{1-42}$ = β-amyloid peptide 1–42; AD = Alzheimer disease; CN = cognitively normal; LP = lumbar puncture; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; POD = Pfeffer Outpatient Disability scale.
Data are mean (SD) or % (n).

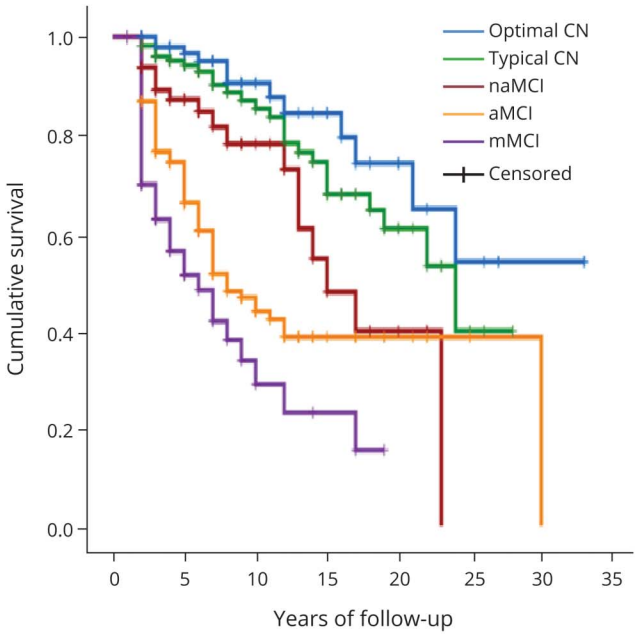
survival curve and differed significantly from the aMCI group ($p = 0.01$) and the other 3 groups ($p < 0.001$). The aMCI group had a steeper survival curve than the naMCI group ($p = 0.007$) and the 2 CN groups ($p < 0.001$). The naMCI group had a steeper survival curve than the tCN ($p = 0.02$) and oCN ($p = 0.001$) groups.

With regard to type of dementia, 145 of the 172 (84.3%) who progressed received a consensus diagnosis of probable AD based on NINCDS-ADRDA criteria.[25,26] Eighteen participants progressed to a non-AD dementia (9 DLB or PDD; 2 frontotemporal dementia; 4 vascular; 2 other CNS disorder) and 9 progressed to a mixed AD dementia (AD plus vascular, PDD, or DLB) based on clinical diagnosis. χ^2 analysis showed significant group differences in type of dementia ($p = 0.02$), as the naMCI group was more likely to progress to a non-AD dementia (37%) than all other cluster groups (0%–11%), which did not differ from one another (see Table 2).

CSF Biomarkers

Analyses of baseline CSF data in a subset of the sample (n = 197) revealed significant differences between the cluster-derived groups in concentrations of tau ($p < 0.001$) and the tau/$A\beta_{1-42}$ ratio ($p = 0.001$; see Table 2). There were no significant group differences for $A\beta_{1-42}$ ($p = 0.11$). For tau, Tukey honestly significant difference (HSD) post hoc testing showed that the aMCI group had a trend toward a higher level of tau compared to the oCN group ($p = 0.08$), while the mMCI group had the highest level compared to all other groups (oCN/tCN/naMCI: $p < 0.001$; aMCI: $p = 0.03$; see Figure 3). For the tau/$A\beta_{1-42}$ ratio, Tukey HSD post hoc testing showed that the aMCI group had a higher ratio compared to the oCN and naMCI groups ($p < 0.05$), while the mMCI group had the highest ratio compared to oCN,

Figure 2 Kaplan-Meier Survival Curves Showing Risk of Progression to Dementia in the Cluster-Derived Groups

