Clinical-Neuroimaging Characteristics of Dysexecutive Mild Cognitive Impairment

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Objective: Subgroups of mild cognitive impairment (MCI) have been proposed, but few studies have investigated the nonamnestic, single-domain subgroup of MCI. The goal of the study was to compare clinical and neuroimaging characteristics of two single-domain MCI subgroups: amnestic MCI and dysexecutive MCI.

Methods: We compared the cognitive, functional, behavioral, and brain imaging characteristics of patients with amnestic MCI (n = 26), patients with dysexecutive MCI (n = 32), and age- and education-matched control subjects (n = 36) using analysis of variance and χ^2 tests. We used voxel-based morphometry to examine group differences in brain magnetic resonance imaging atrophy patterns.

Results: Patients with dysexecutive MCI had significantly lower scores on the majority of executive function tests, increased behavioral symptoms, and left prefrontal cortex atrophy on magnetic resonance imaging when compared with control subjects. In contrast, patients with amnestic MCI had significantly lower scores on tests of memory and a pattern of atrophy including bilateral hippocampi and entorhinal cortex, right inferior parietal cortex, and posterior cingulate gyrus when compared with control subjects.

Interpretation: Overall, the clinical and neuroimaging findings provide support for two distinct single-domain subgroups of MCI, one involving executive function and the other involving memory. The brain imaging differences suggest that the two MCI subgroups have distinct patterns of brain atrophy.

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Mild cognitive impairment (MCI) refers to a decline in cognition in older adults that is not of sufficient magnitude to meet criteria for dementia. Early studies focused on MCI patients with predominant memory impairment and the risk for progression to Alzheimer's disease (AD).[1] Recent studies, however, suggest that MCI is a clinically heterogeneous syndrome,[2] and the prodromal stage of several neurodegenerative disorders may begin with nonamnestic cognitive decline.[3] In 2003, an international working group expanded the concept of MCI and proposed subgroups based on patterns of cognitive impairment.[4,5] This classification system broadly differentiates four MCI subgroups: amnestic (single and multiple domain) and nonamnestic (single and multiple domain).

Few studies have investigated nonamnestic presentations of MCI, which is defined as either a predominant impairment in one nonmemory cognitive domain (eg, executive function, language, or visuospatial skills) or impairment in multiple, nonamnestic domains. Estimates of nonamnestic single-domain MCI range from 7 to 14% in MCI patients.[6,7] Yaffe and colleagues[8] found that single-domain, nonamnestic MCI patients were less likely to convert to dementia but had greater rates of death over 5 years than amnestic MCI (aMCI) patients. Several authors hypothesize that the subgroups will have different causative factors and outcomes.[4,7] Clinical studies have been used to distinguish MCI subgroups, but few studies have evaluated brain atrophy patterns. Thus, the goal of this study was to prospectively investigate the clinical and neuroimaging characteristics of two single-domain MCI subgroups, dysexecutive MCI (dMCI) and aMCI. Based on previous finding that AD patients with disproportionate impairment on executive functioning had greater-than-expected neuropathology in the frontal cortex,[9] we hypothesized that MCI patients with isolated executive dysfunction would have atrophy of the frontal cortex,

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whereas MCI patients with prominent memory impairment would have temporoparietal atrophy.

Subjects and Methods

Subjects and Diagnostic Procedure

The subjects were recruited prospectively for a study about MCI subgroups. Subjects were referred from the University of California, San Francisco Memory and Aging clinic or from a community screening clinic (where subjects responded to a newspaper advertisement). The clinic and community subjects had identical evaluations. Healthy control subjects were recruited through the community screening clinic and received the same evaluation as patients. All subjects were diagnosed after an extensive clinical evaluation including a detailed history, physical, and neurological examination, including the Unified Parkinson's Disease Rating Scale–Part III Motor Scale,[10] neuropsychological screening, and study partner interview. Study partners had regular contact and knew the subject for at least 10 years. As a part of the neurological examination, all subjects and study partners were queried about the first and current symptoms. We categorized the first and current symptoms as follows: (1) memory, (2) executive, (3) behavioral, (4) language, (5) visuospatial, (6) motor, and (7) other. The 1-hour neuropsychological screening battery assessed multiple domains of cognition, including memory, executive function, language, and visuospatial skills.[11] The interview with the study partner involved the Clinical Dementia Rating (CDR)[12] to assess functional abilities and the Neuropsychiatric Inventory to evaluate behavior.[13] Screening for depression was done using the 30-item Geriatric Depression Scale[14] (self-report) and an interview with the study partner. Diagnosis was determined by consensus involving the neurologist, neuropsychologist, and nurse using only the diagnostic information described earlier.

