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Using the Montreal Cognitive Assessment to Identify Individuals With Subtle Cognitive Decline

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Objective: Dementia is a devastating neurological disease that may be better managed if diagnosed earlier when subclinical neurodegenerative changes are already present, including subtle cognitive decline and mild cognitive impairment. In this study, we used item-level performance on the Montreal Cognitive Assessment (MoCA) to identify individuals with subtle cognitive decline. ***Method:*** Individual MoCA item data from the Alzheimer's Disease Neuroimaging Initiative was grouped using *k*-modes cluster analysis. These clusters were validated and examined for association with convergent neuropsychological tests. The clusters were then compared and characterized using multinomial logistic regression. ***Results:*** A three-cluster solution had

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77.3% precision, with Cluster 1 (high performing) displaying no deficits in performance, Cluster 2 (memory deficits) displaying lower memory performance, and Cluster 3 (compound deficits) displaying lower performance on memory and executive function. Age at MoCA (older in compound deficits), gender (more females in memory deficits), and marital status (fewer married in compound deficits) were significantly different among clusters. Age was not associated with increased odds of membership in the high-performing cluster compared to the others. ***Conclusions:*** We identified three clusters of individuals classified as cognitively unimpaired using cluster analysis. Individuals in the compound deficits cluster performed lower on the MoCA and were older and less often married than individuals in other clusters. Demographic analyses suggest that cluster identity was due to a combination of both cognitive and clinical factors. Identifying individuals at risk for future cognitive decline using the MoCA could help them receive earlier evidence-based interventions to slow further cognitive decline.

Key Points

Question: This study investigated a heterogenous group of individuals classified as cognitively unimpaired via cluster analysis of individual-item Montreal Cognitive Assessment (MoCA) performance. ***Findings:*** Individuals were organized into three clusters with 77.3% precision; the lowest performing cluster was characterized by lower scores on memory and executive function items, older age, and less common married status. ***Importance:*** This study sorted individuals categorized as cognitively unimpaired into three distinct clusters according to an easy-to-administer global cognitive test, thus providing a basis for clinicians to quickly and cost-effectively assess their patients' risk for future cognitive decline. ***Next Steps:*** Future research should focus on the neurodegenerative correlates of cluster membership, including amyloid-β deposition and cortical atrophy.

Keywords: Montreal Cognitive Assessment, subtle cognitive decline, Alzheimer's disease, cluster analysis, machine learning

With over 47 million people living with a diagnosis and costs of over $600 billion yearly in the U.S. alone, dementia is a major public health priority worldwide (Alzheimer's Disease International et al., 2012). Individuals with cognitive impairment may progress from unimpaired to mild cognitive impairment (MCI) to dementia, though presentation is heterogeneous (Farias et al., 2009). Subtle cognitive decline[1] represents a stage of cognitive decline in which individuals show evidence of cognitive deterioration but do not yet meet criteria for MCI (Lin et al., 2019; Pan et al., 2020). Whereas MCI may represent a period of accelerated cognitive deterioration, subtle cognitive decline represents a period of slow memory and other cognitive domain worsening (Howieson et al., 2008; Sperling et al., 2011). Individuals with early subtle cognitive decline progress to dementia at a faster rate than those with entirely unimpaired cognition and have been observed to have pathological Alzheimer's disease (AD) biomarkers present, including cerebral spinal fluid amyloid-β, magnetic resonance imaging (MRI) atrophy, and positron emission tomography (PET) amyloid-β deposition and hypometabolism (Bilgel et al., 2018; Li et al., 2017; Roe et al., 2018; Röhr et al., 2017; Thomas et al., 2018; Toledo et al., 2015; Wolfsgruber et al., 2020). Thus, subtle cognitive decline represents a stage at which neurodegenerative processes are present but are not yet causing deficits severe enough to be classified as MCI.

Identifying cognitive decline at an early stage may improve symptom management and potentially slow disease progression, as well as improve financial, legal, lifestyle, and ethical planning (Dubois et al., 2015; Jutkowitz et al., 2017; Leifer, 2003; Mattsson et al., 2010; Rasmussen & Langerman, 2019; Weimer & Sager, 2009). Multiple pharmacologic therapies are being tested for AD, and evidence is emerging that these agents may be effective in slowing pathological changes in preclinical stages such as subtle cognitive decline (Briggs et al., 2016). Furthermore, lifestyle changes and cognitive training may have effects at early stages (Gates & Sachdev, 2014; Rasmussen & Langerman, 2019). Total and familial costs for dementia care are significantly higher than those for other diseases, including heart disease, and are also disproportionally higher for Black individuals and those with fewer years of education (Kelley et al., 2015). Early identification of subtle cognitive decline offers opportunity to decrease these costs by reducing residential care home admission, facilitating earlier, lower cost treatment, or reducing indirect caregiver costs (Dubois et al., 2015; Jutkowitz et al., 2017; Schaller et al., 2015; Weimer & Sager, 2009). Earlier detection can also aid in identifying end-of-life goals and documenting advanced care planning to ease patients' and families' experiences (Dickinson et al., 2013; Mattsson et al., 2010).

