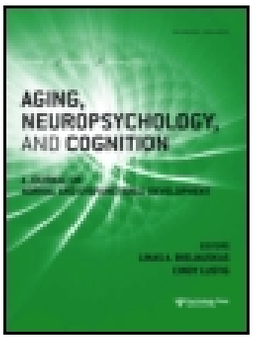

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Aging, Neuropsychology, and Cognition
A Journal on Normal and Dysfunctional Development

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/nanc20

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To cite this article: Jessica Pommy, L. Conant, A. M. Butts, A. Nencka, Y. Wang, M. Franczak & L. Glass-Umfleet (2023): A graph theoretic approach to neurodegeneration: five data-driven neuropsychological subtypes in mild cognitive impairment, Aging, Neuropsychology, and Cognition, DOI: 10.1080/13825585.2022.2163973

To link to this article: https://doi.org/10.1080/13825585.2022.2163973

AGING, NEUROPSYCHOLOGY, AND COGNITION
https://doi.org/10.1080/13825585.2022.2163973

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A graph theoretic approach to neurodegeneration: five data-driven neuropsychological subtypes in mild cognitive impairment

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ABSTRACT

Mild cognitive Impairment (MCI) is notoriously heterogenous in terms of clinical presentation, neuroimaging correlates, and subsequent progression. Predicting who will progress to dementia, which type of dementia, and over what timeframe is challenging. Previous work has attempted to identify MCI subtypes using neuropsychological measures in an effort to address this challenge; however, there is no consensus on approach, which may account for some of the variability. Using a hierarchical community detection approach, we examined cognitive subtypes within an MCI sample (from the Alzheimer's Disease Neuroimaging Initiative [ADNI] study). We then examined whether these subtypes were related to biomarkers (e.g., cortical volumes, fluorodeoxyglucose (FDG)-positron emission tomography (PET) hypometabolism) or clinical progression. We identified five communities (i.e., cognitive subtypes) within the MCI sample: 1) predominantly memory impairment, 2) predominantly language impairment, 3) cognitively normal, 4) multidomain, with notable executive dysfunction, 5) multidomain, with notable processing speed impairment. Community membership was significantly associated with 1) cortical volume in the hippocampus, entorhinal cortex, and fusiform cortex; 2) FDG PET hypometabolism in the posterior cingulate, angular gyrus, and inferior/middle temporal gyrus; and 3) conversion to dementia at follow up. Overall, community detection as an approach appears a viable method for identifying unique cognitive subtypes in a neurodegenerative sample that were linked to several meaningful biomarkers and modestly with progression at one year follow up.

ARTICLE HISTORY
Received 20 April 2022
Accepted 26 December 2022

KEYWORDS
Mild cognitive impairment; graph theory; cognitive subtype; Alzheimer's disease; heterogeneity

Introduction

Mild Cognitive Impairment (MCI) represents an intermediate stage between normal aging and dementia, characterized by an objective decline in cognition, despite intact

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*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Supplemental data for this article can be accessed online at https://doi.org/10.1080/13825585.2022.2163973

functioning in daily life (Petersen & Morris, 2005; Petersen, 2016; Petersen et al., 2014). Heterogeneity in the present clinical symptoms (Nordlund et al., 2005; Panza et al., 2007), underlying pathology (Ezzati et al., 2020; Nettiksimmons et al., 2014) and clinical course (Ellendt et al., 2017; Hu et al., 2017; Thomas et al., 2019) has made it difficult to assess the effectiveness of possible interventions (Blanken et al., 2020; Christa Maree Stephan et al., 2013; Visser et al., 2005) and may make it harder to identify novel targets for treatment. A better understanding of the heterogeneity in MCI would be helpful, not only for clinical care (such as being able to provide an accurate estimate of progression, improved management of the condition), but could potentially result in the identification of MCI cognitive phenotypes which could be impactful for treatment research (e.g., identification of treatment targets, enhanced evaluation of treatment effectiveness), and ultimately help inform the field's understanding of the underlying processes driving the disease.

The variability in both the pattern and degree of impairment across neuropsychological measures has been used to clarify aspects of MCI heterogeneity (Bondi et al., 2014; Kim et al., 2019; Nation et al., 2019). Frequently, these efforts have placed an emphasis on a specific cognitive weakness (e.g., presence or absence of memory impairment) or the additive impact of impairments across multiple domains. Impaired verbal memory, for instance, has been linked to underlying pathology, namely, Alzheimer's Disease (AD) related biomarkers (Eliassen et al., 2017; Michaud et al., 2017) and the subsequent development of Alzheimer's Disease (Jak, Bangen, et al., 2009; Oltra-Cucarella et al., 2018; Petersen, 2004). Alternatively, single domain non-memory profiles have been linked to higher rates of reversion to normal (Ellendt et al., 2017; Overton et al., 2019). When the *number* of cognitive domains is examined, results have suggested dementia risk is greater when multiple cognitive domains are impaired (Bermejo-Pareja et al., 2016; Ganguli et al., 2011), with the greatest risk for multidomain amnestic profiles (Gothlin et al., 2017) (though results are not always consistent (Glynn et al., 2021)). Out of this work, four clinical subtypes have been identified based on: 1) presence or absence of memory impairment (amnestic or non-amnestic), and 2) impairment in one or multiple cognitive domains (single or multidomain) (Bondi et al., 2014; Petersen & Morris, 2005). While this approach continues to influence clinical and research efforts, these subtypes have largely focused on severity and extent of impairment, are complicated by mixed etiologies, and there has been concern this approach may lack specificity (Tatsuoka et al., 2013).

