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Featured Article

Neuropsychological subtypes of incident mild cognitive impairment in the Mayo Clinic Study of Aging

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Abstract

Introduction: We evaluated whether incident mild cognitive impairment (MCI) subtypes could be empirically derived in the Mayo Clinic Study of Aging.
Methods: We performed cluster analysis on neuropsychological data from 506 participants with incident MCI.
Results: The 3-cluster solution resulted in (1) amnestic, (2) dysexecutive, (3) dysnomic subtypes. The 4-cluster solution produced these same three groups and a fourth group with subtle cognitive impairment (SCI). The SCI cluster was a subset of the amnestic cluster and distinct from well-matched cognitively unimpaired participants based on memory and global z-score area under the receiver operating characteristic curve analyses and probability of progression to MCI/dementia.
Discussion: We empirically identified three neuropsychological subtypes of MCI that share some features with MCI subtypes identified in the Alzheimer's Disease Neuroimaging Initiative. The fourth subtype with SCI in the Mayo Clinic Study of Aging differed from the fourth cluster-derived normal group in Alzheimer's Disease Neuroimaging Initiative and could represent a group to target with early interventions.

Keywords: Mild cognitive impairment; MCI; Neuropsychology; Cluster analysis; Subtle cognitive impairment

1. Introduction

The aging and dementia field is increasingly focused on identifying and characterizing the earliest and subtlest cognitive changes that occur as individuals transition from cognitively unimpaired (CU) to mild cognitive impairment (MCI), especially since the introduction of "subtle cognitive/behavioral decline" (in addition to amyloidosis and neuronal injury) as one of the features of preclinical Alzheimer's disease [1]. A new National Institute on Aging and Alzheimer's Association research framework was introduced in 2018 [2]. This framework uses a numeric clinical staging scheme with six stages to describe individuals in the Alzheimer's continuum with stage 2 characterized by "transitional cognitive decline" defined by a decline in previous level of function despite normal performance within the expected range on objective cognitive tests. Conceptually, this is similar to "stage 3 preclinical AD" from the 2011 National Institute on Aging–Alzheimer's Association guidelines.

In an attempt to more fully operationalize the spectrum of MCI in a nonbiased manner, several studies have used empirical, and specifically cluster-analytic techniques, on

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neuropsychological test data rather than theoretical prespecified cut-points in one or more cognitive domains. Delano-Wood (2009) [3] was one of the first to provide evidence for three distinct groups of MCI in their clinic-based sample: memory/language, executive/processing speed, and pure memory. These subtypes also showed a dissociation of white matter lesion type in the two most impaired groups, with the memory/language group showing higher periventricular lesions and the executive/processing speed group showing higher deep white matter lesions. Libon et al. [4] performed a cluster analysis on patients self-referred to an outpatient memory clinic and diagnosed with single-domain and multidomain MCI based on subjective complaints of cognitive decline, ≤24 on the Mini-Mental State Examination [5], no impairment in activities of daily living, and a neuropsychological test performance of ≤1.5 SD on any of six neuropsychological tests [6]. Their cluster analysis revealed a group of patients with amnestic MCI, a second with dysexecutive MCI, and a third with mixed/multidomain MCI. This study supported previous work suggesting the existence of single-domain and multidomain MCI subtypes [7]. Another study using hierarchical cluster analysis on a large sample of patients from twenty memory clinics who presented with subjective or objective memory impairment also found evidence for single-domain and multidomain amnestic MCI subtypes as well as another group with subjective cognitive impairments and very mild to no objective cognitive deficits [8].

Additional studies using cluster-analytic techniques have also identified individuals with normal cognition who were diagnosed with MCI. For example, Clark et al. [9] compared conventional (i.e., ≤1.5 SD below normal on one test with a domain) [6] versus comprehensive criteria (<1 SD below normal in two tests within a domain) [10] in a community-based sample of patients with prevalent MCI. Both criteria revealed an amnestic subtype and mixed subtype that captured individuals with advanced stages of MCI given their impaired scores on measures of memory, executive function, language, and visuospatial function. The comprehensive criteria also yielded dysexecutive and visuospatial subtypes while the conventional criteria produced a cluster-derived normal group. Bondi et al. [11] applied conventional versus comprehensive criteria for defining MCI in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. They again found that both criteria produced a mildly impaired amnestic subtype and a more severely impaired dysexecutive/mixed subtype. The comprehensive criteria also uniquely identified a language subtype, whereas the conventional criteria produced a third subtype of individuals (which comprised nearly a third of the sample) performing within normal limits. Edmonds et al. [12] also performed a cluster analysis on 825 ADNI participants diagnosed with MCI at their initial screening based on ADNI diagnostic criteria [13] and identified three subtypes of MCI in the ADNI sample: (1) dysnomic, (2) dysexecutive, and (3) amnestic, as well as fourth cluster-derived normal group (See Appendix 1).

