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Heterogeneous cortical atrophy patterns in MCI not captured by conventional diagnostic criteria

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ABSTRACT

Objective: We investigated differences in regional cortical thickness between previously identified empirically derived mild cognitive impairment (MCI) subtypes (amnestic MCI, dysnomic MCI, dysexecutive/mixed MCI, and cluster-derived normal) in order to determine whether these cognitive subtypes would show different patterns of cortical atrophy.

Methods: Participants were 485 individuals diagnosed with MCI and 178 cognitively normal individuals from the Alzheimer's Disease Neuroimaging Initiative. Cortical thickness estimates were computed for 32 regions of interest per hemisphere. Statistical group maps compared each MCI subtype to cognitively normal participants and to one another.

Results: The pattern of cortical thinning observed in each MCI subtype corresponded to their cognitive profile. No differences in cortical thickness were found between the cluster-derived normal MCI subtype and the cognitively normal group. Direct comparison between MCI subtypes suggested that the cortical thickness patterns reflect increasing disease severity.

Conclusions: There is an ordered pattern of cortical atrophy among patients with MCI that coincides with their profiles of increasing cognitive dysfunction. This heterogeneity is not captured when patients are grouped by conventional diagnostic criteria. Results in the cluster-derived normal group further support the premise that the conventional MCI diagnostic criteria are highly susceptible to false-positive diagnostic errors. Findings suggest a need to (1) improve the diagnostic criteria by reducing reliance on conventional screening measures, rating scales, and a single memory measure in order to avoid false-positive errors; and (2) divide MCI samples into meaningful subgroups based on cognitive and biomarkers profiles—a method that may provide better staging of MCI and inform prognosis. *Neurology*® 2016;87:2108–2116

GLOSSARY

AD = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **ANCOVA** = analysis of covariance; **CDN** = cluster-derived normal; **CDR** = Clinical Dementia Rating; **MANCOVA** = multivariate analysis of covariance; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **MTL** = medial temporal lobe; **NC** = normal controls; **ROI** = region of interest; **WMS-R** = Wechsler Memory Scale–Revised.

Mild cognitive impairment (MCI), a prodromal state between normal aging and dementia,[1] is typically divided into amnestic or nonamnestic subtypes, with single-domain or multi-domain distinctions.[2,3] A limitation of this conventional classification system is that it combines patients with very different cognitive profiles. Previous research has identified considerable heterogeneity beyond the amnestic/nonamnestic distinction with respect to neuropsychological performance in MCI samples.[4–7] In a recent study,[7] cluster analysis was performed on 825 individuals with MCI from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Although nearly all participants (99.8%) were originally classified simply as amnestic MCI by conventional criteria,[2,8] results showed 4 cognitive phenotypes. This included 3 impaired subtypes: amnestic MCI (34.9%), dysnomic MCI (18.5%), and dysexecutive/mixed MCI (12.5%). A large fourth cluster

Supplemental data at Neurology.org

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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 the ADNI and/or provided data but did not participate in analysis or writing of this article. A complete listing of ADNI investigators can be found at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

(34.2%) was characterized by intact neuropsychological performance. This cluster-derived normal (CDN) group performed within normal limits on all neuropsychological measures examined, despite other performances on screening measures that led to their MCI diagnosis. The existence of this group, which comprises over one-third of the ADNI MCI cohort, indicates that the conventional diagnostic criteria for MCI may be highly susceptible to false-positive errors, especially in light of this group's normal CSF Alzheimer disease (AD) biomarker profiles[7] and normal amyloid imaging scans using florbetapir PET.[9] In addition, longitudinal data over an average of roughly 2 years showed that the CDN group demonstrated a lower rate of progression to AD (10.7%) and a higher rate of reversion to cognitively normal (9.2%) relative to the impaired MCI groups (progression rate 35%–56%; reversion rate 1%–2%).[7]

It has been proposed that individuals with nonamnestic subtypes of MCI will progress to non-AD forms of dementia, such as vascular dementia, dementia with Lewy bodies, or frontotemporal dementia.[2] In the MCI subtypes identified in the ADNI sample,[7] all 3 impaired subtypes demonstrated memory impairment (i.e., there was no nonamnestic group). Of those who progressed to dementia, nearly all received a diagnosis of AD as opposed to another form of dementia. Thus, the amnestic MCI, dysnomic MCI, and dysexecutive/mixed MCI subtypes may represent different stages rather than distinct disease trajectories. Although interest in characterizing MCI subtypes continues to increase, whether ordered patterns of cortical atrophy exist across these cognitive subtypes has not been established. The current study aimed to investigate regional cortical thickness patterns among the empirically derived MCI subtypes.[7]

METHODS Data were obtained from the ADNI database (adni.loni.usc.edu). ADNI is the result of efforts of many coinvestigators from a range of academic institutions and private corporations. Further information about ADNI is available in the e-Methods at Neurology.org or at adni-info.org.

Standard protocol approvals, registrations, and patient consents. The ADNI study was approved by an ethical standards committee on human experimentation at each institution. Written informed consent was obtained from all participants or authorized representatives.