Data-driven cognitive approaches have been explored as a way to more precisely characterize heterogeneity in MCI (Blanken et al., 2020; Bondi et al., 2014; Eppig et al., 2017; Giraldo et al., 2021; Jak, Bondi, et al., 2009; Machulda et al., 2019; Oltra-Cucarella et al., 2018; Tatsuoka et al., 2013). Across different study cohorts, typically, three (Delano-Wood et al., 2009; Edmonds et al., 2019, 2021; Eppig et al., 2017) to four MCI subtypes are identified (Blanken et al., 2020; Bondi et al., 2014; Clark et al., 2013; Edmonds et al., 2021; Jak et al., 2016; Jak, Bondi, et al., 2009; Machulda et al., 2019) based on how one operationalizes MCI, the specific neuropsychological measures examined, and the use of normative samples (Clark et al., 2013; Jak, Bondi, et al., 2009). Generally, an amnestic MCI subtype (focal weakness in memory) (Bondi et al., 2014; Machulda et al., 2019), or memory and language (Clark et al., 2013; Delano-Wood et al., 2009)) a dysexecutive/mixed (Clark et al., 2013) or dysexecutive subtype (Machulda et al., 2019), and a cognitively normal subtype (Bondi et al., 2014; Clark et al., 2013) (sometimes characterized as a subtle cognitive complaints subtype (Machulda et al., 2019)) is identified. A distinct dysnomic

subtype (Bondi et al., 2014; Machulda et al., 2019) has also been reported, though somewhat less consistently. Efforts to link these data-driven cognitive subtypes with pathology (e.g., biomarkers of AD (Bondi et al., 2014; Machulda et al., 2020)) and clinical course have been explored (Ezzati et al., 2020; Guo et al., 2020; Lee et al., 2020) and are promising, though results are inconsistent and often are differentially related to demographic variables (Blanken et al., 2020; Bondi et al., 2014). Overall, despite various approaches to classify MCI subtypes, these efforts have not led to identification of additional novel MCI subtypes (Diaz-Mardomingo et al., 2017) and alternative approaches to subtyping MCI are of interest. Within the neurodevelopmental literature, community detection, a metric founded in graph theory has shown great promise for identifying alternative subtypes within neurodevelopmental and psychiatric diagnoses, and we hypothesize this approach may be useful for MCI. Generally, neuropsychological tests measure multiple interacting cognitive processes, rather than discrete unitary skills. The subtyping approaches described frequently rely on a limited set of neuropsychological variables derived from a larger test battery and often utilize cut scores, making more fine-grained analysis less feasible. Methods that would enable one to consider the interrelationships between different cognitive processes and integrate biomarker data would be most consistent with clinical practice and in theory, have the potential to identify new subtypes. Further, the inclusion of additional neuropsychological measures typically enables more sensitive detection of cognitive subtypes (e.g., Machulda et al., 2019), methods that can detect subtle variation in less comprehensive datasets would be useful.

Computational approaches, including "community structure", have shown promise as a method for identifying subtypes within heterogenous datasets by finding relationships between interacting components of a larger system, such as neuropsychological measures and biomarkers. Briefly, networks are said to have community structure when subsets of nodes (i.e., communities) within that network are more densely connected to other nodes within that particular community relative to other nodes in the network but outside of the community (Fair et al., 2012; Feczko & Fair, 2020; Feczko et al., 2018, 2019). In contrast to traditional clustering approaches, community detection does not require a priori number of clusters to be entered into the model, it allows for the possibility for identifying no clusters (e.g., a unitary dataset), and can more readily detect presence of smaller sized clusters. Within neurodegenerative research, network-based analyses have been applied to biomarker data (e.g., data-driven phenotypes based on cortical atrophy (Guo et al., 2020)) with cognitive data examined after or used in conjunction with select cognitive screener measures (Nezhadmoghadam et al., 2021) (e.g., machine learning methods). However, to our knowledge, this approach has not yet been applied as a means of identifying cognitive subtypes within MCI. Therefore, the purpose of the current study is to assess for cognitive subtypes within the MCI cohort from Alzheimer's Disease Neuroimaging Initiative (ADNI) Study using community detection. Specifically, we hypothesize this approach will result in detection of several distinct communities in the MCI sample.

As mentioned, the definition of MCI varies across studies. As the primary aims of ADNI focused on Alzheimer's Disease, the selection criteria for "Mild Cognitive Impairment" were based on the presence of memory changes (presence of a subjective memory concern and an objective memory problem based on education-corrected score on delayed story memory recall). Individuals characterized as MCI in this study demonstrated

broadly intact general cognitive functions and activities of daily living based on study clinician judgment and individuals were expected to score a 0.5 on the Clinical Dementia Rating (CDR) (with at least a 0.5 on memory box).

Methods

Study sample

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

Data included in the present analyses are from the first wave of the Alzheimer's Disease Neuroimaging Initiative (ADNI) study having 822 participants, ages 55–90 years of age, across 27 sites. Readers are referred to http://www.adni-info.org/Scientists/ADNIGrant/ProtocolSummary.aspx for information regarding ADNI study eligibility criteria and diagnostic procedures.

Group membership was determined at the screening visit. Present analyses were restricted to individuals enrolled into the MCI or HC groups during the first wave of ADNI. Enrollment criteria at screening visit for the larger ADNI study are as follows: participants were between ages 55–90 years old, consented to undergo all study procedures, had a study partner able to provide collateral information regarding daily functioning, spoke English or Spanish, and were not depressed.

More specifically, individuals within the HC group were required to have a Clinical Dementia Rating Scale (CDR) total score of 0, to be cognitively intact (no subjective memory complaints, normal performance on WMS-I Story Memory), and to have Mini-Mental State Exam (MMSE) score between 24 and 30. Individuals within the MCI group met the following criteria at the screening visit: 1) presence of a subjective memory complaint (based on self or informant report), 2) evidence of objective memory loss based on WMS-I Story Memory (education adjusted cutoff scores are as follows: less than or equal to 2/25 points for 0 to 7 years of education; less than or equal to 4/25 points for 8 to 15 years of education; less than or equal to 8/25 for 16 or more years of education at screening visit, 3) Clinical Dementia Rating of 0.5 (memory box score must be at least 0.5), 4) MMSE score between 24 and 30, and 5) based on study physician's judgment, general cognitive abilities and independent living skills were intact (meaning that "physician could not diagnose Alzheimer's disease"). All participants then underwent baseline neuropsychological testing (within 28 days of screening visit). Of note, the study protocol allowed for changes in group membership based on study clinician judgment at baseline neuropsychological visit as well. None of the participants in our analyses demonstrated impaired functional living skills (based on the FAQ). All participants then underwent baseline neuropsychological testing (within 28 days of screening visit). Present analyses included participants for whom all baseline visit neuropsychological data was collected and available d the first wave, which resulted in 388 individuals with MCI and 226 Our

analyses were limited to English-speaking participant. MRI and PET data were available for a subset of the sample (baseline neuroimaging visit within 14 days of baseline neuropsychological testing visit, follow up visits scheduled up to 72 months later).