Identification of subtle cognitive decline is challenging, with lengthy, comprehensive neuropsychological testing as the clinical gold standard (Allan et al., 2017; Ferreira et al., 2015; MacAulay et al., 2018; O'Connor et al., 2020; Schindler et al., 2017; Shea & Remington, 2018). This is limited by typically brief medical encounters and long waitlists for specialist evaluation. Shorter, global neuropsychological screening tests such as the Mini-Mental State Examination (MMSE) and the Mini-Cog are cited as the most commonly used tools, despite their relative lack of sensitivity for early cognitive decline (vs. MCI or dementia) using a single summative score (Borson et al., 2000; Judge et al., 2019a, 2019b; Pan et al., 2020). More specific biomarker-based methods, such as cerebral spinal fluid analysis and PET imaging, are invasive

[1] To be distinguished from subjective cognitive decline, which refers to the self-reported experience of this decline (Sperling et al., 2011). Whereas subtle cognitive decline refers to objective cognitive change, subjective cognitive decline is, by definition, without objective cognitive impairment (Edmonds et al., 2015).

and costly, especially as health insurance plans often do not cover these procedures for evaluation of AD (Alzheimer's Association, 2014; CardinalHealth, 2010; Frisoni et al., 2017; Judge et al., 2019b; Palmqvist et al., 2015).

The Montreal Cognitive Assessment (MoCA) offers a potential solution for identifying subtle cognitive decline. This 30-point global cognitive test assesses abilities in visuospatial/executive function skills (e.g., cube drawing), attention (e.g., digit repetition), language (e.g., naming, fluency), abstraction, episodic memory (e.g., word recall), and orientation (Nasreddine et al., 2005). Though the global score is used more commonly in diagnosing MCI and dementia, subscores such as the memory index score have been shown to have utility for earlier stage diagnosis (Freitas et al., 2014; Julayanont et al., 2014; Kaur et al., 2018; Ritter et al., 2017). Compared to the MMSE, the MoCA is more sensitive for detecting subclinical cognitive changes with less ceiling effect (Aggarwal & Kean, 2010; Ciesielska et al., 2016; Trzepacz et al., 2015). Furthermore, the MoCA has been established as having an inverse relationship with amyloid-β PET burden (Eguchi et al., 2019; Jung et al., 2014; Nair et al., 2018; Ramaswamy et al., 2018). The MoCA is of further utility as it can be administered at many points of care by a variety of providers, including medical assistants, nurses, physician assistants, primary care physicians, and neurologists (Nasreddine et al., 2005; S. J. Vogel et al., 2015). It also has several alternate forms to minimize practice effects with repeat testing and versions in almost 100 languages ("FAQ | MoCA Montreal—Cognitive Assessment, n.d.; Siciliano et al., 2019).

The objective of this study was to identify subgroups of individuals with subtle cognitive decline based on MoCA performance. This was achieved using cluster analysis, an unsupervised machine learning technique (Chiu et al., 2009). We hypothesized that these clusters represent unique cognitive subgroups that can be identified clinically according to MoCA item scores and other clinical information. These findings will help to inform clinical practice by identifying those who may experience future cognitive decline and may benefit from more support or preventative medical intervention.

Materials and Method

Data and Variable Selection

Participants

Data were derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI; www.adni.loni.usc.edu; ADNI | About, n.d.). This multicenter, longitudinal research project studies cognition, imaging, and other biomarkers across all stages of cognitive function (Weiner et al., 2010). Data included individuals aged 55–90 recruited from 57 sites across the United States and Canada who had undergone a series of cognitive, imaging, and biomarker evaluations every 3–12 months with ongoing annual follow-up (ADNI | About, n.d.). The database is open to researchers upon request. Informed consent was obtained from all participants at time of study enrollment. In an effort to comply with Transparency and Openness Promotion guidelines, we report how we determined our sample size, all data manipulations, and all measures in the study, in addition to the analytic methods. This study was not preregistered.