Participants. Participants included all ADNI MCI (n = 825) and normal controls (NC; n = 284) from our original sample.[7] The NC group contained participants who remained classified as cognitively normal for the duration of their participation in the ADNI study (range of 1–7 years of follow-up). Local quality inspection was performed on all 1,109 baseline scans, and high-quality scans (e.g., those without significant motion artifact or poor segmentation; see e-Methods) were identified and included in the sample. The final sample of 663 participants represents 60.1% of the original amnestic MCI group, 60.8% of the original dysnomic MCI group, 60.8% of the original dysexecutive/mixed MCI group, 55.7% of the original CDN group, and 62.7% of the original NC group.

MRI processing and analysis. All image processing and analyses were performed at the Multimodal Imaging Laboratory, University of California, San Diego. Images were downloaded from the ADNI database and processed using FreeSurfer software (v 5.3.0; surfer.nmr.mgh.harvard.edu).[10] Cortical thickness measurements were obtained using well-known and validated procedures, as described previously[11] (also see e-Methods).

Cortical thickness estimates for each individual were computed at each vertex (~1 mm spacing) across the cortical mantle and within 32 gyral-based regions of interest (ROIs) per hemisphere, as described by Desikan et al.[12] Mean thickness for each ROI was calculated by averaging the cortical thickness measurements based on the unsmoothed data within a given ROI.

Statistical analyses. The cluster groups were originally derived using 2 language measures, 2 attention/executive function measures, and 2 memory measures from participants' baseline neuropsychological evaluation[7] (see e-Methods). For the subsample (n = 663) in the current study, differences in clinical and biomarker characteristics were examined using χ^2 analysis, analysis of variance, and analysis of covariance (ANCOVA) adjusted for age and education. Bonferroni-corrected post hoc tests were conducted for significant omnibus tests (corrected for 9 pairwise comparisons; $\alpha = 0.05/9 = 0.006$).

To create statistical group maps for cortical thickness, individual surfaces were resampled into a common spherical coordinate system that aligned cortical folding patterns across participants.[13] The surface maps were compared between NCs and each cluster-derived group using a general linear model. A series of one-way multivariate ANCOVAs (MANCOVAs) was conducted to compare each cluster-derived group separately to the NCs on mean thickness values in the ROIs. We also compared the MCI subtypes to one another using a series of one-way MANCOVAs. Covariates included age, education, sex, and scanner field strength (n = 311 with a 1.5T scan; n = 352 with a 3T scan). Bonferroni correction was applied to each analysis to account for multiple ROI comparisons (corrected for 64 ROI comparisons; $\alpha = 0.05/64 = 0.0008$).

RESULTS **Demographics and neuropsychological performance.** Demographic characteristics are presented in table 1. Mean performance for each group on the 6 neuropsychological measures is shown in table 1 (raw scores) and figure 1 (age- and education-adjusted z scores). Group performance in this subsample (n = 663) is nearly identical to the full original sample (n = 1,109)[7]; see also e-Results.

Performance on diagnostic measures. Three measures are considered in ADNI's diagnosis of MCI: Wechsler Memory Scale–Revised (WMS-R) Logical Memory–II

Table 1 Demographic, neuropsychological, biomarker, and clinical outcome characteristics of the cluster groups and normal control group

