




Research Article

Exploring symptom clusters in mild cognitive impairment and dementia with the NIH Toolbox

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Abstract

Objective: Symptom clustering research provides a unique opportunity for understanding complex medical conditions. The objective of this study was to apply a variable-centered analytic approach to understand how symptoms may cluster together, within and across domains of functioning in mild cognitive impairment (MCI) and dementia, to better understand these conditions and potential etiological, prevention, and intervention considerations. **Method:** Cognitive, motor, sensory, emotional, and social measures from the NIH Toolbox were analyzed using exploratory factor analysis (EFA) from a dataset of 165 individuals with a research diagnosis of either amnesic MCI or dementia of the Alzheimer's type. **Results:** The six-factor EFA solution described here primarily replicated the intended structure of the NIH Toolbox with a few deviations, notably sensory and motor scores loading onto factors with measures of cognition, emotional, and social health. These findings suggest the presence of cross-domain symptom clusters in these populations. In particular, negative affect, stress, loneliness, and pain formed one unique symptom cluster that bridged the NIH Toolbox domains of physical, social, and emotional health. Olfaction and dexterity formed a second unique cluster with measures of executive functioning, working memory, episodic memory, and processing speed. A third novel cluster was detected for mobility, strength, and vision, which was considered to reflect a physical functioning factor. Somewhat unexpectedly, the hearing test included did not load strongly onto any factor. **Conclusion:** This research presents a preliminary effort to detect symptom clusters in amnesic MCI and dementia using an existing dataset of outcome measures from the NIH Toolbox.

Keywords: adults; aged; cognition; emotion; sensory function; pain assessment; social support; psychomotor performances; statistical factor analyses

(Received 22 March 2023; final revision 1 December 2023; accepted 12 January 2024; First Published online 16 February 2024)

There has been interest by the healthcare science community in recent years in looking closely at how symptoms cluster together within and across clinical conditions as a way to understand the potential shared etiologies, possible preventive strategies, and treatment interventions that may be useful (Miaskowski et al., 2007; 2017). This has been driven particularly strongly within oncology and nursing research, where so-called “symptom clustering” approaches have been used to understand the patient experience of their outcomes holistically when numerous co-occurring symptoms—such as pain, fatigue, insomnia, and depression—go undetected and unaddressed if the primary clinical focus is elsewhere, as in the case of cancer treatment (Dodd et al., 2001; Ho et al., 2015; Huang & Lin, 2009; Illi et al., 2012; Kim et al., 2005). The clinical challenges posed by complex, comorbid, and chronic conditions are familiar to clinical and health psychologists

and neuropsychologists (Ashworth et al., 2015; Ford, 2018; Miles et al., 2021), although the concept of a “symptom cluster” as defined by these allied health research traditions (see Table 1) may be a novel framing (Barsevick, 2016; 2007; Dodd et al., 2001; Harris et al., 2022; Miaskowski et al., 2017).

In symptom clusters research, exploratory factor analysis (EFA) has been a preferred approach for detecting clusters of symptoms that may not be expected based on traditional diagnostic groupings or severity delineations (Harris et al., 2022). Considered one of several “variable-centered approaches” of symptom clusters research (in contrast to other “patient-centered approaches,” such as latent profile analysis), EFA allows for statistical understanding of how an array of symptoms can be grouped to reveal the underlying structure of symptoms and how they may be related or caused by shared etiologies (Barsevick, 2016; Harris et al., 2022;

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Cite this article: Tyner C.E., Boulton A.J., Slotkin J., Cohen M.L., Weintraub S., Gershon R.C., & Tulsky D.S. (2024) Exploring symptom clusters in mild cognitive impairment and dementia with the NIH Toolbox. *Journal of the International Neuropsychological Society*, 30: 603–614, <https://doi.org/10.1017/S1355617724000055>

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Table 1. Definitions of a symptom cluster in the literature

Definition	Source
“The first definition of a symptom cluster was proposed to be ‘three or more concurrent symptoms’ that ‘are related to each other The symptoms within a cluster are not required to share the same etiology.’”	Harris et al., 2022 p. 2 (quoting Dodd et al., 2001 p. 465)
“A stable group of concurrent symptoms that are related to one another and distinct from other symptom clusters (Kim et al., 2005). Symptoms in a cluster may be related through a common etiology or mechanism, shared variance, or a common outcome (Miaskowski et al., 2007).”	Barsevick, 2016 p. 334–335
“Given the presence of clinically and statistically meaningful symptom pairs and the potential for others, it makes sense to include symptom pairs in the definition of a symptom cluster.”	
“Two or more concurrent symptoms Stable group of symptoms Independent of other clusters May have shared underlying mechanism(s) May have shared outcome(s) Temporal dimension [may be relevant]”	Miaskowski et al., 2017; Table 1, p.2

Oh et al., 2016; Skerman et al., 2012). In the psychometric and neuropsychological assessment traditions, EFA is often used for identifying “domains” for assessment, for psychometric validation of tests or batteries, or for further interpretation of assessments, such as developing composite scores (Ma et al., 2021; Strauss & Fritsch, 2004). While the language used for describing these approaches may differ between these research communities—trading “domains” for “symptom clusters”—the underlying clinical interest is a shared one: to use patient-centered assessments and advanced statistical techniques to better understand complex presentations of symptoms that may offer novel targets for assessment, intervention, and improvement in quality of life.