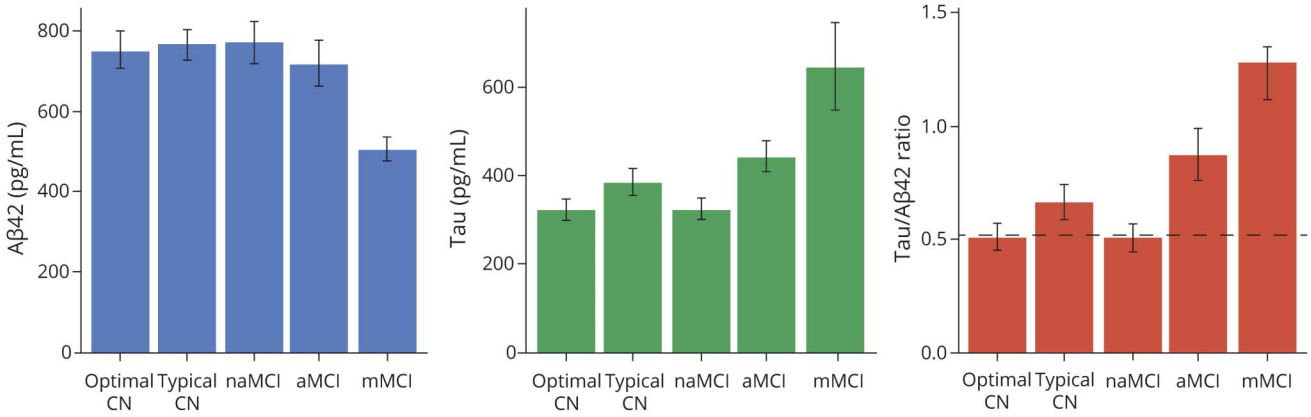


Number entering interval (number progressed during interval):

130 (2)	75 (4)	33 (2)	20 (2)	10 (2)	5 (0)	2 (0)
204 (7)	99 (6)	52 (7)	34 (5)	11 (2)	3 (0)	0 (0)
104 (9)	41 (3)	17 (4)	8 (2)	4 (1)	0 (0)	0 (0)
216 (44)	90 (28)	33 (5)	11 (0)	5 (0)	2 (0)	1 (1)
84 (26)	23 (7)	7 (2)	3 (1)	0 (0)	0 (0)	0 (0)

All groups differed significantly from one another, with the exception of the optimal cognitively normal (CN) and typical CN groups. aMCI = amnestic mild cognitive impairment; mMCI = mixed mild cognitive impairment; naMCI = nonamnestic mild cognitive impairment.

Figure 3 Concentrations of CSF β-Amyloid (Aβ)1–42 (pg/mL), Tau (pg/mL), and the Tau/Aβ1–42 Ratio for Each Cluster-Derived Group



The dotted line represents the cut point for biomarker positivity for the tau/$A\beta_{1-42}$ ratio (>0.52). aMCI = amnestic mild cognitive impairment; CN = cognitively normal; mMCI = mixed mild cognitive impairment; naMCI = nonamnestic mild cognitive impairment.

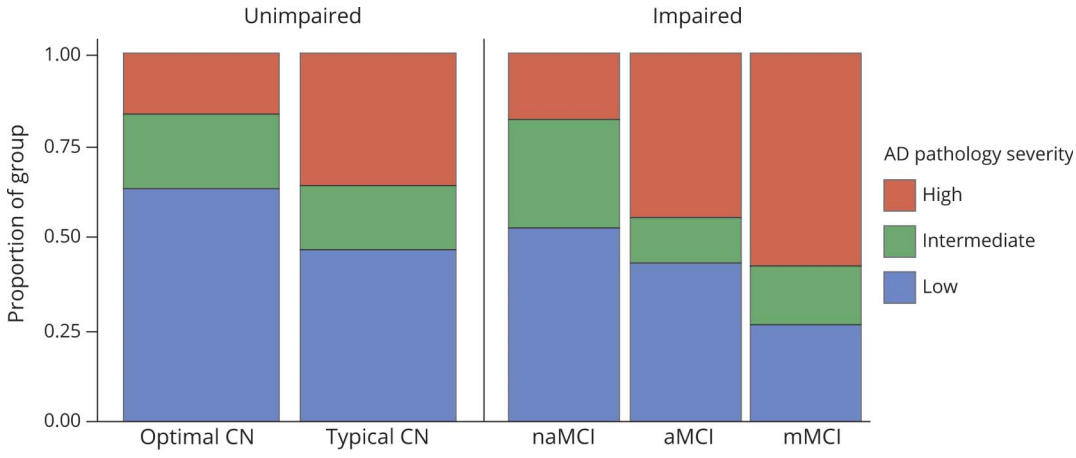
tCN, and naMCI ($p < 0.01$) but not aMCI ($p = 0.22$; see Figure 3).

When the cut point for biomarker positivity was applied to the tau/$A\beta_{1-42}$ ratio, χ^2 analysis with FDR adjustment demonstrated that the mMCI group had a higher rate of biomarker positivity relative to the oCN/tCN ($p < 0.001$) and naMCI ($p = 0.06$) groups (see Table 2). The oCN, tCN, and naMCI groups did not differ significantly from each other on any of the CSF biomarker variables.