The evidence thus far suggests there are subtypes of prevalent MCI that can be empirically identified. The most frequently identified subtypes are amnestic and dysexecutive MCI [3,4,8,9,11,12], with two studies also identifying a language subtype on the ADNI data set [11,12] and one identifying a visuospatial subtype in a community-based sample [9]. The clusters are contingent upon the neuropsychological measures included in the analyses as well as criteria used to operationalize MCI. Some studies show that the oversensitivity of conventional diagnostic criteria may result in misclassification of individuals as having MCI when in fact these individuals are CU [9,11,12]. A limitation of the studies carried out to date is that they are based on prevalent MCI, and impairment in some cognitive domains may have progressed further for some individuals with MCI compared with others. This study expands on the research to determine the reproducibility of empirically derived MCI subtypes in a population-based sample and to characterize the cognitive changes that occur in incident MCI. The objective of this study was to use cluster analysis to identify neuropsychological subtypes of incident MCI in the Mayo Clinic Study of Aging (MCSA) [14].

2. Methods

2.1. Study sample

2.1.1. Cluster analysis participants

Participants were from the MCSA which is a longitudinal population-based study of cognitive aging in Olmsted County, Minnesota [14]. All participants were aged ≥50 years at their baseline assessment and classified as CU. Given the emphasis on evaluating cognitive changes that occur as participants transition from CU to MCI, we first identified a cohort of participants with incident MCI. We required that all MCI participants have at least one prior visit at which they were classified as CU. We also required that all MCI participants have at least one subsequent visit after the initial visit at which they were diagnosed with incident MCI so that we could examine reversion rates. The Mayo Clinic and Olmsted Medical Center Institutional Review Boards approved these studies, which also followed Health Insurance Portability and Accountability Act guidelines. Every participant provided written informed consent.

2.2. Materials and procedure

2.2.1. Evaluation

Participants completed comprehensive evaluations at approximately 15-month intervals which included a physician examination, an interview by a study coordinator, and neuropsychological testing [14]. The physician examination included a medical history review, complete neurologic examination, and administration of the Short Test of Mental Status [15]. The study coordinator interview included