Measures

Neuropsychological Measures: As detailed in the ADNI protocol summary (http://www.adni-info.org/Scientists/ADNIGrant/ProtocolSummary.aspx), a battery of neuropsychological and cognitive measures was administered to participants at the baseline visit (completed within one month of the screening visit). Readers are referred to Park and colleagues for analyses of the factor structure of the neuropsychological variables collected for ADNI (Park et al., 2012). Consistent with prior approaches, since WMS Story Memory was used to diagnose MCI, it was not included in community detection analyses to avoid criterion contamination (Eppig et al., 2017). The reader is referred to Table 1 for further information regarding selected measures. Differences in reading using American National Adult Reading Test (ANART) (Nelson & O'Connell, 1978), Functional Assessment Questionnaire (FAQ), and MMSE scores were later examined in post-hoc analyses.

Please Note: WAIS-R = Weschler Adult Intelligence Scale-Revised.

Data reduction methods

The clinical practice of neuropsychology relies heavily on standardized scores generated using normative reference groups. In an effort to parallel clinical methods when possible, linear regressions were run within the healthy control group for each neuropsychological variable (dependent variable) with age, gender, and education entered as predictors (independent variables). The standard error of the estimate of the model and the unstandardized beta coefficients for age, gender and education from each regression were then used to generate standard scores with age-, gender-, and education-corrections for participants in MCI sample.

Table 1. Neuropsychological Variables.

Domain	Test Name	Variable
Memory	Rey Auditory Verbal Learning Test	Immediate recall: sum of 1–5 learning trials
		Delayed recall: total number of correct words recalled after 30-minute delay
		Recognition discrimination score
		Number of true positives – number of false positives
Language	Boston Naming Test	Total number of words correctly named spontaneously and with stimulus cue
	Animal Fluency	Total number of correct animal names within 60 seconds
	Vegetable Fluency	Total number of correct vegetable names within 60 seconds
Working Memory	WAIS-R Digit Span	Digit Span Forward: Total number of points for digit span forward trials (auditory working memory capacity)
		Digit Span Backward: Total number of points for digit span backward trials (complex auditory working memory)
Processing Speed	Trail Making Test	Time in seconds to complete Trails A
	WAIS-R Digit Symbol Substitution	Total number of correct items completed in X seconds
Executive Function	Trail Making Test	Time in seconds to complete Trails B (speeded set shifting)
	Clock Drawing	Accuracy of drawing scored 1-5

Note: WAIS-R = Weschler Adult Intelligence Scale-Revised.

Community detection methods

The presence of cognitive subtypes within the MCI cohort was examined using the map equation (Rosvall et al., 2009). Demographic analyses were examined in SPSS. Graph analyses were conducted using Matlab and Infomap (Edler et al., 2014; Rosvall et al., 2009). Each element in the matrix represented the similarity, or link, between one participant's neuropsychological profile with another participant's neuropsychological profile. Negative weights were replaced with zeros. This resulted in a 388×388 matrix. We utilized the map equation, a hierarchical community detection method available using Infomap (Rosvall et al., 2009,) and was employed as part of the analyses conducted in neurodevelopment samples (Feczko et al., 2019). Infomap was run using the multi-level algorithm which performs recursive multilevel search to find optimal multilevel hierarchical partitioning. For present analysesthe number of outer-most loops (N) run set to 100, the number of core loops set to 1000, and no limit set for core level (L) or tune iteration (T). One can select parameters designed to optimize speed or a more modular solution over accuracy. We chose parameters to optimize accuracy over speed (did not select preference for fast hierarchical solution or inner parallelization). As participants in the ADNI sample were recruited based on presence of memory concern, potentially, this MCI sample might be expected to be more homogeneous than a broader cohort (e.g., one that enrolled participants with other cognitive concerns beyond memory). Thus we selected parameters to favor accuracy over modularity (i.e., did not favor more modular solutions). Additional parameters settings included the following: (a) nodes without module assignment were not assigned to module assignment of neighboring node, (b) flow was distributed from bipartite node to primary nodes, (c) self-links were ignored, (d) teleportation probability was 0.15, (e) Markov time was set to 1, and (f) multi-layer relax rate probability was 0.15.

The most appropriate thresholding approach in this context has not yet been established, therefore, connectivity was examined across a variety of thresholds (similar to approaches used by Feczko et al., 2019). More specifically, community structure was examined across multiple weight thresholds (links below a given weight threshold were ignored) and across multiple proportional thresholds (only links at or above given proportion of all links were included) under the reachability assumption as was previously employed by Fair and colleagues to confirm findings were not dependent on thresholding method.

The neuropsychological profiles of each community were first examined visually to determine the presence of any defining cognitive weaknesses relative to the overall HC group means (i.e., profiles were characterized descriptively based on how many standard deviations they scored below the control group means). Second, neuropsychological scores were compared statistically across MCI communities. Communities were then characterized by defining feature(s) (i.e., instances when the community's score on a given measure is significantly different than all other communities in pairwise comparisons). As mentioned, cognitive weaknesses were defined based upon age-, gender-, and education-corrected scores derived based on the HC sample mean, as opposed to a more traditionally employed normative sample (e.g., Heaton normative sample).

ANOVAs, Kruskal-Wallis, and Chi-Square tests were run in the MCI cohorts separately to examine the relationships between demographic variables and community membership (e.g., age, education, gender, race, ethnicity). Cognitive profiles of each community were characterized first using ANOVAs to examine the relationship between community membership and the 12 age-, gender-, and education-corrected neuropsychological variables. Pair-wise comparisons were examined for significant main effects. Select biomarkers were examined between the identified communities within the MCI group using several ANOVAS. Cortical volume measurements reflect bilateral volumes. All reported *p* values were corrected for multiple comparisons using Bonferroni correction.