Neuropathology

In the subset of the sample (n = 157) with neuropathologic assessment available, the oCN and tCN groups had a significantly longer interval between baseline neuropsychological evaluation and autopsy (15 years) relative to the 3 MCI groups (7–12 years). The 5 cluster groups differed at autopsy in their Braak stage ($p = 0.03$) and the proportion of participants with a high level of AD pathology based on NIA-Reagan consensus criteria[35] ($p = 0.01$). Specifically, the mMCI group showed a greater proportion of participants with a high level of AD pathology relative to the oCN ($p = 0.01$) and naMCI ($p = 0.03$) groups, while the aMCI group showed a greater proportion relative to the oCN group ($p = 0.03$) (see Figure 4). However, these patterns fell to trend level after FDR adjustment for multiple comparisons; this may reflect the fact that autopsies in general are more likely to occur in those with an advanced

Figure 4 Neuropathologic Findings Showing Alzheimer Disease (AD) Pathology Severity Based on National Institute on Aging–Reagan Consensus Criteria in the Mild Cognitive Impairment (MCI) and Cognitively Normal (CN) Groups



Note that the optimal and typical CN groups had a significantly longer interval between baseline neuropsychological evaluation and autopsy (15 years) relative to the 3 MCI groups (7–12 years). aMCI = amnestic mild cognitive impairment; mMCI = mixed mild cognitive impairment; naMCI = nonamnestic mild cognitive impairment.

Table 3 Comparison of Cluster-Derived Groups to Consensus Diagnoses at Baseline

Cluster-derived group	Consensus diagnosis, n (%)			
	CN	Impaired–not MCI	MCI	Total
oCN	123 (94.6)	0 (0.0)	7 (5.4)	130 (100)
tCN	179 (87.7)	3 (1.5)	22 (10.8)	204 (100)
naMCI	89 (85.6)	1 (1.0)	14 (13.5)	104 (100)
aMCI	122 (56.5)	5 (2.3)	89 (41.2)	216 (100)
mMCI	27 (32.1)	3 (3.6)	54 (64.3)	84 (100)

Abbreviations: aMCI = amnestic mild cognitive impairment; CN = cognitively normal; MCI = mild cognitive impairment; mMCI = mixed mild cognitive impairment; MMSE = Mini-Mental State Examination; naMCI = nonamnestic mild cognitive impairment; oCN = optimal cognitively normal; tCN = typical cognitively normal.

stage of dementia, regardless of which cluster classification they originated from. Other pathologic findings in the sample were common, particularly vascular disease, but there were no significant group differences in the presence of vascular, Lewy body, or other (hippocampal sclerosis, FTLD, etc.) pathologies (Table 2).

Comparisons to Consensus Diagnosis

Comparison of the cluster-derived groups to consensus diagnoses at baseline are shown in Table 3. The majority of participants in the oCN and tCN clusters were also classified as CN by consensus diagnosis (95% and 88%, respectively). There was less consistency between diagnostic methods for MCI. Participants in the naMCI group were classified as CN by the consensus diagnosis in 86% of cases. The aMCI group was split between a consensus diagnosis of MCI (41%) and CN (57%). For mMCI, the majority were classified with MCI based on consensus diagnosis (64%), although approximately one-third were classified as CN (32%). The impaired–not MCI assignment did not correspond to any particular cluster group. Overall, cluster analysis classified 54.7% of the sample with MCI compared to 25.2% of the sample classified via consensus diagnosis.

For individuals in the subset of the sample identified as robust CN for the purposes of generating the neuropsychological *z* scores, 64% were classified into one of the CN groups (28% oCN, 36% tCN), while 36% were classified into one of the MCI groups (14% naMCI, 18% aMCI, 5% mMCI). These findings are consistent with the poor agreement between cluster analysis and consensus diagnoses.

For the 172 participants who progressed to dementia, 133 (77%) participants were classified as MCI at baseline by the cluster analysis (19 naMCI, 78 aMCI, 36 mMCI), while only 94 (55%) were classified as MCI at baseline by the consensus criteria (plus 3 impaired–not MCI).