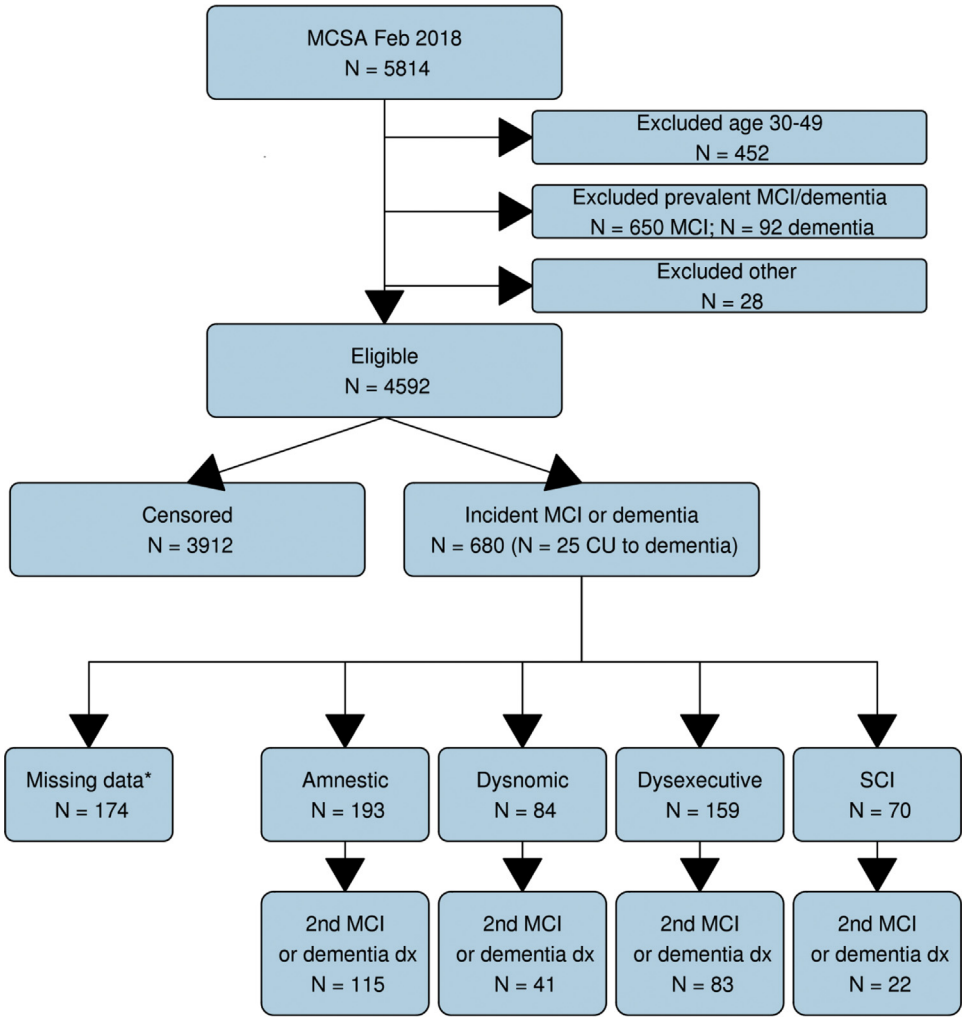

Fig. 1. Study flow chart. *Ineligible for clustering due to missing data. Abbreviations: MCI, Mild cognitive impairment; CU, cognitively unimpaired; SCI, subtle cognitive impairment; MCSA, Mayo Clinic Study of Aging.

demographic information, medical history, and questions about memory to the participant using the Blessed Memory Test [16] and the informant using the Clinical Dementia Rating Scale [17] and the Functional Activities Questionnaire [18].

Neuropsychological testing included nine measures assessing four cognitive domains: (1) memory (AVLT Delayed Recall [19], WMS-R Logical Memory II, and Visual Reproduction II) [20], (2) language (Boston Naming Test [21], Category Fluency [22]), (3) attention/executive (Trail Making Test B [22,23], WAIS-R Digit Symbol [24]), (4) visuospatial (WAIS-R Picture Completion & Block Design [24]). For each participant, cognitive performance in each domain was compared with age-adjusted scores of individuals previously obtained using Mayo's Older American Normative Studies [25–27]. This approach relies on prior normative work and extensive experience with the measurement of cognitive abilities in an independent sample of participants from the same population. Given that we were clustering participants on neuropsychological test data, we had the strict requirement that all participants have data from $\geq$8 of the 9 cognitive tests administered at each study visit. This resulted in excluding 174 participants (Fig. 1).

The criteria used to diagnose MCI were those described in the article by Petersen [7] and follow the outline mentioned previously, with history from the participant and interview of a study partner to determine if there has been (1) a change in cognition, (2) objective scores in the -1.0 SD below the mean range that the clinicians believe are below what would be expected for that individual in one or more cognitive domains based on the normative data we use, (3) functionally intact, and (4) does not meet Diagnostic and Statistical Manual of Mental Disorders-IV criteria for dementia. In addition, these criteria are consistent with the recent evidence-based review of the literature [28]. A final decision to diagnose CU or MCI was based on a consensus agreement among study coordinator, examining physician, and neuropsychologist, after taking into account education, prior occupation, or visual or hearing deficits

and reviewing all other participants' clinical information [7,14]. A diagnosis of dementia was based on published criteria [29]. All raters are blinded to the previous diagnosis of the participant.

2.2.2. Genetic characterization

All participants underwent a blood draw at their baseline visit. DNA extraction and apolipoprotein E (*APOE*) genotyping were performed for each participant using standard methods [30]. The *APOE* ε4 carrier group included participants with one or two copies of the ε4 allele (i.e., ε2ε4, ε3ε4, ε4ε4).

2.3. Statistical analyses

2.3.1. Cluster analysis

Neuropsychological test z-scores were computed and averaged by domain and referenced to 3686 MCSA 2004-2012 CU from the 50-89 cohort and weighted to the 2013 Olmsted County population by age and sex. We performed agglomerative hierarchical clustering with Euclidean distance and Ward's linkage on the MCI participants' neuropsychological domain z-scores [31]. Based on our desire to capture a reasonably sized, fairly mild MCI group, we determined that four clusters were better than three. We conducted a discriminant function analysis to quantitatively examine the ability of the cognitive domain scores to discriminate the cluster subgroups. The stability of the cluster solution was also evaluated using the leave-one-out cross-validation procedure which minimizes the potential bias of using the same participants to develop the cluster solution as used to compute the discriminant function [32]. We then calculated analysis of variance or chi-square goodness of fit test to assess group differences in baseline demographic features.

2.3.2. Area under the receiver operating characteristic curve

We calculated the area under the receiver operating characteristic curve (AUROC) as a nonparametric measure of effect size [33] and calculated 95% confidence intervals for each AUROC estimate [34].