Results

Demographic characteristics of study sample

The sample was predominantly White, Non-Hispanic, English-speaking adults. There was a significant difference in gender between the two diagnostic groups (X^2 (1) = 8.127, p = 0.005) with more males in the MCI sample. There were no significant differences in ethnicity (X^2 (2) = 2.881, p = 0.237) or race between diagnostic groups (X^2 (6)> = 0.746, p = 0.993). Findings from one-way ANOVAs suggested trend level differences in age [F (1,612) = 3.837, MSE = 169.179, p = .051, η^2 = .006] with the healthy control sample approximately one year older than the MCI sample, and no differences in years of education by diagnosis F(1,612) = 2.179, MSE = 18.603, p = .140, η^2 = .004]. See Table 2 for more information.

Please Note: HC=Healthy Control; MCI=Mild Cognitive Impairment; N=Sample size; SD=Standard Deviation.

Table 2. Demographics.

Demographic Variable	HC	MCI	Total Sample	Significance
Age, years	75.85 (5.05)	74.76 (7.41)	75.16 (6.66)	.051
Mean (SD)				
Education, years	16.06 (2.86)	15.70 (2.96)	15.83 (2.93)	.140
Mean (SD)				
Gender	118, 108	248, 140	366, 248	.005
Males, Females				
Ethnicity (N)	2	11	13	.237
Hispanic/Latino	223	374	597	
Not Hispanic/Latino	1	3	4	
Unknown				
Race (N)	0	1	1	.260
American Indian	3	8	11	
Asian	16	15	31	
Black	207	364	571	
White				

Note: HC=Healthy Control; MCI=Mild Cognitive Impairment; N=Sample size; SD=Standard Deviation.

Table 3. Normative Weaknesses by MCI Community.

Neuropsychological Test Variable	1 (N = 240)		2 (N=29)		3 (N=22)		4 (N=30)		5 (N=67)		Total	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Immediate Recall	-1.60	(-0.85)	-0.79	(-1.14)	0.09	(-1.29)	-1.31	(-1.03)	-1.37	(-1.05)	-1.38	(-1.04)
Delayed Recall	-1.58	(-0.67)	-0.50	(-0.93)	0.56	(-0.93)	-1.00	(-0.85)	-1.11	(-0.94)	-1.25	(-0.94)
Recognition	-1.98	(-1.46)	-0.02	(-0.94)	0.65	(-0.56)	-0.80	(-1.46)	-1.20	(-1.28)	-1.46	(-1.57)
Naming	-0.58	(-1.11)	**-3.51**	**(-2.54)**	0.39	(-0.57)	-1.55	(-1.55)	-1.64	(-1.84)	-1.01	(-1.67)
Animals	-0.63	(-0.92)	-1.46	(-0.71)	-0.24	(-0.85)	-0.86	(-0.76)	-0.94	(-0.93)	-0.74	(-0.93)
Vegetables	-1.00	(-0.93)	-1.54	(-0.94)	-0.10	(-1.21)	-0.86	(-0.98)	-1.20	(-1.00)	-1.01	(-1.00)
Digit Span Forward	-0.15	(-1.07)	-0.45	(-1.34)	-0.97	(-0.84)	-0.32	(-1.03)	-0.36	(-1.07)	-0.27	(-1.09)
Digit Span Backward	-0.31	(-0.10)	-0.50	(-0.86)	-1.02	(-0.66)	-0.56	(-0.78)	-0.66	(-0.92)	-0.45	(-0.96)
Digit Symbol	-0.63	(-1.08)	-0.94	(-1.17)	-0.70	(-1.06)	-1.13	(-1.10)	-1.92	(-1.22)	-0.92	(-1.21)
Trails A	-0.11	(-0.91)	-0.39	(-1.06)	-0.24	(-0.83)	-0.83	(-1.31)	**-2.62**	**(-2.68)**	-0.62	(-1.69)
Trails B	-0.36	(-1.06)	-0.25	(-1.11)	-0.33	(-0.82)	-1.50	(-1.52)	**-3.68**	**(-1.76)**	-1.01	(-1.76)
Clock	-0.44	(-1.27)	-0.60	(-1.23)	-0.26	(-0.79)	**-3.81**	**(-1.71)**	-0.99	(-1.83)	-0.79	(-1.66)

Legend	-4.00	-3.75	-3.50	-3.25	-3.00	-2.75	-2.50	-2.25	-2.00	-1.75	-1.50	-1.25	-1.00

Please note: Numbers across the top row correspond to MCI community number with sample size of each community in parentheses. Values within each cell correspond to the mean standard score per neuropsychological variable with standard deviation provided in parentheses. Values are rounded for display purposes. Significant pairwise comparisons are bolded. Cells with scores greater than standard deviation below the control group mean are shaded using heatmap with intensity of shade and equivalent value provided in the legend.

Descriptive statistics between MCI and HC groups

As expected, the MCI cohort performed significantly more poorly than the HC cohort across cognitive measures. The multivariate result was significant for diagnosis, Pillai's Trace =.681, $F = 91.409$, $df = (14, 599)$, $p <= .001$, and post-hoc univariate analyses revealed the MCI group performed significantly worse on all neuropsychological measures examined (see Tables 3 and 4 for additional detail).

Please Note: Numbers across the top row correspond to MCI community number. Values within each cell correspond to the mean difference between MCI communities per neuropsychological variable. Significant pairwise comparisons are bolded. Bonferroni-corrected p-values are in parentheses.

Community detection

Within the MCI group, communities were examined across multiple thresholds to minimize influence of thresholding. The results presented reflect the five communities that were identified most consistently across different thresholds and within the reachability limit. More specifically, results revealed the presence of five communities consistent with reachability (no node was isolated) across multiple weighted thresholds (0.30 to 0.55, in increments of 0.05) and proportional thresholds (10% to 35%; increments of 5). The reported results for the communities are based on use of a weighted threshold of 0.4.

