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Clinical-Neuroimaging Characteristics of Dysexecutive Mild Cognitive Impairment

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Abstract

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

Methods—We compared the cognitive, functional, behavioral and brain imaging characteristics of patients with aMCI (n=26), dMCI (n=32) and age- and education-matched controls (n=36) using analysis of variance and chi-squared tests. We used voxel-based morphometry (VBM) to examine group differences in brain MRI atrophy patterns.

Results—Patients with dMCI had significantly lower scores on the majority of executive function tests, increased behavioral symptoms, and left prefrontal cortex atrophy on MRI when compared to controls. In contrast, patients with aMCI 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 to controls.

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.

Introduction

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 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 non-amnesic 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: amnesic (single and multiple domain) and non-amnesic (single and multiple domain).

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Few studies have investigated non-amnestic presentations of MCI, which is defined as either a predominant impairment in one non-memory cognitive domain (e.g., executive function, language, or visuospatial skills) or impairment in multiple, non-amnestic domains. Estimates of non-amnestic single domain MCI range from 7–14% in MCI patients.^{6,7} Yaffe and colleagues⁸ found that single-domain non-amnestic MCI patients were less likely to convert to dementia but had higher rates of death over five years than amnestic MCI. Several authors hypothesize that the subgroups will have different etiologies 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 amnestic MCI (aMCI) and compare with healthy controls. Based on previous finding that Alzheimer's disease 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 frontal cortex, 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 controls 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 (UPDRS-III),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 are queried about the first and current symptoms. We categorized the first and current symptoms into the following: 1) memory, 2) executive, 3) behavioral, 4) language, 5) visuospatial, 6) motor, and 7) other. The one-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 (NPI) to evaluate behavior.¹³ Screening for depression was done using the 30-item Geriatric Depression Scale (GDS)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 above.

Subjects were excluded if they met criteria for dementia (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 MRI, defined as a Longstreth¹⁶ grade ≥ 4 (out of 8), were excluded. The controls included in the study underwent an identical evaluation to the MCI patients and had a CDR of 0 and a Mini-Mental State Examination (MMSE)¹⁷ score ≥ 28 . All subjects scored within the normal range (within 1 SD) on neuropsychological testing. Patients diagnosed with MCI were further classified according 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 cut-off (1.28 standard deviations), which has been used in other studies of non-amnestic 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 (*i.e.*, modified Trailmaking Test B, modified Stroop interference, number of D words in one minute, or abstractions).¹¹ In addition, patients with dMCI had to score within the normal range (within one SD from norms mean) on tests of memory (*i.e.*, 20-minute delayed recall or recognition on California Verbal Learning Test¹⁸ and 10-minute recall of modified Rey-Osterrieth figure), language (*i.e.*, 15-item Boston Naming Test¹⁹ or syntax comprehension) and visuospatial skills (*i.e.*, copy of modified Rey-Osterrieth figure and Number Location subtest from The Visual Object and Space Perception Battery (VOSP)).²⁰ In contrast, patients were classified as aMCI if scores were at or below the 10th percentile on the screening tests of memory (described above) and within the normal range on tests of executive function, language, and visuospatial skills. The study sample included 32 individuals with dMCI, 26 with aMCI, and 36 healthy controls.

The following outcome measures were also collected but were not used in diagnosis. Within three months of the diagnostic visit, a 1.5T MRI of the brain was completed. We obtained apolipoprotein E (*APOE*) genotypes through 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 (*e.g.*, distractibility, impulsivity, difficulty planning) on a four-point scale (from "never" to "very often"), with higher 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 (FAQ)²⁴ was used to assess IADLs.

Statistical Methods for Clinical Data

An analysis of variance (ANOVA) was used, together with Tukey HSD pairwise posthoc comparisons, to evaluate possible group differences in clinical variables. A chi-squared test was used to assess differences in gender and *APOE* status. We used Statistical Package for the Social Sciences (SPSS) 16.0 to conduct the statistical analysis.

Brain MRI and Voxel-based Morphometry

MR Image Acquisition—Images were collected on a Siemens Vision 1.5T MRI scanner (Siemens, Iselin, NJ). T1-weighted 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) images were acquired (TI/TR/TE=300/9.7/4 (ms); flip angle=15°; FOV 256 × 256 mm² with 1.0 × 1.0 mm² inplane resolution; 154 partitions with 1.5mm slice thickness).