2.3.3. Cox Proportional Hazards

We also considered the probability of diagnosing participants as MCI at their future visit. To do this, we compared the proportion of CU participants with incident MCI or dementia and the proportion of the MCI groups having a confirmatory diagnosis of MCI or dementia (i.e., a diagnosis of MCI or dementia at the next visit.) *P* values to assess pairwise group differences were attained by fitting a Cox proportional hazards model on time to recurrence of MCI or dementia with age as the time scale and adjusting for sex. To correctly account for multiple events per person, robust standard errors were estimated using the Huber sandwich estimator. We entered cluster membership as a time-dependent covariate, with group membership assigned at first occurrence of MCI or dementia. All analyses were completed in R version 3.4.2 (https://www.r-project.org).

3. Results

3.1. Demographics

This study included 506 participants who received a diagnosis of incident MCI. Fig. 1 provides a flow chart of the steps used to derive the study sample. Table 1 provides demographics and clinical characteristics for the four cluster solution and the CU group.

3.2. Cluster analysis

Given that we wanted to examine incident MCI, the cluster assignment occurred at the first diagnosis of MCI. The 3-cluster solution produced the following groups: (1) amnestic (n = 263); (2) dysexecutive (n = 159); (3) dysnomic (n = 84). The 4-cluster solution produced these same three clusters with comparable performance in the four cognitive domains and a fourth cluster labeled as subtle cognitive impairment (SCI; n = 70) that was a subset of the amnestic cluster and distinct from the other groups with respect to the level of cognitive performance and degree of functional impairment. This resulted in 193 participants in the amnestic cluster in the 4-cluster solution. Fig. 2 shows the median z-score by domain for the 3- and 4-cluster solutions. Fig. 3 shows the boxplots of neuropsychological domains z-scores for the four-cluster solution. The 5-cluster solution was comparable to the 4-cluster solution, with the exception of an additional cluster that essentially replicated the dysexecutive subtype.

The amnestic, dysexecutive, and dysnomic clusters had a reversion rate to CU of ∼30% at the next visit, whereas the SCI cluster had a reversion rate of ∼70%, which is not unexpected given that the degree of cognitive change is much milder than the other clusters and the blindedness of the evaluators to previous performance.

3.3. Discriminant function analysis

We performed linear discriminant analysis which showed that the four-cluster solution model accurately classified 87% of the participants. A leave-one-out cross-validation estimated accuracy at 86%, indicating a bias of overfitting.

3.4. Matching procedure

To examine whether participants in the SCI cluster differed from CU individuals, we identified 5 CU controls for each SCI case, matching age (±5 years), sex (exact), and number of exposures to neuropsychological tests (exact for 1 to 5+) from the group of censored individuals in Fig. 1. The five-year caliper was generous—most of our participants were exactly matched on visit. To get 5 CU matches, we allowed CU at the second visit to match the

Table 1
Demographics of incident MCI clusters referenced to 50 + CU weighted to Olmsted County

Feature	Amnestic (N = 193)	Dysnomic (N = 84)	Dysexecutive (N = 159)	SCI (N = 70)	*P* value*	CU† (N = 3912)
Age, yrs						
Median (Q1, Q3)	82 (76, 86)	86 (80, 89)	84 (81, 88)	81 (76, 84)	<.001‡	72 (63, 78)
Education, yrs						
Median (Q1, Q3)	13 (12, 16)	12 (12, 14)	13 (12, 15)	15 (12, 18)	<.001‡	14 (12, 16)
Sex						
Female	90 (47%)	48 (57%)	71 (45%)	30 (43%)	.231§	1988 (51%)
CDR Sum of Boxes						
Median (Q1, Q3)	0.5 (0, 1)	0.5 (0, 1.5)	1 (0, 1.5)	0.5 (0, 1)	.009‡,¶,#	0 (0, 4)
APOE status						
Carrier	73 (38%)	29 (35%)	59 (38%)	23 (33%)	.857§	900 (25%)
STMS total						
Median (range)	31 (25, 38)	29 (19, 36)	30 (22, 36)	33 (26, 37)	<.001‡	36 (34, 37)
MCSA cycle						
Median (Q1, Q3)	3 (2, 4)	3 (2, 5)	3 (2, 4)	4 (3, 5)	.023‡	1 (1, 1)
Global z						
Median (Q1, Q3)	−1.4 (−1.7, −1.1)	−2.7 (−3.5, −2.2)	−2.4 (−2.8, −1.8)	−0.4 (−0.8, −0.1)	<.001‡	0.1 (−0.6, 0.7)
Memory z						
Median (Q1, Q3)	−1.8 (−2.2, −1.2)	−2.1 (−2.6, −1.7)	−1.3 (−1.9, −0.6)	−0.6 (−1.7, −0.1)	<.001‡	−0.0 (−0.7, 0.7)
Language z						
Median (Q1, Q3)	−1.1 (−1.5, −0.6)	−3.1 (−3.8, −2.5)	−1.4 (−1.9, -0.9)	−0.1 (−0.6, 0.3)	<.001‡	0.0 (−0.6, 0.7)
Attention z						
Median (Q1, Q3)	-0.9 (−1.6, −0.4)	−2.0 (−3.1, −1.4)	−3.4 (−3.8, −2.8)	−0.4 (−0.8, 0.0)	<.001‡	0.1 (−0.6, 0.7)
Visuospatial z						
Median (Q1, Q3)	-0.7 (−1.2, −0.3)	−1.7 (−2.4, −1.3)	−1.4 (−2.0, −0.7)	0.2 (−0.7, 0.7)	<.001‡	0.1 (−0.6, 0.7)
FAQ total (0-30)						
Median (Q1, Q3)	0 (0, 2)	0 (0, 4)	1 (0, 5)	0 (0, 1)	<.001‡	0 (0, 0)

