FEATURED ARTICLE

Cortical atrophy patterns of incident MCI subtypes in the Mayo Clinic Study of Aging

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Abstract

Introduction: We examined differences in cortical thickness in empirically derived mild cognitive impairment (MCI) subtypes in the Mayo Clinic Study of Aging.

Methods: We compared cortical thickness of four incident MCI subtypes (n = 192) to 1257 cognitive unimpaired individuals.

Results: The subtle cognitive impairment cluster had atrophy in the entorhinal and parahippocampal cortex. The amnestic, dysnomic, and dysexecutive clusters also demonstrated entorhinal cortex atrophy as well as thinning in temporal, parietal, and frontal isocortex in somewhat different patterns.

Discussion: We found patterns of atrophy in each of the incident MCI clusters that corresponded to their patterns of cognitive impairment. The identification of MCI subtypes based on cognitive and structural features may allow for more efficient trial and study designs. Given individuals in the subtle cognitive impairment cluster have less structural changes and cognitive decline and may represent the earliest group, this could be a unique group to target with early interventions.

KEYWORDS

cluster analysis, cortical thickness, mild cognitive impairment, neuropsychology

1 | INTRODUCTION

Numerous studies have examined imaging characteristics of single- and multi-domain amnestic mild cognitive impairment (aMCI) using voxel-based morphometry[1-7] and cortical thickness.[8-11] As is now well established, aMCI most commonly involves the medial temporal lobe and surrounding structures, with extension into posterior temporal, parietal, and frontal lobes depending on the criteria used to define mild cognitive impairment (MCI; most often Petersen criteria[12]) and symptom duration.

We and others have performed hierarchical cluster analysis on neuropsychological data which revealed three similar MCI subtypes in both the Mayo Clinic Study of Aging (MCSA) and Alzheimer's Disease Neuroimaging Initiative (ADNI): amnestic, dysnomic, and dysexecutive.[13,14] These two studies were discrepant, however, on the fourth MCI subtype identified by cluster analysis. In the ADNI sample on prevalent MCI, their fourth cluster was a cluster-derived normal group that performed within normal limits on cognitive testing, had fewer apolipoprotein E (APOE) $\varepsilon 4$ carriers, had normal cerebrospinal fluid (CSF) Alzheimer's disease (AD) biomarker profiles, and had fewer members who progressed to dementia.[13] In contrast in the MCSA sample on incident MCI, the fourth cluster defined as subtle cognitive impairment had lower memory and global cognitive scores and an increased probability of progressing to MCI or dementia relative to their robustly matched cognitively unimpaired (CU) peers.[14]

Edmonds et al. subsequently reported on cortical thickness patterns of the MCI subtypes in the ADNI sample and showed an ordered pattern of cortical atrophy in the amnestic, dysnomic, and dysexecutive clusters while their cluster derived normal group did not differ from the cognitively normal group.[8] Evaluating structural brain changes in empirically derived cognitive subtypes of MCI has the potential to enhance our understanding of specific prodromes of dementia. Therefore, the aim of this study was to examine cortical thickness patterns of empirically derived incident MCI subtypes in the MCSA. We specifically were interested in examining whether we could detect any structural changes in the subtle cognitive impairment cluster.

RESEARCH IN CONTEXT

1. Systematic review: We reviewed previously published manuscripts that focused on voxel-based morphometry and cortical thickness measures for evaluating structural brain changes in mild cognitive impairment (MCI) defined by conventional/internal consensus criteria and/or cluster analysis. Most studies use samples of individuals with prevalent MCI and therefore the degree of atrophy may have progressed for some individuals more than others.

2. Interpretation: All incident MCI cluster subtypes had entorhinal cortex thinning. The amnestic, dysnomic, and dysexecutive clusters also showed thinning in temporal, frontal, and parietal isocortex that corresponded to their patterns of cognitive impairment. Each MCI subtype had differing degrees of involvement of the cognitive domains as well as different patterns of cortical thinning, suggesting that there may be cognitive and structural trajectories that are unique to each group that cannot be explained solely by symptom duration

3. Future directions: We will continue to follow our cohort of neuropsychologically derived MCI subtypes to assess longitudinal outcome. Future analyses will examine markers of cerebrovascular and tau pathology.

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2 | METHODS

2.1 | Study sample

2.1.1 | Participants

Participants were enrolled in the MCSA, a longitudinal population-based study of cognitive aging in Olmsted County, Minnesota.[15] All participants are assessed approximately every 15 months and given a consensus diagnosis. Given the emphasis on evaluating changes in cortical thickness as participants transition from CU to MCI, we first identified a cohort of participants with incident MCI—which allowed us to assess cortical thinning in MCI with homogenous (and minimal) disease duration. Participants who had a diagnosis of MCI at the time of enrollment into the MCSA were considered prevalent MCI and excluded. Thus, we required that all MCI participants in this study have ≥1 prior visits at which they were classified as CU.