Subjects were excluded if they met criteria for dementia (*Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition [DSM-IV]),[15] a history of a neurological disorder, current psychiatric illness, head trauma with loss of consciousness greater than 10 minutes, severe sensory deficits, substance abuse, or were taking medications that affect cognition. In addition, subjects with significant vascular lesions on brain magnetic resonance imaging (MRI), defined as a Longstreth[16] grade ≥ 4 (of 8), were excluded. The control subjects included in the study underwent an identical evaluation to the MCI patients and had a CDR of zero and a Mini-Mental State Examination[17] score ≥ 28. All control subjects scored within the reference range (within one standard deviation [SD]) on neuropsychological testing. Patients diagnosed with MCI were further classified according to the predominant domain(s) of cognitive impairment using the recently proposed MCI diagnostic scheme.[5] Two single-domain MCI groups were included in this study: aMCI and dMCI. We used a 10th percentile cutoff (1.28 SDs), which has been used in other studies of nonamnestic MCI patients,[7] to determine the primary cognitive domain of impairment. Patients were classified as dMCI with relatively focal executive dysfunction, which was operationally defined as scores at or below the 10th percentile of control performance on at least one of four screening tests of executive function (ie, modified Trail Making Test B, modified Stroop interference, number of D words in 1 minute, or abstractions).[11] In addition, patients with dMCI had to score within the reference range (within one SD from norms mean) on tests of memory (ie, 20-minute delayed recall or recognition on California Verbal Learning Test (CVLT)[18] and 10-minute recall of modified Rey–Osterrieth figure), language (ie, 15-item Boston Naming Test[19] or syntax comprehension), and visuospatial skills (ie, copy of modified Rey–Osterrieth figure and Number Location subtest from The Visual Object and Space Perception Battery.[20] In contrast, patients were classified as aMCI if scores were at or below the 10th percentile on the screening tests of memory (described earlier) and within the reference range on tests of executive function, language, and visuospatial skills. The study sample included 32 patients with dMCI, 26 with aMCI, and 36 healthy control subjects.

The following outcome measures were also collected but were not used in diagnosis. Within 3 months of the diagnostic visit, 1.5-Tesla MRI of the brain was completed. We obtained apolipoprotein E *(ApoE)* genotypes though the Alzheimer's Disease Research Center. All informants completed additional measures of behavior and instrumental activities of daily living (IADLs). We used the informant-based Dysexecutive Questionnaire (DEX)[21] and the Frontal Behavioral Inventory (FBI)[22] to evaluate dysexecutive symptoms. The DEX is a 20-item questionnaire that assesses the frequency of dysexecutive symptoms in everyday living (eg, distractibility, impulsivity, difficulty planning) on a four-point scale (from "never" to "very often"), with greater scores reflecting more dysexecutive symptoms. The DEX has been validated in patients with brain injury and behavioral symptoms.[23] We administered the DEX to the study partner. The informant-based FBI is a 24-item questionnaire designed to measure behavior in patients with frontotemporal dementia. The Functional Activities Questionnaire[24] was used to assess IADLs.

Statistical Methods for Clinical Data

An analysis of variance was used, together with Tukey's honestly significant difference pairwise post hoc comparisons, to evaluate possible group differences in clinical variables. A χ^2 test was used to assess differences in sex and *ApoE* status. We used Statistical Package for the Social Sciences 16.0 to conduct the statistical analysis.

Brain Magnetic Resonance Imaging and Voxel-Based Morphometry

MAGNETIC RESONANCE IMAGE ACQUISITION.

Images were collected on a Siemens Vision 1.5-Tesla MRI scanner (Siemens, Iselin, NJ). T1-weighted, three-dimensional, magnetization-prepared rapid acquisition gradient-echo images were acquired (TI/TR/TE = 300/9.7/4 milliseconds); flip angle = 15 degrees; field of view = $256 \times 256\text{mm}^2$ with $1.0 \times 1.0\text{mm}^2$ inplane resolution; 154 partitions with 1.5mm slice thickness).

IMAGING DATA ANALYSIS.

Voxel-based morphometry (VBM) analysis was performed on the T1-weighted images using Statistical Parametric Mapping (SPM5) software (Wellcome Department of Imaging Neuroscience, University College London, London, UK;

Table 1. **Demographic and Screening Results**

Characteristics	Control Subjects	aMCI Patients	dMCI Patients	*p*
n	36	26	32	NA
Mean age (SD), yr	64.8 (8.2)	68.0 (6.6)	63.8 (7.8)	0.099
Sex, M/F	13/23	13/13	20/12	0.094[a]
Mean education (SD), yr	17.0 (2.0)	17.5 (1.7)	17.1 (2.7)	0.631
Mean CDR-sum of boxes (maximum 18) (SD)	0	1.1 (1.0)[b]	1.3 (0.9)[b]	<0.0001
Mean Geriatric Depression Scale (maximum 30) score (SD)	2.6 (2.9)	5.5 (4.3)[b]	5.0 (5.0)	0.014
Mean UPDRS-III score (SD)	0.8 (1.7)	1.3 (2.4)	3.7 (6.4)[b]	0.036
Frequency of ApoE ε4 allele carriers	12%	52%	37%	0.005[a]

Statistical results from an analysis of variance test.
[a]*p* value from a χ^2 statistic.
[b]Different from control subjects, Tukey's honestly significant difference post hoc comparison, $p < 0.05$.
aMCI = amnestic mild cognitive impairment; dMCI = dysexecutive mild cognitive impairment; NA = not applicable; SD = standard deviation; CDR = Clinical Dementia Rating; UPDRS = Unified Parkinson's Disease Rating Scale; ApoE = apolipoprotein.