Abbreviations: SCI, Subtle cognitive impairment; CDR, Clinical Dementia Rating scale; STMS, Short Test of Mental Status; FAQ, Functional Activities Questionnaire; CU, cognitively unimpaired; SCI, subtle cognitive impairment; MCI, mild cognitive impairment; APOE, apolipoprotein E; MCSA, Mayo Clinic Study of Aging.

*P value testing differences among the 4 clusters.

†Censored CU participants; IQR = interquartile range.

‡Linear model ANOVA.

§Pearson's Chi-squared test.

¶Wilcoxon rank-sum test, dysnomic < SCI.

#Wilcoxon rank-sum, dysexecutive < SCI.

SCI cluster at the third visit. This matching procedure allowed us to correct for any demographic differences that might explain our results. The demographic information of the SCI cluster matched to CU participants is provided in Appendix 2.

3.5. AUROC analyses

We then calculated the area under the receiver operating characteristic curve (AUROC) for the SCI cluster versus the matched CU group and tested whether it was significantly different from 0 at the $P = .05$ level. The most striking difference between the groups was in the memory z-score (AUROC, 0.76; $P \leq .001$) indicating that 76% of the time, a participant in the SCI cluster performed worse than their matched CU peer. There was also a significant difference on the global z-score (AUROC, 0.67; $P \leq .001$), indicating that 67% of the time, a participant in the SCI cluster performed worse than their matched CU peer. There were no differences in the language z (AUROC, 0.56; $P = .13$), attention z (AUROC, 0.55; $P = .21$), or visuospatial z (AUROC, 0.50; $P = .58$) scores.

3.6. Cox Proportional Hazards

Table 2 shows the percentage of individuals receiving a diagnosis of MCI at a future visit and hazard ratios. Of the 4592 participants who entered the study as CU, the probability of being classified as incident MCI/dementia was 15%. The absolute probabilities of receiving a second MCI/dementia diagnosis in the following 15 – 30 months after the initial MCI/dementia diagnosis for participants in the amnestic, dysnomic, and dysexecutive clusters were 60%, 49%, and 53%, respectively. For participants in the SCI cluster, the absolute probability of being classified as MCI/dementia at a future visit was 31%. The SCI cluster had an approximate 2-fold increased risk of a subsequent diagnosis of MCI/dementia, whereas the amnestic, dysnomic, and dysexecutive clusters had an approximate 6-fold increased risk of a subsequent diagnosis of MCI/dementia. Comparisons of hazard ratios between groups are provided in Table 3. The hazard ratios differed between the SCI and MCI clusters but not among the MCI clusters. Including APOE carrier status in the model did not impact results in a qualitative manner.