For the present analyses, inclusion criteria were as follows: (a) a Clinical Dementia Rating (CDR) of 0 (indicating no or subclinical cognitive impairment, see Measures below); (b) available MoCA and 18-Florbetapir amyloid-β PET scan; (c) CDR, MoCA, and PET within 18 months of each other (Morris, 1997). As the ADNI study spanned many years, some individuals had multiple assessments. For individuals with multiple CDR scores, we selected the CDR closest to MoCA administration and PET scan to ensure that our sample consisted of cognitively unimpaired individuals at the time of assessment. Individuals were excluded if they had confounding medical illness, including other neurological illness and traumatic brain injury.

Measures

The CDR was used as gold standard for identifying individuals without MCI or dementia. This measure collects qualitative data in six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care) from both the patient and an informant (Morris, 1993, 1997). A global score (range: 0–3; 0 = no impairment, 0.5 = questionable impairment/MCI, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia) was calculated to indicate overall functional status. This structured interview was administered by a study coordinator to both the participant and their informant/study partner. Only individuals with a CDR rating of zero were included in the present analyses.

The MoCA is scored according to performance in seven domains: visuospatial/executive, naming, attention, language, abstraction, memory, and orientation (Table 1). A global score, range: 0–30, was calculated according to individual item performance. Higher scores are indicative of better cognitive performance.

Demographic information at the time of MoCA administration was gathered from the ADNI data set: age, years of education, self-identified gender, handedness, self-identified race, ethnicity, and marital status. Data also contained a first-degree family history of dementia and the Geriatric Depression Scale (GDS) short form score (range: 0–15, higher scores indicate more depressive symptoms; Sheikh & Yesavage, 1986).

Raw neuropsychological test scores collected within 18 months of MoCA administration were included in the data for convergent cluster validation. These tests were chosen based on both availability in the data and relative purity of the neuropsychological construct being validated (e.g., testing only a single neuropsychological domain). Logical memory delayed recall (range: 0–25, higher scores

Table 1
MoCA Items Per Domain

Cognitive domain	MoCA items
Visuospatial/executive	Trail making, cube drawing, clock drawing (contour, numbers, hands)
Naming	Lion, rhinoceros, camel
Attention	Digit span (forward, backwards), letters, serial 7 s
Language	Repeat (1–2), *F* fluency
Abstraction	Transportation, measurement
Memory	Word recall 1–5
Orientation	Date, month, year, day, place, city

Note. MoCA = Montreal Cognitive Assessment.

indicate better performance), a measure of episodic memory, assesses an individual's ability to recall a short story after a 30–40 min delay (Wechsler, 1987). The clock drawing test (range: 0–5, higher scores indicate better performance) asks individuals to draw a clock indicating the time "ten past eleven," which requires a mix of executive function and visuospatial abilities to complete (Mainland et al., 1998; Shulman, 2000). MMSE orientation score (range: 0–10, higher scores indicate better performance) is a subset of the MMSE, which asks individuals to recount details of place and time. Decline in orientation is associated with more severe cognitive decline and therefore should be nonimpaired in individuals without MCI or dementia (Dumurgier et al., 2016; Folstein et al., 1975).

Imaging

Amyloid-β PET data included whole cerebral standardized uptake value ratio (SUVR), the standard method of amyloid-β burden quantification (Klein et al., 2015). As part of the ADNI study at the University of California at Berkeley, dynamic, 3D PET images of four 5 min frames were acquired 50–70 min after administration of 370 MBq Florbetapir (ADNI | PET Analysis, n.d.). Image processing was completed at the University of California at Berkeley using Freesurfer (version 5.3.0) reference regions to calculate SUVR; cortical SUVR was standardized according to whole cerebellum (Landau & Jagust, 2015). Amyloid-β positivity was defined as cortical SUVR $\geq$ 1.11, according to established cutoffs (Joshi et al., 2012; Landau & Jagust, 2015). Only PET scans using the Florbetapir amyloid-β tracer were included to maximize available PET variables.

Statistical Analysis

To identify groups of individuals based on item-level MoCA performance, we conducted cluster analysis. Because the MoCA data contained binary and categorical items, we used *k*-modes cluster analysis (R version 4.0.2, package klaR), which uses characteristics of each observation to form groups on the basis of dissimilarity. In this method, clusters are formed according to feature modes, matching dissimilarity, and frequencies (Chaturvedi et al., 2001; Madhuri et al., 2014). Individual MoCA items were used as cluster features. We conducted analyses with two to five clusters and chose the best solution. This solution was chosen quantitatively using the elbow method and qualitatively as that which had the largest cluster sizes (e.g., minimizing small clusters, which contribute to model overfitting), the most unique clusters (e.g., no two clusters with the same MoCA total score), and was substantively meaningful, with individual scores following established cognitive patterns (Marutho et al., 2018; Shi et al., 2021; Syakur et al., 2018). The final cluster solution was then cross-validated 10-fold.