www.fil.ion.ucl.ac.uk) implemented within Matlab 7 (MathWorks, Natick, MA). SPM5 uses a unified segmentation process in which image registration, tissue classification, and bias correction are combined making the need to perform "optimized VBM" unnecessary.[25] Furthermore, in SPM5, prior probability maps that are relevant to tissue segmentation are warped to the individual brains, eliminating the need for a study-specific template.[26] All images were normalized, modulated, and segmented images in Montreal Neurological Institute stereotactic space using the default International Consortium for Brain Mapping template. We applied an isotropic Gaussian smoothing kernel of 12mm full-width at half-maximum to minimize individual anatomical variability and reduce the chance of false-positive results.[27] All images were reviewed before statistical analysis to ensure quality of the segmentation process.

The preprocessed images were passed up to voxel-wise statistical comparison. We first investigated differences in patterns of gray matter (GM) atrophy between the MCI subgroups and control subjects using SPM5. Based on previous studies[28–30] and our hypotheses that dMCI patients would have frontal atrophy and aMCI would have medial temporal atrophy, we identified five a priori regions of interest (ROIs) that included the left superior and middle frontal gyri, medial temporal lobe, posterior cingulate gyrus, and precuneus/parietal cortex. We created ROI-based masks using the aal atlas in the Wake Forest University (WFU) Pickatlas toolbox.[31] All ROIs were assessed at the $p < 0.05$, family-wise error rate (FWE)–corrected threshold. To eliminate selection bias, we also applied each ROI mask to the nonhypothesized patient group (eg, medial temporal lobe mask applied to dMCI analysis). No ROIs were significant in this cross comparison. In addition, we performed a whole-brain analysis of differences between our two patient groups at an anticonservative threshold of $p < 0.001$, because we expect the differences between nondemented patient groups to be subtle.

We conducted a multiple regression analysis with age, sex, and intracranial volume as nuisance variables. We conducted our planned comparisons of control subjects versus dMCI patients and control subjects versus aMCI patients. For exploratory purposes, we also investigated the contrast of dMCI and aMCI.

Results

Demographics and Screening

Tables 1 and 2 summarize the demographic and neuropsychological screening test results. There were no significant group differences in education, but there was a trend for group difference in age. Therefore, age was used as a covariate in the neuroimaging analyses. There were no group differences in sex. However, there were group differences on the CDR-sum of boxes, and both MCI groups had significantly higher CDR-sum of boxes scores than control subjects. Two dMCI and four aMCI patients were missing CDR scores. Eighty-five percent of the aMCI and 90% of the dMCI patients had a CDR of 0.5, and the remainder of MCI subjects had a CDR of zero. For the aMCI patients with a CDR of zero, both subjects had objective memory impairment on the screening cognitive testing and reported memory deficits, but their study partners did not endorse observing memory deficits. All patients or study partners endorsed changes in cognition. Informants or patients with dMCI all described recent difficulty with planning, multitasking, attention/concentration, or disorganization. However, 66% of these patients also reported difficulty remembering recent events or misplacing objects. As expected, deficits in concentration or attention can affect memory performance. In contrast, all patients and informants of the aMCI patients reported changes in memory, but only 31% reported changes in executive function. The aMCI patients had significantly greater Geriatric Depression Scale scores compared with control subjects;

Table 2. **Screening Neuropsychological Test Results**

Test	Control Subjects	aMCI Patients	dMCI Patients	*p*
Mean Global score (SD)				
MMSE (maximum 30)	29.8 (0.6)	28.7 (1.2)[a]	28.9 (1.3)[a]	<0.0001
Mean Memory score (SD)				
CVLT Long Delay free recall (maximum 16)	13.1 (2.4)	7.4 (4.0)[a,b]	9.8 (3.1)[a]	<0.0001
CVLT hits (maximum 16)	15.1 (1.5)	12.8 (2.9)[a]	14.1 (2.0)	<0.0001
Modified Rey–Osterrieth figure recall (maximum 17)	12.1 (3.1)	8.1 (3.8)[a,b]	11.8 (3.0)	<0.0001
Mean Executive Function score (SD)				
Modified Trail Making Test B (maximum 120 seconds)	25.4 (11.3)	31.1 (16.1)	41.9 (22.5)[a]	0.001
Modified Stroop Interference (number correct in 1 minute)	56.7 (14.2)	48.2 (11.7)	45.0 (4.9)[a]	0.001
Letter fluency (D words in 1 minute)	16.9 (5.1)	15.5 (3.7)	14.1 (4.9)	0.051
Abstractions (maximum 6)	5.0 (1.1)	5.1 (1.0)	4.5 (1.5)	0.156
Mean Visuospatial score (SD)				
Copy of modified Rey–Osterrieth figure (maximum 17)	15.9 (1.1)	15.8 (1.0)	15.7 (1.3)	0.873
VOSP Number Location (maximum 10)	9.2 (1.4)	9.1 (1.3)	9.1 (1.4)	0.909
Mean Language score (SD)				
Modified Boston Naming Test (maximum 15)	14.6 (0.8)	13.8 (1.8)	13.9 (1.2)	0.023
Syntax Comprehension (maximum 5)	4.8 (0.4)	4.7 (0.5)	4.6 (0.6)	0.209
Mean other scores (SD)				
Calculations (maximum 5)	4.9 (0.4)	4.8 (0.5)	4.7 (0.6)	0.477