Imaging Data Analysis—Voxel-based morphometry analysis was performed on the T1-weighted images using SPM5 software (Wellcome Department of Imaging Neuroscience, University College London, UK, 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 Further, 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 MNI (Montreal Neurological Institute) stereotactic space using the default ICBM template. We applied an isotropic Gaussian smoothing kernel of 12mm FWHM to minimize individual anatomical variability and reduce the chance of false positives.²⁷ All images were reviewed prior to 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 atrophy between the MCI subgroups and controls 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 (ROI) 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 WFU Pickatlas toolbox.³¹ All regions of interest were assessed at the $p < .05$, family-wise error rate (FWE)-corrected threshold. To eliminate selection bias, each ROI mask was also applied to the non-hypothesized patient group (e.g. medial temporal lobe mask applied to dMCI analysis). No regions of interest were significant in this cross comparison. In addition, we performed a whole-brain analysis of differences between our two patient groups at an anti-conservative threshold of $p < 0.001$, as we expect the differences between non-demented patient groups to be subtle.

We conducted a multiple regression analysis with age, gender, and intracranial volume as nuisance variables. We conducted our planned comparisons of controls vs. dMCI and controls vs. aMCI. For exploratory purposes, we also investigated the contrast of dMCI and aMCI.

Results

Demographic and Screening

Tables 1 and 2 summarize the demographic and neuropsychological screening test results. There were no significant group difference 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 gender. However, there were group differences on the CDR-sum of boxes, and both MCI groups had significantly higher CDR-sum of boxes scores than controls. Two dMCI and four aMCI were missing CDR scores. Eighty-five percent of the aMCI and 90% of the dMCI patients had a CDR = 0.5, and the remainder of MCI subjects had a CDR = 0. For the aMCI patients with a CDR=0, both subjects had objective memory impairment on the screening cognitive testing and complained about 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 complained of recent difficulty with planning, multi-tasking, attention/concentration, or disorganization. However, 66% of these patients also complained of 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% complained of changes in executive function. The aMCI patients had significantly higher GDS scores when compared to controls; however, subjects who were clinically depressed were excluded, and the GDS scores fell below the cut-off for depression. The dMCI patients had higher UPDRS-III than controls. Fifty-two percent of the aMCI, and 37% of the dMCI patients had at least one *APOE* $\epsilon 4$ allele, but this difference was not significant. In contrast, only 12% of the controls had an *APOE* $\epsilon 4$ allele, which was significantly lower than aMCI and dMCI patients.

On the neuropsychological screening battery (see Table 2), both MCI groups scored significantly below controls on the MMSE. Both MCI groups scored significantly below controls 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 controls, the scores obtained by the dMCI patients fell within the normal range according to published norms.¹⁸ In addition, the aMCI patients scored significantly below both the controls and dMCI patients on the CVLT recognition trial (hits), and there was a trend for aMCI to score lower than dMCI patients on the recognition trial. The aMCI patients scored significantly below both the controls 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 Trailmaking Test B and Stroop interference tests and a trend for group differences on phonemic fluency. Only the dMCI patients significantly scored lower than controls on the modified Trailmaking Test B and modified Stroop interference. There was a trend for the dMCI patients to score lower than the aMCI patients on the modified Trailmaking Test B. There were no group differences on the abstractions task. There were also no group differences on tests of visuospatial skills (*i.e.*, 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 differences. 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 controls on the majority of tests of executive function. (see Table 3) Patients with dMCI scored significantly lower than controls 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 controls on the 30-minute delayed trial. There was a trend for group differences on the immediate recall trial, with the aMCI patients scoring lower than controls. There were no group differences on the Digit Span task.

Behavior and IADLs

Compared to controls, the dMCI patients had significantly higher scores on the DEX, and there was a trend for aMCI patients to also score higher than controls. (see Table 4) The dMCI patients also had significantly more behavioral symptoms on the FBI, but the aMCI patients did not differ from the controls or the dMCI patients. With regards to group differences on IADLs, the aMCI patients had significantly higher scores on the FAQ than controls. There was also a trend for the dMCI patients to score higher than controls, but the MCI groups did not differ from each other.

