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Clinical and radiological characteristics of early versus late mild cognitive impairment in patients with comorbid depressive disorder

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Abstract

Objective—The classification of mild cognitive impairment (MCI) continues to be debated though it has recently been subtyped into late (LMCI) versus early (EMCI) stages. Older adults presenting with both a depressive disorder (DEP) and cognitive impairment (CI) represent a unique, understudied population. Our aim was to examine baseline characteristics of DEP-CI patients in the DOTCODE trial, a randomized controlled trial of open antidepressant treatment for 16 weeks followed by add-on donepezil or placebo for 62 weeks.

Methods/Design—Key inclusion criteria were diagnosis of major depression or dysthymic disorder with Hamilton Depression Rating Scale (HAM-D) score >14, and cognitive impairment defined by MMSE score ≤ 21 and impaired performance on the WMS-R Logical Memory II test. Patients were classified as EMCI or LMCI based on the 1.5 SD cutoff on tests of verbal memory, and compared on baseline clinical, neuropsychological, and anatomical characteristics.

Results—79 DEP-CI patients were recruited of whom 39 met criteria for EMCI and 40 for LMCI. The mean age was 68.9 and mean HAM-D was 23.0. LMCI patients had significantly worse ADAS-Cog ($p < 0.001$), MMSE ($p = 0.004$), Block Design ($p = 0.024$), Visual Rep II ($p = 0.006$), CFL Animal ($p = 0.006$), UPSIT ($p = 0.051$), as well as smaller right hippocampal volume ($p = 0.037$) compared to EMCI patients. MRI indices of cerebrovascular disease did not differ between EMCI and LMCI patients.

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Conclusions—Cognitive and neuronal loss markers differed between EMCI and LMCI among patients with DEP-CI, with LMCI being more likely to have the clinical and neuronal loss markers known to be associated with Alzheimer's disease.

Keywords

Early mild cognitive impairment; late mild cognitive impairment; depression

1. Introduction

Depression (DEP) and cognitive impairment (CI) are the most common neuropsychiatric disorders in older adults, with a co-occurrence that may exceed chance ^{1,2}. Patients presenting with DEP-CI represent a unique, understudied population that is difficult to diagnose, treat and estimate prognosis. CI is associated with poor antidepressant response in depressed older adults ³. In most but not all studies, depression in individuals with CI consistently increases the risk of transition to a diagnosis of dementia ^{4,5}. DEP-CI patients convert to dementia at a greater rate than elderly non-depressed patients with MCI ⁶, lending support to the idea that late-life depression may be a risk factor for later dementia or represent a prodromal condition in many patients with dementia because depressive symptoms often accompany rather than precede cognitive decline ⁷.

Within MCI, amnesic (aMCI) and non-amnesic (naMCI) subtypes have been delineated with the distinction based on poor performance relative to standardized norms on either memory tests (aMCI) or non-memory tests (naMCI) ^{8,9}. Patients with aMCI are thought to be more likely to transition to a clinical diagnosis of AD, whereas patients with naMCI are considered to be more likely to transition to non-AD dementia, such as vascular dementia or dementia with Lewy bodies ¹⁰. Due to growing interest in early intervention and prediction, aMCI has been further subtyped into early aMCI (EMCI) and late aMCI (LMCI). While distinctions between aMCI and naMCI have been extensively studied ¹¹, little information is available on the distinction between EMCI and LMCI, and, in particular, a lack of information on differences in the presence of comorbid depression.

EMCI and LMCI subtypes are distinguished by the severity of amnesic impairment with LMCI requiring memory test performance greater than 1.5 SD below standardized norms on memory tests and EMCI requiring memory test performance between 1.0 – 1.5 SD below standardized norms. This classification has been used in the Alzheimer's Disease Neuroimaging Initiative (ADNI) studies, and is related to the distinction between aMCI and naMCI that is the predominant subtyping classification in the literature on MCI¹². While LMCI is essentially synonymous with the longstanding definition of aMCI, EMCI does not necessarily equate with naMCI in which deficits in non-memory cognitive domains need to reach the 1.5 SD threshold ¹³. EMCI patients have milder verbal memory impairment than LMCI and are thought to represent a very early stage of disease that may be optimal for disease-modification treatments. These subtype differences may have implications for differences in biomarker abnormalities, likely clinical course, and treatment response in patients with comorbid depression and cognitive impairment.