Thus, in the present study, a symptom clustering framework was chosen to study the experience of people with amnesic mild cognitive impairment (aMCI) or dementia of the Alzheimer type (DAT), as it offers an opportunity to understand patient experiences beyond the lines of traditional domains as typically approached in neuropsychological research. The objective of this research is to detect and examine the presence of possible symptom clusters within and across individuals with a research diagnosis of either aMCI or mild DAT (Weintraub et al., 2022). Given the known wide array of symptoms that can be experienced by patients with these diagnoses, which can span cognitive, emotional, motor, sensory, and social challenges (American Psychiatric Association, 2013; Lezak et al., 2012; Thomas et al., 2020), using an exploratory symptom clustering approach offers the potential to detect groups of symptoms that may cut across domains. While most symptom clusters research has been performed in oncology populations (Harris et al., 2022), this theoretical and methodological approach has been applied in other clinical groups—such as HIV, heart disease, lung disease, and kidney disease—and symptom clusters have been found that correlate with important patient-centered outcomes including quality of life and health care utilization (Miaskowski et al., 2017). Furthermore, the National Institutes of Health (NIH) has recently supported several initiatives to examine other chronic disease groups for relevant symptom clusters (National Institutes of Health, 2017), with the goal to understand what can be learned about these clinical groups through application of these methods. The present study reports on one of these recent projects.

Historically, research on symptom clusters (or domains of functioning) in dementia has primarily focused on using neuropsychological assessments to distinguish similar clinical syndromes with unique neuropathological causes (such as frontotemporal dementia, semantic dementia, and DAT) by

comparing neuropsychiatric symptoms that support the diagnosis of one syndrome over another (Kramer et al., 2003; Marra et al., 2007). More recent research on symptom clusters relevant to MCI and dementia has focused primarily on understanding how patterns of cognitive functioning change with aging—for example, the distinct patterns of fluid cognition seen in adults with and without dementia (Ma et al., 2021; McDonough et al., 2016)—and lifestyle predictors of cognitive decline, such as the connections between engaging in cognitive leisure activities and lower rates of dementia (Lee & Chi, 2016). Furthermore, research has shown the relevance of associated symptoms in *noncognitive* domains—such as motor, sensory, mood, social functioning—to the daily functioning and quality of life of these patients (Dyer et al., 2020; Elovainio et al., 2022; Insha et al., 2022; Hwang et al., 2020; Rostamzadeh et al., 2022; Vaingankar et al., 2017; van der Linde et al., 2010). There has nevertheless been limited research exploring the associations of symptoms across cognitive and noncognitive domains in MCI and dementia. One study, for example, found a connection between vestibular functioning and visuospatial functioning, with worse performance in one domain associated with worse performance in the other (Bigelow et al., 2015). These findings are likely more than correlational; there is increasingly rigorous evidence to indicate that domains of noncognitive functioning (e.g., hearing; physical fitness) may be modifiable risk factors of cognitive decline and dementia (Cohen et al., 2021; Livingston et al., 2020). Thus, we believe that exploration of symptom clusters within and across domains in these populations may be fruitful for understanding targets for intervention, prevention, and as possible markers of etiology.

For the purpose of measuring symptoms within and across domains, there have been important test development efforts for standardizing systems of comprehensive symptom assessments, including the NIH Toolbox[®] (Gershon et al., 2010; 2013). The NIH Toolbox (NIHTB), which includes tests that span a wide range of cognitive, sensory, motor, emotional, and social domains, appears to have significant potential for exploring symptom clusters. The NIHTB tests are self-contained and conormed, and score corrections can be made based on demographics and/or premorbid ability estimates (Holdnack et al., 2017; Nitsch et al., 2017). This widely researched battery benefits from being a computerized assessment by having high precision for measuring reaction times, and automated administration and scoring that can reduce user bias. The NIHTB has been validated previously in healthy aging (Scott et al., 2019) and dementia research (Ma et al., 2021), including a recent publication supporting the validity of the

NIHTB in individuals aged 85 and older (Nolin et al., 2023), which further supports its utility for this study. For these reasons, we anticipate that the NIHTB will offer a useful assessment approach for symptom clusters research generally, and specifically in aging research, and we aim to evaluate it for this purpose with the current project. We hypothesize that by using an existing dataset, which was collected as part of the Advancing Reliable Measurement in Alzheimer's Disease and Cognitive Aging (ARMADA) study (Weintraub et al., 2022), and a variable-oriented symptom clustering approach, we expect we will detect clusters of symptoms within and potentially across domains that may have relevance to understanding potential etiological factors, prevention targets, and intervention strategies for MCI and dementia.

Methods

Participants

Participants for this study were drawn from the ongoing data collection for the ARMADA study and included individuals recruited from nine established Alzheimer's Disease Research Centers (ADRCs) across the United States. Although the ARMADA study includes several participant groups, only data from 165 individuals aged ≥ 60 with a research diagnosis of aMCI (single or multidomain) or mild DAT were included in the present study. Diagnoses of aMCI and mild DAT were based on the 2011 NIA–Alzheimer's Association criteria (Albert et al., 2011; McKhann et al., 2011) following the procedures of the National Alzheimer's Coordinating Center (Morris et al., 2006; Weintraub et al., 2018; 2009), with the Clinical Dementia Rating Scale (CDR; Morris, 1993) global score of 0.5 required for aMCI and 1.0 for mild DAT. Participants were excluded for acute neurological disorders that could lead to cognitive impairment, a history of major psychiatric illness, or substance use disorder (see Weintraub et al., 2022, for full details on sample recruitment, inclusion/exclusion criteria, and diagnostic classification procedures). The study was approved by the institutional review boards at each of the participating data collection sites and was completed in accordance with Helsinki declaration.

Study design, measures, and procedures

Data used for these analyses come from the baseline assessment timepoint of the ARMADA project and included administration of the NIHTB (English language version) and a detailed inventory of demographics and health history (in many cases this was the Uniform Data Set [UDS] assessment). Table 2 presents details on the NIHTB assessments administered in the baseline assessment of the ARMADA study, including scoring metrics and directions. Analyses were conducted on all measures in NIHTB version 2.0 except the Standing Balance test, which was only completed by a minority of participants. Only cases in which the NIHTB and demographic/health history data were collected within a 130-day window were included in the present analyses.