Next, we examined the convergent validity of the clusters to establish that cluster differences were consistent with major cognitive domains as assessed by commonly used neuropsychological tests. Specifically, word recall scores on MoCA, which rely on episodic memory, were validated against logical memory delayed recall, and cube drawing was validated against clock drawing. MMSE orientation was used as a control, as performance on this measure should be consistent in individuals without overt cognitive impairment. Scaled logical memory scores were determined based on normative values according to age, sex, and years of education (Shirk et al., 2011). Clock Drawing scores were categorized according to normed cutoffs by age and education (Mazancova et al., 2017). Raw and scaled neuropsychological test scores were compared across clusters using Kruskall–Wallis tests and post hoc using Mann–Whitney tests. Comparisons were considered to be significant at $p < .05$.

We examined demographics across clusters to gain an understanding of cluster characteristics and factors that may correlate with cluster membership. We used Kruskall–Wallis and Mann–Whitney tests (for continuous data, Omnibus and post hoc, respectively) and chi-square and Fisher's exact tests (for categorical data) with Bonferroni correction for multiple comparisons. In order to understand demographic and neuropsychological contributions to cluster identity, cluster demographics and convergent validation neuropsychological tests were then used to jointly predict cluster membership using multinomial logistic regression with training (70%) and testing (30%) subsets, from which adjusted odds ratios (*OR*) were calculated with 95% confidence intervals (CI).

Results

Sample Characteristics

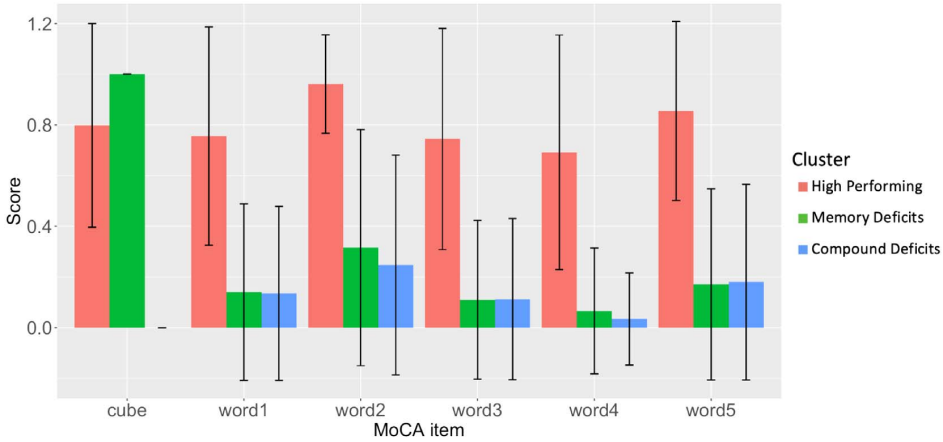
Five hundred and ninety-nine subjects met inclusion criteria and were included in cluster analysis. Subjects had a M_{age} of 74.4 [standard deviation (*SD*) = 7.0] years and education of 16.6 (*SD* = 2.6) years; 53.8% identified as female, 9.52% identified as belonging to a racial minority, and 4.20% identified as Hispanic. A total of 89.3% of subjects were right-handed and 72.1% were married. A family history of dementia was identified in 60.4% of subjects. Mean GDS was 0.96 (*SD* = 1.26); 34.7% of subjects were identified as amyloid-β PET positive.

Mean MoCA sum was 25.6 (*SD* = 2.8, range: 17–30). $M \pm SD$ raw neuropsychological scores were as follows: logical memory delayed = 12.9 ± 4.0 (range: 1–24); clock drawing test = 4.7 ± 0.6 (range: 2–5); MMSE orientation = 9.7 ± 0.5 (range: 7–10). $M \pm SD$ scaled neuropsychological scores were as follows: logical memory delayed *z*-score = 0.50 ± 1.00 (range: −2.372 to 3.469); clock drawing test percentile = 88.2 ± 19.3 (range: 2–98).