Cardiovascular disease, which is a risk factor for both late-life depression and dementia, may contribute to the development of both conditions by disrupting prefrontal systems governing executive functions and mood regulation. One subtype coined as “vascular depression” is characterized by deficits in executive functioning, presence of white matter hyperintensities, and poor antidepressant treatment response¹⁴. The vascular depression subtype, however, has been explored primarily in the context of non-amnesic MCI and amnesic MCI has typically been excluded in most studies of vascular depression. Therefore, patients in these studies may not represent the full range of patients with DEP-CI^{15–17}. There is also an established association between vascular disease and the development of vascular dementia, with major depressive disorder occurring in approximately 20% of patients with vascular dementia¹⁸. Thus, vascular depression might fall on a continuum that would include vascular disease, vascular MDD itself, post-stroke depression, and vascular dementia. Indeed, Steffens and colleagues have reported in a case study of an elderly woman the progression of subcortical ischemic disease from vascular depression to vascular dementia¹⁹.

Several neuroanatomical factors have been identified as predictors of the transition from MCI to AD. The medial temporal lobe contains several regions involved in declarative memory. Amongst these are the hippocampus and parahippocampal gyrus. In MCI, and to a greater extent AD, there is volumetric loss in these areas, which is associated with poor performance on measures of verbal learning, memory, and olfactory identification. In patients with MCI, those who convert to AD have greater rate of atrophy in the hippocampus and entorhinal cortex than those who remain cognitively stable²⁰. Further, those with DEP-CI who transition to a clinical diagnosis of AD do so at a younger age and with greater hippocampal volume loss than patients with MCI alone⁶. Taken together, these reports suggest that volumetric atrophy in the medial temporal lobe increases the risk of transition to AD, and depressive symptoms may exacerbate this tendency.

To clarify the clinical and radiological correlates of patients with DEP-CI, we examined differences between EMCI and LMCI in a sample of patients with depression and cognitive impairment participating in a clinical trial. At baseline, we hypothesized that there will be worse global cognitive functioning (ADAS-Cog, MMSE) in LMCI than EMCI. We also expected smaller medial temporal lobe volume in LMCI than EMCI. Finally, we evaluated whether cerebrovascular pathology differs between EMCI compared to LMCI by examining white matter hyperintensities in the two groups.

2. Materials and Methods

2.1 Inclusion Criteria

The full DOTCODE study procedures have been described elsewhere²¹. The study was approved by the New York State Psychiatric Institute/Columbia University Institutional Review Board and the Duke University Medical Center Institutional Review Board. The study is registered at ClinicalTrials.gov (NCT01658228). The targeted sample size based on power analysis for the clinical trial was 80 patients with depression and cognitive impairment; 81 patients were recruited but two patients did not complete baseline

procedures, leaving a final sample of 79 patients. Of these 79 patients, 39 participated at the NYSPI/Columbia site and 40 participated at Duke.

Patients were eligible if they were age 55–95, had 8 years minimum of education, met diagnosis for major depression or dysthymic disorder (based on SCID-P evaluation), had a minimum score of 14 on the 24-item Hamilton Rating Scale for Depression, presented with subjective memory or other cognitive complaints, met criteria for CI (defined as a score ≥ 11 for delayed recall on the Wechsler Memory Scale-Revised Logical Memory II test), Folstein Mini Mental State Exam (MMSE) score ≥ 21 , received a Clinical Dementia Rating of 0.5, and were willing and capable of giving informed consent. Patients were excluded if they met criteria for dementia (DSM-IV), probable Alzheimer's Disease (NINCDS-ADRDA criteria), schizophrenia, schizoaffective disorder, psychotic depression, other psychosis, bipolar I, alcohol or substance dependence or abuse (current or within the past 6 months), active CNS infections (such as meningitis, encephalitis, septicemia, or any other infectious process), post-traumatic dementia (with clear temporal relationship to severe head injury with loss of consciousness), Huntington's disease, multiple sclerosis, Parkinson's disease, other neurological disorders with focal signs, mental retardation, or any acute medical condition. Additionally, patients were excluded if they had active suicidal ideation or made a suicide attempt in the last 6 months, had a stroke with residual neurological defects, use medications that would interact in a clinically significant manner with the study medications (warfarin or monoamine oxidase inhibitors), use medication definitely known to negatively impact cognition (benzodiazepines in lorazepam equivalents ≥ 2 mg daily, narcotics, and anticholinergics) and deemed the likely cause of cognitive impairment, were currently taking an effective antidepressant, or had QTc >460 ms on baseline EKG. If both citalopram and venlafaxine were contraindicated, the patient would be ineligible. Patients with hypertension (BP $> 140/90$) were excluded unless their primary care physician was comfortable with the patient's blood pressure being above 140/90 but below 150/100 mm Hg. Full medical exclusion criteria, phases of treatment with antidepressant medication and subsequent randomization to add-on donepezil or placebo have been described in detail elsewhere²¹, and are not discussed further in this paper.