Statistical results from an analysis of variance test.
[a]Different from control subjects, Tukey's honestly significant difference post hoc comparison, $p < 0.05$.
[b]Different from dMCI, Tukey's honestly significant difference post hoc comparison, $p < 0.05$. aMCI = amnestic mild cognitive impairment; dMCI = dysexecutive mild cognitive impairment; SD = standard deviation; MMSE = Mini-Mental State Examination; CVLT = California Verbal Learning Test; VOSP = Visual Object and Space.

however, subjects who were clinically depressed were excluded, and all Geriatric Depression Scale Scores fell below the cutoff for depression. The dMCI patients had greater Unified Parkinson's Disease Rating Scale–Part III Motor Scale than control subjects. Fifty-two percent of the aMCI and 37% of the dMCI patients had at least one *ApoE* ε4 allele, but this difference was not significant. In contrast, only 12% of the control subjects had an *ApoE* ε4 allele, which was significantly lower than aMCI and dMCI patients.

On the neuropsychological screening battery (see Table 2), both MCI groups scored significantly less than control subjects on the Mini-Mental State Examination. Both MCI groups scored significantly less than control subjects on the CVLT delayed recall. The aMCI subjects also recalled significantly fewer words on the delayed recall than the dMCI subjects. Although the dMCI patients recalled fewer words on the CVLT than control subjects, the scores obtained by the dMCI patients were within the reference range according to published norms.[18] In addition, the aMCI patients scored significantly less than both the control subjects and dMCI patients on the CVLT recognition trial (hits), and there was a trend for aMCI patients to score less than dMCI patients on the recognition trial. The aMCI patients scored significantly less than both the control subjects and dMCI patients on the test of visual memory (delayed recall of the modified Rey–Osterrieth figure).

On screening tests of executive function, there were group differences on modified Trail Making Test B and Stroop interference tests, and a trend for group differences on phonemic fluency. Only the dMCI patients significantly scored less than control subjects on the modified Trail Making Test B and modified Stroop interference. There was a trend for the dMCI patients to score less than the aMCI patients on the modified Trail Making Test B. There were no group differences on the abstractions task. There were also no group differences on tests of visuospatial skills (ie, copy of modified Rey–Osterrieth figure and number location subtest) or calculations. There were group differences on the Boston Naming Test; however, post hoc tests did not support significant pairwise group differ-

Table 3. **Experimental Neuropsychological Measures**

Test	Control Subjects	aMCI Patients	dMCI Patients	*p*
Mean Executive Function score (SD)				
WAIS-III Digit Symbol–scaled	13.8 (2.0)	11.9 (2.9)	10.7 (3.1)[a]	0.002
WAIS-III Matrix Reasoning–scaled	14.5 (2.1)	13.3 (2.3)	12.6 (2.5)[a]	0.031
DKEFS Design Fluency Switching–scaled	12.8 (2.7)	11.7 (2.6)	10.5 (2.7)[a]	0.006
WAIS-III Similarities–scaled	14.4 (2.6)	13.7 (2.5)	12.9 (2.6)	0.181
Mean Memory score (SD)				
WMS Visual Reproductions–immediate recall (scaled)	11.7 (3.3)	9.8 (3.9)	9.7 (3.2)	0.073
WMS Visual Reproductions–30-minure delayed recall (scaled)	12.4 (3.6)	9.8 (4.0)[a]	10.6 (3.3)	0.042
WAIS-III Digit Span–scaled	12.9 (2.6)	12.3 (2.6)	11.8 (3.2)	0.383

Statistical results from an analysis of variance test.
[a]Different from control subjects, Tukey's honestly significant difference post hoc comparison, $p < 0.05$.
aMCI = amnestic mild cognitive impairment; dMCI = dysexecutive mild cognitive impairment; SD = standard deviation; WAIS = Wechsler Adult Intelligence Scale; DKEFS = Delis Kaplan Executive Function System; WMS = Wechsler Memory Scale.

ences. There were no group differences on the test of syntax comprehension.

Experimental Neuropsychological Test Results

When considering additional neuropsychological test results that were not used in diagnosis, the dMCI patients performed significantly worse than control subjects on the majority of tests of executive function (Table 3). Patients with dMCI scored significantly less than control subjects on Digit Symbol, Matrix Reasoning, and the switching condition of Design Fluency. There were no group differences on the Similarities subtest.

In contrast, the aMCI patients scored significantly worse than control subjects on the 30-minute delayed trial. There was a trend for group differences on the immediate recall trial, with the aMCI patients scoring less than control subjects. There were no group differences on the Digit Span task.