Participants in this study represent a subset of those from a previous article in which we used agglomerative hierarchical clustering with Euclidean distance and Ward's linkage to identify neuropsychological subtypes of MCI.[14] For the present study, both CU and MCI participants were included if they completed a magnetic resonance imaging (MRI). Of our original sample of 506 MCI participants, 192 had imaging data. The current sample of 192 participants represents 38% (27/70) of the original subtle cognitive impairment cluster, 44% (84/193) of

the amnestic cluster, 37% (31/84) of the dysnomic cluster, and 31% (50/159) of the dysexecutive cluster.

2.1.2 | Standard protocol approval and patient consents

The Mayo Clinic and Olmsted Medical Center Institutional Review Boards approved these studies, which also followed Health Insurance Portability and Accountability Act (HIPAA) guidelines. Every participant provided written informed consent.

2.2 | Materials and procedure

2.2.1 | Evaluation

For the MCSA, participants complete comprehensive evaluations approximately every 15 months, including a physician examination, an interview by a study coordinator, and neuropsychological testing.[15] The physician examination included a medical history review, complete neurologic examination, and administration of the Short Test of Mental Status.[16] The study coordinator interview included collection of demographic information, medical history, and questions about memory to the participant using the Blessed Memory Test[17] and the informant

using the Clinical Dementia Rating Scale[18] and the Functional Activities Questionnaire.[19] Participants also completed the Beck Depression Inventory.[20]

Neuropsychological testing included nine measures assessing four cognitive domains: (1) Memory (AVLT Delayed Recall,[21] WMS-R Logical Memory II & Visual Reproduction II),[22] (2) Language (Boston Naming Test,[23] Category Fluency[24]), (3) Attention/Executive (Trailmaking Test B,[24,25] WAIS-R Digit Symbol[26]), (4) Visuospatial (WAIS-R Picture Completion & Block Design[26]). For each participant, cognitive performance in each domain was compared with age-adjusted scores of individuals previously obtained using Mayo's Older American Normative Studies (MOANS).[27,28] This approach relies on prior normative work and extensive experience with the measurement of cognitive abilities in an independent sample of participants from the same population. There was no overlap between individuals from which the MOANS were derived and the participants in the current study. For the original cluster analysis, we had the strict requirement that all participants have data from ≥8 of the 9 cognitive tests administered at each study visit.[14]

The criteria used to diagnose MCI were those described by Petersen[29] and follow the outline above, with (1) history from the participant and interview of a study partner to determine whether there has been a change in cognition, (2) objective scores in the −1.0 standard deviation (SD) below the mean range that the clinicians believe are below what would be *expected for that individual* in one or more cognitive domains based on the normative data we use, (3) functionally intact, and (4) does not meet *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for dementia. In addition, these criteria are consistent with the recent practice guideline update on MCI.[30] A final decision to diagnose CU or MCI was based on a consensus agreement among study coordinator, examining physician, and neuropsychologist, after taking into account education, prior occupation, visual or hearing deficits, and reviewing all other participant clinical information.[15,29] A diagnosis of dementia was based on published criteria.[31] All raters were blinded to the previous diagnosis of the participant.

2.2.2 | Genetic characterization

All participants underwent a blood draw at their baseline visit. DNA extraction and *APOE* genotyping was performed for each participant using standard methods.[32] The *APOE* $\varepsilon 4$ carrier included participants with one or two copies of the $\varepsilon 4$ allele (ie, $\varepsilon 2 \varepsilon 4$, $\varepsilon 3 \varepsilon 4$, $\varepsilon 4 \varepsilon 4$).

2.2.3 | Structural MRI

All MRI were performed using General Electric 3T scanners with a three-dimensional T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo sequence. Regional cortical thickness measurements were estimated using FreeSurfer 5.3 software with default settings.[33] Cortical thickness measures were estimated for the following: temporal (entorhinal, parahippocampal, banks of superior temporal sulcus, fusiform, inferior temporal, insula, middle temporal, superior temporal, temporal pole, transverse temporal), frontal (regions of interest [ROIs] from caudal middle frontal, frontal pole, lateral orbitofrontal, medial orbitofrontal, pars opercularis, pars orbitalis, pars triangularis, rostral middle frontal, superior frontal), and parietal (ROIs from inferior parietal, precuneus, superior parietal, supramarginal).[34]

2.3 | Statistical analyses

To compare cortical thinning by group we fit linear regression models on thickness including group as a categorical covariate having five levels of which four were the MCI subtypes and also a reference level of CU individuals. The reference group included CUs ≥ 70 who remained CU and had a MCSA visit with imaging data, for example, MRI, available. To have a single visit per participant while maximizing the available data, we selected the earliest visit with imaging data. In our sample, the median visit was second visit for CU and third for MCIs (36% and 42% of the samples, respectively, were on their fourth visit or greater.)