2.2. Measures

The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) was administered to document medical burden in the major organ systems. The University of Pennsylvania Smell Identification Test (UPSIT, scratch and sniff 40-item multiple-choice test) was the primary odor identification measure. The Functional Activities Questionnaire was given to both patients and informants to evaluate instrumental and social/cognitive activities of daily living. A neuropsychological test battery was used to tap into deficits in both DEP and CI. The ADAS-Cog (13-item version, max score 85) was administered to determine cognitive functioning across multiple domains. Non-verbal learning and memory were assessed using the WMS-III Visual Reproduction subtest. Visuospatial skills were measured using the WAIS-III Block Design subtest. The 15-item Boston Naming Test (total spontaneous responses) was used to assess confrontation naming ability. Letter and Animal naming (60-second trials) were used to evaluate verbal fluency. Trails A served as an estimate of attention. Trails B and the Stroop Color-Word Interference Test were used to evaluate

executive functioning. WAIS-III Digit Symbol measured processing speed. Apolipoprotein E genotype was determined through the laboratory of the Human Genetics Resources Core (HGRC) at Columbia University using blood samples.

2.3. Cognitive Impairment Subtyping

Patients were classified as late MCI (LMCI) according to the ADNI definition^{12,22}, which is consistent with amnesic MCI, if they scored ≥ 1.5 SD below norms on the WMS-R Logical Memory II test or the FC-SRT conducted at screening. All other patients who met the above inclusion criteria for cognitive impairment were classified as early MCI (EMCI).

2.4. MRI

Images were acquired on a GE Signa 3 Tesla whole body scanner with the following sequences: 1) 3-Plane localizer repetition time (TR) = 23.4 ms, echo time (TE) = 1.7 ms, flip angle = 30°, bandwidth = 31.3 MHz, field of view (FOV) = 24 × 24 cm, thickness = 5.0 mm, Spacing = 1.5 mm, 9 slices per volume (3 axials, 3 sagittals, 3 coronals), matrix 256 × 128, 2) 3D SPGR anatomical sequence TI 500 ms, TR 5 ms, TE minimum (1.3 ms), flip angle 11°, bandwidth 31.25 MHz, FOV 26 × 26, slice thickness 1.1 mm, spacing 0.0, 128 slices per volume, 1 NEX images × 2 (acquisitions averaged off line), matrix 256 × 256 coronal oblique orientation, aligned to the long axis of the hippocampus, and 3) T2 FLAIR: 2D IR axial images, TR = 10,000 msec, TE = 122 msec, TI = 2000 msec, FOV = 24, matrix = 320 × 256, NEX = 1, slice thickness = 5 mm, 31 slices.

Regions of interest (ROIs), chosen a priori, were based on published studies identifying regions predicting increased risk of dementia in MCI. A single trained, experienced technician drew the hippocampus, parahippocampal gyrus, and entorhinal cortex ROIs using atlas based approaches on MRI scans. This technician established high interrater reliability with other trained expert raters (ICC=.90–.96) and high intrarater reliability over one year (ICC=.97–.99)²³.