	Amnestic MCI (n = 173)	Dysnomic MCI (n = 93)	Dysexecutive/ mixed MCI (n = 62)	Cluster-derived normal (n = 157)	Normal control (n = 178)	*F* or χ^2	Significance, *p* value	Effect size
Demographics[a]								
Age, y	72.6 (6.9)	74.7 (7.1)	73.7 (7.8)	72.4 (8.0)	74.1 (5.2)	$F = 2.7$	0.03	$\eta_p^2 = 0.02$
Education, y	16.1 (2.6)	16.2 (2.9)	14.9 (3.5)	16.2 (2.5)	16.5 (2.6)	$F = 3.9$	0.004	$\eta_p^2 = 0.02$
% Female	38.7	43.0	38.7	41.4	44.9	$\chi^2 = 1.7$	0.79	$\varphi_c = 0.05$
Cognitive measures (raw)[a]								
Animal fluency	16.5 (4.4)	14.4 (4.0)	13.7 (4.2)	20.2 (4.7)	21.1 (5.5)	$F = 57.3$	<0.001	$\eta_p^2 = 0.26$
BNT	27.4 (1.7)	22.5 (2.7)	23.5 (4.7)	28.6 (1.4)	28.2 (2.1)	$F = 157.4$	<0.001	$\eta_p^2 = 0.49$
TMT, part A, s	41.5 (13.1)	37.9 (9.4)	69.8 (27.8)	31.9 (9.7)	33.8 (10.7)	$F = 100.4$	<0.001	$\eta_p^2 = 0.38$
TMT, part B, s	105.0 (38.0)	105.6 (42.4)	247.7 (52.7)	78.5 (24.7)	80.9 (36.6)	$F = 286.3$	<0.001	$\eta_p^2 = 0.64$
AVLT recall	2.0 (2.4)	2.6 (2.8)	2.5 (2.8)	7.0 (4.0)	7.7 (3.8)	$F = 105.0$	<0.001	$\eta_p^2 = 0.39$
AVLT recognition	9.0 (3.2)	9.7 (3.3)	9.0 (3.8)	13.1 (1.7)	13.0 (2.2)	$F = 82.4$	<0.001	$\eta_p^2 = 0.33$
Diagnostic measures (raw)[a]								
MMSE	27.5 (1.8)	26.9 (1.8)	26.8 (1.7)	28.3 (1.5)	29.1 (1.0)	$F = 48.4$	<0.001	$\eta_p^2 = 0.23$
CDR-sum of boxes	1.6 (0.9)	1.6 (0.9)	1.8 (0.9)	1.2 (0.7)	0.0 (0.1)	$F = 12.1$[b]	<0.001	$\eta_p^2 = 0.07$
LM II recall	4.9 (3.2)	4.3 (3.3)	3.8 (3.3)	7.5 (2.8)	13.6 (3.3)	$F = 243.9$	<0.001	$\eta_p^2 = 0.60$
CSF[c]**/genetic**[d] **biomarkers**								
% High p-tau$_{181p}$	59.8	67.3	86.1	40.2	32.4	$\chi^2 = 44.3$	<0.001	$\varphi_c = 0.35$
% Low A$\beta_{1\text{-}42}$	70.7	59.2	86.1	35.9	37.3	$\chi^2 = 49.1$	<0.001	$\varphi_c = 0.36$
% High p-tau$_{181p}$/A$\beta_{1\text{-}42}$	70.7	73.5	88.9	41.3	40.2	$\chi^2 = 48.4$	<0.001	$\varphi_c = 0.36$
% *APOE* ε4 carriers	62.6	52.7	54.8	39.1	26.6	$\chi^2 = 52.4$	<0.001	$\varphi_c = 0.28$
Clinical outcome[e]								
% Progression to AD	36.0	39.8	53.2	12.9	—	$\chi^2 = 41.2$	<0.001	$\varphi_c = 0.30$
% Reversion to normal	1.2	2.4	1.6	10.2	—	—	—	—
Length of follow-up, mo	22.5 (18.8)	24.6 (18.8)	21.3 (18.1)	27.7 (22.7)	—	$F = 2.3$	0.07	$\eta_p^2 = 0.02$

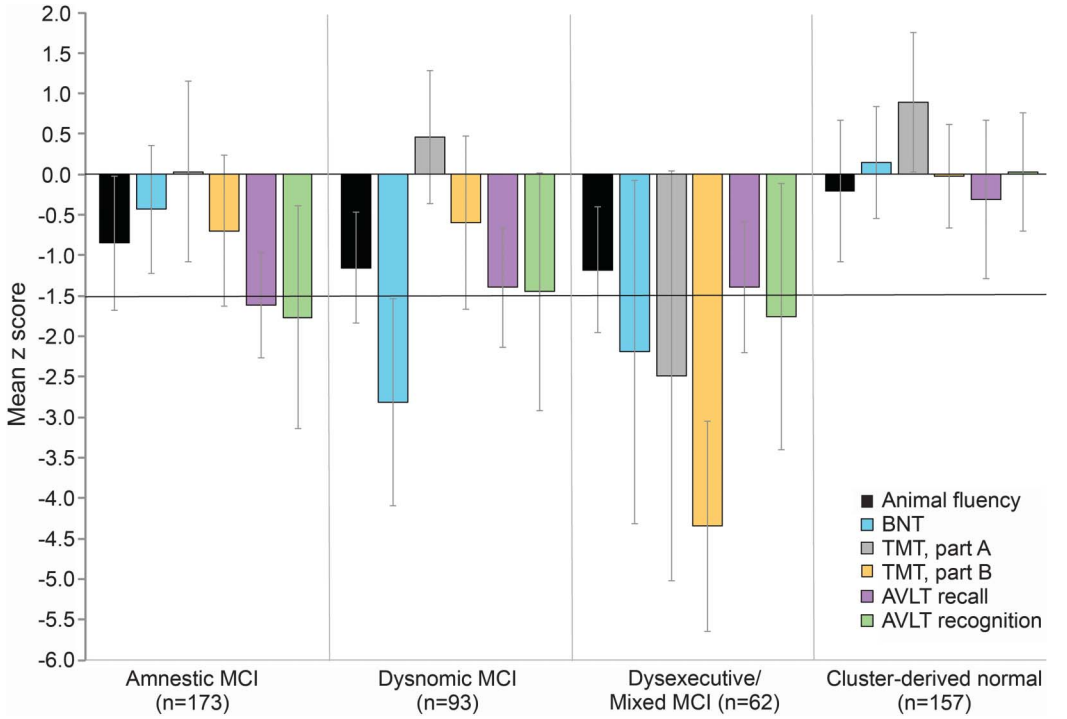
Abbreviations: A$\beta_{1\text{-}42}$ = β-amyloid; AVLT = Rey Auditory Verbal Learning Test; BNT = Boston Naming Test; CDR = Clinical Dementia Rating; LM = Logical Memory; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; p-tau$_{181p}$ = hyperphosphorylated tau; TMT = Trail-Making Test.
[a] Data are mean (SD), unless otherwise indicated.
[b] Normal controls were not included in the *F* test for CDR-sum of boxes, given the small SD relative to the other groups.
[c] Number of participants for CSF analysis: amnestic: n = 92, dysnomic: n = 49, dysexecutive/mixed: n = 36, cluster-derived normal: n = 92, normal control: n = 102.
[d] Number of participants for *APOE* analysis: amnestic: n = 171, dysnomic: n = 91, dysexecutive/mixed: n = 62, cluster-derived normal: n = 156, normal control: n = 177.
[e] Number of participants with follow-up data for clinical outcome analyses: amnestic: n = 164, dysnomic: n = 83, dysexecutive/mixed: n = 62, cluster-derived normal: n = 147. The normal controls were not included in the progression analyses since individuals this group were selected on the basis of remaining cognitively normal (did not progress/revert) throughout the course of their participation in the Alzheimer's Disease Neuroimaging Initiative.