Separate models were fit in each of 46 regions of interest (23 in each hemisphere) and adjusted for age, sex, and years of education. Regions were not averaged over left and right hemispheres to allow for detection of asymmetric thinning. The natural log transformation was applied to thickness to account for skewness in the data, which allows the group differences to be interpreted as approximate proportional differences.[35] For example, a coefficient of −0.05 for a one unit difference of X where X is subtype 1 referenced to CU corresponds to an approximate 5% (0.05 * 100) reduction in thickness. In simpler terms, thickness in subtype 1 is ≈5% less than CUs.[35] In the demographics table, comparisons are made across all the groups, and superscripts indicate *P*-values from pairwise comparisons between CU and each cluster. All analyses were completed in R statistical software version 3.4.2 (https://www.r-project.org).

3 | RESULTS

3.1 | Demographic characteristics and neuropsychological performance

Figure 1 provides a flow chart of the steps used to derive the initial study sample of 506 participants with incident MCI on which the cluster analysis was performed. The cluster analysis produced the following MCI cluster subtypes: amnestic, dysnomic, dysexecutive, subtle cognitive impairment, which we describe in our previous paper.[14] The current analysis is based on a subset of these individuals who had imaging at the time of the incident MCI diagnosis (n = 192), and a group of CU participants who had imaging data available. Demographics and cognitive domain z-scores are listed in Table 1. Group values in this subsample (N = 192) did not meaningfully differ from the original sample (N = 506) on age, sex, APOE genotype, education, and cognitive test z-scores. The frequency of an APOE $\varepsilon 4$ allele did not differ by cluster.
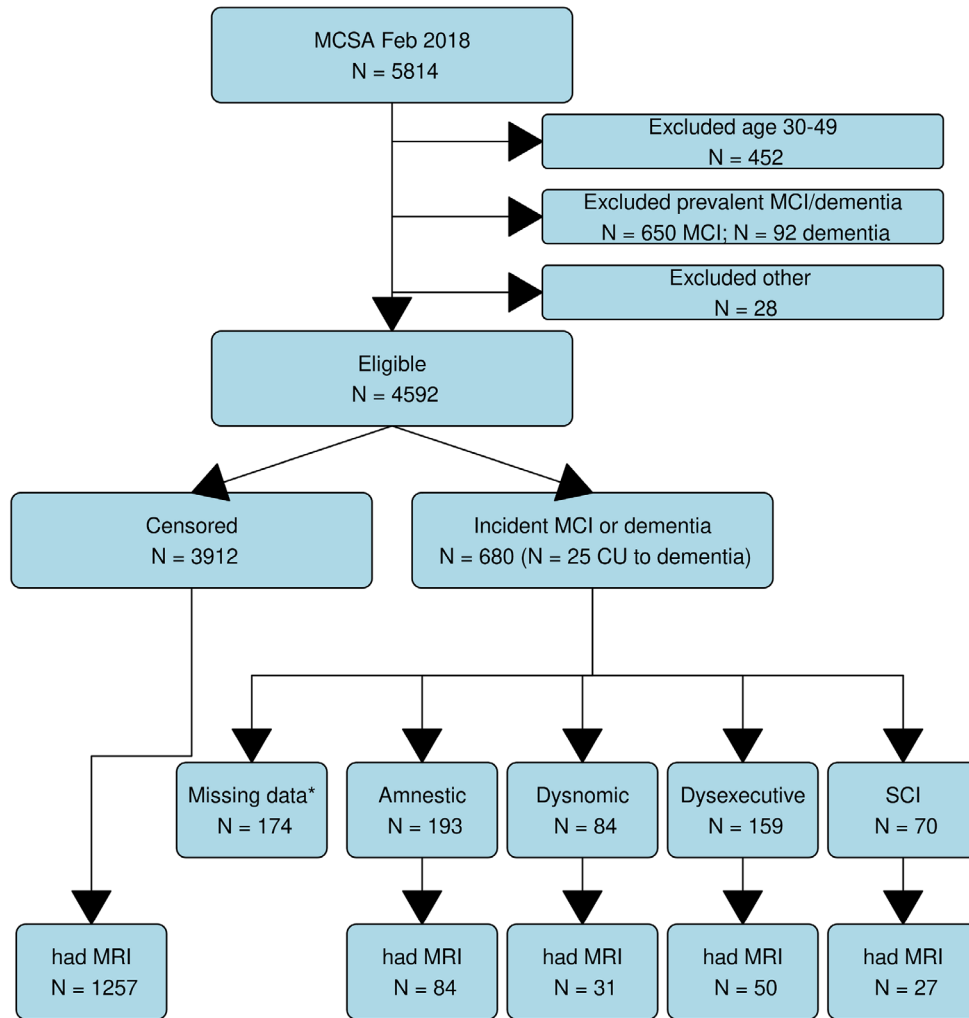
FIGURE 1 Study flow chart. *Ineligible for clustering due to missing data.