With regard to CSF biomarkers, of the 74 participants who were positive for the tau/$A\beta_{1-42}$ ratio, 43 (58%) were classified as MCI at baseline by the cluster analysis (11 naMCI, 21 aMCI, 11 mMCI), while 31 (42%) were classified as MCI at baseline by the consensus criteria.

With regard to neuropathology, of the 58 participants who had a high level of AD pathology at autopsy based on NIA-Reagan consensus criteria, 42 (72%) were classified as MCI at baseline by the cluster analysis (3 naMCI, 27 aMCI, 12 mMCI), while 32 (55%) were classified as MCI at baseline by the consensus criteria (plus 1 impaired–not MCI).

Discussion

Through application of cluster analytic techniques to comprehensive neuropsychological data within a large cohort of older adult participants drawn from the UCSD ADRC, we identified MCI and CN subgroups with differing cognitive and CSF AD biomarker profiles, as well as differing rates of progression to dementia (mMCI > aMCI > naMCI). The mMCI subtype represented the most at-risk participants at baseline given multidomain cognitive impairment coupled with the highest rate of progression to dementia over time (i.e., 43% progressed over an average of 4 years) and a trend toward a more severe level of AD pathology at autopsy approximately 7 years postbaseline. This group also had the fewest years of formal education, potentially contributing to lower cognitive reserve. In contrast, the aMCI subtype appeared to be earlier in the course of the disease at baseline, with cognitive impairment largely affecting memory and language domains, consistent with early clinical manifestations of AD.

The cluster-derived naMCI subtype showed neuropsychological impairments in executive function and visuospatial domains, but intact memory abilities. Interestingly, this group was largely classified as CN by the consensus diagnosis, likely given the ADRC's primary focus on memory impairment in their diagnostic strategy. The naMCI cluster group did not progress to dementia at the rate of aMCI and mMCI; however, they were at an increased risk of progression relative to CN participants. While probable AD was the primary cause of dementia in all 3 MCI subtypes, participants in the naMCI group were more likely than other cluster groups to progress to non-AD dementia based on clinical diagnosis.

Our findings complement those of a previous study[37] that used latent class analysis to identify subgroups within participants who received a consensus diagnosis of MCI in the National Alzheimer's Coordinating Center (NACC). Results of that study revealed 7 MCI subtypes based not only on neuropsychological but also functional and neuropsychiatric profiles. The MCI subgroups with multidomain cognitive impairments progressed to dementia at the highest rate, consistent with our findings, along with amnestic MCI

participants who had concurrent functional and neuropsychiatric symptoms.[37]

In addition to the 3 MCI subtypes, we identified 2 groups of CN participants: those with neuropsychological scores in the high average range across 5 cognitive domains, and those with scores in the average range. We speculated that these groups may reflect optimal and typical cognitive aging, respectively. Interestingly, there were no clear differences between the 2 groups in terms of demographics, *APOE* genotype, CSF biomarkers, or neuropathologic findings. The finding of 2 cognitively normal clusters is similar to those of a previous study[14] that applied latent profile analysis to neuropsychological test scores and found 5 cognitive subgroups, including a high-normal cognition and a low-normal cognition group. Unlike our study, the low-normal cognition group was significantly older and showed a higher rate of progression to dementia than the high-normal cognition group over a mean follow-up period of 3.4 years.[14] Key differences that may account for the discrepancy between studies include the differing length of follow-up, as well as the previous study being conducted in a memory clinic vs a community-based sample.

The ability of neuropsychological profiles to identify meaningful cognitive subgroups was supported by biomarker and neuropathologic findings in a subset of the sample. CSF concentrations of both tau and the tau/$A\beta_{1-42}$ ratio differed across MCI subtypes, with the mMCI group in particular showing a high rate of CSF biomarker positivity (92%) based on the tau/$A\beta_{1-42}$ ratio, although the small number of participants in this group should be noted. Both the aMCI and mMCI groups showed greater severity of AD pathology at autopsy relative to the oCN group. Among the 3 MCI groups, mMCI showed more severe AD pathology than the naMCI group, with aMCI falling between the two. Although these group comparisons fell to trend level after FDR adjustment, it is remarkable that participants' baseline cognitive performance was associated with their eventual autopsy findings an average of 7–15 years later. Other neuropathologies including Lewy bodies and vascular disease were observed in 17% and 31% of participants, respectively, who had undergone autopsy; these proportions correspond well with previous research.[38]

An unexpected finding was the lack of difference in *APOE* genotype across the cognitive subgroups. One factor that may have contributed to this finding is a relatively high rate of *APOE* ε4 positivity in ADRC control participants due to selection bias. Individuals who have family history of AD, or who know their *APOE* ε4 status and are concerned about their own risk, may be compelled to volunteer for research. Indeed, 31% of participants classified as CN based on the ADRC's consensus diagnosis, and 34% of participants classified as oCN/tCN based on our cluster analysis, were *APOE* ε4 carriers, which is higher than reported prevalence rates (e.g., 24% in European Americans[39]).