Data analyses

EFA was used to analyze the data. All EFA models were fit in R using the *lavaan* package (version 0.6-16; Rosseel, 2012). Rates of missing data were generally low ($< 5\%$), although a small number of assessments had slightly higher rates of missingness (e.g., Picture Sequence Memory = 18%). Full-information maximum likelihood (FIML) was used for model estimation and used all available information in the dataset. We examined EFA solutions that varied

between 1 and 9 factors being extracted. Several criteria were used for factor extraction, as employing multiple criteria simultaneously may be optimal, compared to reliance on any single criterion alone (Auerswald & Moshagen, 2019). First, we conducted a parallel analysis (Horn, 1965). Second, we compared global model fit between adjacent solutions, as indicated by the chi-square test statistic χ^2 , the root-mean-square error of approximation (RMSEA; Steiger & Lind, 1980), and the Tucker-Lewis index (TLI; Tucker & Lewis, 1973). Conventional fit index cutoffs—despite their known limitations (Marsh et al., 2004)—were used to pinpoint solutions that exhibited acceptable fit to the data: nonsignificant χ^2 , RMSEA values below .06, TLI values greater than .95 (Hu & Bentler, 1999). We also noted the solution in which the lower bound of the 90% confidence interval for the RMSEA dipped below .05 (Preacher et al., 2013). Comparative model fit was indexed by the Bayesian information criterion (BIC; Schwarz, 1978), with the lowest BIC value indicating an optimal balance between model fit and parsimony. Finally, the interpretability of each EFA solution was given the largest weight when deciding how many factors to extract. Following extraction, factor loadings were rotated using oblimin, a common oblique rotation method, as we expected the extracted factors to be correlated. Following extraction, factor scores were computed using empirical Bayes estimation and compared (*t*-test, Cohen's *d*) between the aMCI and DAT subsamples.

Results

Demographic characteristics of the analysis sample are shown in Table 3. Participant age was approximately normally distributed between 60 and 94 years of age. Participant gender was roughly evenly distributed, with a slighter higher proportion of males in each diagnostic category. The sample was predominantly non-Hispanic and White. A majority of the sample reported high levels of educational attainment (4-year college degree or higher). Descriptive statistics for the primary outcome variables are shown in Table 4 (descriptive statistics within each diagnostic category are available in the Supplementary Material). Apart from the 9-Hole Pegboard Test and Odor Identification tests, all variables exhibited skewness and kurtosis indices between 2 and 2. Moderate floor effects were also observed for three measures: Picture Sequence Memory, Pain Interference, and Friendship.

Parallel analysis suggested the extraction of four factors (Fig. 1). Model fit results, shown in Table 5, were mixed. The chi-square test statistic was significantly different from zero for all solutions except the 7-, 8-, and 9-factor solutions. The RMSEA index fell below .06 in the 5-factor solution, and the lower bound of the 90% RMSEA confidence interval fell below .05 in this solution as well. The BIC was lowest for the 4-factor solution, although the TLI index did not show acceptable fit until the 7-factor solution. Given these conflicting answers, factor loading patterns for the 5-, 6-, 7-, 8-, and 9-factor solutions were inspected, and the 6-factor solution was considered the most interpretable solution. This solution exhibited acceptable fit for the RMSEA statistic and nearly met the conventional .95 threshold for the TLI.

Rotated factor loadings for the 6-factor solution are shown in Table 6—a second oblique rotation method (geomin) was inspected and produced similar rotated loading values—and interfactor correlations are provided in Table 7. The factor loadings largely adhered to a simple structure pattern, with very few secondary loadings greater than .3. communalities, which represent the proportion of variance accounted for in each indicator variable by

Table 2. NIH Toolbox measures by battery and domain

Battery & subtest	Domain	Metric	Scoring direction - higher scores
Cognition module			
Picture vocabulary	Language	Uncorrected ss	Better function, fewer symptoms
Oral reading recognition	Language	Uncorrected ss	Better function, fewer symptoms
Flanker inhibitory control and attention	Executive function-attention	Uncorrected ss	Better function, fewer symptoms
Dimensional change card sort	Executive function-set-shifting	Uncorrected ss	Better function, fewer symptoms
List sorting working memory	Working memory	Uncorrected ss	Better function, fewer symptoms
Picture sequence memory	Episodic memory	Uncorrected ss	Better function, fewer symptoms
Pattern comparison processing speed	Processing speed	Uncorrected ss	Better function, fewer symptoms
Motor module			
9-hole pegboard dexterity test	Dexterity	Uncorrected ss - dominant hand	Better function, fewer symptoms
Grip strength test	Strength	Uncorrected ss - dominant hand	Better function, fewer symptoms
2-minute walk endurance test	Endurance	Uncorrected ss	Better function, fewer symptoms
4-meter walk gait speed test	Locomotion	Raw score (meters/second)	Worse function, more symptoms
Sensory module			
Pain interference	Pain	T-score	Worse function, more symptoms
Odor identification	Olfaction	Uncorrected ss	Better function, fewer symptoms
Visual acuity	Vision	Logmar	Worse function, more symptoms
Words-in-noise	Audition	Better ear threshold	Worse function, more symptoms
Emotion module			
Anger (affect)	Negative affect	T-score	Worse function, more symptoms
Fear (affect)	Negative affect	T-score	Worse function, more symptoms
Sadness	Negative affect	T-score	Worse function, more symptoms
Positive affect	Positive affect	T-score	Better function, fewer symptoms
General life satisfaction	Positive affect	T-score	Better function, fewer symptoms
Meaning & purpose	Positive affect	T-score	Better function, fewer symptoms
Perceived stress	Stress	T-score	Worse function, more symptoms
Emotional support	Social relationships-social support	T-score	Better function, fewer symptoms
Friendship	Social relationships-companionship	T-score	Better function, fewer symptoms
Loneliness	Social relationships-companionship	T-score	Worse function, more symptoms

Notes. Uncorrected SS = uncorrected standardized scores ($M = 100, SD = 15$) and T-scores ($M = 50, SD = 10$) are weighted to the 2010 Census; Better Ear Threshold for the Words-In-Noise Test is defined as the lowest threshold score observed for either ear, in the unit decibels of signal-to-noise ratio (dB S/N).