Patterns of gray matter atrophy

Dysexecutive MCI subgroup—Overall, the dMCI patients had significantly less gray matter in the left dorsolateral prefrontal cortex when compared to controls ($p < 0.05$, FWE-corrected). Additionally, a region in the dorsomedial prefrontal cortex of patients with dMCI showed a trend for less gray matter when compared to controls ($p = 0.05$, FWE-corrected) (Fig. 1a, Table 5).

Amnesic MCI subgroup—As expected, patients with aMCI had significantly less gray matter in the posterior temporoparietal regions when compared to controls. Bilateral medial temporal lobes, including hippocampus and entorhinal cortex, showed significant atrophy when compared to controls ($p < 0.05$, FWE-corrected) (Fig. 1b, Table 5). Gray matter atrophy was also observed in the right posterior cingulate gyrus when compared to controls (both $p < 0.05$, FWE-corrected). Finally, there was gray matter loss in the right inferior parietal cortex in the aMCI group ($p < 0.05$, FWE-corrected).

Direct patient group comparison: dMCI vs. aMCI—When comparing the extent of gray matter atrophy in our MCI groups, the caudate nucleus was smaller in dMCI than aMCI ($p < 0.001$, uncorrected) (Fig. 1c, Table 6). In contrast, the right inferior parietal cortex had less gray matter in the aMCI than dMCI patients ($p < 0.001$, uncorrected) (Fig. 1c, Table 6).

Individual gray matter concentration—Figure 3 shows the distribution of the individual subject gray matter (GM) values, unadjusted for age, gender 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, we show the distribution in left dorsolateral and dorsomedial prefrontal cortices, and for the aMCI and control comparisons, we show the distribution in left hippocampus and right posterior cingulate gyrus. As expected, the distribution of GM values in the patient groups is generally greater than controls with a significant degree of overlap. It is important to keep in mind that the raw VBM gray matter values are not adjusted for age, gender, or total intracranial brain volume.

Discussion

Overall, dysexecutive MCI patients who had low scores on screening tests of executive function (but not memory) had increased behavioral and motor symptoms and left prefrontal cortex atrophy on MRI when compared to controls. In contrast, the amnesic MCI 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 to controls. In addition, the aMCI patients had slightly more IADL impairment than controls 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 controls; however, the dMCI patients may exhibit even higher 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 colleagues³³ found increased rates of sleep disorders and hallucinations (on the NPI) in non-amnesic MCI patients when compared to amnesic MCI patients. The dMCI patients also had higher scores on the UPDRS-III and included slightly fewer carriers of the *APOE* ϵ 4 allele when compared with aMCI patients. The lower prevalence of *APOE* ϵ 4 carriers in the dMCI patients was not significant but should be investigated in a larger study. Other studies have found an increase in motor symptoms³³ and lower rates of *APOE* ϵ 4³⁴ in non-amnesic MCI patients. Thus, the cognitive, behavioral, and genetic profiles of non-amnesic 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 prefrontal cortex when compared to controls. In contrast, the aMCI patients showed the typical pattern of gray matter atrophy involving bilateral hippocampi and entorhinal cortex, right inferior parietal cortex, and posterior cingulate gyrus when compared to controls. 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 the current 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 which influence the statistical findings, such as age, gender, 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 prefrontal cortex (PFC). Specifically, the Trailmaking test used in the present study has been linked to the left PFC. For example, patients with focal lesions in the left lateral PFC have difficulty on the Letter-Number Switching condition of the DKEFS Trailmaking test.³⁹ Patients with left frontal-lobe epilepsy are also impaired on the Trailmaking switching condition when compared to temporal-lobe epilepsy patients and healthy controls.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 controls.⁴¹ Functional neuroimaging studies have also documented PFC activation while completing measures of executive function. For example, Phelps and colleagues⁴² found left PFC activation during a letter fluency task in healthy subjects using functional MRI (fMRI). A similar result was reported in a PET study in which verbal fluency was shown to activate a similar region in healthy middle-aged adults.⁴³ Lastly, an fMRI study found the Trailmaking test was related to neural activity to 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 gray matter volume in the left prefrontal cortex.