Story A, Mini-Mental State Examination (MMSE), and Clinical Dementia Rating scale (CDR). There were no differences on these measures among amnestic, dysnomic, and dysexecutive/mixed MCI. However, all 3 groups scored worse than the CDNs and the NCs ($p < 0.001$). The CDN group also scored worse than the NCs on ADNI's diagnostic measures ($p < 0.001$), which accounts for their original MCI classification.[7]

Biomarker characteristics and longitudinal clinical outcomes. Table 1 shows the prevalence of abnormal CSF biomarkers (based on established cutpoint concentrations[14]), *APOE* genotype, and progression/regression rates for the subsample. There were no differences among the amnestic, dysnomic, and dysexecutive/mixed MCI groups in CSF biomarkers or *APOE* status; there were also no significant differences between the CDNs and NCs (see also e-Results). The CDN group showed the lowest rate of progression to AD and highest rate of reversion to normal. These biomarker and progression results are similar to findings in the original full sample.[7]

Regional cortical thickness patterns relative to NCs. Significant differences in regional cortical thickness

Figure 1 Neuropsychological performance for the cluster groups



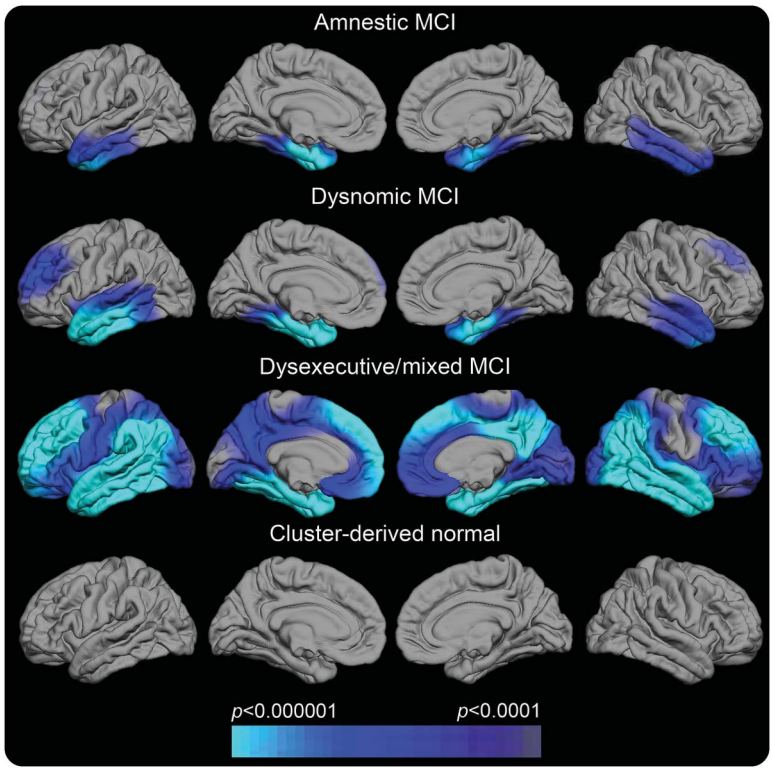
Mean *z* scores for the cluster groups on neuropsychological measures included in the cluster analysis. Error bars denote SDs. The horizontal dotted line indicates the typical cutoff for impairment (−1.5 SDs). AVLT = Rey Auditory Verbal Learning test; BNT = Boston Naming Test; MCI = mild cognitive impairment; TMT = Trail-Making Test.

between each cluster-derived MCI subtype relative to the NCs are displayed at the vertex-wise level on the lateral and medial surface maps in figure 2, and at the ROI level in table 2. (See table e-1 for cortical thickness values for all 32 ROIs per hemisphere.) For amnestic MCI, thinning was observed primarily in medial and lateral temporal lobe regions bilaterally ($p < 0.0001$). Additional atrophy was seen in some parietal and frontal regions ($p < 0.0008$); these findings reached significance in the ROI analyses but were subthreshold on the surface maps. The dysnomic MCI group demonstrated thinning primarily in medial and lateral temporal lobe regions ($p < 0.0001$), with greater atrophy in the left lateral temporal cortex relative to the right (comparison of left vs right lateral temporal ROIs: $t[92] = 6.18$, $p < 0.0001$, $d = 0.64$), as well as atrophy in frontal lobe regions ($p < 0.0001$). For dysexecutive/mixed MCI, a widespread pattern of cortical thinning was observed including atrophy in frontal, temporal, parietal, and cingulate cortices bilaterally ($p < 0.0001$), with relative sparing of occipital and paracentral regions. There were no significant differences between the CDNs and the NCs.