Behavior and Instrumental Activities of Daily Living

Compared with control subjects, the dMCI patients had significantly greater scores on the DEX, and there was a trend for aMCI patients to also score higher than control subjects (Table 4). The dMCI patients also had significantly more behavioral symptoms on the FBI, but the aMCI patients did not differ from the control subjects or the dMCI patients. About group differences on IADLs, the aMCI patients had significantly greater scores on the Functional Activities Questionnaire than control subjects. There was also a trend for the dMCI patients to score higher than control subjects, but the MCI groups did not differ from each other.

Patterns of Gray Matter Atrophy

DYSEXECUTIVE MILD COGNITIVE IMPAIRMENT SUBGROUP.

Overall, the dMCI patients had significantly less GM in the left dorsolateral prefrontal cortex (PFC) compared with control subjects ($p < 0.05$, FWE corrected) (Fig 1A–1B; Table 5). In addition, a region in the dorsomedial PFC of patients with dMCI showed a trend for less GM compared with control subjects ($p = 0.05$, FWE corrected) (Fig 1C–1E; Table 5).

AMNESTIC MILD COGNITIVE IMPAIRMENT SUBGROUP.

As expected, patients with aMCI had significantly less GM in the posterior temporoparietal regions compared with control subjects. Bilateral medial temporal lobes, including hippocampus and entorhinal cortex, showed significant atrophy compared with control subjects ($p < 0.05$, FWE corrected) (Fig 1C; Table 5). GM atrophy was also observed in the right posterior cingulate gyrus when compared with control subjects (both $p < .05$, FWE corrected) (Fig 1D; Table 5). Finally, there was GM loss in the right inferior parietal cortex in the aMCI group ($p < 0.05$, FWE corrected) (Fig 1E; Table 5).

DIRECT PATIENT GROUP COMPARISON: DYSEXECUTIVE MILD COGNITIVE IMPAIRMENT VERSUS AMNESTIC MILD COGNITIVE IMPAIRMENT.

When comparing the extent of GM atrophy in our MCI groups, the caudate nucleus was smaller in dMCI than aMCI ($p < 0.001$, uncorrected) (Fig 2D; Table 6). In contrast, the right inferior parietal cortex had less GM in the aMCI than dMCI patients ($p < 0.001$, uncorrected) (Fig 2B; Table 6).

Table 4. **Behavior and Instrumental Activities of Daily Living Results**

Test	Control Subjects	aMCI Patients	dMCI Patients	*p*
Mean Behavior score (SD)				
DEX (maximum 80)	1.6 (2.1)	8.7 (8.7)	12.7 (10.1)[a]	<0.0001
FBI (maximum 72)	0.8 (1.8)	6.5 (8.0)	9.1 (9.2)[a]	0.003
Mean IADLs (SD)				
FAQ (maximum 30)	0.04 (0.2)	2.0 (4.2)[a]	1.7 (2.2)[a]	0.002

Statistical results from an analysis of variance test.
[a]Different from control subjects, Tukey's honestly significant difference post hoc, $p < 0.05$. aMCI = amnestic mild cognitive impairment; dMCI = dysexecutive mild cognitive impairment; SD = standard deviation; DEX = Dysexecutive Questionnaire; FBI = Frontal Behavioral Inventory; IADLs = instrumental activities of daily living; FAQ = Functional Activities Questionnaire.

INDIVIDUAL GRAY MATTER CONCENTRATION.
Figure 3 shows the distribution of the individual subject GM values, unadjusted for age, sex, and total intracranial volume (covariates included in the VBM analysis). The GM values of the peak voxel (as shown in Table 5) within four key ROIs are plotted for each group comparison. For the dMCI and control comparisons, the distribution in left dorsolateral and dorsomedial prefrontal cortices is shown, and for the aMCI and control comparisons, the distribution in left hippocampus and right posterior cingulate gyrus is shown. As expected, the distribution of GM values in the patient groups is generally greater than for control subjects with a significant degree of overlap. It is important to keep in mind that the raw VBM GM values are not adjusted for age, sex, or total intracranial brain volume.

Discussion

Overall, dMCI patients who had low scores on screening tests of executive function (but not memory) had