Hyperintensities on axial T2 FLAIR images were rated using the Fazekas-modified Coffey Rating Scale²⁴, a qualitative rating of lesion severity. Deep white matter hyperintensities (DWM) are scored as 0 (absent), 1 (punctate foci), 2 (beginning confluence of foci), and 3 (large confluent areas); subcortical gray matter hyperintensities in the basal ganglia (SCG) are scored as 0 (absent), 1 (punctate), 2 (multipunctate), and 3 (diffuse); periventricular hyperintensities (PVH) are scored as 0 (absent), 1 (caps), 2 (smooth halo), and 3 (irregular and extending into the deep white matter). Additionally, T2 FLAIR lesion volume was measured on a parallel, semi-automated version of this scale using MRIcro²⁵. Our group has published extensively using these methods^{26,27} and raters using this semi-automated approach have achieved excellent interrater reliability (ICC=.98).

2.5. Statistical analyses

Means and standard deviations were computed to describe continuous variables, while frequencies and percentages were used for categorical variables. All statistical tests were performed at $\alpha=0.05$ for inference using the Statistical Package for the Social Sciences version 23 software. The chi square test for independence and the independent samples t-test

were used to evaluate differences between sites on demographic characteristics of age, sex, race, and education. ANCOVA was used to compare EMCI and LMCI groups on continuous clinical, neuropsychological, and anatomical variables. Logistic regression was used for nominal anatomical variables. All ANCOVA and logistic regression models included age, sex, HAM-D, and years of education as covariates.

3. Results

3.1. Baseline, demographic, and clinical characteristic

Descriptive statistics for demographic characteristics, clinical surveys, neuropsychological assessments, and brain tissue volumes are presented in Tables 1–3. The average age was 68.9 (SD 9.0) years, with 51.9% of the sample being male and 48.1% female. There was no difference between the two sites in age [$t(77)=-0.5$, $p=.62$], sex [$\chi^2(2, n=79)=0.1$, $p=.81$], or education [$t(77)=-0.5$, $p=.60$]. In terms of marital status, 35.4% were single or never married, 24.1% were divorced or separated, 29.1% were married or living with a partner, and 11.4% were widowed. 36.7% were currently employed, 46.8% were retired, and 16.5% were unemployed or disabled. All patients were living at home.

The mean ADAS-Cog score was 14.3 and the mean 24-item HAM-D score was 23.0. Many patients had a family history of depression (50.6%), dementia (45.6%), or Alzheimer's disease (16.5%). On the CIRS-G, patients had a mean score of 7.4, with 10.1% reporting current mild or past significant vascular problems, and 25.3% reporting moderate disability or comorbidity as a result of their vascular illness. The mean FAQ – Patient Score was 4.0 and the mean FAQ – Informant Score was 3.1, indicating that patients were generally able to complete instrumental activities of daily living with minimal difficulty and were not consistently dependent upon others. 29.5% of patients possessed a homozygous or heterozygous genotype for the ApoE4 allele.

3.2. Anatomical Characteristics

Fifty-five patients completed MRIs. Of these, 24 were EMCI and 31 were LMCI. Patients possessed varying severities of deep white matter hyperintensities: 5.5% were rated as 3, 10.9% as 2, 60.0% as 1, and 23.6% were rated as having none. Periventricular hyperintensities were absent in only 7.3% of the sample, with 47.3% having a rating of 1, 30.9% had a rating of 2, and 14.5% had a rating of 3. Subcortical grey matter hyperintensities occurred in a single patient. For hyperintensity volumes obtained using the semi-automated method, patients had means of 5.6, 28.5, and 34.1 cc for deep white, periventricular, and total hyperintensity volumes respectively.

3.3. EMCI versus LMCI Analyses

39 patients met criteria for EMCI and 40 met criteria for LMCI. Both subtypes were comparable in terms of demographic features including age, sex, education, race, marital status, and employment status (Table 1). No differences between the subtypes were found for family histories of depression or dementia, prevalence of vascular problems, baseline depression severity, or ApoE genotype (Table 1). There were also no differences between the groups on self-reported or informant-reported instrumental activities of daily living. In terms

of cognitive functioning, there was a statistically significant difference between groups on ADAS-Cog (Figure 1), MMSE, Block Design, Digit Symbol, Animal fluency, Visual Reproduction II, and UPSIT performance. No differences between the groups were found for Digit Symbol, Letter fluency, Visual Reproduction I, measures of executive functioning (Trails or Stroop), or Boston Naming Test (Table 2).