Regional cortical thickness comparisons among MCI subtypes. Significant differences in regional cortical thickness between the amnestic MCI and dysexecutive/mixed MCI groups are displayed at the vertex-wise level in figure 3. ROI analyses showed that the dysexecutive/mixed MCI group had greater cortical thinning relative to the amnestic MCI group in frontal (left caudal middle frontal gyrus), lateral temporal (left superior temporal gyrus, left middle temporal gyrus, left inferior temporal gyrus), and parietal regions (left supramarginal gyrus, left and right inferior parietal cortex, and right precuneus); all *p*s < 0.0008. No significant differences were found between amnestic vs dysnomic MCI, or between dysnomic vs dysexecutive/mixed MCI, once Bonferroni correction was applied. In comparison to the CDN group, the amnestic MCI and dysnomic MCI groups demonstrated thinning in medial and lateral temporal lobe regions; see table 2. The dysexecutive/mixed MCI group showed atrophy primarily in frontal, temporal, and parietal cortices relative to the CDN group; see table 2.

DISCUSSION This study examined patterns of cortical atrophy in empirically derived MCI subtypes. Findings revealed heterogeneous patterns of cortical thinning in MCI participants that are not captured by conventional diagnostic criteria. Importantly, the pattern of cortical thinning observed for each subtype corresponded to their cognitive profile, suggesting that cognitive impairments accumulate in a systematic manner that is commensurate with the accumulation

Figure 2 Regional cortical thickness maps for the cluster groups relative to normal controls



Regional cortical thickness on the left and right lateral and medial pial surfaces for each cluster-derived group relative to the normal control (NC) group (n = 178). The scale indicates group differences in cortical thickness at $p < 0.0001$. The cyan/blue shades represent areas where the MCI subgroup has thinner cortex than NCs. MCI = mild cognitive impairment.

of region-specific atrophy. Consistent with their isolated deficits in episodic memory, the amnestic MCI group showed significant medial temporal lobe (MTL) thinning. These findings provide an important anchoring of our results to previous studies,[15,16] and validation of cluster analytic techniques for identifying reliable cognitive phenotypes. In the dysnomic MCI group, the finding of lateral temporal lobe atrophy with greater left hemisphere involvement is consistent with the observed naming deficit. Although language was their primary impairment, the dysnomic MCI group also demonstrated poor memory, which fits with their thinning in MTL. A previous study examining patterns of gray matter atrophy in MCI[17] demonstrated similar results, with atrophic changes predominantly affecting the left MTL in a language-impaired subgroup of nonamnestic MCI. Findings also dovetail with another study[18] that found gray matter loss in bilateral temporal regions as well as frontal and subcortical regions in a language variant of nonamnestic MCI. The dysnomic MCI subtype may represent a more intermediate stage of cognitive decline consistent with the Braak staging scheme in which stages III and IV begin to demonstrate neurofibrillary tangles spreading from entorhinal/medial temporal cortex to adjacent inferolateral temporal and frontal cortices.

The dysexecutive/mixed MCI group exhibited a fairly widespread pattern of atrophy. This reflects their neuropsychological profile, which is characterized by poor performance across all cognitive domains tested. These finding are consistent with those of a previous study[19] that found greater cortical thinning in superior and lateral frontoparietal regions in a dysexecutive-predominant MCI subgroup relative to memory impairment-predominant participants. Our findings in the dysexecutive/mixed MCI group also corroborate previous studies of multidomain amnestic MCI. In addition to bilateral MTL atrophy, multidomain amnestic MCI typically involves widespread thinning within parietal, temporal, and frontal regions.[17,18,20,21] However, the pattern of thinning in the dysexecutive/mixed MCI group was less consistent with previous studies of the conventional nonamnestic MCI subtype, in which heterogeneous patterns of gray matter loss and less MTL focus have been noted.[17,18] The current study did not include a purely dysexecutive group, as all subtypes demonstrated memory impairment, limiting our ability to examine nonamnestic forms of MCI. The dysexecutive/mixed MCI group would be expected to have even more Braak staging-related pathology compared to the amnestic MCI and dysnomic MCI subtypes, given the severity of their cognitive impairments and the widespread distribution of cortical thinning.