3.2 | Clinical categorization at next visit

Table 2 provides the diagnostic category for each MCI subtype at the study visit following the visit at which the incident MCI diagnosis was made. This represents a subset of the imaging study sample because not all participants had an MCSA visit after their imaging visit. Similar to our previous paper, the subtle cognitive impairment cluster had the highest rate of being classified as CU at the next visit, followed by the amnestic, dysnomic, and dysexecutive clusters, respectively. Conversely, the dysexecutive group had the highest rate of progression to dementia at the next study visit. The time interval between visits did not significantly differ between the MCI subtypes.

3.3 | Regional cortical thickness patterns

Compared to CU, the subtle cognitive impairment cluster had thinning in entorhinal and parahippocampal cortex. The amnestic cluster had thinning in the entorhinal cortex, the fusiform and infe-

rior/middle/superior temporal gyri, temporal pole, rostral middle frontal, medial orbitofrontal, and superior frontal gyri, and the inferior parietal lobe. The dysnomic cluster showed thinning in the entorhinal cortex—relative more left than right—and bilateral thinning of inferior/middle/superior temporal gyri, temporal pole, frontal pole, pars triangularis, caudal/rostral middle frontal, superior frontal, inferior parietal, precuneus, and supramarginal regions. The dysexecutive cluster showed bilateral cortical thinning in entorhinal and parahippocampal cortex, bilateral fusiform/lingual gyri, middle/superior temporal gyri, right temporal pole, bilateral caudal/rostral middle frontal gyri, left frontal pole, right lateral orbitofrontal, and bilateral medial orbitofrontal, superior frontal, inferior parietal, and supramarginal gyri. Figure 2 provides results from linear regression models on thickness adjusted for age, sex, and education for each region. Figure 3 shows the cortical thickness maps that represent the difference between each cluster and CU. All neuropsychologically derived incident MCI clusters demonstrated entorhinal cortex thinning, while the amnestic, dysnomic, and dysexecutive clusters showed thinning in temporal, frontal, and parietal isocortex, albeit in somewhat different patterns.

TABLE 1 Demographic and cognitive characteristics

Feature	Amnestic (N = 84)	Dysnomic (N = 31)	Dysexecutive (N = 50)	SCI (N = 27)	CU (N = 1257)	P value
Age at first MRI						
Mean (Q1, Q3)	81 (77, 85)	84 (80, 88)	83 (80, 87)	80 (78, 84)	79 (74, 83)	<0.001[a,c,e]
Education, years						
Median (Q1, Q3)	13 (12, 15)	12 (9, 13)	13 (12, 14)	17 (15, 18)	14 (12, 16)	<0.001[a,c,g]
Sex						
Male	48 (57.1%)	17 (54.8%)	32 (64.0%)	20 (74.1%)	645 (51.3%)	0.05[h]
CDR sum of boxes						
Median (Q1, Q3)	0.5 (0, 1)	0.5 (0, 1)	0.5 (0, 1.5)	0.5 (0, 0.75)	0 (0, 0)	<0.001[a,c,e,g]
APOE ε4 carrier						
Yes	31 (36.9%)	13 (41.9%)	22 (44.0%)	10 (37.0%)	291 (23.4%)	<0.05[b,d,f]
STMS						
Median (Q1, Q3)	31 (30, 33)	30 (28, 32)	30 (28, 32)	33 (32, 34)	35 (34, 37)	<0.001[a,c,e,g]
FAQ Total						
Median (Q1, Q3)	0 (0, 3)	0 (0, 2)	1 (0, 4)	0 (0, 0.75)	0 (0, 0)	<0.001[a,c,e,g]
BDI						
Total ≥ 13	6 (7.1%)	3 (9.7%)	9 (18.0%)	3 (11.1%)	66 (5.3%)	NS
Global z						
Median (Q1, Q3)	−1.3 (−1.6, −1.1)	−2.8 (−3.3, −2.4)	−2.3 (−2.8, −1.8)	−0.3 (−.7, −0)	−0.1 (−.7, 0.4)	<0.001[a,c,e]
Memory z						
Median (Q1, Q3)	−1.8 (−2.2, −1.3)	−2.3 (−2.6, −1.8)	−1.2 (−1.8, −.5)	−0.8 (−2.1, −.3)	0.0 (−.71, 0.62)	<0.001[a,c,e,g]
Language z						
Median (Q1, Q3)	−1.1 (−1.4, −.5)	−3.2 (−3.9, −2.5)	−1.5 (−2.0, −1.1)	−0.1 (−.6, 0.5)	−0.1 (−.7, 0.5)	<0.001[a,c,e]
Attention z						
Median (Q1, Q3)	−0.9 (−1.5, −.2)	−2 (−2.6, −1.5)	−3.3 (−3.9, −2.9)	−0.2 (−.6, 0.5)	−0.2 (−.8, −.3)	<0.001[a,c,e]
Visuospatial z						
Median (Q1, Q3)	−0.6 (−1, −.1)	−1.6 (−2.4, −1.1)	−1.3 (−2, −.5)	0.4 (0, 0.77)	−0.1 (−.7, 0.5)	<0.001[a,c,e]