Five communities were identified. Univariate analyses revealed a significant effect of community membership for each of the neuropsychological measures. The cognitive profile of each MCI community was then characterized in two ways: 1) based on standardized cognitive weaknesses identified relative to the healthy control group (i.e., profiles

Table 4. Mean Differences on Neuropsychological Scores Between the Five MCI Communities.

	1-2	1-3	1-4	1-5	2-3	2-4	2-5	3-4	3-5	4-5
Immediate Recall	**−0.814**	**−1.697**	−0.296	−0.232	**−0.883**	0.517	0.582	**1.401**	**1.465**	0.064
	(<0.001)	**(<0.001)**	(1.0)	(0.785)	**(<0.001)**	(0.376)	(0.063)	**(<0.001)**	**(<0.001)**	(1.0)
Delayed Recall	**−1.076**	**−2.135**	**−0.576**	**−0.470**	**−1.059**	0.500	**0.606**	**1.559**	**1.665**	0.106
	(<0.001)	**(<0.001)**	**(0.001)**	**(<0.001)**	**(<0.001)**	(0.130)	**(0.004)**	**(<0.001)**	**(<0.001)**	(1.0)
Recognition	**−1.963**	**−2.632**	**−1.182**	**−0.780**	−0.670	0.781	**1.182**	**1.450**	**1.852**	0.402
	(<0.001)	**(<0.001)**	**(<0.001)**	**(<0.001)**	(0.832)	(0.286)	(0.001)	**(0.002)**	**(<0.001)**	(1.0)
Naming	**2.921**	**−0.972**	**0.964**	**1.059**	**−3.893**	**−1.957**	**−1.862**	**1.936**	**2.031**	0.095
	(<0.001)	**(0.024)**	**(0.005)**	**(<0.001**	**(<0.001)**	**(<0.001)**	**(<0.001)**	**(<0.001)**	**(<0.001)**	(1.0)
Animals	**0.829**	−0.389	0.232	0.310	**−1.218**	−0.596	−0.518	0.621	**0.699**	0.078
	(<0.001)	(0.511)	(1.0)	(0.123)	**(<0.001)**	(0.106)	(0.093)	(0.136)	**(0.015)**	(1.0)
Vegetables	**0.538**	**−0.899**	−0.142	0.204	**−1.437**	−0.680	−0.335	0.757	**1.103**	0.345
	(0.048)	(<0.001)	(1.0)	(1.0)	**(<0.001)**	(0.071)	(1.0)	(0.054)	**(<0.001)**	(1.0)
Digit Span Forward	0.298	**0.820**	0.163	0.207	0.522	−0.135	−0.091	−0.657	−0.613	0.044
	(1.0)	**(0.007)**	(1.0)	(1.0)	(0.872)	(1.0)	(1.0)	(0.304)	(0.211)	(1.0)
Digit Span Backwards	0.192	**0.707**	0.250	0.345	0.515	0.058	0.154	−0.457	−0.362	0.095
	(1.0)	**(0.009)**	(1.0)	(0.085)	(0.545)	(1.0)	(1.0)	(0.858)	**(1.0)**	(1.0)
Digit Score	0.301	0.061	0.498	**1.288**	−0.240	0.197	**0.987**	0.437	**1.227**	**0.790**
	(1.0)	(1.0)	(0.215)	**(<0.001)**	(1.0)	(1.0)	**(<0.001)**	(1.0)	**(<0.001)**	(0.014)
Trails A	0.289	0.131	0.724	**2.514**	−0.157	0.435	**2.225**	0.592	**2.382**	**1.790**
	(1.0)	(1.0)	(0.085)	**(<0.001)**	(1.0)	(1.0)	**(<0.001)**	(1.0)	**(<0.001)**	**(<0.001)**
Trails B	−0.115	−0.029	**1.141**	**3.320**	0.085	**1.256**	**3.434**	**1.171**	**3.349**	**2.179**
	(1.0)	(1.0)	**(<0.001)**	**(<0.001)**	(1.0)	**(0.001)**	**(<0.001)**	**(0.008)**	**(<0.001)**	**(<0.001)**
Clock	0.161	−0.180	**3.378**	**0.558**	−0.340	**3.217**	0.397	**3.557**	0.737	**−2.820**
	(1.0)	(1.0)	**(<0.001)**	**(0.041)**	(1.0)	**(<0.001)**	(1.0)	**(<0.001)**	(0.322)	**(<0.001)**

Note: Numbers across the top row correspond to MCI community number. Values within each cell correspond to the mean difference between MCI communities per neuropsychological variable. Significant pairwise comparisons are bolded. Bonferroni-corrected p-values are in parentheses.

examined for scores that were greater than one standard deviation below the control group means), and 2) based on statistically significant differences in scores relative to other MCI communities. Based on the pattern of neuropsychological findings, these communities will subsequently be referred to by their most appropriate neuropsychological identification: Please see Figures 1 and 2 for visual representation of each MCI community's profiles.

The first community (Community 1) was characterized by mean memory scores (Immediate Recall, Delayed Recall, and Recognition Index from AVLT) that were more than one standard deviation below the HC group means. Relative to other communities, Community 1 was characterized by significantly lower AVLT Delayed Recall and Recognition Index scores (Delayed Recall: $p < .000$for Community 2, 3, and 5; $p = .001$for Community 4; Recognition Index $p < .000$for all Communities). This first community will be subsequently referred to as "predominantly memory impairment."

The second community (Community 2) was characterized by a mean Boston Naming Test (BNT) Total score that was more than 3 standard deviations below the HC group's mean, as well as, by mean Vegetable Fluency and Animal Fluency scores that were more than 1 standard deviation below the HC group mean. Relative to other communities, Community 2 was characterized by significantly lower BNT Total score ($p < .000$ for all communities). This community will subsequently be referred to as the "predominantly language impairment."