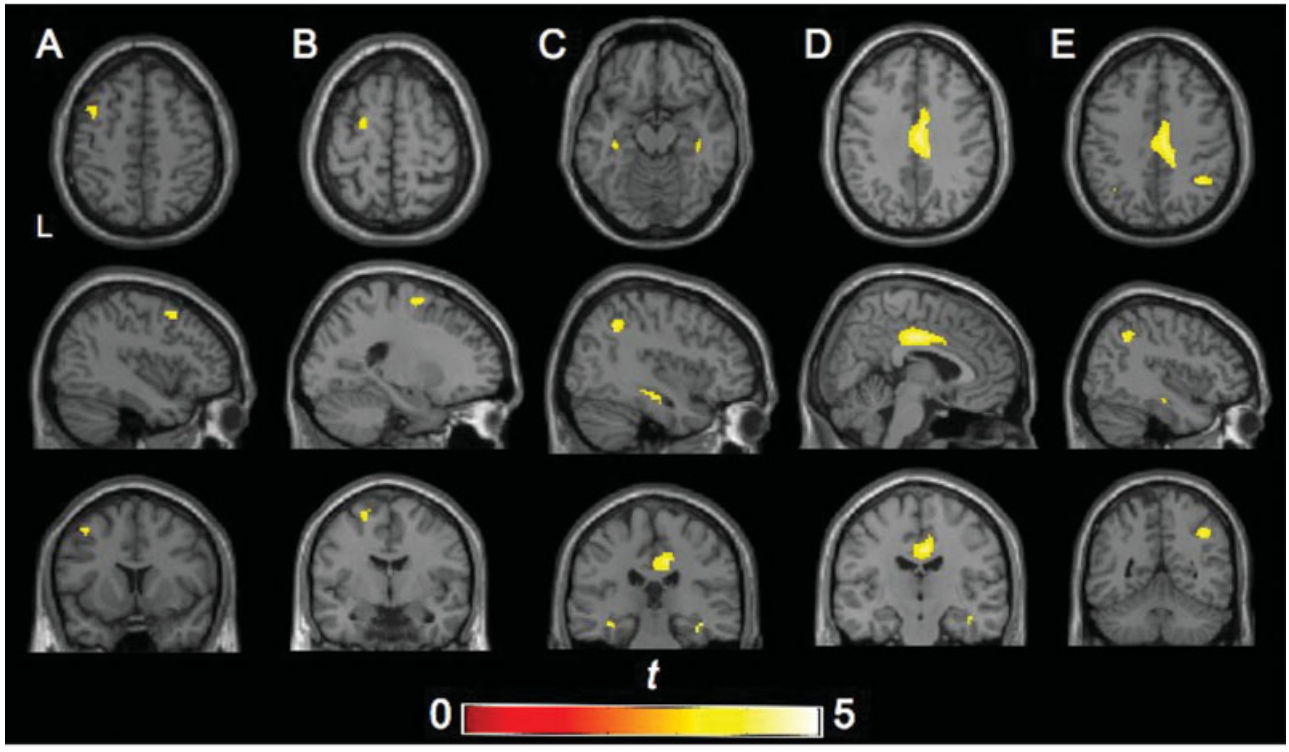

Fig 1. Gray matter loss in mild cognitive impairment (MCI) subgroups when compared with control subjects. (A) Gray matter loss in dorsolateral prefrontal cortex in dysexecutive MCI (dMCI) compared with control subjects. (B) Gray matter loss in dorsomedial prefrontal cortex in dMCI compared with control subjects. (C) Gray matter loss in bilateral hippocampus in amnestic MCI (aMCI) compared with control subjects. (D) Gray matter loss in the posterior cingulate gyrus in aMCI compared with control subjects. (E) Gray matter loss in right parietal cortex in aMCI compared with control subjects.

Table 5. **Regions of Gray Matter Loss in Mild Cognitive Impairment Subgroups versus Control Groups**

Brain Region	*x*	y	z	t Statistic	z Value
dMCI > control subjects					
Left dorsolateral prefrontal cortex	−44	10	50	3.76	3.61
Left dorsomedial prefrontal cortex	−20	−4	64	3.73	3.59[a]
aMCI > control subjects					
Left hippocampus	−38	−26	−14	4.02	3.84
Right hippocampus	40	−22	−18	3.98	3.81
Right posterior cingulate gyrus	6	−16	38	4.39	4.16
	12	−28	38	4.2	4
	8	−4	38	4.19	3.99
Right inferior parietal lobe	38	−54	40	4.23	4.03

Voxel coordinates represent the peak voxel in local maxima; coordinates are expressed in Montreal Neurological Institute stereotactic space. $p < 0.05$, family-wise error rate (FWE) corrected.
[a] $p = 0.05$, FWE corrected. aMCI = amnestic mild cognitive impairment; dMCI = dysexecutive mild cognitive impairment.

increased behavioral and motor symptoms, and left PFC atrophy on MRI when compared with control subjects. In contrast, the aMCI patients who had low scores on screening tests of memory (but not executive function) had a pattern of brain atrophy including bilateral hippocampus and entorhinal cortex, right inferior parietal cortex, and posterior cingulate gyrus when compared with control subjects. In addition, the aMCI patients had slightly more IADL impairment than control subjects but did not exhibit significantly more behavioral symptoms as measured by the DEX and FBI. These results suggest that the aMCI and dMCI subgroups can be differentiated using clinical and neuroimaging measures.

Patients with dMCI also had increased behavioral symptoms on the DEX and FBI, two questionnaires that specifically measure dysexecutive behaviors. There was a trend for aMCI patients to have higher behavioral symptoms on the DEX, but the difference did not reach statistical significance. These results suggest that MCI patients, in general, have increased behavioral symptoms compared with control subjects; however, the dMCI patients may exhibit even greater rates of behavioral change than aMCI patients. Several studies report that behavioral symptoms are increased in MCI,[32] but few studies directly compare MCI subgroups. Rozzini and colleagues[33] found increased rates of sleep disorders and hallucinations (on the Neuropsychiatric Inventory) in nonamnestic MCI patients when compared with aMCI patients. The dMCI patients also had higher scores on the Unified Parkinson's Disease Rating Scale–Part III Motor Scale and included slightly fewer carriers of the *ApoE* ε4 allele when compared with aMCI patients. The lower prevalence of *ApoE* ε4 carriers in the dMCI patients was not significant but should be investigated in a larger study. Other studies have found an increase in motor symptoms[33] and lower rates of *ApoE* ε4[34] in nonamnestic MCI patients. Thus, the cognitive, behavioral, and genetic profiles of nonamnestic MCI patients may differ from MCI with predominant memory symptoms.