Identification of MoCA Clusters

A three-cluster solution had 77.3% precision with 10-fold cross-validation. Compared to a four-cluster solution, this solution was also well distributed, with relatively large clusters, no clusters with the same total MoCA score, and cluster individual scores falling along established types of decline (e.g., memory difficulties grouped together); furthermore, this *k* was best according to the elbow method. Individuals in Cluster 1 ("high performing," $n = 282$) had a modal MoCA score of 30 out of 30, with no items of score 0, indicating the most common score across all individuals in the cluster was 1 for each item. Individuals in Cluster 2 ("memory deficits," $n = 228$) had a modal MoCA score of 25 out of 30, with a modal score of 0 on word recall items one through five, indicating a most common score of 0 across all individuals in the cluster for word recall items. Individuals in Cluster 3 ("compound deficits," $n = 89$) had a modal MoCA score of 24 out of 30 with a score of 0 on word recall items one through five and cube drawing, indicating the most common score was 0 across all individuals in the cluster for cube drawing and word recall items. Figure 1 shows the relative

Figure 1
Select MoCA Item Distributions by Cluster



Note. Score = probability of scoring 1 on each item. Word 1–5 = word recall items. MoCA = Montreal Cognitive Assessment. See the online article for the color version of this figure.

distributions of these MoCA items across the three clusters: Although lower word recall scores were observed for the compound and memory deficits clusters compared to the high-performing cluster, the compound deficits cluster performed consistently lower on cube drawing than the high-performing and memory deficits clusters.

Tests of convergent validity with raw and scaled scores from several commonly used neuropsychiatric measures supported cognitive differences among clusters (Table 2). Logical memory (memory domain; cognitively equivalent to MoCA word recall items one through five) was significantly lower in the compound and memory deficits clusters compared to the high-performing cluster ($p < .001$ for raw and scaled) but did not significantly differ between the compound and memory deficits clusters (raw $p = .09$, scaled $p = .95$). Clock drawing (executive function and visuospatial domain; cognitively equivalent to cube drawing) was significantly lower in the compound deficits cluster compared to the high-performing and memory deficits clusters (raw $p = .002$ and $p < .001$, respectively; scaled $p = .003$ and $p = .001$, respectively) and did not significantly differ between the high-performing and memory deficits clusters (raw $p = .91$, scaled $p = .84$). MMSE orientation (control) did not significantly differ among or between any clusters ($p > .05$).

Demographic Correlates and Predictive Models of MoCA Clusters

Mean age at MoCA, self-identified gender (female), and marital status (married) were significantly different among clusters ($p < .05$, Table 3). Post hoc analysis revealed that the compound and memory deficits clusters were significantly older than the high-performing cluster ($p < .001$), but there was no significant difference in age between the compound and memory deficits clusters ($p = .49$). There were significantly more females in the high-performing cluster versus the memory deficits cluster ($p < .001$). Significantly fewer individuals were married in the compound deficits cluster compared to the high-performing cluster ($p = .002$). There were no significant differences among clusters according to education, handedness (right), self-identified race (minority), ethnicity (Hispanic), first-degree family history of dementia, or GDS score. Though not statistically significant ($p = .24$), individuals in the compound deficits cluster were more often amyloid-β PET positive, with 41.6% positive compared to 28.3% in the high-performing cluster and 35.5% in the memory deficits cluster.

In multinomial logistic regression, individuals in the high-performing cluster were more likely to be younger relative to individuals in the memory deficits cluster, $OR = 1.07$, 95% CI [1.04–1.11], $p < .001$, and compound deficits cluster, $OR = 1.09$, 95% CI [1.04–1.13], $p < .001$). No differences in age were observed between individuals in the memory and compound deficits clusters (Table 4). Higher scores on Logical Memory were associated with lower odds of belonging to the compound and memory deficits clusters compared to the high-performing cluster, with $OR = 0.86$, 95% CI [0.80–0.91], and $OR = 0.86$, 95% CI [0.79–0.93], respectively. Furthermore, higher scores on Clock Drawing were associated with lower odds of belonging to the compound deficits cluster compared with the high-performing and memory deficits clusters, with $OR = 0.61$, 95% CI [0.39–0.96] and $OR = 0.45$, 95% CI [0.28–0.73], respectively. Higher MMSE orientation scores were not associated with cluster membership.