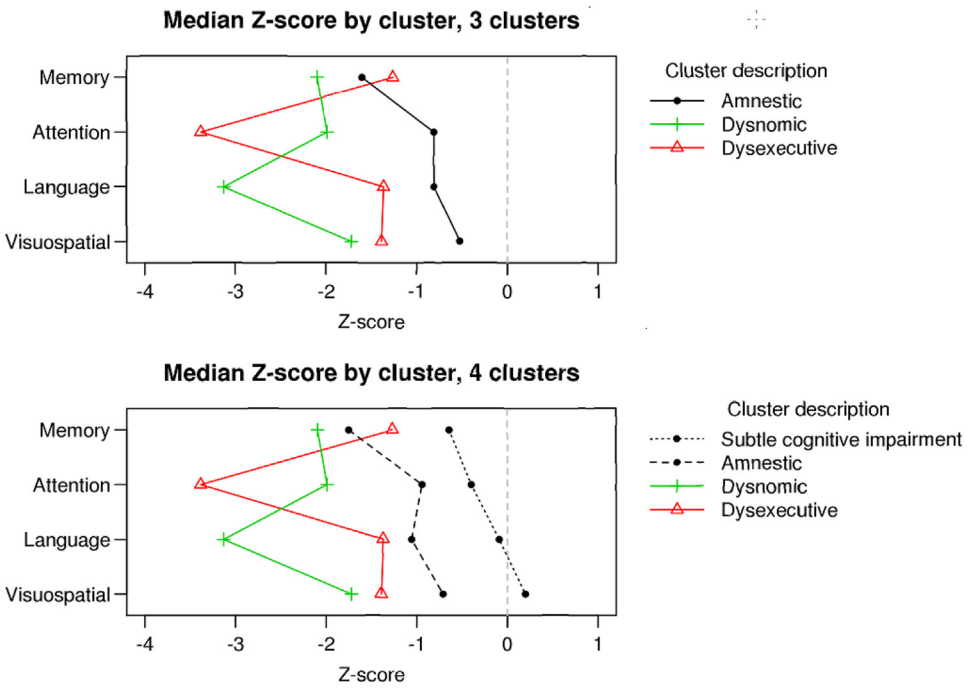

Fig. 2. Plots of median Z-scores by domain for 3-cluster and 4-cluster solutions.

4. Discussion

In this prospective, population-based, longitudinal study of participants with incident MCI (1) we empirically identified three distinct neuropsychological subtypes (amnestic, dysexecutive, and dysnomic), as well as a fourth group with SCI that differed from those who remained CU; (2) participants in the SCI cluster had lower memory and global z-scores relative to their robustly matched CU peers; (3) participants in the SCI cluster had an increased probability of progressing to MCI or dementia relative to their matched CU peers; and (4) the three distinct neuropsychological

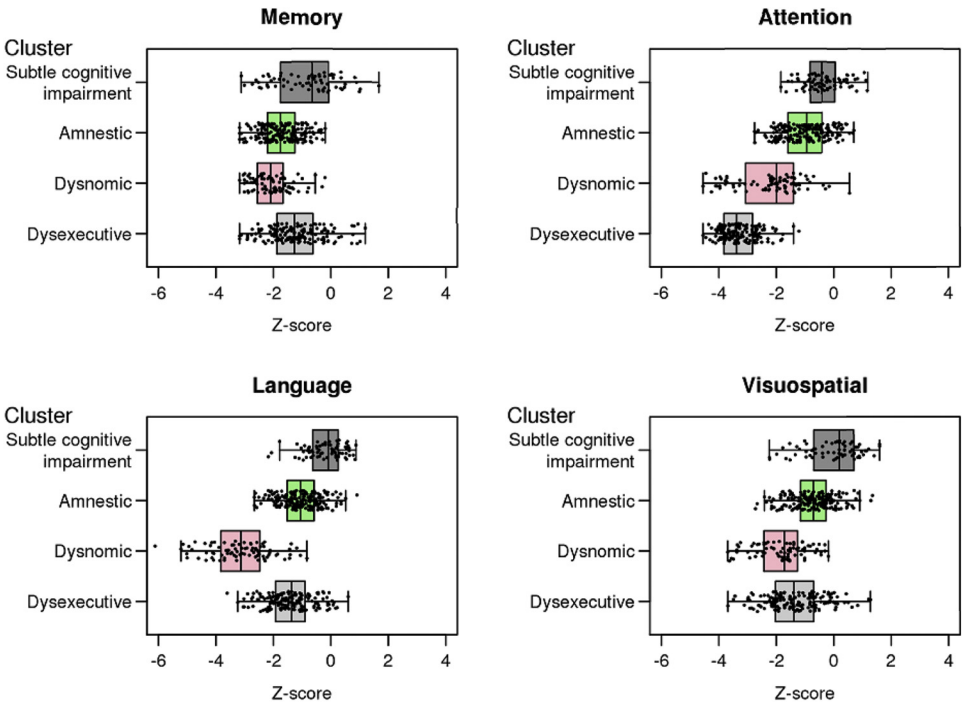

Fig. 3. Boxplots of neuropsychological domain z-scores for the 4-cluster solution.

Table 2
Count (%) testing as MCI at a future visit and hazard ratio

Group	N (%)	HR (95% CI)	*P* value*
CU (reference group)	680 (15%)	1.0	<.001
SCU	22 (31%)	2.1 (1.3, 3.2)	.001
Amnestic	115 (60%)	6.2 (5.1, 7.8)	<.001
Dysnomic	41 (49%)	6.0 (4.3, 8.2)	<.001
Dysexecutive	83 (53%)	6.1 (5.0, 7.4)	<.001

Abbreviations: CU, cognitively unimpaired; SCI, subtle cognitive impairment; MCI, mild cognitive impairment; HR, hazard ratio; CI, confidence interval.

**P* value from a Cox proportional hazards model.

subtypes (amnestic, dysexecutive, and dysnomic) share features with the subtypes identified by Edmonds et al. in the ADNI data set [12].