The LMCI group had statistically significantly less volume in the right hippocampus (Table 3). All other regions had comparable volumes in EMCI and LMCI, including the bilateral entorhinal cortex, bilateral parahippocampal gyrus, left hippocampus, and total hippocampus (Figure 2). For white matter hyperintensities, there were no statistically significant group differences in lesion severity for DWM, PVH, or SCG using the Fazekas-modified Coffey Rating Scale. In terms of lesion volume, there were also no statistically significant differences between the LMCI and EMCI groups.

4. Discussion

This is the first report to describe the characteristics of EMCI versus LMCI subjects in patients with depressive disorder. Our sample of older adults (mean age 68.9, SD 9.0) demonstrated moderate levels of depression and met broad criteria for mild cognitive impairment. Risk factors such as family history of AD, presence of the ApoE 4 allele, and cardiovascular disease were commonly reported by patients. Notably, the LMCI group had worse global cognitive functioning and smaller right hippocampal volume than the EMCI group. White matter hyperintensity burden did not vary between LMCI and EMCI.

Consistent with expectations, patients with LMCI performed worse on measures of global cognitive functioning. This supports the notion that decline in verbal memory ability is associated with decline in other cognitive domains in most patients²⁸. At the domain level, those with LMCI had reduced visuospatial ability, semantic fluency, and delayed nonverbal memory. There was also worse olfactory identification performance in the LMCI group compared to the EMCI group. This is in line with reports from other studies which find that olfactory impairment is linked with both incident LMCI and progression from LMCI to dementia, but not with incident naMCI²⁹. Despite these broad differences in cognitive abilities, the two groups did not differ with respect to instrumental activities of daily living.

Smaller medial temporal lobe volume was predicted for patients with LMCI. Indeed, smaller right hippocampus volume was observed in the LMCI group, which has been reported by other groups^{30,31}. The right hippocampus is involved in spatial memory whereas the left hippocampus plays a greater role in verbal memory³², making it somewhat surprising that no difference was found for the left hippocampus, seeing as our groups were formed on the basis of verbal memory functioning. Visual Reproduction II, a measure of spatial memory, did differ across groups. Consideration should be given to the possibility that early volume loss in the right hippocampus alongside dysfunction in visual memory ability are unique characteristics of DEP-CI. Follow-up studies may need to consider classifying amnesic patients based on any memory modality as EMCI or LMCI, instead of verbal memory impairment alone. There was no group difference for volume in the entorhinal cortex, which is a region located within the parahippocampal gyrus. Given the susceptibility of the

entorhinal cortex to decay earlier and at a faster rate than the hippocampus in patients with LMCI³³, and the role of the entorhinal cortex in delayed recall, it is unexpected to find no difference between our LMCI group and EMCI group. The entorhinal cortex is a small structure and small degrees of atrophy at the MCI stage can sometimes be difficult to measure accurately³⁴.

We hypothesized greater white matter hyperintensity volume amongst patients with LMCI, yet found no differences between the groups in terms of WMH volume or Fazekas ratings. There were also no group differences in reported vascular problems. naMCI is generally thought to largely comprise vascular cognitive impairment that is often a prodrome to vascular dementia, whereas aMCI is thought to be more likely to indicate future transition to AD. As such, naMCI is presumed to have a greater occurrence of cardiovascular health problems and greater WHM load, while aMCI is believed to have greater temporal lobe volume reductions. This was not the case for our amnesic sample of DEP-CI, where only temporal lobe volumes were different across the EMCI and LMCI subtypes. Because cardiovascular disease and WMHs are strongly linked with executive dysfunction in DEP and CI, the equivalence of these factors across groups may partially explain their comparable performance on tests of executive functioning, such as Trails B and Stroop. This sample was selected specifically for memory complaints and patients with more than moderate levels of hypertension were excluded, thereby limiting the severity of cardiovascular disease and perhaps reducing the prevalence of MRI-defined cerebrovascular pathology in our sample.