Abbreviations: ANOVA, analysis of variance; BDI, Beck Depression Inventory; CDR, Clinical Dementia Rating scale; CU, cognitively unimpaired; FAQ, Functional Activities Questionnaire; NS, not significant; Q, quartile; SCI, subtle cognitive impairment; STMS, Short Test of Mental Status.

[a]Amnestic versus CU, Linear Model ANOVA.
[b]Amnestic versus CU, Pearson Chi-squared test.
[c]Dysnomic versus CU, Linear Model ANOVA.
[d]Dysnomic versus CU, Pearson Chi-squared test.
[e]Dysexecutive versus CU, Linear Model ANOVA.
[f]Dysexecutive versus CU, Pearson Chi-squared test.
[g]SCI versus CU, Linear Model ANOVA.
[h]SCI versus CU, Pearson Chi-squared test.

Compared to subtle cognitive impairment, the amnestic cluster had relatively more thinning in the fusiform gyrus, the dysnomic cluster had more thinning in middle/superior temporal gyri, inferior parietal lobe, and supramarginal gyri, and the dysexecutive cluster had more thinning in the medial orbitofrontal gyri, inferior parietal lobe, and supramarginal gyri. The dysnomic cluster had more thinning in the left entorhinal cortex relative to the amnestic cluster, and the dysexecutive cluster had slightly more thinning in the left frontal pole and left supramarginal gyrus compared to the amnestic cluster (see Figure 2). There were no significant differences in cortical thickness values between the dysnomic and dysexecutive clusters.

Because of the exploratory nature of this study, we did not want to strongly control for the rate of false-positive findings at the expense of

false negatives.[36] With 46 regions, the Bonferroni adjustment would consider $P < 0.05/46 = 0.0011$ as statistically significant. Thickness estimated mean differences for each region are provided in Table S1 in supporting information.

4 | DISCUSSION

We found patterns of atrophy in each of the neuropsychologically derived incident MCI clusters that corresponded to their patterns of cognitive impairment. The cortical thinning in the entorhinal and parahippocampal cortices in the subtle cognitive impairment cluster is consistent with the cognitive profile of this group showing very mild,

TABLE 2 Diagnostic category at next visit

	Amnestic (N = 72)	Dysnomic (N = 22)	Dysexecutive (N = 38)	SCI (N = 24)	P value[a]
Clinical outcome					0.002[b]
MCI to CU	29 (40.3%)	8 (36.4%)	8 (21.1%)	18 (75.0%)	
MCI to MCI	38 (52.8%)	13 (59.1%)	23 (60.5%)	5 (20.8%)	
MCI to DEM	5 (6.9%)	1 (4.5%)	7 (18.4%)	1 (4.2%)	
First to second visit, months					0.696[c]
Median (Q1, Q3)	15.9 (15, 17)	15.7 (14.7, 16.8)	16 (15, 17.1)	15.3 (14.7, 16.4)	

[a]P value testing differences among the four clusters.
[b]Linear Model ANOVA.
[c]Pearson Chi-squared test, Q, quartile
NOTE: Not all participants had an MCSA visit after their first imaging visit.
Abbreviations: ANOVA, analysis of variance; CU, cognitively unimpaired; DEM, dementia; MCI, mild cognitive impairment; SCI, subtle cognitive impairment.

focal involvement of memory. These results are also consistent with pathologic data showing that the first region to develop neurofibrillary tangles is the transentorhinal region[37] though we cannot confirm that this is the pathologic substrate for the cortical thinning in our sample. Our findings provide structural evidence that this group does not represent false positives (with respect to possessing evidence of underlying neurodegenerative disease) despite the high likelihood of receiving a diagnosis of CU at the next visit. There were no significant differences between the subtle cognitive impairment cluster and the other three clusters on percentage of participants with clinically elevated scores on the Beck Depression Inventory. Therefore, it's also unlikely that the entorhinal/parahippocampal thinning is due to affective symptoms.