The third community (Community 3) was characterized by a Digit Span Backwards score that was more than one standard deviation below the HC group's mean. Relative to other communities, Community 3 profile was characterized by significantly *higher* BNT

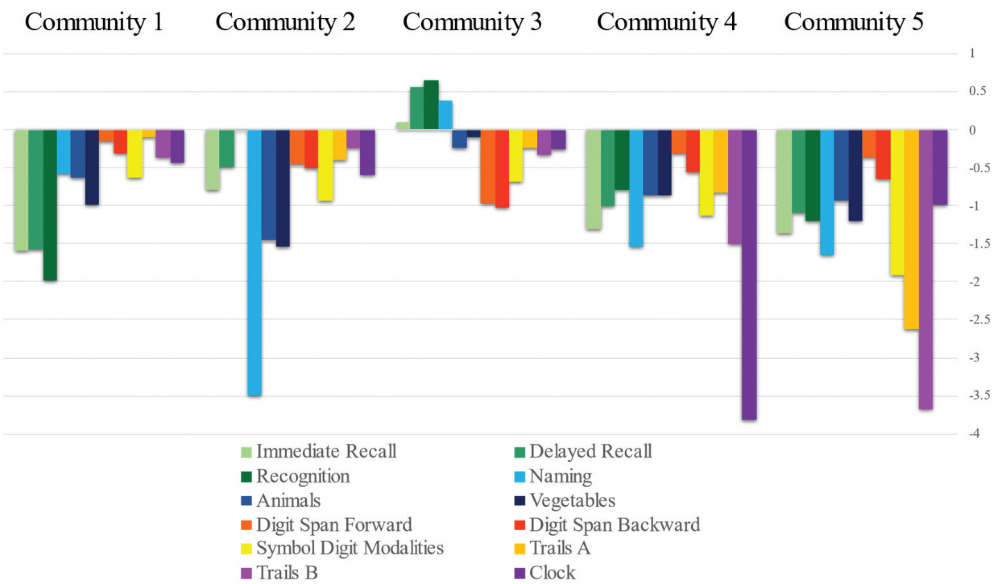

Figure 1. The neuropsychological profiles for the five communities. Colour bars are grouped by cognitive domain (memory is green, language is blue, working memory is red, processing speed is yellow, and executive function is purple). Each community's cognitive profile for each cognitive measure is represented along the X axis.

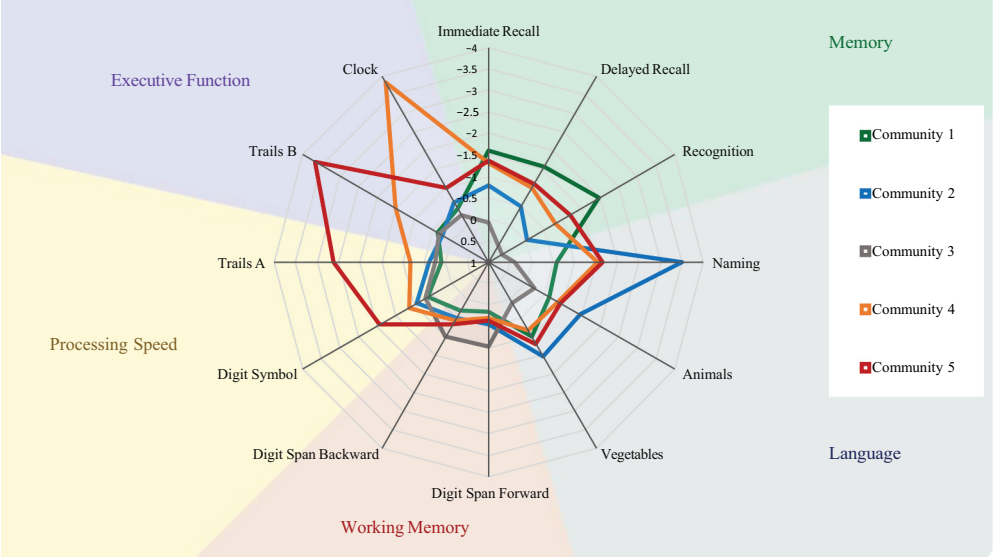

Figure 2. The radar graph displays the neuropsychological profiles for five communities. Background panel colours correspond to cognitive domain (memory is green, language is blue, working memory is red, processing speed is yellow, and executive function is aqua). The y-axis represents standardized scores on each measure. The community mean for each cognitive measure is represented along the y axis as a standardized score based on control group performance. The green line corresponds to MCI Community 1 (predominantly memory impairment), the blue line corresponds to MCI Community 2 (predominantly language impairment), the purple line corresponds to MCI Community 3 (cognitively normal), the orange line corresponds to MCI Community 4 (multidomain, with notable executive dysfunction), and the red line corresponds to MCI Community 5 (multidomain, with notable processing speed impairment).

Total score and AVLT Delayed Recall scores (BNT Total: $p = .024$for Community 1; $p < .000$for Community 2, 4, and 5; AVLT Delayed Recall: $p < .000$for all communities). This community will subsequently be referred to as the "cognitively normal," though it is recognized that this community was enrolled in the MCI group and thus would have scored in the impaired range on a memory measure at the screening visit.

The fourth community (Community 4) was characterized by a mean Clock Drawing score that was more than three standard deviations below the HC group mean. Additionally, relative to HC mean: BNT Total and Trails B scores were greater than 1.5 SD below, and Digit Symbol Modalities, AVLT Immediate Recall and AVLT Delayed Recall were greater than one standard deviation below the HC group means. Relative to other communities, Community 4 was characterized by significantly lower Clock scores ($p < .000$ for all communities). This community will subsequently be referred to as "multidomain, with notable executive dysfunction."

The fifth community (Community 5) was characterized by a mean Trails B score that was greater than three standard deviations below the HC group mean and a Trails A score that was more than two standard deviations below the HC group mean. Additionally, compared to the HC means: Digit Symbol Modality and Confrontation naming scores were greater than 1.5 SD below the mean, and AVLT Immediate Recall, AVLT Delayed

Recall, AVLT Recognition Index, and Vegetable Fluency were more than one standard deviation below the HC group mean. Relative to other communities, Community 5 was characterized by significantly lower Trails A, Trails B, and Digit Symbol Modalities scores (Trails A and Trails B: $p < .000$for all communities; Digit Symbol: $p = .014$for Community 4, $p = .001$for Community 2, $p < .000$for Communities 1 and 3). This community will subsequently be referred to as "multidomain, with notable processing speed impairment."