We used two methods to validate that the SCI cluster does not represent a group of false-positive participants. The first was an ROC curve analysis which used a robust matching procedure wherein we matched the participants with SCI to CU participants by age, sex, and number of exposures to previous neuropsychological tests given the known effects of previous test exposure on performance [35,36]. Results revealed that participants in the SCI cluster performed more poorly than their matched CU peer 76% of the time on the memory z-score and 67% of the time on the global z-score. Furthermore, results from the Cox proportional hazards model revealed that the SCI cluster had a slightly greater than 2-fold increased probability of progression to MCI/dementia than the CU group.

Our group previously showed that even when a neuropsychological domain cut score of z = -0.5 was used (which is slightly greater than the memory z-scores of the SCI cluster with median = -0.6), there was an increased risk of incident dementia. The incidence rates at this cut score were very low, but for multidomain patterns, the hazard ratios were significant [37]. We also previously showed that a group of participants that developed incident MCI/dementia had lower baseline scores in all cognitive domains relative to those who remained CU, and the memory domain z-score at baseline of participants with incident MCI/dementia was over a half-standard deviation lower than that of the group that remained CU (i.e., a z-score difference of .72) [36].

Several studies show that individuals with MCI who revert to normal have an increased risk for receiving another MCI classification or developing dementia [38–43], and the reversion rates are higher in community-based samples [38,41,43]. Although participants in the SCI cluster had a higher rate of reversion to CU than participants in the other three clusters (70% vs. 30% reversion rate), they were much more likely to receive a classification of MCI at the following visit than participants in the CU group. Because of inherent day-to-day variability in test-taking performance, the performance of persons with impending MCI may fluctuate in a range that straddles the cut-point between CU and MCI [39,44]. The observation of reversion to CU does not invalidate the concept of MCI but rather reflects an inherent clinical feature of incident MCI due to variability in the participants' ability to benefit from previous exposure to the testing [36], transient, and/or reversible conditions present on the day of the evaluation, the informant's perception of the participant, and interactions between the participant and clinicians [39]. Those individuals who revert to CU may already have some degree of underlying brain pathology given that individuals with MCI, including those who revert to CU, have a higher risk of progressing to dementia than those who have never received a diagnosis of MCI [38–42].

Table 3
Comparisons of hazard ratios between groups

Group	SCI	Amnestic	Dysnomic	Dysexecutive
CU	0.001	<0.001	<0.001	<0.001
SCI		<0.001	<0.001	<0.001
Amnestic			0.90	0.86
Dysnomic				>0.99

Abbreviations: CU, Cognitively unimpaired; SCI, subtle cognitive impairment.

The amnestic, dysexecutive, and dysnomic clusters we identified in the MCSA data set have some similarities and differences relative to those derived from the ADNI cohort [12] aside from the SCI cluster. Both the ADNI and MCSA data sets resulted in a cluster with isolated memory impairment. The MCSA dysexecutive cluster had relatively mild impairment in memory, language, and visuospatial function in addition to the prominent attention/executive impairment, whereas in the ADNI dysexecutive cluster, memory was mildly impaired, but language was substantially impaired. The MCSA dysnomic cluster had mild to moderate impairment in the memory, attention/executive, and visuospatial domains in addition to language, whereas the ADNI dysnomic cluster also had impairment in memory but not in attention or executive function. This could also be due to slight differences in the neuropsychological tests used to derive the clusters. Nonetheless, the empirical identification of amnestic, dysexecutive, and dysnomic clusters in these two large data sets provides support for reproducible MCI subtypes that, when accounted for in clinical trials, may uncover stronger relationships among biomarkers, pathology, and outcomes, thus improving trial efficiency. Longitudinal evaluation of participants in these clusters will also provide additional insight into the clinical phenotypes of these groups.

Unlike the studies using the ADNI data set, we did not identify a group of "cluster-derived normal" participants [11,12]. There are several important methodological differences between the study by Edmonds et al. [12] on the ADNI data and the MCSA that may shed light on why the participants in the SCI cluster in our study indeed likely represent early MCI rather than false positives. (1) We examined only participants diagnosed with incident MCI based on prospective ratings blinded to previous diagnosis,

whereas the ADNI participants had prevalent MCI diagnosed at their initial screening evaluation. (2) ADNI determines abnormal memory function based on a single memory score (i.e., delayed recall of story A from WMS-R Logical Memory with cutoffs that are education but not age-corrected). As explained by Edmonds et al., the use of only one memory measure to identify memory impairment is a possible shortcoming that could account for low specificity and the large number of false-positive classifications [13]. In contrast, the MCSA uses a composite score based on three age-adjusted measures [27] to assess memory (AVLT Delayed Recall, WMS-R Logical Memory II (both paragraphs), and WMS-R Visual Reproduction II). (3) ADNI assesses general cognitive function with only the Mini-Mental State Examination, whereas the MCSA uses the Short Test of Mental Status [15] and performance on neuropsychological measures of language, attention/executive, visuospatial function, and memory when determining cognitive status. (4) ADNI recruits participants from universities and medical centers [13], whereas the MCSA is an epidemiologic community-based sample [14]. (5) Finally, ADNI includes only participants with amnestic MCI who must have a Clinical Dementia Rating of 0.5 to enter the study. The MCSA, being population-based, did not have any restrictions on entry.