Table 3. Demographic characteristics

		aMCI		DAT		Total	
		($n = 92$)	($n = 92$)	($n = 73$)	($n = 73$)	($n = 165$)	($n = 165$)
Age ($n, \%$)	60–64	1	(1.1)	2	(2.7)	3	(1.8)
	65–69	17	(18.5)	16	(21.9)	33	(20.0)
	70–74	18	(19.6)	16	(21.9)	34	(20.6)
	75–79	25	(27.2)	17	(23.3)	42	(25.5)
	80–84	13	(14.1)	15	(20.5)	28	(17.0)
	85–89	16	(17.4)	4	(5.5)	20	(12.1)
Gender ($n, \%$)	Female	36	(39.1)	32	(43.8)	68	(41.2)
	Male	56	(60.9)	41	(56.2)	97	(58.8)
Ethnicity ($n, \%$)	Hispanic	2	(2.2)	2	(2.7)	4	(2.4)
	Not Hispanic	90	(97.8)	63	(97.3)	161	(97.6)
Race ($n, \%$)	White	77	(83.7)	66	(90.4)	143	(86.7)
	Black or African American	15	(16.3)	4	(5.5)	19	(11.5)
	Asian	0	(0.0)	1	(1.4)	1	(0.6)
	Other	0	(0.0)	1	(1.4)	1	(0.6)
	More than one race	0	(0.0)	1	(1.4)	1	(0.6)
Education ($n, \%$)	Some high school or less	1	(1.1)	0	(0.0)	1	(0.6)
	High school graduate/GED	4	(4.3)	10	(13.7)	14	(8.5)
	Some college/associate's degree	19	(20.7)	14	(19.2)	33	(20.0)
	Bachelor's degree (e.g., BA, AB, BS)	29	(31.5)	28	(38.4)	57	(34.5)
	Master's degree (e.g., MA, MS, Med, MSW, MBA)	24	(26.1)	12	(16.4)	36	(21.8)
	Professional degree or doctorate (e.g., PhD, EdD, MD, DDS, JD)	15	(16.3)	9	(12.3)	24	(14.5)

all extracted factors (symbolized as h^2) were largest ($> .5$) for emotional, social, and cognitive performance outcomes, and smallest for motor and sensory outcomes—in particular, the tests of visual acuity (Visual Acuity Test; $h^2 = .14$) and auditory function (Words-in-Noise; $h^2 = .17$) had the lowest communalities.

Measures from the Cognition battery loaded onto two factors reflecting *Fluid Intelligence* (Factor 1) and *Crystallized Intelligence* (Factor 2). Along with the five cognitive tests of fluid intelligence,

one motor and one sensory test (9-Hole Pegboard, Odor Identification) also exhibited weak/moderate loadings on *Fluid Intelligence* (Factor 1). The relationships between olfaction with cognitive decline in aging and with frontal-lobe structural integrity appear potentially relevant for understanding this factor (Bathini et al., 2019; Cynthia et al., 2021; Roberts et al., 2016; Sohrabi et al., 2012; Yap et al., 2022). Regarding *Crystallized Intelligence* (Factor 2), the loading for Picture Vocabulary dominated the factor (rounded-

Table 4. Descriptive statistics

Battery & subtest	N	M	SD	Median	Min	Max	% Min	% Max	Skew	Kurtosis
Cognition module										
Picture vocabulary	163	110.7	10.4	112.0	74.0	135.0	0.6	0.6	-0.7	0.7
Oral reading recognition	163	107.2	7.3	109.0	84.0	119.0	0.6	1.8	-0.7	0.1
Flanker inhibitory control and attention	162	81.5	13.7	85.0	48.0	108.0	0.6	0.6	-0.7	-0.6
Dimensional change card sort	163	87.4	15.6	92.0	46.0	119.0	0.6	0.6	-0.9	-0.1
List sorting working memory	149	76.2	16.2	74.0	40.0	109.0	0.6	2.4	0.2	-0.9
Picture sequence memory	136	82.1	6.5	79.0	76.0	109.0	24.2	0.6	1.3	1.6
Pattern comparison processing speed	165	72.3	15.7	71.0	38.0	109.0	0.6	1.2	0.0	-0.7
Motor module										
9-Hole pegboard dexterity test	162	86.3	17.3	90.0	-23.0	110.0	0.6	0.6	-2.5	11.1
Grip strength test	165	96.1	10.3	95.0	72.0	129.0	0.6	0.6	0.5	-0.1
2-Minute walk endurance test	138	80.6	15.5	83.0	39.0	126.0	0.6	0.6	-0.2	0.1
4-Meter walk gait speed test	140	1.1	0.3	1.1	0.4	2.1	0.6	0.6	0.5	1.2
Sensory module										
Pain interference	164	49.4	8.1	50.0	39.0	76.0	26.7	0.6	0.3	-0.4
Odor identification	156	66.6	24.9	69.0	11.0	115.0	1.2	3.6	0.0	-0.8
Visual acuity	159	50.0	10.0	48.8	31.2	78.0	0.6	1.2	0.8	0.3
Words-in-noise	157	13.3	6.0	11.6	4.4	26.0	1.2	3.0	0.6	-0.8
Emotion module										
Anger (affect)	163	47.2	10.2	47.0	27.0	77.0	6.1	0.6	0.1	-0.1
Fear (affect)	163	50.1	9.9	49.0	27.0	77.0	4.2	0.6	-0.1	0.2
Sadness	163	48.7	10.1	48.0	30.0	73.0	9.7	2.4	0.1	-0.1
Positive affect	165	48.1	7.9	48.0	28.0	71.0	0.6	3.6	0.9	1.2
General life satisfaction	165	54.4	9.9	55.0	32.0	76.0	0.6	4.2	0.2	-0.4
Meaning & purpose	165	49.3	9.1	49.0	29.0	71.0	0.6	6.1	0.6	0.3
Perceived stress	163	46.1	10.1	46.0	23.0	75.0	1.8	0.6	0.1	-0.1
Emotional support	165	47.0	8.2	46.0	22.0	62.0	0.6	11.5	0.0	0.0
Friendship	163	50.2	8.5	50.0	28.0	67.0	0.6	6.7	0.1	-0.4
Loneliness	163	49.9	9.7	51.0	37.0	75.0	25.5	0.6	0.2	-0.7