Demographic and clinical variables

Community profiles did not differ on age [$F(4,378) = .281$, $p = .890$], gender (X^2 (4) = 1.907, $p = 0.753$), race (X^2 (12) = 18.594, $p = 0.099$), or ethnicity (X^2 (8) = 12.722, $p = 0.122$). There was a significant effect for education (Kruskal-Wallis Test, (X^2 (4) = 13.184, $p = .01$) and community membership. Follow-up analyses revealed Community 5 (multidomain, with notable processing speed impairment) had a lower education level compared to Community 1 (predominantly memory impairment) ($p = .014$) and Community 3 (cognitively normal) ($p = .009$). Community membership was not significantly associated with functional living skills measured by the FAQ [$F(4,374) = 0.526$, $p = .717$], Clinical Dementia Rating Scale score [$F(4,377) = 1.290$, $p = .273$], or MMSE score [$F(4,377) = 1.566$, $p = .183$].

Biomarkers

One-way ANCOVAs controlling for intracranial volume (ICV), age, and gender revealed community membership were significantly associated with hippocampal ($F(4,299) = 5.081$, $p = .001$), entorhinal ($F(4,299) = 5.655$, $p < .000$) and fusiform gyrus ($F(4,299) = 2.850$, $p = .024$) volumes. Pairwise comparisons revealed smaller hippocampal and entorhinal volumes in Community 1 (predominantly memory impairment) compared to Community 3 (cognitively normal) ($p = .005$, $p = .002$) and Community 2 (predominantly language impairment) ($p = .018$, $p = .018$). In addition, smaller fusiform gyrus volume was seen in Community 5 (multidomain impairment with notable processing speed impairment) compared to Community 1 (predominantly memory impairment) ($p = .019$). FDG-PET levels in the posterior cingulate, angular gyrus, inferior/middle temporal gyrus were associated with community membership ($F(4,190) = 3.775$, $p = .006$). Pairwise comparisons revealed lower FDG-PET levels (i.e., greater hypometabolism) in angular gyrus, temporal, and posterior cingulate in Community 5 (multidomain, with notable processing speed impairment) compared to Community 2 (predominantly language impairment) ($p = .006$) as well as a trend toward significance relative to Community 1 (predominantly memory impairment) ($p = .061$). Community membership was not significantly related to other biomarkers examined (tau: $F(4,168) = 1.659$, $p = .162$; ABETA: $F(4,154) = 1.108$, $p = .355$; APOE4 Status: X^2 (8) = 5.605, $p = 0.691$).

Conversion at follow up

Stable MCI diagnosis (relative to baseline) versus conversion to dementia was significantly associated with community membership at 18-, 24-, and 36-month follow- up visits (X^2 (4) = 17.944, $p = 0.001$; X^2 (4) = 16.194, $p = 0.003$; X^2 (4) = 11.087, $p = 0.026$;), but not at 6-month, 12-month or 48-months (X^2 (4) = 3.20, $p = 0.525$; X^2 (4) = 8.445, $p = 0.077$; X^2 (4) = 5.180, $p = 0.269$). Additionally, amongst individuals that subsequently converted to dementia, months from baseline visit to first diagnosis of dementia visit was significantly associated with community membership ($F(4,165) = 3.009$, $p = .020$). Pair-wise

comparisons revealed months to initial dementia diagnosis were significantly greater for Community 3 (cognitively normal, mean conversion rate: 33.6 months) relative to Communities 1 (predominantly memory impairment, mean conversion rate: 20.1 months), 5 (multidomain, with notable processing speed impairment, mean conversion rate: 17.3 months), and 2 (predominantly language impairment, mean conversion rate: 15.6 months) ($p = .042$, $p = .012$, $p = .044$), but not community 4 (multidomain, with notable executive dysfunction, mean conversion rate: 20.5 months) ($p = .106$).

Discussion

This is the first study to examine cognitive subtypes in MCI using a community detection approach, to the best of our knowledge. Five distinct cognitive MCI subtypes were identified, each characterized first by the pattern of weaknesses relative to the healthy control group and second, by examining the unique, defining cognitive features relative to the other MCI communities. Community membership was significantly associated with multiple biomarkers and progression rates at some, but not all, time points.

The first and largest subtype, predominantly memory impairment, was characterized by lower verbal memory scores compared to both the healthy control sample, and compared to the other four MCI communities. This profile is consistent with single, domain amnestic MCI syndrome frequently identified as a precursor to Alzheimer's Disease (Jak, Bangen, et al., 2009; Oltra-Cucarella et al., 2018; Petersen, 2004). Given the emphasis on recruiting individuals at heightened risk for AD for entry into ADNI, this profile is expected. The second subtype identified, predominantly language impairment, was characterized by lower language scores (confrontation naming, two category fluency measures) compared to both the HC group sample and compared to the other four MCI communities. In the context of AD, confrontation naming weaknesses frequently co-occur with verbal memory weaknesses, and together, have been hypothesized to reflect more broadly, a decline in semantic knowledge associated with AD (Lin et al., 2014). More predominant language weaknesses, could also, theoretically reflect alternative neurodegenerative etiologies (e.g., primary progressive aphasia) (Gorno-Tempini et al., 2011; Mesulam et al., 2012), though further language measures would be necessary to assess this and present analyses did not include information pertaining to differential etiologies. The third subtype, cognitively normal, was characterized by relatively "normal" scores compared to the HC group (only one score, digit span backwards, was 1 standard deviation below the HC group mean). Further, when compared to other four MCI communities, this profile was characterized by relative strengths in language and memory. Of note, participants in this community would have been enrolled in the study based on the presence of a low story memory score at the screening visit (within 14 days of neuropsychological baseline testing) and based upon presence of a subjective decline in memory. Intraindividual cognitive variability is of interest (Casaletto et al., 2019; Costa et al., 2019), and potentially, this profile could be a reflection of greater intraindividual variability over time. Alternatively, this profile could reflect the earliest stage of AD, the Subjective Memory Complaints, stage (Jessen et al., 2020; Petersen et al., 2021) (given enrollment in ADNI required presence of memory concerns and poor performance logical memory).