Discussion

In this study, we identified three cognitively distinct clusters of individuals categorized as having unimpaired cognition (CDR = 0) based on item-level MoCA performance. The compound deficits cluster represented a group at highest risk for future cognitive decline, or poor performance on neuropsychological testing, due to lower executive performance relative to the other two clusters and lower memory performance relative to the high-performing cluster. Though the compound deficits cluster was characterized by older age, relative to the other clusters, joint predictive models suggested that membership within this cluster was also associated with poorer cognitive performance. There was no difference in age between the compound and memory deficits clusters. Our results were consistent

Table 2
Cluster Convergent Validation

MoCA domain[a]	Validation Measure	Score	Cluster			Omnibus test	Post hoc comparisons[c]		
			HP	MD	CD	*p* value[b]	HP versus MD	MD versus CD	HP versus CD
Memory: word recall 1–5	Logical memory delayed	Raw	14.2 ± 3.8	11.9 ± 3.8	10.6 ± 3.2	**<.001**	**<0.001**	0.09	**<0.001**
		Scaled[d]	0.80 ± 0.96	0.23 ± 0.97	0.23 ± 0.92	**<.001**	**<0.001**	0.95	**<0.001**
Visuospatial and executive function: Cube drawing	Clock drawing	Raw	4.7 ± 0.5	4.7 ± 0.5	4.4 ± 0.7	**.002**	0.91	**0.002**	**<0.001**
		Scaled[e]	89.6 ± 17.7	89.3 ± 18.4	81.4 ± 24.5	**.002**	0.84	**0.003**	**0.001**
Control	MMSE orientation	Raw	9.7 ± 0.5	9.7 ± 0.5	9.7 ± 0.6	.37	0.27	0.23	0.65

Note. All values are given as mean ± standard deviation. Significant *p* values (<.05) are indicated in bold. MoCA = Montreal Cognitive Assessment; HP = high performing; MD = memory deficits; CD = compound deficits; MMSE = Mini-Mental State Examination.
[a] MoCA domain corresponding to the validation measure. [b] Kruskall–Wallis test. [c] Mann–Whitney test. [d] Scaled according to gender, education, and age; represented as *z*-score with standard deviation. [e] Scaled according to normative percentiles for age and education; represented as percentile with standard deviation.

with other studies that have found deficits in memory and executive function among individuals with subtle cognitive decline (Toledo et al., 2015; Weiner et al., 2017). Individuals in the memory deficits cluster showed lower memory performance than individuals in the high-performing cluster. Taken together, the compound deficits cluster may represent a group of individuals who were characterized as unimpaired based on CDR but may be at heightened risk for future cognitive deterioration. Individuals in the compound deficits cluster displayed a more "multi-domain" pattern of decline, which has been shown to indicate quicker conversion to worse cognitive status and presence of more pathological biomarkers, such as amyloid-β PET burden, than those with memory decline alone (Toledo et al., 2015).

As optimal MoCA cutoffs to indicate cognitive impairment vary within the literature, especially in racial and ethnic minority groups, the modal MoCA score of 24/30 in the compound deficits cluster and 25/30 in the memory deficits cluster could potentially be used as cutoffs to screen for MCI if diagnosis was based on total score alone (Milani et al., 2019; Nasreddine et al., 2005). In a recent meta-analysis, a cutoff score of 23/30 showed the best diagnostic accuracy in distinguishing unimpaired cognition versus MCI (Carson et al., 2018). Other studies have identified the standard cutoff of 26/30 as too high when compared to performance on comprehensive neuropsychological testing (Carson et al., 2018; Elkana et al., 2020). In community-dwelling elders, a cutoff of 22 has been shown to accurately identify those with functional impairment (Doyon Dolinar et al., 2016). Total MoCA scores often overlap between unimpaired individuals and individuals with MCI, thus making it difficult to define a clear screening cutoff (Rossetti et al., 2011; Trzepacz et al., 2015; Wong et al., 2015). These discrepancies further underscore the ambiguity in cognitive diagnosis for individuals with CDR = 0 (grossly cognitively unimpaired) and lower MoCA score, supporting the use of additional cognitive testing to identify individual cognitive status. Moreover, these discrepancies underlie the importance and relevance of using *individual* MoCA items when utilizing this easy-to-administer screening test, such as those specified in our cluster analysis, for identifying those with subtle cognitive decline, as inconsistent total score cutoffs across providers could potentially result in inaccurate MCI diagnoses. For example, identifying that someone scored lower in memory items and executive function items (such as cube drawing) may have better diagnostic utility than assessing their cognitive status based on total score alone. Therefore, we suggest that it is important to weigh both overall score and individual item patterns when assessing MoCA performance.