Perhaps our most striking and novel finding was the lack of difference in cortical thickness between the CDNs and the NCs in any ROI examined. In addition, there were significant differences between the CDNs and the 3 impaired MCI subtypes, paralleling the neuropsychological differences found between CDNs and other MCI groups. The normal cortical thickness profile in the CDN group is consistent with their intact cognitive performance coupled with our previous findings that these individuals evidenced CSF AD biomarker profiles that did not differ from the normative reference group, had low rates of progression to AD relative to the other empirically derived groups, and were equally as likely to revert to cognitively normal as they were to progress to dementia.[7] Taken together, these findings offer additional support for the premise that conventional diagnostic criteria are susceptible to a high rate of false-positive diagnostic errors. Given that the CDN group comprises roughly one-third of ADNI's total MCI sample, including these individuals in research studies of MCI will undoubtedly weaken or obscure meaningful findings. Indeed, we have shown that removing these false-positive diagnoses by applying a novel actuarial diagnostic method[22] to ADNI's MCI cohort results in stronger relationships between cognition, biomarkers, and rates of progression to AD.[23]

Table 2 Cortical thickness values for the cluster-derived mild cognitive impairment (MCI) subtypes and normal controls in regions of interest with significant differences

	Amnestic MCI	Dysnomic MCI	Dysexecutive/ mixed MCI	Cluster-derived normal	Normal controls
Frontal					
LH superior frontal gyrus	2.50[a] (0.15)	2.46[b] (0.15)	2.42[b] (0.14)	2.52 (0.16)	2.55 (0.15)
LH rostral middle frontal gyrus	2.15[a] (0.14)	2.12[b] (0.14)	2.07[b,d] (0.15)	2.19 (0.14)	2.21 (0.14)
LH caudal middle frontal gyrus	2.34 (0.16)	2.33 (0.17)	2.24[b,d] (0.15)	2.38 (0.17)	2.39 (0.16)
LH pars orbitalis	2.48 (0.22)	2.50 (0.21)	2.43[a] (0.18)	2.54 (0.22)	2.55 (0.22)
LH medial orbitofrontal cortex	2.21 (0.16)	2.20 (0.16)	2.14[b,d] (0.15)	2.24 (0.15)	2.26 (0.14)
RH superior frontal gyrus	2.48 (0.16)	2.45[b] (0.15)	2.42[b] (0.13)	2.50 (0.15)	2.53 (0.15)
RH rostral middle frontal gyrus	2.14 (0.15)	2.12[a] (0.14)	2.07[b] (0.14)	2.15 (0.15)	2.19 (0.14)
RH caudal middle frontal gyrus	2.33[a] (0.17)	2.31[b] (0.16)	2.26[b] (0.16)	2.35 (0.17)	2.39 (0.16)
RH pars opercularis	2.39 (0.19)	2.40 (0.17)	2.33[a] (0.16)	2.44 (0.16)	2.44 (0.14)
RH pars orbitalis	2.49 (0.20)	2.49 (0.22)	2.40[b] (0.23)	2.48 (0.20)	2.53 (0.20)
RH medial orbitofrontal cortex	2.19 (0.17)	2.17[a] (0.15)	2.16[a] (0.17)	2.22 (0.19)	2.24 (0.15)
Medial temporal					
LH entorhinal cortex	3.09[b,d] (0.47)	2.90[b,d] (0.54)	3.05[b] (0.46)	3.30 (0.42)	3.35 (0.31)
LH parahippocampal gyrus	2.49[a] (0.37)	2.44[b] (0.40)	2.43[b] (0.34)	2.63 (0.37)	2.63 (0.33)
LH fusiform gyrus	2.51[b] (0.19)	2.46[b] (0.22)	2.40[b,d] (0.20)	2.58 (0.17)	2.58 (0.15)
LH temporal pole	3.43[b] (0.33)	3.31[b,d] (0.44)	3.39[a] (0.38)	3.54 (0.30)	3.57 (0.29)
RH entorhinal cortex	3.22[b,d] (0.54)	3.10[b,d] (0.57)	3.17[b,c] (0.53)	3.48 (0.44)	3.52 (0.34)
RH parahippocampal gyrus	2.49 (0.34)	2.44 (0.35)	2.41[b] (0.35)	2.63 (0.33)	2.59 (0.29)
RH fusiform gyrus	2.52[b] (0.18)	2.50 (0.21)	2.41[b,d] (0.22)	2.61 (0.19)	2.59 (0.17)
RH temporal pole	3.53[b] (0.36)	3.45[b] (0.44)	3.48[b] (0.39)	3.64 (0.35)	3.70 (0.30)
Lateral temporal					
LH superior temporal gyrus	2.55[b] (0.18)	2.47[b,d] (0.23)	2.42[b,d] (0.19)	2.62 (0.17)	2.61 (0.16)
LH middle temporal gyrus	2.63[b,c] (0.18)	2.56[b] (0.22)	2.52[b,d] (0.20)	2.72 (0.16)	2.72 (0.14)
LH inferior temporal gyrus	2.60[b] (0.19)	2.54[b] (0.21)	2.48[b,d] (0.18)	2.65 (0.18)	2.66 (0.14)
LH banks superior temporal sulcus	2.27 (0.20)	2.21[b,c] (0.22)	2.15[b,d] (0.24)	2.35 (0.18)	2.33 (0.17)
RH superior temporal gyrus	2.58[a] (0.19)	2.53[b] (0.19)	2.49[b] (0.18)	2.62 (0.18)	2.64 (0.16)
RH middle temporal gyrus	2.66[b] (0.19)	2.64[b] (0.20)	2.56[b,d] (0.20)	2.72 (0.16)	2.75 (0.14)
RH inferior temporal gyrus	2.62[b] (0.19)	2.59[b] (0.21)	2.53[b,d] (0.18)	2.69 (0.18)	2.69 (0.15)
RH banks superior temporal sulcus	2.38[a] (0.20)	2.34[b] (0.22)	2.27[b,c] (0.25)	2.44 (0.17)	2.45 (0.16)
Parietal					
LH supramarginal gyrus	2.32[a] (0.17)	2.30[a] (0.18)	2.21[b,d] (0.17)	2.38 (0.18)	2.38 (0.14)
LH superior parietal cortex	1.99 (0.16)	1.95 (0.18)	1.91[b] (0.18)	2.03 (0.17)	2.02 (0.14)
LH inferior parietal cortex	2.20[a] (0.16)	2.18 (0.19)	2.08[b,d] (0.20)	2.26 (0.15)	2.25 (0.14)
LH precuneus cortex	2.11[a] (0.16)	2.09 (0.20)	2.02[b,d] (0.19)	2.18 (0.16)	2.17 (0.14)
RH supramarginal gyrus	2.33 (0.17)	2.31 (0.17)	2.25[b] (0.17)	2.36 (0.17)	2.37 (0.15)
RH superior parietal cortex	1.98 (0.16)	1.94 (0.18)	1.90[b] (0.16)	2.02 (0.17)	2.02 (0.15)
RH inferior parietal cortex	2.21[b] (0.17)	2.20 (0.19)	2.11[b,d] (0.18)	2.26 (0.17)	2.28 (0.14)
RH precuneus cortex	2.14[b] (0.16)	2.13 (0.17)	2.04[b,d] (0.17)	2.21 (0.16)	2.20 (0.15)
Occipital					
LH lingual gyrus	1.80 (0.15)	1.76 (0.15)	1.71[b,c] (0.13)	1.83 (0.15)	1.80 (0.13)
RH lateral occipital cortex	2.00 (0.16)	1.99 (0.18)	1.91[b,c] (0.19)	2.06 (0.17)	2.03 (0.16)