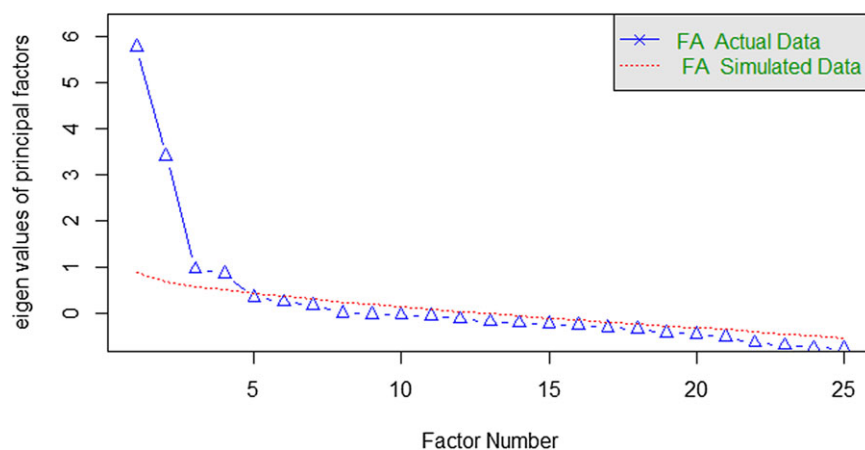


Figure 1. Parallel analysis scree plot. In this figure, the triangles represent eigenvalues obtained across the 25 NIHTB measures. The dotted line represents average eigenvalues obtained from randomly generated datasets. Four of the observed eigenvalues were greater than the average of random samples, and thus the parallel analysis suggests retention of four factors, although a 6-factor structure was ultimately chosen as a more interpretable solution.

1.00); a similar factor loading pattern was observed for this factor by Ma et al. (2021) in individuals with MCI/dementia.

Measures from the Emotion battery loaded onto three factors that were interpreted as indicators of *Negative Affect* (Factor 3), *Positive Affect/Life Satisfaction* (Factor 4), and *Social Health* (Factor 5). Although these factors were quite homogeneous (i.e., indicated by variables with strong primary loadings and weak secondary loadings), both Pain Interference and Loneliness exhibited moderate loadings on *Negative Affect* (Factor 3). Loneliness also exhibited a moderate loading on *Social Health* (Factor 5). The remaining sixth factor included several *Physical Function* outcomes across motor (gait speed/ambulation endurance, manual motor strength) and sensory (visual acuity) domains (Factor 6), although the factor loading pattern suggests

the factor is strongly indicated by lower extremity function (ambulation endurance). The auditory perception outcome measure, Words-in-Noise Test, did not load clearly on any factor, although the highest loading (absolute value = .25) observed for this test was for the *Physical Function* factor (Factor 6).

Interfactor correlations ranged between .51 and .41 (see Table 7); the strongest correlations were observed among the three factors indicated by the Emotion battery measures (Factors 1, 4, and 5). The proportion of variance accounted for in the NIHTB tests by each factor is shown in the diagonal in Table 7. These proportions ranged between .07 and .15, with the highest value of .15 observed for *Negative Affect* and the lowest value of .07 observed for *Crystallized Intelligence* and *Positive*

Table 5. Model fit

Factors extracted	χ^2	df	p	RMSEA with 90% CI	TLI	BIC
1	1124.2	275	< .01	.137 [.129, .145]	.491	29,450.5
2	693.8	251	< .01	.103 [.094, .113]	.709	29,142.6
3	516.0	228	< .01	.087 [.077, .098]	.792	29,082.3
4	372.3	206	< .01	.070 [.058, .081]	.867	29,050.8
5	280.0	185	< .01	.056 [.042, .069]	.915	29,065.8
6	212.6	165	< .01	.042 [.023, .057]	.952	29,100.5
7	160.2	146	0.20	.024 [.000, .045]	.984	29,145.1
8	128.1	128	0.48	.002 [.000, .038]	1.000	29,204.9
9	101.3	111	0.73	.000 [.000, .030]	1.014	29,265.0

Note. BIC = Bayesian information criterion, CI = confidence interval, df = degrees of freedom, p = p-value, RMSEA = root-mean-square error of approximation, TLI = Tucker-Lewis index, χ^2 = chi-square goodness of fit test statistic.