Within the compound deficits cluster, 41.6% of individuals were amyloid-β PET positive. However, individuals in this cluster were not overall significantly more likely to be amyloid-β PET positive than individuals in other clusters, which is not surprising based on previous literature. For example, in a study of cognitively unimpaired older adults who underwent sequential fluorodeoxyglucose (FDG) and amyloid-β PET scans, individuals were found to have alterations in FDG metabolism and cognition up to 20 years before meeting the conventional threshold for amyloid-β positivity (Insel et al., 2017). This suggests that some cognitively unimpaired individuals may experience progressive neurodegenerative changes, as measured by FDG PET, and subtle cognitive changes, even if they do not meet thresholds for AD amyloid-β pathology. As we continue to study these clusters, we will assess amyloid-β burden

Table 3
Cluster Demographics

Subject characteristics	Cluster			Omnibus test	Post hoc comparisons		
	HP	MD	CD	*p* value	HP versus MD	MD versus CD	HP versus CD
Age at MoCA[a]	72.6 ± 6.3	75.8 ± 6.7	76.6 ± 7.8	**<.001**	**<0.001**	0.49	**<0.001**
Education[a]	16.7 ± 2.5	16.6 ± 2.5	15.9 ± 3.0	.09	0.59	0.08	0.03
Gender—female (self-identified)[b]	176 (62.4%)	95 (41.7%)	51 (57.3%)	**<.001**	**<0.001**	0.02	0.46
Handedness—right[b]	252 (89.4%)	203 (89.0%)	80 (89.9%)	.98	1.0	0.99	1.0
Race—minority (self-identified)[b]	29 (10.3%)	19 (8.4%)	9 (10.1%)	.74	0.55	0.79	1.0
Ethnicity—Hispanic[c]	15 (5.4%)	9 (4.0%)	1 (1.1%)	.23	0.59	0.29	0.13
Marital status—married[b]	208 (73.8%)	172 (75.4%)	52 (58.4%)	.007	0.74	0.009	**0.002**
Dementia family history[b]	182 (64.5%)	130 (57.0%)	50 (56.2%)	.15	0.10	0.99	0.20
Geriatric Depression Scale (range: 0–15)[a]	0.84 ± 1.1	1.03 ± 1.3	1.16 ± 1.5	.24	0.17	0.69	0.16
PET status—amyloid positive[b]	90 (28.3%)	81 (35.5%)	37 (41.6%)	.24	0.45	0.39	0.12

Note. All values are given as $M \pm SD$ for continuous data or N (percentage) for categorical data. Significant p values are indicated in bold ($p < .005$). MoCA = Montreal Cognitive Assessment; PET = positron emission tomography; HP = high performing; MD = memory deficits; CD = compound deficits.
[a] Omnibus Kruskall–Wallis/post hoc Mann–Whitney tests. [b] Among groups/post hoc chi-square tests. [c] Omnibus/post hoc Fisher exact tests.

beyond binary PET positivity to better understand any organic brain changes in these individuals.

The compound deficits cluster represents a distinct group of subtle cognitive decline that can potentially be identified clinically. In addition to a homogenously low performance on MoCA cube drawing relative to the memory deficits and high-performing clusters and lower MoCA memory performance compared to the high-performing cluster, these individuals were also older and more commonly unmarried than individuals in other clusters. These characteristics could be combined to identify individuals at the greatest risk for subtle cognitive decline to provide earlier interventions, which have been shown to benefit patients' quality of life and financial situations by extending quality time at home and avoiding long-term institutionalization (Borson et al., 2013; Dubois et al., 2015; Leifer, 2003; Olsen et al., 2016; Rasmussen & Langerman, 2019; A. Vogel et al., 2006). As the total MoCA score alone has poor sensitivity for identifying individuals with subtle cognitive decline, the combination of individual item performance and demographic characteristics represents a novel clinical decision-making opportunity for clinicians looking to provide early intervention for individuals with subtle cognitive decline at risk for future neurodegeneration (Pan et al., 2020). Thus, early evidence-based treatments, such as cognitive training and select pharmacotherapy, may slow disease progression and could be targeted toward those individuals in the compound deficits cluster (Gates & Sachdev, 2014; Gauthier, 2005). Caregiver assistance and support can also be initiated early to decrease caregiver burden and stigma in future cognitive decline (Chu, 2012; Conde-Sala et al., 2014; Martín-Carrasco et al., 2009; Werner et al., 2012).

Cognitively unimpaired individuals in the lowest performing cluster can be identified at many levels of care, as the MoCA and clinical information are easy and inexpensive to collect and categorize. Unlike a comprehensive neuropsychological assessment, these data can be collected by a physician, nurse, medical assistant, or other healthcare professional at a yearly wellness visit. Physician consensus is mixed regarding yearly cognitive screening despite patient appreciation for this information (Ashford et al., 2006; Borson et al., 2013; Galvin et al., 2020; Larner, 2018). Our results further underscore the necessity for screening even in the absence of cognitive complaints, as individuals in the compound deficits cluster were classified as cognitively unimpaired on CDR but had distinct cognitive deficits on the MoCA.