Importantly, cluster analysis classified 29.5% more of the sample with MCI compared to the ADRC's consensus diagnosis. Longitudinal follow-up showed that actuarial methods captured a greater proportion of individuals who progressed to dementia relative to conventional consensus diagnostic methods. While the primary source of discrepancy between the 2 methods was the existence of the naMCI group, there were also more participants captured within our memory-impaired subgroups (aMCI and mMCI) relative to those with a consensus diagnoses of MCI. These findings are consistent with recent work from our laboratory that compared actuarial vs consensus diagnoses using data from the NACC Uniform Data Set[40]; we found that approximately one-third of individuals diagnosed as CN by consensus diagnosis met neuropsychological criteria for MCI.[41]

Results of the current study have several important clinical and research implications. First, our findings show that the ADRC's method of consensus diagnosis underestimates MCI in its participant sample. One potential explanation for underdiagnosis is that clinical judgment may reduce the likelihood of an MCI diagnosis if the participant and the study partner do not report concerns about cognitive or functional change, even in the presence of impaired neuropsychological test scores. Indeed, there is evidence that scores on the Clinical Dementia Rating (CDR) scale, a subjective measure of a participant's functioning, correspond more closely with consensus diagnoses than with performance on neuropsychological testing,[41] suggesting that the CDR is weighted more heavily than cognitive performance when determining consensus diagnoses. In addition, while the consensus method used by the ADRC/NACC includes consideration of a participant's neuropsychological performance, the final diagnostic decision may rely more heavily on measures of global cognition such as the MMSE, which is limited in its ability to distinguish CN from MCI[42] and typically does not show changes until later in the course of the disease.

Second, the cluster-based classifications outperformed consensus diagnoses in identifying at-risk participants. Specifically, for the subset of the sample who progressed to dementia, had abnormal CSF biomarkers, or had a high level of AD pathology at autopsy, cluster analysis identified a greater percentage of these individuals as at risk (i.e., MCI) relative to the consensus diagnosis. In addition, the cluster-derived naMCI group represents an at-risk group of participants who could potentially benefit from early lifestyle/behavioral-focused interventions and clinical follow-up; however, they would be missed by widely used, conventional methods of MCI diagnosis. Another concern is that these naMCI individuals would be included in "cognitively normal" comparison samples in research studies or clinical trials, thereby adding noise and potentially attenuating significant treatment effects.

Third, the delineation of subgroups of CN may allow for further exploration of protective factors in aging. While additional research on oCN individuals may reveal clues to maintaining optimal brain health, identification of the tCN group could also be beneficial, as this classification may include a subset of individuals who are experiencing subtle cognitive decline, suggestive of a preclinical phase of AD.[43,44] As clinical trials shift their focus to earlier phases of the disease process, objective methods of identifying which CN individuals are most appropriate for enrollment would be valuable from both a scientific and a cost-savings perspective.

Our data show that actuarial/statistical methods confer several advantages over consensus diagnosis, including the removal of subjective judgments, the potential to identify groups of participants with more subtle cognitive changes, and the ability to consistently apply data-driven methods across sites, all of which would enhance the identification of participants who are most at risk for progression to dementia. Nonetheless, clinical context is important when diagnoses are made at an individual level as there are a number of factors that could contribute to low cognitive test scores aside from neurodegenerative disease (e.g., low premorbid functioning, psychiatric conditions, cultural factors). On the other hand, individuals who have a high level of premorbid functioning but have declined cognitively will be missed by actuarial methods that rely solely on impaired scores. Thus, actuarial and clinical approaches may prove to be most useful as a complement to one another, with actuarial methods providing initial classifications that could then be modified as appropriate based on clinical context.