Continued

Table 2 Continued

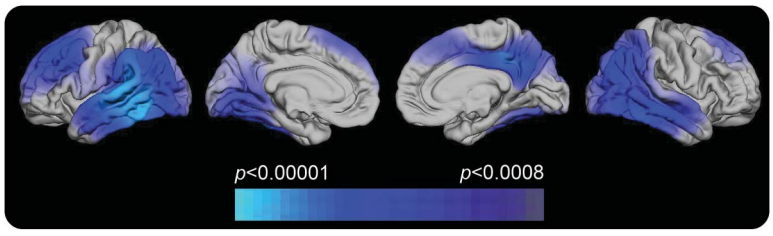
	Amnestic MCI	Dysnomic MCI	Dysexecutive/ mixed MCI	Cluster-derived normal	Normal controls
Cingulate					
LH posterior cingulate cortex	2.29 (0.17)	2.32 (0.18)	2.23[a] (0.21)	2.35 (0.17)	2.33 (0.16)
LH isthmus cingulate cortex	2.21 (0.21)	2.17 (0.23)	2.10[a] (0.24)	2.26 (0.22)	2.24 (0.22)
RH posterior cingulate cortex	2.27 (0.17)	2.27 (0.18)	2.18[b,c] (0.19)	2.31 (0.16)	2.30 (0.15)
RH isthmus cingulate cortex	2.18 (0.20)	2.13 (0.21)	2.06[b] (0.23)	2.23 (0.23)	2.21 (0.20)

Abbreviations: LH = left hemisphere; RH = right hemisphere.
Data are summarized as mean (SD).
[a] Mean is significantly different from normal controls at $p < 0.0008$.
[b] Mean is significantly different from normal controls at $p < 0.0001$.
[c] Mean is significantly different from cluster-derived normals at $p < 0.0008$.
[d] Mean is significantly different from cluster-derived normals at $p < 0.0001$.

Another notable finding from the current study was the lack of difference between the impaired MCI subtypes on the 3 measures used by ADNI to arrive at an MCI diagnosis, despite significant variability in cortical atrophy profiles. All groups performed comparably on the MMSE and WMS-R Logical Memory. On the CDR, participants in all 3 impaired MCI groups were given a global CDR score of 0.5, and their scores on the CDR sum of boxes also did not differ from one another. Based on these measures alone, it appears that these individuals represent a homogenous sample of MCI participants. However, it is clear from the cortical thickness maps and performance on the neuropsychological battery (e.g., naming; executive function) that there is substantial cognitive and neuropathologic heterogeneity within the sample. The dysexecutive/mixed MCI group, in particular, demonstrated greater severity in neuropsychological deficits and more widespread cortical thinning. One might expect that individuals in this more impaired group would also show poorer scores on the diagnostic measures, or perhaps even be classified as having early AD. Instead, their scores are comparable to the less impaired MCI groups and, even more concerning, fall into the same general range as the nonimpaired CDN group. Limitations of the CDR have been described previously, including one study[24] which found that global CDR scores of 0.5 masked variability within an MCI sample in terms of functional abilities, cognitive test performance, cortical thinning in frontal and parietal lobe regions, and rates of progression to dementia. ADNI has expanded its diagnostic scheme by classifying participants as either early MCI or late MCI (determined by the WMS-R Logical Memory). However, the data suggest that these labels do not improve clarity or accuracy of the diagnosis, as 42% of the CDN group was classified as late MCI, and 20% of the dysexecutive/mixed MCI group was considered early MCI. Our data suggest that these coarse diagnostic measures are not capturing the variability in biomarkers or cognitive profiles that exists within MCI. Nonetheless, the conventional diagnostic criteria for MCI are routinely used in large-scale research studies, clinical trials, and clinical practice.