In addition to expected medial temporal lobe involvement, the amnestic cluster showed cortical thinning in the rest of the temporal lobe as well as frontal and parietal regions. This pattern is comparable to findings from other studies of prevalent MCI[9,10,38] that used conventional criteria for diagnosing MCI.[29] The degree of thinning in our amnestic cluster was similar in the left versus right entorhinal and parahippocampal cortices. Some studies report a predilection for more prominent left than right medial temporal involvement in amnestic MCI.[6,8-10,38] In contrast, two others found right-sided predominant atrophy[1,39] and another found right medial temporal lobe atrophy but left parietal lobe atrophy.[2] Some of the variability in findings could be due to the measures used to assess memory.

Previous studies have found left lateralized[4,8] and bilateral findings[3] in MCI with prominent language involvement. Other investigators have also showed multiple brain regions were affected in multi-domain MCI, including medial/lateral temporal, parietal and frontal regions[3,4,9,11] and specifically, bilateral cortical thinning in a dysexecutive subtype.[8] The lack of substantial thinning of the temporal poles and precuneus, areas included in the AD-signature region,[40,41] along with relatively more involvement of lateral frontal regions than the other MCI subtypes suggests that individuals in the dysexecutive MCI cluster may be on a unique trajectory compared to the subtle cognitive impairment, amnestic MCI, and dysnomic MCI subtypes. Despite considerable overlap in the brain regions involved in the amnestic, dysnomic, and dysexecutive clusters, there are important

regions where they do not overlap, which is informative and relates to the cognitive profiles we observe after clustering.[14]

Other studies have also shown the ability to detect structural differences prior to a formal diagnosis of MCI. For example, Dickerson et al. found cortical thinning among CU participants who later developed AD dementia in AD-signature regions, including medial temporal cortex, inferior temporal gyrus, temporal pole, angular gyrus, superior frontal gyrus, superior parietal lobule, supramarginal gyrus, precuneus, and inferior frontal sulcus.[42] A previous study that included a group diagnosed as "pre-MCI" (ie, physician cognitive diagnosis of MCI based on participants' entire clinical history and functional status, neuropsychological diagnosis of normal) reported that this group had lower left hippocampal volumes compared to CU participants.[5] A more recent paper reported smaller hippocampal volume in ADNI CU participants with neuropsychological decline compared to CU participants without neuropsychological decline.[7]