Another advantage of actuarial/statistical methods for identifying MCI subtypes is that they go beyond the conventional labels for MCI subtypes[1,2] (i.e., single- and multidomain amnestic MCI; single- and multidomain nonamnestic MCI). In this study, if we had restricted our groups to the conventional labels, then both the aMCI and mMCI groups would have been considered multidomain aMCI (because our aMCI group had both memory and language impairments), despite their differing cognitive and biomarker profiles, which suggest they may represent earlier and later stages of the disease process.[45]

Strengths of the current study include the use of comprehensive neuropsychological data and data-driven methods to identify subtypes in both MCI and CN participants as well as the extensive longitudinal follow-up period. Another strength is the relatively large sample of participants with CSF and neuropathologic data, although it should be noted that only a fraction of the overall sample had CSF (27%) and neuropathologic data (21%) available. A limitation of the current study is that the sample was largely White and well-educated, which limits generalizability, particularly given previous findings showing that racial/ethnic groups differ on variables such as incidence of AD, clinical presentation, timing of diagnosis, and course of disease.[46] In addition, other key relationships may differ across racial groups, such as the association between cognition and CSF biomarkers.[47] Therefore, further research is critical to determine the utility of cluster-derived cognitive subgroups in racially and socioeconomically diverse samples. Another limitation is that we did not use an independent reference group to create the demographically adjusted neuropsychological *z* scores. While there is a risk of circulatory from the overlapping reference and cluster samples, this concern is attenuated by the finding that the robust CNs were spread across the cluster-derived groups. Future longitudinal studies examining stability of cluster groups over time will be informative to determine whether individuals progress through different subtypes toward a diagnosis of dementia.

Our results suggest that actuarial neuropsychological methods have utility for producing reliable cognitive phenotypes in older adults, and data from a subset suggest that these phenotypes are associated with clinical outcome, CSF AD biomarkers, and eventual neuropathologic findings as much as a decade or more later. Findings indicate that data-driven algorithms could enhance diagnostic sensitivity by identifying empirically derived at-risk groups of individuals for enrollment in clinical trials, including those with nonamnestic forms of MCI, those with subtle cognitive deficits, and those who do not report subjective concerns but have nonetheless experienced meaningful cognitive changes.

Study Funding

This work was supported by the US Department of Veterans Affairs Clinical Sciences Research and Development Service (Career Development Award-2 1IK2CX001415 to E.C.E.; 1IK2CX001865 to K.R.T.; and Merit Award 1I01CX001842 to K.J.B.), NIH grants (P30 AG062429 to D.P.S., D.R.G., and M.W.B.; R01 AG049810 to M.W.B.; R01 AG063782 to K.J.B.; R03 AG070435 to K.R.T), and the Alzheimer's Association (AARF-17-528918 to K.R.T.).

Disclosure

M.W. Bondi is a consulting editor for the *Journal of the International Neuropsychological Society* and receives royalties from Oxford University Press. D.R. Galasko serves as editor for *Alzheimer's Research and Therapy* and as a paid consultant on Data Safety Monitoring Boards for Pfizer, Inc., Elan, Inc., and Balance Pharmaceuticals, Inc. D.P. Salmon serves as a paid consultant for Biogen, Inc. and Takeda Pharmaceuticals. The other authors report no disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* February 5, 2021. Accepted in final form July 1, 2021.

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Denis S. Smirnov, BS	University of California San Diego	Analysis and interpretation of data; drafting/revising the manuscript for intellectual content
Kelsey R. Thomas, PhD	VA San Diego Healthcare System; University of California San Diego	Interpretation of data; revising the manuscript for intellectual content
Lisa V. Graves, PhD	VA San Diego Healthcare System; University of California San Diego	Interpretation of data; revising the manuscript for intellectual content
Katherine J. Bangen, PhD	VA San Diego Healthcare System; University of California San Diego	Interpretation of data; revising the manuscript for intellectual content
Lisa Delano-Wood, PhD	VA San Diego Healthcare System; University of California San Diego	Study concept; interpretation of data; revising the manuscript for intellectual content
Douglas R. Galasko, MD	VA San Diego Healthcare System; University of California San Diego	Study concept; major role in acquisition of data; interpretation of data; revising the manuscript for intellectual content
David P. Salmon, PhD	University of California San Diego	Study concept; major role in acquisition of data; interpretation of data; revising the manuscript for intellectual content
Mark W. Bondi, PhD	VA San Diego Healthcare System; University of California San Diego	Study concept and design; major role in acquisition of data; interpretation of data; revising the manuscript for intellectual content

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