Most importantly, the MCI subgroups had distinct patterns of atrophy on brain MRI. The dMCI patients had atrophy in the left dorsolateral and a trend for atrophy in the dorsomedial PFC when compared with control subjects. In contrast, the aMCI patients showed the typical pattern of GM atrophy involving bilateral hippocampi and entorhinal cortex, right inferior parietal cortex, and posterior cingulate gyrus when compared with control subjects. This pattern of atrophy in temporoparietal cortex has been well-documented in other VBM studies of aMCI patients.[30,35–37] Although the aMCI patients in this study are younger than patients in other aMCI studies, the patterns of atrophy are similar. When directly comparing the MCI groups, the dMCI patients had less volume in the caudate nucleus, supporting the role of the basal ganglia in executive functioning.[38] In contrast, the aMCI patients had less volume in the right inferior parietal cortex, suggesting a more AD-like pattern of atrophy. The distribution of peak GM values in individual subjects displays the overlap between patient and control groups. It is important to note that these plots do not account for key factors that influence the statistical findings, such as age, sex, and total intracranial volume. The overlap between patient and control groups supports the idea that a high degree of variability exists in both normal aging and MCI populations.

Numerous studies link deficits in executive functioning to damage in the PFC. Specifically, the Trail Making test used in this study has been linked to the left PFC. For example, patients with focal lesions in the

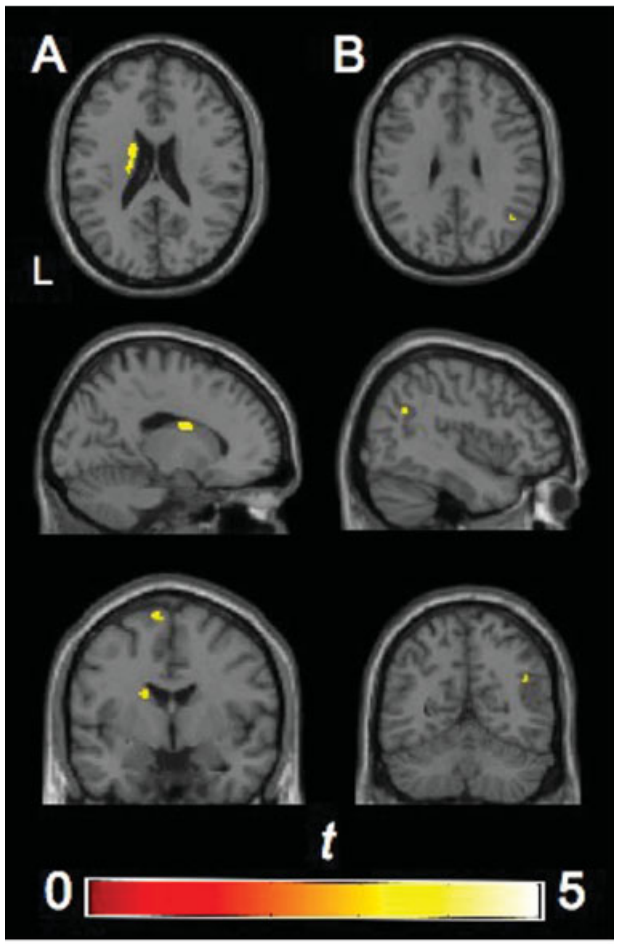

Fig 2. Gray matter loss in the mild cognitive impairment (MCI) subgroup (direct patient) comparison. (A) Dysexecutive MCI (dMCI) shows gray matter loss in caudate nucleus compared with amnestic MCI (aMCI), and (B) aMCI shows slightly more gray matter loss in the right inferior parietal lobe.

left lateral PFC have difficulty on the Letter-Number Switching condition of the DKEFS Trail Making test.[39] Patients with left frontal-lobe epilepsy are also impaired on the Trail Making switching condition when compared with temporal-lobe epilepsy patients and healthy control subjects.[40] Another study found an association between frontal lobe volume and performance on the switching condition of the DKEFS Design Fluency test in patients with neurodegenerative disease and control subjects.[41] Functional neuroimaging studies have also documented PFC activation while completing measures of executive function. For example, Phelps and colleagues[42] found left PFC activation during a letter fluency task in healthy subjects using functional MRI. A PET study showed that verbal fluency activated a similar region in healthy middle-aged adults.[43] Lastly, an fMRI study found the Trail Making test was related to neural activity in the left dorsolateral and medial frontal regions.[44] Taken together, these studies from both clinical and healthy populations support our finding that a dysexecutive subgroup of MCI would likely show decreased GM volume in the left PFC.