Table 6. Factor loadings for 6-factor solution

NIHTB Module	Measure	Factors						h^2	u^2
		1	2	3	4	5	6		
Cognition	Flanker inhibitory control and attention	0.87	0.02	-0.05	0.01	-0.04	-0.04	0.75	0.25
Cognition	Dimensional change card sort	0.71	0.08	-0.06	-0.15	0.04	0.05	0.60	0.40
Cognition	Pattern comparison processing speed	0.72	-0.06	0.05	0.00	0.07	0.05	0.52	0.48
Cognition	List sorting working memory	0.60	0.15	0.03	0.09	-0.12	0.08	0.51	0.49
Motor	9-hole pegboard dexterity – dominant	0.43	-0.04	0.09	0.17	-0.04	0.25	0.30	0.70
Cognition	Picture sequence memory	0.43	0.16	0.08	0.02	-0.05	-0.04	0.26	0.74
Sensory	Odor identification	0.35	0.04	0.18	0.27	-0.01	0.10	0.22	0.78
Cognition	Picture vocabulary	0.03	1.00	0.03	0.02	0.03	-0.02	1.00	0.00
Cognition	Oral reading recognition	0.06	0.62	-0.16	-0.14	0.06	0.09	0.50	0.50
Emotion	Fear (affect)	0.03	-0.07	0.87	-0.04	0.04	0.04	0.77	0.23
Emotion	Anger (affect)	-0.05	0.01	0.83	-0.01	0.04	0.02	0.68	0.32
Emotion	Perceived stress	-0.03	0.04	0.82	-0.09	-0.05	0.03	0.81	0.19
Emotion	Sadness	0.03	0.02	0.83	-0.06	-0.09	-0.03	0.82	0.18
Sensory	Pain interference	0.15	-0.09	0.49	-0.04	0.18	-0.25	0.28	0.72
Emotion	Loneliness	-0.10	0.09	0.49	0.05	-0.49	-0.02	0.69	0.31
Emotion	General life satisfaction	-0.09	0.06	-0.23	0.66	0.06	0.04	0.71	0.29
Emotion	Positive affect	0.06	-0.05	-0.12	0.60	0.20	-0.14	0.64	0.36
Emotion	Meaning & purpose	0.00	-0.07	-0.14	0.55	0.27	0.07	0.67	0.33
Emotion	Friendship	-0.05	0.05	0.07	0.10	0.81	0.02	0.69	0.31
Emotion	Emotional support	-0.01	0.07	-0.11	0.13	0.65	0.05	0.63	0.38
Motor	2-minute walk endurance	0.05	-0.03	0.02	-0.05	0.05	0.97	0.95	0.05
Motor	4-meter walk gait speed	-0.02	-0.11	0.04	-0.16	0.06	-0.63	0.50	0.50
Motor	Grip strength - dominant	-0.10	0.10	-0.04	-0.23	-0.01	0.42	0.23	0.78
Sensory	Visual acuity	0.10	-0.04	-0.08	-0.10	0.04	-0.36	0.14	0.86
Sensory	Words-in-noise	0.03	-0.16	-0.19	-0.20	0.13	-0.25	0.17	0.83

Note. h^2 = communality: collective proportion of variance in NIH Toolbox test accounted for by all extracted factors. u^2 = uniqueness: proportion of variance in NIH Toolbox test not accounted for by extracted factors. Factor loading absolute values > .3 are highlighted in boldface.

Table 7. Factor correlations for 6-factor solution

	Fluid intelligence	Crystallized intelligence	Negative affect	Positive affect / life satisfaction	Social health	Physical function
Fluid intelligence	.11					
Crystallized intelligence	.41	.07				
Negative affect	-.00	-.04	.15			
Positive affect / life satisfaction	-.03	.01	-.50	.07		
Social health	.04	-.05	-.50	.49	.08	
Physical function	.31	.34	.01	.06	.06	.08

Note. Interfactor correlations are shown in the lower diagonal. The proportion of variance accounted for in the entire variable set by each factor is shown on the diagonal.

Affect/Life Satisfaction. Overall, the factor loading patterns and communality estimates suggest the outcomes from the Emotion and Cognition batteries form rather tight-knit clusters, whereas the Motor and Sensory outcome measures form less cohesive clusters that may be dominated by a single measure. Nevertheless, we believe that the cross-domain factor loadings

may be useful for understanding patterns of symptoms that cluster together in meaningful ways in these populations. Finally, factor score comparisons between the aMCI and DAT subsamples are shown in Table 8. The DAT group exhibited significantly worse functioning compared to the aMCI group on three factors: *Fluid Intelligence* (Factor 1), *Crystallized*

Table 8. Mean comparisons

Factor	aMCI		DAT		<i>T</i>	<i>df</i>	<i>p</i>	<i>d</i> [95% C.I.]
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>				
Fluid intelligence	.41	.70	-.52	.94	-7.00	129.2	<.01	-1.14 [-1.47, -.80]
Crystallized intelligence	.15	.92	-.19	1.07	-2.10	142.9	.04	-.34 [-.65, -.02]
Negative affect	-.03	.90	.03	1.05	.39	142.0	.72	.06 [-.25, .37]
Positive affect / life satisfaction	.01	.92	.01	.89	.09	157.3	.97	.01 [-.30, .32]
Social health	.04	.94	-.06	.89	-.70	158.0	.53	-.11 [-.42, .20]
Physical function	.15	.96	-.19	.89	-2.35	158.8	.02	-.37 [-.68, -.05]

Note. Negative values for *d* indicate lower average factor scores for the DAT group compared to the aMCI group and vice versa.

Intelligence (Factor 2), and *Physical Function* (Factor 6); effect sizes (absolute values) ranged from .01 to 1.14.

Discussion

This study provides a novel contribution by highlighting several cross-domain symptom clusters using the NIHTB in a clinical sample of individuals with either aMCI or mild DAT. We found that measures of sensory and motor functioning were associated with cognitive, emotional, and social functioning in these populations; instead of forming homogeneous factors, measures from the NIHTB Sensory and Motor batteries spread across several factors, although they exhibited somewhat lower associations.

Specifically, Pain Interference loaded primarily on a factor along with three measures of Negative Affect, a measure of Stress, and a measure of Social Relationships. Taken together, Sadness, Fear, Anger, Stress, Loneliness, and Pain Interference could therefore be considered a symptom cluster indicative of the complexities of negative emotional experiences in aMCI and DAT, which are influenced by both physical and social health. Loneliness was the one measure in this EFA that had dual loadings > 0.30, contributing both to this symptom cluster of Negative Affect and Pain as well as a negative loading with two other measures of Social Health: Friendship and Emotional Support.