Somewhat unexpectedly, we did not identify a cluster with predominant visuospatial impairment despite including two measures that assess this domain, although both the dysexecutive cluster (visuospatial mean z = -1.34) and the dysnomic cluster (visuospatial mean z = -1.83) had below average to mildly impaired visuospatial z-scores. In a previous article that examined prognosis in elderly persons without dementia in both the MCSA and Framingham Heart Study, the lowest rates of incident dementia occurred with the single-domain nonamnestic profile in the visuospatial domain while single-domain nonamnestic attention/executive function had a comparable prognosis to the single-domain amnestic profile, suggesting that visuospatial function does not add much to prognosis as attention/executive function and memory [37]. Conversely, Clark et al. [9] identified a visuospatial/visual memory subgroup using comprehensive (vs. conventional) MCI criteria that was characterized by lower performance [z = -1.0 (1.6)] only on Block Design which they speculated might represent an emerging non-AD dementia or AD-related condition such as Dementia with Lewy bodies.

In addition to identifying empirical MCI subtypes in the MCSA, our results underscore the value of identifying the earliest stage at which an individual begins to show evidence for cognitive decline, even if this decline does not yet meet a clinical threshold. We used the first diagnosis of MCI or dementia which allowed us to capture participants just as they were transitioning from a classification of CU to MCI. Although participants in the SCI cluster had a lower probability of being classified as MCI/dementia at a subsequent visit relative to the other MCI groups, they had a higher probability (i.e., double) than CU participants. The characteristics of the SCI cluster may represent the transitional cognitive decline of stage 2 of the new National Institute on Aging–Alzheimer's Association AD Research Framework [2] and thus could be a group to target with early interventions given they are showing the earliest manifestations of cognitive decline.

Strengths of our study include a large sample of participants from a population-based design and in-depth characterization including neuropsychological evaluation of four cognitive domains, information from an informant, a physician examination, and diagnosis made by a consensus process. Our ability to identify a separate cluster with SCI from the amnestic cluster underscores the importance of a thorough examination of memory and not relying solely on a single memory measure or preset cutoff score, subjective cognitive complaints, or subjective rating scales for identifying MCI. Participants were assessed at multiple time points, and at each assessment, the raters did not know participants' previous classification or the other raters' classification. We also used a rigorous matching procedure for identifying CU participants against which to compare our SCI cluster. A limitation of this study is that our participants may be healthier than nonparticipants based on their ability to remain active in the MCSA for several years.

A future direction of our work will be to examine imaging biomarkers of our empirically derived MCI clusters to better understand the underlying pathophysiology, especially the group with SCI. Specifically, the next step of our work will be to examine differences in cortical thickness in each of the cluster-derived incident MCI subtypes. Based on a previous study by Edmonds et al. [45], we predict that the amnestic and dysnomic clusters will have atrophy relatively restricted to the temporal lobe, whereas the dysexecutive cluster will have atrophy in temporal, frontal, and parietal regions. Given that our SCI cluster has very mild memory impairment, we expect that this group will also have temporal lobe atrophy, albeit less extensive than the amnestic cluster.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2019.03.014.

RESEARCH IN CONTEXT

1. Systematic review: We reviewed the literature in PubMed which focused on empirical methods for classifying mild cognitive impairment (MCI) subtypes based on conventional versus comprehensive criteria and the oversensitivity of conventional criteria that may result in misclassification of individuals as having MCI. However, these studies are based on prevalent MCI, and impairment in some cognitive domains may have progressed more than in others.
2. Interpretation: The incident MCI cluster subtypes identified in the Mayo Clinic Study of Aging share some similarities and differences with those derived from the Alzheimer's Disease Neuroimaging Initiative cohort, with the most notable difference being a cluster-derived normal group in the Alzheimer's Disease Neuroimaging Initiative versus a group with subtle cognitive decline in the Mayo Clinic Study of Aging that differed from a matched cognitively unimpaired group.
3. Future directions: The identification of replicable MCI subtypes as well as individuals with subtle cognitive decline may allow for more precision in characterizing groups to target with early interventions.

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