Only one other study has investigated MRI patterns in nonamnestic MCI. Whitwell and colleagues[34] identified nine patients with an executive/attention subgroup of MCI, and found atrophy in the basal forebrain and hypothalamus when compared with control subjects. In the current study, we found atrophy in the PFC but did not identify atrophy in the basal forebrain and hypothalamus as in Whitwell and colleagues'[34] study. However, when comparing the MCI groups, we found less volume in the caudate nucleus in the dMCI when compared with the aMCI patients. There are several differences between this study and the Whitwell and colleagues'[34] study. Specifically, this study had younger subjects and a larger sample size of dMCI patients than Whitwell and colleagues'[34] study. It is also important to point out that the age of the MCI patients in our study is generally younger than the other studies in the literature. The differences in our findings may also be because of heterogeneity in underlying causative factors in the dMCI group.[45] Whitwell and colleagues[34] report that three patients converted to dementia with Lewy bod-

***Table 6.* Regions of Gray Matter Loss in Mild Cognitive Impairment Subgroup Comparison**

Brain Region	*x*	y	z	t Statistic	z Value
dMCI > aMCI					
Caudate nucleus	−18	0	22	3.55	3.42
aMCI > dMCI					
Right inferior parietal lobe	44	−60	30	3.36	3.25[a]

Voxel coordinates represent the peak voxel in local maxima; coordinates are expressed in Montreal Neurological Institute stereotactic space. $p < 0.0001$, uncorrected.
[a]$p < 0.001$, uncorrected.
aMCI = amnestic mild cognitive impairment; dMCI = dysexecutive mild cognitive impairment.

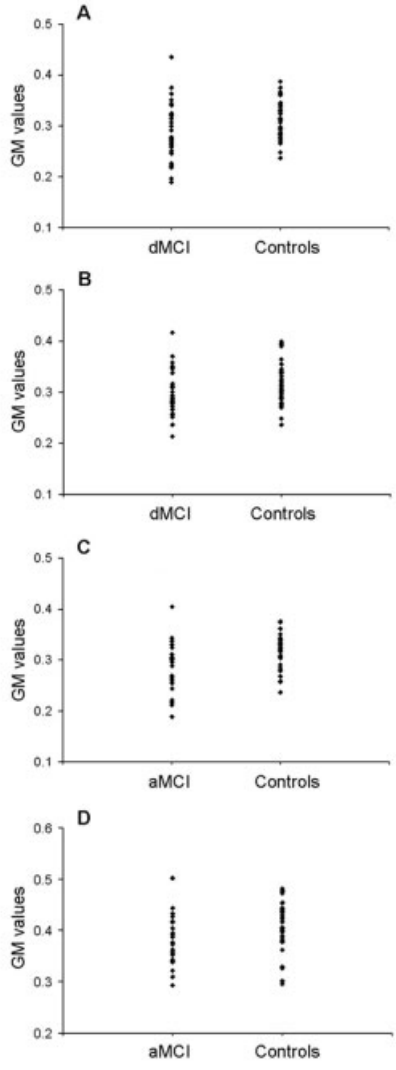

Fig 3. The gray matter (GM) values of each subject for each peak voxel are plotted for four key regions of interest: (A) left dorsolateral prefrontal cortex, (B) left dorsomedial prefrontal cortex, (C) left hippocampus, and (D) right posterior cingulate gyrus for each patient and control group comparison. This represents the distribution of GM values in each group and does not control for age, sex, and total intracranial volume (covariates included in the voxel-based morphometric analysis). aMCI = amnestic mild cognitive impairment; dMCI = dysexecutive mild cognitive impairment.

ies and three converted to AD. Patients with dMCI may also convert to other non-AD dementias, such as progressive supranuclear palsy, vascular dementia, and Parkinson's disease. The increase in motor symptoms and a trend for lower rates of *ApoE* ε 4 alleles also support this hypothesis.

Isolated executive dysfunction can be a prodromal stage of several neurodegenerative diseases, such as Parkinson's disease, frontotemporal dementia, progressive supranuclear palsy, and AD. We are currently observing our cohort to determine the longitudinal clinical outcomes. Executive dysfunction has also been linked to white matter lesions in healthy adults and MCI patients.[46] However, white matter burden did not differentiate MCI subgroups in one study.[47] Further, in this study, we excluded subjects with significant white matter damage. When considering whether patients with dMCI perform worse than control subjects on more challenging tests of executive function (not used in diagnosis), we found that the patients with dMCI scored lower than control subjects on tests that measure several subcomponents of executive functioning, such as nonverbal reasoning, visuomotor attention, and the switching condition in design generation.

The clinical and neuroimaging findings provide evidence for two distinct single-domain subgroups of MCI, one involving executive function and the other involving memory. These findings thus support the general framework of distinct *single*-domain MCI patients as proposed by the International MCI Working Group.[4] The neuroimaging findings in the dMCI patients are consistent with the prominent executive dysfunction. The loss of PFC tissue suggests that some of the dMCI patients may represent a distinct subgroup of MCI who may progress to non-AD dementias or AD with disproportionate neuropathology in the frontal cortex. Future studies should yield additional information about the clinical outcomes of MCI patients with different cognitive profiles.

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