One sensory domain, Olfaction, and one motor domain, Dexterity, were found to load with the *Fluid Intelligence* factor. Both domains are known to be associated with frontal lobe functioning, so the association of Olfaction and Dexterity on a symptom cluster with the fluid cognition measures of Executive Functioning, Working Memory, Episodic Memory, and Processing Speed is not surprising. Odor identification has long been proposed as a biomarker of cognitive impairment that may be useful for early screening (Bathini et al., 2019; Roberts et al., 2016; Yap et al., 2022), so we believe these associations could be fruitful for future research on noninvasive predictive biomarkers of cognitive decline.

When the sensory domains of Vision and Hearing were evaluated for associations with other domains across the NIHTB, the Visual Acuity Test loaded meaningfully on a factor with Strength, Locomotion, and Endurance, which together formed what we considered to be a *Physical Function* factor. Interpreted through the lens of symptom clustering, vision appears to form a meaningful symptom cluster with mobility and strength in aMCI and DAT as markers of physical decline and frailty that have been shown in prior research to meaningfully impact the quality of life and overall health (Liljas et al., 2017). The aMCI group performed significantly better on the *Physical Function* factor than the DAT group (Factor 6; effect size = .34), which highlights the relevance of

declining physical functioning (specifically strength, locomotion, endurance, and vision) for individuals with dementia (Auyeung et al., 2008; Wang et al., 2006).

Hearing was expected to be similarly relevant as vision across domains in this clinical sample, given prior research documenting the relevance of auditory functioning to cognitive performance in older adults (O'Brien et al., 2021). However, the NIHTB test of audition, the Words-In-Noise Test, did not load strongly on any of the identified factors. This measure is more complex cognitively than a simple hearing test, as it requires listeners to identify spoken words heard with multitalker background noise of increasing volume (Zecker et al., 2013). Future, prospective research is needed to determine if a pure hearing test—such as the recently developed Hearing Threshold Test for the NIHTB (Wiseman et al., 2022)—would be relevantly associated with performance tests or symptoms in other domains.

Mirroring the structure of the NIHTB Cognition Battery, our results support separate factors for *Fluid* and *Crystallized Intelligence* (Mungas et al., 2014). This study also replicated the finding of a discrepancy between NIHTB fluid and crystallized cognition in clinical and preclinical MCI and dementia samples that has been documented in recent research (Ma et al., 2021; McDonough et al., 2016). The aMCI group was found to perform significantly better than the DAT group on both *Fluid Intelligence* (Factor 1; effect size = 1.14) and *Crystallized Intelligence* (Factor 2; effect size = .34). Thus, the discrepancy in fluid and crystallized intelligence appears to increase in magnitude with cognitive decline/worse cognitive performance. Specifically, the difference between fluid and crystallized cognition mean scores observed in this sample was .26 for aMCI and .33 for the DAT group (see Table 8). Moderation analysis could be used to further elucidate this trend.

On the *Fluid Intelligence Factor* in this study (which included both Odor Identification and the 9-Hole Pegboard Dexterity Test), one notable finding was that Picture Sequence Memory had the weakest loading (0.43), and List Sorting Working Memory the second weakest loading (0.60), compared with the three other fluid cognition tests on this factor (range 0.72–0.87; see Table 6). As two of the more challenging tests in the NIHTB cognition battery, Picture Sequence Memory and List Sorting Working Memory have been shown previously to have reduced completion rates in cognitively impaired samples (Hackett et al., 2018; Ma et al., 2021). This was also seen in our study, with 17.6% and 9.7% of the sample missing scores on Picture Sequence Memory and List Sorting Working Memory tests, respectively. We suspect this is most likely attributable to the discontinue criterion applied for both tests after the sample items, such that the test is not attempted unless the test taker can accurately complete the practice component of the test. Nevertheless, we suspect that the attenuation of these loadings is

primarily due to the difficulty of these tasks, although this should be evaluated in future research.

On the *Crystallized Intelligence* factor, Picture Vocabulary was the dominant contributor (1.00), with a strong loading of Oral Reading (0.62) also observed. The loadings for these two crystallized cognition tests were less balanced than has been shown in prior research on the NIHTB in a general population adult sample. For example, Mungas *et al.* (2014) documented loadings of 0.84 for Vocabulary (Picture Vocabulary Test and PPVT-R) and 0.99 for Reading (Oral Reading Recognition Test and WRAT-R) on the Crystallized Intelligence factor in their study. The larger split between the loadings of these two tests on Factor 6 found in our study may suggest a weakening of the association of vocabulary knowledge and reading ability with cognitive decline, which was also observed by Ma *et al.* (2021).

Potential clinical implications and future directions

This study represents an initial step toward improving patient care for aMCI and DAT using data-driven symptom science. The results, although exploratory in nature, suggest that multidomain assessment of each patient—considering their symptoms holistically including emotional, social, and physical symptoms in addition to cognitive functioning—should continue to be the standard of care for neuropsychological assessment in MCI and DAT. The results also suggest potential shared targets for intervention and assessment. In particular, several of the symptoms loading on Factor 3 may be modifiable with a shared treatment approach. As one example, the symptoms of Pain, Sadness, and Fear may be symptoms of a shared underlying problem that could be improved with antidepressant and/or anxiolytic medication (Feeney, 2004; Lin *et al.*, 2003). Alternatively, the symptoms of Anger, Stress, and Loneliness on Factor 3 could be appropriate targets for a socially based intervention, such as a support group or community engagement activity (O'Rourke *et al.*, 2018). Recent reviews of social interventions for older adults have cited the need to expand the theoretical understanding of how social and emotional symptoms are related in older adults (Gardiner *et al.*, 2018), and for understanding how the symptoms of social and emotional health experienced by older adults may be unique for those individuals with cognitive impairments (Cohen-Mansfield & Perach, 2015). We anticipate that our results could be useful for supporting the design of a future study to evaluate and potentially validate psychosocial interventions for these patients.