Our findings of substantial variability in MCI are consistent with those from a study[25] that used cluster analysis to identify biomarker profiles in the ADNI MCI cohort. Results of that study revealed 4 unique clusters based on 11 biological variables (e.g., cortical thinning, CSF values, white matter hyperintensities). One cluster showed the poorest biomarker profile, with means similar to the AD group on some measures, and significant cognitive decline longitudinally. A healthy cluster group was also identified which had biomarkers similar to the NC group and showed stable or improved cognitive performance over time. These 2 clusters from this previous study[25] appear remarkably similar to our dysexecutive/mixed MCI group and CDN group, respectively. These complementary methodologies provide compelling evidence for the enormous diversity of cognitive and biomarker profiles in samples classified as MCI based on conventional criteria. Considerable heterogeneity exists not only at the level of MCI, but even within autopsy-confirmed AD, as one study[26] found that 2 atypical variants—coined limbic-predominant

Figure 3 Regional cortical thickness maps for dysexecutive/mixed mild cognitive impairment (MCI) relative to amnestic MCI



Regional cortical thickness on the left and right lateral and medial pial surfaces for dysexecutive/mixed MCI relative to amnestic MCI. The scale indicates group differences in cortical thickness at $p < 0.0008$. The blue/purple shades represent areas where dysexecutive/mixed MCI has thinner cortex than amnestic MCI.

and hippocampal-sparing subtypes—accounted for 25% of AD cases. Thus, better characterization of MCI subtypes may be critical not only for staging MCI severity, but perhaps also for identifying individuals with different underlying variants of AD.

In the current study, the comparison of each MCI subgroup to the NCs suggested a differential pattern of cortical thinning for each MCI subgroup. However, direct comparison between the MCI subtypes only partially confirmed this impression and more strongly suggested an ordered pattern of cortical atrophy. Specifically, cortical thickness patterns across the 3 impaired MCI groups appear to reflect increasing disease severity within the MCI cohort—from mild (amnestic) to severe (dysexecutive/mixed), with a possible intermediate moderate stage (dysnomic). This is consistent with the behavioral data showing increasing neuropsychological impairment across groups. While results suggest our group differences are likely more quantitative than qualitative in nature, the word "subtype" is used to remain consistent with existing MCI literature that makes similar distinctions (e.g., single-domain vs multi-domain amnestic MCI subtypes) for patients along a disease continuum.

The presence of heterogeneous cortical atrophy patterns in our empirically derived MCI subtypes suggests a strong need to (1) improve the diagnostic criteria by reducing reliance on conventional screening measures, rating scales, and a single memory measure in order to avoid false-positive errors; and (2) divide MCI samples into meaningful subgroups based on cognitive and biomarkers profiles—a method that may provide better staging of MCI and inform prognosis. A limitation of this study is the lack of assessment of visuospatial functioning, as early visuospatial deficits may be indicative of prodromal AD. The possibility of type II error is also a consideration, given our rigorous threshold for statistical significance. Notable strengths of the study include the large number of MRI scans that were analyzed, and careful manual inspection locally with rigorous quality control procedures in order to ensure optimal quality of all imaging data. A future direction of this line of research will be to examine changes in cortical thickness longitudinally in our CDN group and each cognitive subtype in order to determine how changes are related to risk of progression to dementia. Information gleaned from such studies could have important clinical utility, as knowledge of regional cortical thickness and cognitive profiles could be useful for establishing the diagnosis or stage of MCI, or for predicting prognosis at an individual level.

AUTHOR CONTRIBUTIONS

E.C.E.: study concept and design, analysis and interpretation of data, drafting/revising the manuscript for content, acquisition of data, statistical analysis. J.E.: analysis and interpretation of data, drafting/revising the manuscript for intellectual content. M.W.B.: study concept and design, analysis and interpretation of data, drafting/revising the manuscript for intellectual content, obtained funding. K.M.L.: analysis and interpretation of data, drafting/revising the manuscript for intellectual content. B.G.: analysis and interpretation of data. L.D.-W.: study concept and design, analysis and interpretation of data, drafting/revising the manuscript for intellectual content. C.R.M.: study concept and design, analysis and interpretation of data, drafting/revising the manuscript for intellectual content, study supervision and coordination, obtained funding.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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