This study is novel compared to previous studies of structural changes in MCI because to our knowledge, we are the first to show changes in cortical thickness that correspond to empirically derived cognitive phenotypes in a large cohort of individuals with incident MCI. Our findings reflect changes in cortical thickness just as participants are transitioning from CU to MCI and differs from the majority of other structural imaging studies on MCI that have examined prevalent MCI.[1-5,8-11] A previous study on incident MCI was not based on empirically derived MCI subtypes.[6] It is unlikely that the different patterns and extent of cortical involvement in our cohort is simply a reflection of disease severity given that imaging was performed at the first visit at which an MCI diagnosis was made for all participants. Neuroimaging studies performed on individuals with prevalent MCI do not take into account symptom duration, which raises the likelihood that the degree of atrophy may have progressed for some individuals more than others. The fact that each MCI subtype in our sample has differing degrees of involvement of the cognitive domains as well as different patterns of cortical thinning suggests that there may be cognitive and structural trajectories that are unique to each group that cannot be explained solely by symptom duration. Although the notion that multi-domain aMCI is simply more advanced or "late-MCI" makes conceptual sense, our results challenge this assumption.
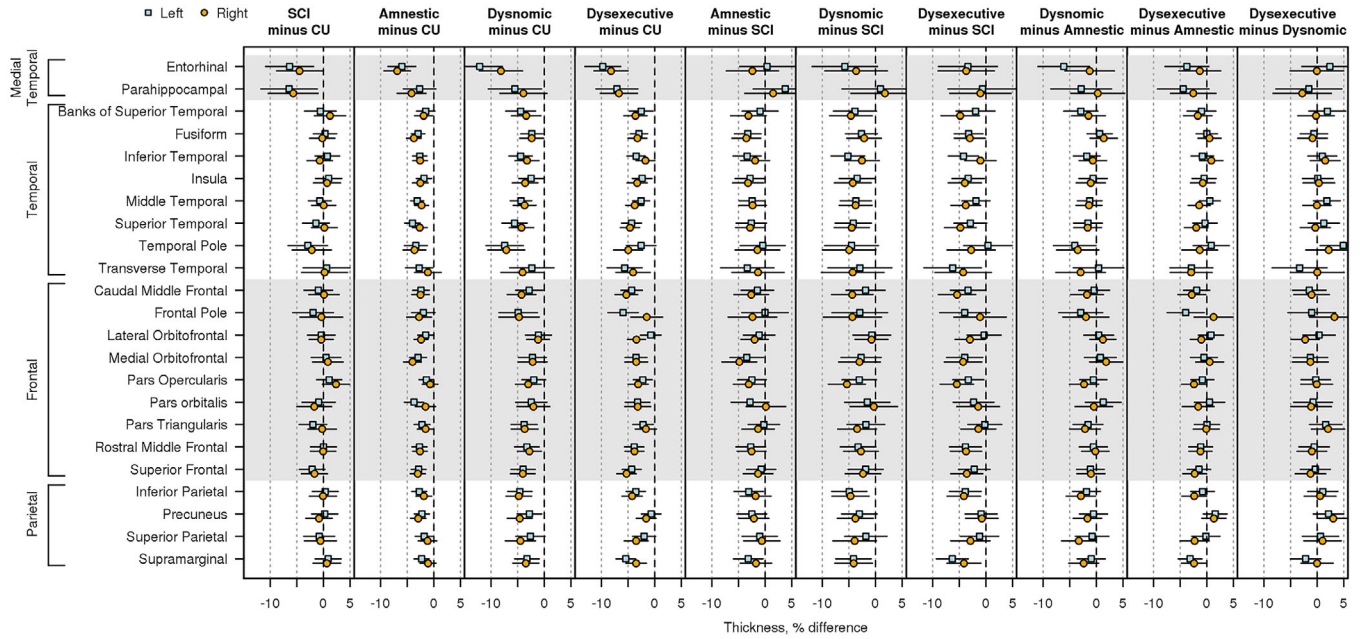
FIGURE 2 Percent differences in cortical thickness between each cluster and cognitively unimpaired and between clusters. Pairwise mean percent difference (point) with 95% confidence interval (CI; black) from linear regression models on thickness adjusted for age, sex, and education and fit separately in each region. Each column header indicates the two groups compared. A log transformation of thickness allows for interpretation of differences on the percent scale
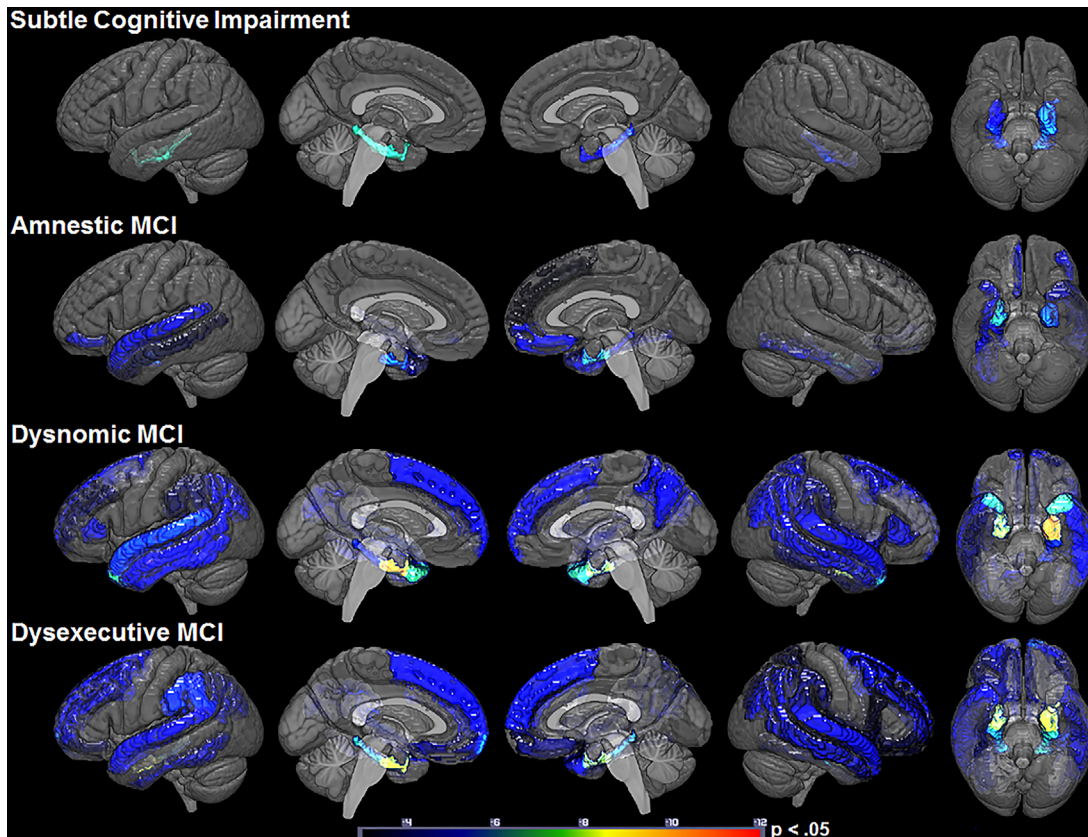

FIGURE 3 Percent thickness difference between each cluster and cognitively unimpaired (CU). Percent thickness differences between each cluster and CU (n = 1257) where negative values indicate the group is thinner. Group-wise differences in thicknesses for each region are displayed using MRIcroGL (https://www.mccauslandcenter.sc.edu/mricrogl/), (P < 0.05)