Only one other study has investigated MRI patterns in non-amnesic MCI. In this study, Whitwell and colleagues³⁴ identified nine patients with an executive/attention subgroup of MCI and found atrophy in the basal forebrain and hypothalamus when compared to controls. In the present study, we found atrophy in the prefrontal cortex but did not identify atrophy in the basal forebrain and hypothalamus as in the Whitwell study. However, when comparing the MCI groups, we found less volume in the caudate nucleus in the dMCI when compared to the aMCI patients. There are several differences between the current study and the Whitwell study. Specifically, the current study had younger subjects and a larger sample size of dMCI patients than the Whitwell 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 due to heterogeneity in underlying etiologies in the dMCI group.⁴⁵ Whitwell and colleagues reported that three patients converted to dementia with Lewy bodies (DLB), 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 disease, frontotemporal dementia, progressive supranuclear palsy and Alzheimer disease. We are currently following our cohort to determine the longitudinal clinical outcomes. Executive dysfunction has also been linked to white matter lesions in healthy adults and MCI.⁴⁶ However, white matter burden did not differentiate MCI subgroups in one study.⁴⁷ Further, in the current study, we excluded subjects with significant white matter damage. When considering whether or not patients with dMCI perform worse than controls on more challenging tests of executive function (not used in diagnosis), we found that the patients with dMCI scored lower than controls on tests that measure several subcomponents of executive functioning, such as non-verbal 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 prefrontal cortex 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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Figure 1.

Gray matter loss in MCI subgroups when compared to controls. (A) Gray matter loss in dorsolateral prefrontal cortex in dMCI compared to controls (B) Gray matter loss in dorsomedial prefrontal cortex in dMCI compared to controls. (C) Gray matter loss in bilateral hippocampus in aMCI compared to controls. (D) Gray matter loss in the posterior cingulate gyrus in aMCI compared to controls. (E) Gray matter loss in right parietal cortex in aMCI compared to controls.

Figure 2. Gray matter loss in the MCI subgroup (direct patient) comparison. (A) dMCI show gray matter loss in caudate nucleus compared to aMCI and (B) aMCI show slightly more gray matter loss in right inferior parietal lobe.

Figure 3.

The 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, gender, and total intracranial volume (covariates included in the VBM analysis).

Table 1
Demographic and Screening Results. Mean and (standard deviations)

	Controls	aMCI	dMCI	<i>p</i>
N	36	26	32	NA
Age (yr)	64.8 (8.2)	68.0 (6.6)	63.8 (7.8)	.099
Sex (males/females)	13 / 23	13 / 13	20 / 12	.094 ⁺
Education (yr)	17.0 (2.0)	17.5 (1.7)	17.1 (2.7)	.631
CDR-sum of boxes (max. 18)	0	1.1 (1.0) [*]	1.3 (0.9) [*]	<0.0001
Geriatric Depression Scale (max. 30)	2.6 (2.9)	5.5 (4.3) [*]	5.0 (5.0)	.014
UPDRS-III	0.8 (1.7)	1.3 (2.4)	3.7 (6.4) [*]	.036
Frequency of APOE ε4 allele carriers	12%	52%	37%	.005 ⁺

Statistical results from an analysis of variance (ANOVA) test

Abbreviations: CDR = Clinical Dementia Rating, UPDRS = Unified Parkinson's Disease Rating Scale, APOE = apolipoprotein

^{*} different from controls, Tukey HSD post-hoc, $p < 0.05$

⁺ p-value from a Chi-squared statistic

Table 2
Screening Neuropsychological Test Results. Mean and (standard deviation)

		Controls	aMCI	dMCI	p
Global	MMSE (max. 30)	29.8 (0.6)	28.7 (1.2) *	28.9 (1.3) *	<0.0001
	CVLT Long Delay free recall (max. 16)	13.1 (2.4)	7.4 (4.0) ^a	9.8 (3.1) *	<0.0001
	CVLT Hits (max. 16)	15.1 (1.5)	12.8 (2.9) *	14.1 (2.0)	<0.0001
	Modified Rey-Osterrieth figure recall (max. 17)	12.1 (3.1)	8.1 (3.8) ^a	11.8 (3.0)	<0.0001
Executive Function	Modified Trailmaking Test B (max. 120 sec)	25.4 (11.3)	31.1 (16.1)	41.9 (22.5) *	.001
	Modified Stroop Interference (number correct in one minute)	56.7 (14.2)	48.2 (11.7)	45.0 (4.9) *	.001
	Letter fluency (D words in one minute)	16.9 (5.1)	15.5 (3.7)	14.1 (4.9)	.051
	Abstractions (max. 6)	5.0 (1.1)	5.1 (1.0)	4.5 (1.5)	.156
Visuo-spatial	Copy of modified Rey-Osterrieth figure (max. 17)	15.9 (1.1)	15.8 (1.0)	15.7 (1.3)	.873
	VOSP Number Location (max. 10)	9.2 (1.4)	9.1 (1.3)	9.1 (1.4)	.909
Language	Modified Boston Naming Test (max. 15)	14.6 (0.8)	13.8 (1.8)	13.9 (1.2)	.023
	Syntax Comprehension (max. 5)	4.8 (0.4)	4.7 (0.5)	4.6 (0.6)	.209
Other	Calculations (max. 5)	4.9 (0.4)	4.8 (0.5)	4.7 (0.6)	.477