Our findings also suggest approaches to screening and assessment for individuals with aMCI and DAT. Research suggests that early identification of Alzheimer's disease is possible and beneficial, given the relevance of modifiable risk factors that can be treated to potentially prevent progression to dementia if identified early (Isaacson *et al.*, 2018; Norton *et al.*, 2014; Rasmussen & Langerman, 2019; Saxton *et al.*, 2004). Although moderate in size, the loadings on Factor 1 in our study suggest that Odor Identification and/or 9-Hole Pegboard Dexterity could potentially be used as screening tests to identify individuals who may benefit from cognitive assessment, with the goal of early detection. There has recently been renewed interest in using sensory measures to detect early brain changes associated with dementia (Bathini *et al.*, 2019; National Institutes of Health, 2022; Yap *et al.*, 2022). Since these sensory tests from the NIHTB are simple to deploy, they could be implemented in a variety of settings by nonneuropsychologist health professionals. Analysis of the sensitivity and

specificity of these measures would be needed to validate the predictive utility of these tests for screening and is an area warranting further research. The results from this study also lend support to the development of a clinically oriented assessment battery based on the NIHTB. This is an area of interest for members of the ARMADA investigator team, and we anticipate this will be explored in future research stemming from this larger project.

Study limitations

This study has several limitations, which stem primarily from the use of an existing dataset as opposed to prospective data collection designed explicitly to evaluate symptom clusters. Ideally, in future research, a broader array of symptom-oriented assessments would be used. Prospective research is needed with the inclusion of prespecified symptom assessments across the domains found to be important in this study, as well as other domains suspected to be salient, to replicate and expand on these findings. For example, we suspect it would be fruitful to expand the assessments, particularly in the sensory domains, to capture subtle differences in hearing and visual acuity, for example, that may contribute to relevant symptom clusters in these populations. Fortunately, future waves of ARMADA data collection will use three additional tests, which were not available in the baseline dataset, but would be relevant for this future research: Face-Name Associative Memory Exam (FNAME; Rentz *et al.*, 2011), Hearing Threshold Test (Wiseman *et al.*, 2022), and Near Visual Acuity (under development). The results from the present study will be useful for shaping future study design and data collection efforts.

Concerns about the accuracy of self-appraisals of symptoms in dementia may also limit the interpretability of symptom cluster research with this population, although the inclusion of participants with *mild* DAT in this study's sample should help partially assuage this concern, given that difficulties with self-awareness (including anosognosia) have been observed to progress with disease burden (Hanseeuw *et al.*, 2020). Finally, the absence of explicit performance validity testing or symptom validity assessment in the NIHTB is an important limitation. Future prospective studies should include measures of performance and symptom validity to elucidate relevant patterns that may be affecting the symptom clusters observed in this study. In fact, symptom clustering approaches may themselves prove useful for this purpose: recent research has demonstrated how "patient-centered approaches" of symptom clusters research (e.g., latent class analysis) can be used to identify patterns of cognitive effort and symptom magnification (Morin & Axelrod, 2017).

Some features of the data and sample may limit the generalizability of these findings. The sample size was modest, skewed slightly older in the aMCI group, and was restricted to individuals with memory impairment in both subgroups. Additionally, the sample was not representative of the diversity of individuals with MCI and DAT in the general population with regards to race, ethnicity, and education. Furthermore, the exclusions based on preexisting neurologic and psychiatric illness also distort the sample makeup. The findings from this study may differ if replicated in a larger, more representative and diverse sample. Replication of these results should include tests of measurement invariance across diagnostic categories and over time. Moderate floor effects were also present for three of the measures, most notably Picture Sequence Memory where a small portion of the sample (17.6%) did not complete the measure (we suspect due to

not passing the sample items) and another 24.2% scored at the floor. While this is not surprising given that memory impairment was consistently demonstrated throughout this aMCI and DAT sample, and we do not suspect results were influenced—except possible attenuation of the relation between this test and the Fluid Intelligence factor—this remains an open question and may be a limitation of the current study.

Last, we believe it may be useful to understand if the factors and loading identified in this study sample would replicate or vary in a meaningful way for older adults *without* cognitive impairment. Although this was not the purpose of the current project, we did explore the applicability of the exploratory model identified in this study in a separate sample of older adults without significant memory impairment collected as part of the same ARMADA study. Specifically, we conducted a separate, *post-hoc* EFA analysis using data from 156 individuals ages 65–85 from the older adult “healthy control” cohort, extracting the same number of factors as was selected for the final aMCI/DAT solution. Factor loadings from this solution were then rotated using Procrustes rotation (Fischer & Karl, 2019) to make it as similar as possible to the rotated solution found in the aMCI/DAT sample. Results of these analyses, including similarities and differences in the factor structure between samples, are provided in the Supplementary Material for interested readers.

Conclusions

This research provides support for using the NIHTB to detect clusters of symptoms that people with aMCI and DAT experience. Researchers and clinicians can use these findings to shape their assessment approaches and considerations for treatment. For example, individuals with symptoms of fear or sadness may also be experiencing pain and life stress that could be targets for intervention to improve quality of life. Future research is needed to validate the utility of symptom clusters for planning assessment and treatment approaches in these patients.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S1355617724000055>.

Acknowledgements. We thank the study participants and their family members for their time and efforts to participate in the original ARMADA study. We also thank the staff at the research sites who helped collect the data.

Funding statement. This work was supported by the National Institute of Nursing Research (D.T., C.T., A.B., J.S., & M.C., grant number R01NR018684), and National Institute on Aging (R.G., S.W., & J.S., grant number U2C AG057441).

Competing interests. None.

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