Table 4
Multinomial Logistic Regression With Demographics and Convergent Validation Neuropsychological Tests Among Clusters

Regression covariates	HP[a] versus MD	MD[a] versus CD	HP[a] versus CD
Age at MoCA	**1.07 [1.04–1.11] [<.001]**	1.01 [0.97–1.06] [.59]	**1.09 [1.04–1.13] [<.001]**
Education	0.98 [0.89–1.07] [.62]	0.91 [0.81–1.02] [.10]	0.89 [0.79–1.00] [.044]
Gender—female (self-reported)	**0.59 [0.36–0.97] [.039]**	0.95 [0.50–1.80] [.86]	0.56 [0.29–1.07] [.077]
Marital status—married	1.13 [0.65–1.98] [.66]	0.51 [0.26–1.00] [.051]	0.58 [0.30–1.13] [.11]
Logical memory delayed	**0.86 [0.80–0.91] [<.001]**	1.00 [0.93–1.08] [.98]	**0.86 [0.79–0.93] [<.001]**
Clock drawing test	1.35 [0.86–2.12] [.19]	**0.45 [0.28–0.73] [.0012]**	**0.61 [0.39–0.96] [.033]**
MMSE orientation	1.09 [0.72–1.64] [.68]	1.27 [0.74–2.16] [.38]	1.38 [0.80–2.37] [.24]

Note. Values are reported as adjusted odds ratio [95% confidence interval] [p value]. Significant odds ratios (defined as CI not crossing 1) are indicated in bold. MoCA = Montreal Cognitive Assessment; HP = high performing; MD = memory deficits; CD = compound deficits; MMSE = Mini-Mental State Examination.
[a] Indicates baseline group for regression.

This study has multiple strengths. A common critique of unsupervised clustering methods is the lack of gold standard for output, which can make model generalizability more difficult. Our study connects MoCA items to convergent neuropsychological tests, which strengthens the generalizability of our results by relating our clusters to performance on commonly used measures. This supports that the differences observed in our clusters are not due to random changes in MoCA performance but rather related to underling cognitive change. Furthermore, as the MoCA has been extensively studied in the context of many cognitive disorders, the neuropsychological constructs measured and observed were relatively distinct (i.e., measuring specific neuropsychological processes; Freitas et al., 2012; S. J. Vogel et al., 2015). The large sample size also facilitates relative cluster homogeneity, providing further strength to the study. Also of note, there were no significant differences in depressive symptoms among our clusters, thus underscoring that the relative differences among clusters are not likely to be due to pseudodementia, as depressive symptoms have been associated with subtle cognitive deficits (Fisman, 1985; Paterniti et al., 2002).

Our study also should be interpreted in the context of several limitations. It is important to consider selection bias in individuals of the ADNI cohort, as this group is not necessarily equivalent to a random epidemiological sample and may represent individuals with more subjective cognitive complaints; the ADNI cohort was also, on average, well educated, which may negatively skew MoCA results (Ardila et al., 2000; Weiner et al., 2010). Additionally, the cohort was largely nonminority race and did not have reliable measures of socioeconomic status. This made it difficult to generalize this model to all race or socioeconomic backgrounds. Though certain demographic differences, such as marital status, were significantly different across clusters, we cannot conclude a causal relationship between a potential lack of social support (in an unmarried individual) and cognitive decline, though this relationship has been explored in the past (Del Brutto et al., 2019; Kotwal et al., 2016). Finally, though we are able to make conclusions regarding long-term cognitive decline based on the neuropsychological profile of our cognitive deficits cluster, we were not able to assess the actual longitudinal development of dementia in this sample due to lack of statistical power and inconsistent follow-up availability for individual participants (Toledo et al., 2015).

In this study, we used cluster analysis to identify three distinct cognitive clusters among those considered to be cognitively unimpaired (CDR = 0) using individual MoCA items. Performance on this easy-to-administer cognitive screening test can potentially be combined with clinical information to aid in clinical decision-making, thus aiding providers in identifying those who may benefit from additional early intervention or lifestyle changes. Future work in these clusters will involve more investigation into amyloid-β PET burden, particularly within brain regions related to the observed MoCA pathologies, as well as into longitudinal validation of our clusters.

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