Statistical results from an analysis of variance (ANOVA) test

Abbreviations: MMSE = Mini-Mental State Examination, CVLT = California Verbal Learning Test, VOSP = Visual Object and Space

* different from controls, Tukey HSD post-hoc, $p < 0.05$

^a different from dMCI, Tukey HSD post-hoc, $p < 0.05$

Table 3
Experimental Neuropsychological Measures (mean and standard deviation)

		Controls	aMCI	dMCI	<i>p</i>
Executive Function	WAIS-III Digit Symbol – scaled	13.8 (2.0)	11.9 (2.9)	10.7 (3.1) *	.002
	WAIS-III Matrix Reasoning – scaled	14.5 (2.1)	13.3 (2.3)	12.6 (2.5) *	.031
	DKEFS Design Fluency Switching - scaled	12.8 (2.7)	11.7 (2.6)	10.5 (2.7) *	.006
	WAIS-III Similarities – scaled	14.4 (2.6)	13.7 (2.5)	12.9 (2.6)	.181
Memory	WMS Visual Reproductions – immediate recall (scaled)	11.7 (3.3)	9.8 (3.9)	9.7 (3.2)	.073
	WMS Visual Reproductions – 30 min. delayed recall (scaled)	12.4 (3.6)	9.8 (4.0) *	10.6 (3.3)	.042
	WAIS-III Digit Span – scaled	12.9 (2.6)	12.3 (2.6)	11.8 (3.2)	.383

Statistical results from an analysis of variance (ANOVA) test
Abbreviations: WAIS = Wechsler Adult Intelligence Scale, DKEFS = Delis Kaplan Executive Function System, WMS = Wechsler Memory Scale
* different from controls, Tukey HSD post-hoc, $p<0.05$

Table 4
Behavior and IADL Results. Mean and (standard deviation)

		Controls	aMCI	dMCI	<i>p</i>
Behavior	DEX (max. 80)	1.6 (2.1)	8.7 (8.7)	12.7 (10.1) *	<0.0001
	FBI (max. 72)	0.8 (1.8)	6.5 (8.0)	9.1 (9.2) *	.003
IADLs	FAQ (max. 30)	0.04 (0.2)	2.0 (4.2) *	1.7 (2.2)	.002

Statistical results from an analysis of variance (ANOVA) test
Abbreviations: DEX = Dysexecutive Questionnaire, FBI = Frontal Behavioral Inventory, FAQ = Functional Activities Questionnaire
* different from controls, Tukey HSD post-hoc, $p<0.05$

Regions of gray matter loss in MCI subgroups vs. Controls
Voxel coordinates represent the peak voxel in local maxima, coordinates are expressed in Montreal Neurological Institute stereotactic space.

Regions of gray matter atrophy in dMCI and aMCI patients compared to controls					
Brain Region	x	y	z	t Statistic	z Value
<u>dMCI > Controls</u>					
Left dorsolateral prefrontal cortex	-44	10	50	3.76	3.61
Left dorsomedial prefrontal cortex	-20	-4	64	3.73	3.59*
<u>aMCI > Controls</u>					
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

p<0.05, FWE-corrected;
* indicates *p*=0.05, FWE-corrected.

Regions of gray matter loss in MCI subgroup comparison
Voxel coordinates represent the peak voxel in local maxima, coordinates are expressed in Montreal Neurological Institute stereotactic space.

Regions of gray matter atrophy in MCI patient comparison				
Brain Region	x	y	z	t Statistic
<u>dMCI > aMCI</u>				
caudate nucleus	-18	0	22	3.55
<u>aMCI > dMCI</u>				
right inferior parietal lobe	44	-60	30	3.36
				3.25*

$p<0.0001$, uncorrected.
* indicates $p<0.001$, uncorrected.