The remaining two communities identified were characterized by more widespread weaknesses across cognitive domains when compared to the healthy control group. Both

"multidomain" communities demonstrated greater executive dysfunction relative to other three MCI subtypes described above, however, it appeared poor performance on executive function measures for the fifth subtype might, in part, be driven by slowed processing speed (hence the label, multidomain, with notable impairment in processing speed), while the fourth subtype, appeared to have more pronounced impairments in executive function, in the context of relatively better processing speed. The present testing battery was not selected to elucidate visuospatial deficits, however, given the notable weakness on Clock, it is possible this profile could reflect a more visually mediated AD presentation (Salimi et al., 2018)

Relationship between biomarkers and MCI subtypes

Community membership was associated with some, but not all of the biomarkers examined. While measures of cortical volume (hippocampus, entorhinal, and fusiform volumes) and FDG PET in the posterior cingulate, angular gyrus, inferior/middle temporal gyrus (key hubs of the Default Mode Network) were significantly related to community, additional biomarkers (tau, amyloid beta, APOE4 carrier status) were not significantly different across communities.

The predominantly memory impairment community was the largest, with a cognitive profile (single domain, amnestic) and cortical atrophy (smaller hippocampal and entorhinal volumes) most consistent with AD. The multidomain, with pronounced processing speed impairment community, was associated with greater hypometabolism in key hubs of the Default Mode Network (the posterior cingulate, angular gyrus, inferior/middle temporal gyrus) and additionally, had smaller fusiform volumes relative to some comparison profiles. This profile might reflect mixed pathology or more advanced aMCI. Fusiform connectivity has been linked to greater risk for progression to AD in individuals with MCI, potentially, our findings could link to that. Notably, the communities did not differ on clinical measures of severity, however, suggesting communities were not simply a reflection of greater functional impairment. Further, conversion to dementia, at 2- and 3 year- follow up visits was significantly associated with community membership (with strongest converters in the predominantly memory impairment community and the two multidomain communities, though due to limited sample sizes future studies would be needed to confirm this). These findings are consistent with prior research linking greater progression to dementia in single domain aMCI (i.e., predominantly memory impairment community) and multidomain profiles.

Comparisons to alternative approaches

Prior subtyping approaches rely heavily on a priori determination of impaired scores (i.e., cut scores) which influences which subtypes emerge. For instance, depending on criteria selected, Bondi et al. (2014) identified either a relatively normal subtype in MCI or alternatively, a language subtype (without a normal subtype), both of which had different associations with biomarker data. Multiple approaches across datasets reveal an amnestic subtype (Bondi et al., 2014; Machulda et al., 2019) and dysexecutive/mixed (Clark et al., 2013) or dysexecutive subtype (Machulda et al., 2019). The present approach enabled detection of both a language subtype and a relatively normal subtype, along with an

amnestic subtype and two separate dysexecutive subtypes all within a single sample that was initially labeled generally MCI. This approach was successful in detecting these subtypes without use of separate normative data, as the scores were standardized based on the control sample without the use of a priori cut off scores. The strongest associations with biomarker data emerged with FDG-PET levels, suggesting this may be a particularly sensitive biomarker associated with cognitive decline in MCI. These findings suggest that this data driven approach may be useful in differentiating subtypes of MCI which may have subsequent implications for etiologic and treatment determinations. Additional follow-up studies and etiologic classification data are needed to further examine the specific findings reported here.

Study limitations

Study limitations include smaller healthy control sample size relative to MCI sample size. This likely impacted post-hoc analyses for smaller sized communities (as relatively less participants had data for all neuropsychological variables, biomarkers, and follow up information). The smaller sample sizes of some of the communities (e.g., communities with less than 50 people) in combination with smaller sample sizes for individuals with aforementioned biomarkers undoubtedly impacted post-hoc comparisons. As ADNI was developed to examine Alzheimer's Disease, not all neuropsychological domains were equivalently sampled (e.g., no spatial tasks), which impacted the cognitive profiles that could be examined. Lastly, diagnostic criteria for MCI has been shown to impact what subtypes are detected (Bondi et al., 2014), so this also influenced what profiles would be detected. The sample was a predominantly White, Non-Hispanic, English Speaking sample (bilingualism/multilingualism was not assessed) which limits the applicability of these findings to the general population. Given the extent of health disparities in MCI, it is imperative research efforts and financial spending initiatives be directed to rebuilding the trust between minoritized communities and the scientific community, and as such, future studies are needed to expand findings to individuals from minoritized backgrounds.

Conclusions

A better understanding of MCI heterogeneity can be examined by exploring not only cognitive weaknesses relative to a healthy control sample but also by examining within MCI variability. Alternative methodologies, such as community detection, have the potential to detect subtler cognitive variation within MCI that can be readily examined with biomarker variables or clinical metrics. This approach has shown significant utility within neurodevelopmental populations (Fair et al., 2012; Feczko & Fair, 2020; Feczko et al., 2018) and our work supports its extension to MCI as well. Theoretically, with more accurate subtyping approaches, it may be possible to characterize the clinical and etiological heterogeneity within MCI, in ways that could have meaningful clinical applications. More accurate subtyping of MCI has the potential to identify different etiological subtypes and could potentially identify help explain the heterogeneity in treatment response, for instance (Nettiksimmons et al., 2014). While the present community detection analyses were conducted for using neuropsychological data collected at a single time point, future analyses might consider using a trajectory-based subtyping approach which has also

shown utility in developmental samples (Fair et al., 2012; Feczko & Fair, 2020; Feczko et al., 2018). The code used in these analyses has been made available at https://github.com/jpommy/MCI-Subtyping.

Acknowledgments

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. D. Edler, A. Eriksson and M. Rosvall, The MapEquation software package, is available at the mapequation.org.

Disclosure statement

No potential conflict of interest was reported by the authors.

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