Another unique feature of our study is that our results are based on an epidemiologic community-based sample[15] whereas previous studies of empirically derived MCI subtypes have been performed on clinic-based samples; volunteers from the community or research centers; or ADNI, which recruits participants from universities and medical centers.[43]

Similar to the findings by Edmonds et al., with the exception of their cluster-derived normal group which did not differ from the cognitively normal group,[8] all of the clusters in the MCSA dataset showed some degree of involvement of medial temporal lobe structures and memory impairment. Although memory was not the most severely impaired domain in the dysnomic and dysexecutive subtypes, there was still significant cortical thinning in medial temporal regions in these groups. Therefore, a more accurate way to describe these cognitive phenotypes is dysnomic aMCI and dysexecutive aMCI.

Edmonds et al.[8] found significant differences between their dysexecutive/mixed MCI relative to the amnestic MCI, with the dysexecutive group showing more thinning in frontal, lateral temporal, and parietal regions. We found only modest differences between our dysexecutive and amnestic clusters which were in the left frontal pole and left supramarginal gyrus. Possibly underlying these different results are methodological differences between the studies, and that the ADNI dysexecutive cluster had poor performance across all cognitive domains assessed suggesting that this group may be at a more advanced clinical stage whereas the MCSA dysexecutive cluster had severe impairment in attention/executive function but only mild impairment in the memory, language, and visuospatial domains.

Taking into account the unique cognitive and imaging features of these reproducible MCI subtypes has the potential to improve clinical trials by identifying more homogenous groups of participants. Results from previous studies of MCSA participants provide converging evidence that performance on memory measures in the range of $z = −0.5$ places individuals at higher risk of developing MCI[14,44] and for having measurably elevated levels of neurodegeneration.[45] A previous study also examined cognitive profiles of two large independent population-based elderly cohorts (MCSA and Framingham Heart Study).[46] MCI subtypes were defined based on consensus adjudication in both studies. Consistent with the present findings, results showed that there was increased incident dementia even when a threshold of $z < −0.5$ was used. Current results provide imaging evidence that individuals in this range of cognitive function are indeed showing structural changes even though they a had higher reversion rate to CU than participants in the amnestic, dysnomic, and dysexecutive clusters.[14] As we discussed in our previous paper,[14] many studies show that individuals with MCI who subsequently receive a diagnosis of CU are at increased risk for being classified again as MCI and/or eventually developing dementia, implying that they already have some degree of underlying brain pathology.[47-50] Some factors affecting the diagnosis of incident MCI include variability in the individuals' ability to benefit from previous exposure to the assessment procedure and test materials,[45] specific conditions present on the day of testing that are transient or reversible,

the informant's perception of the participant at that point in time, and the interactions between the participant and clinicians.[50] Furthermore, reversion rates are higher in community-based samples such as that used in this study than in memory clinic samples.[47-49]

A significant strength of this study is the measurement of structural brain changes in a large sample of individuals with incident MCI derived from a population-based cohort. A potential weakness of this study is that the features of those who chose to participate in neuroimaging studies may not be reflective of the general population. Another potential limitation is that we performed a large number of comparisons on regional thickness values. However, because this was an exploratory study, we did not want to overly control for false positives at the expense of missing structural brain changes that make conceptual sense and can help guide future studies that focus on hypothesis testing. In addition, cortical thickness provides a measure of neurodegeneration but is not specific for the type(s) of underlying neuropathology. We will continue to follow these individuals longitudinally and examine other biomarkers (ie, cerebrovascular changes, tau) in future studies on this cohort.

AUTHOR CONTRIBUTIONS

MMM: design and conceptualization of the study, data collection, analysis and interpretation of the data, drafting the manuscript, study funding, revising the manuscript. ESL: design and conceptualization of the study, analysis and interpretation of the data, drafting the manuscript, revising the manuscript. SMA: design and conceptualization of the study, analysis and interpretation of the data, drafting the manuscript, revising the manuscript. AJS: analysis of data, revising the manuscript. CS: analysis of data, drafting the manuscript, revising the manuscript. MMM: data collection, analysis and interpretation of the data, revising the manuscript. CRJ: data collection, analysis and interpretation of the data, drafting the manuscript, study funding, revising the manuscript. WKK: analysis and interpretation of the data, drafting the manuscript, study funding, revising the manuscript. PV: revising the manuscript. DSK: data collection, revising the manuscript. DTJ: revising the manuscript. MWB: design and conceptualization of the study, drafting the manuscript, study funding, revising the manuscript. RCP: data collection, analysis and interpretation of the data, drafting the manuscript, study funding, revising the manuscript.

CONFLICTS OF INTEREST

The authors report no disclosures relevant to the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.