This study involved a sample of older adults with co-occurring depression and cognitive impairment. However, in the literature, these two disorders are typically kept separate. Research focused on MCI tends to exclude depression by excluding affective disorders^{35–37}, and research on late-life depression tends to exclude memory disorders and cognitive impairment³⁸ by using a cutoff score for the Mini-Mental State Examination^{27,39–42}. This creates a bias against the study of comorbid depression and cognitive impairment in older adults. Since there is a clear, commonly occurring, association between depression and MCI^{43–45}, it is important to learn more about the characteristics of patients presenting with both conditions.

Previously, the Alzheimer's Disease Neuroimaging Initiative (ADNI) enrolled subjects with LMCI and EMCI who did not meet criteria for a depressive disorder¹². In the ADNI dataset, the LMCI group has significantly worse ADAS-Cog performance and smaller total hippocampal volume than the EMCI group⁴⁶. The discrepant total hippocampal volume findings between our study and ADNI may be due to the unique presentation of DEP-CI, comparably lower statistical power, or differing approaches for obtaining hippocampal volume. Our study employed a manual segmentation approach, whereas Beckett et al. used a fully-automated approach, which tends to estimate greater overall hippocampal volumes than manual methods by expanding the hippocampal ROI to the adjacent white matter⁴⁷.

The DEP-CI subjects presented in this report were enrolled in a longitudinal trial to test the efficacy of combined antidepressant and donepezil therapy versus antidepressant alone. This study contains several limitations balanced by its unique strengths. We did not adjust for multiple comparisons because the subtype analyses are exploratory in nature and we did not

want to risk failing to identify a potentially important finding deserving of future study. However, this increases the risk of potentially spurious findings. Additionally, the exclusive use of memory tests to determine eligibility precludes the sample from representing the full range of possible non-amnestic MCI subtypes. Exclusion of more than moderate levels of hypertension limits the presentations of MCI due to cerebrovascular disease. Nonetheless, the broad inclusion and exclusion criteria for depression and amnestic cognitive impairment increases generalizability to clinical settings. Further longitudinal studies to examine clinical, genetic, neuronal loss and pathological markers of AD in subjects with and without comorbid depression and cognitive impairment are warranted to assess possible interaction of these factors. Such studies may provide critical information to develop personalized treatment for patients with DEP-CI and may provide additional insights to delay the onset of dementia.

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Key Points

- Patients with comorbid depression and cognitive impairment were classified as EMCI or LMCI
- LMCI patients had reduced cognitive functioning across multiple domains
- Smaller right hippocampal volume for LMCI
- MRI indices of cerebrovascular disease did not differ between EMCI and LMCI patients

Figure 1. ADAS-Cog (13 Item) by MCI subtype

The LMCI group had significantly higher (worse) ADAS-Cog Total scores than EMCI group.

Figure 2. Hippocampus volume by MCI subtype

The LMCI group had significantly smaller right hippocampus volume than the EMCI group. No significant group differences were observed for left hippocampal or total hippocampal volume.

Table 1

Baseline demographic and clinical characteristics

Demographic Variable	All Patients (n=79)	EMCI (n=39)	LMCI (n=40)	T-test/Chi Square
Site				$X^2=3.7$, $p=0.056$
NY	39 (49.4%)	15 (38.5%)	24 (60.0%)	
DU	40 (50.6%)	24 (61.5%)	16 (40.0%)	
Age	68.9 (9.0)	67.5 (8.6)	70.2 (9.2)	$t=-1.3$, $p=0.185$
Sex				$X^2=1.0$, $p=0.313$
Male	41 (51.9%)	18 (46.2%)	23 (57.5%)	
Female	38 (48.1%)	21 (53.8%)	17 (42.5%)	
Education	15.3 (2.8)	15.3 (3.2)	15.3 (2.3)	$t=0.1$, $p=0.946$
Race				$X^2=3.7$, $p=0.156$
Caucasian	58 (73.4%)	32 (82.1%)	26 (65.0%)	
Black/African American	12 (15.2%)	5 (12.8%)	7 (17.5%)	
Hispanic	9 (11.4%)	2 (5.1%)	7 (17.5%)	
Marital Status				$X^2=5.9$, $p=0.119$
Single/never married	28 (35.4%)	9 (23.1%)	19 (47.5%)	
Divorced/separated	19 (24.1%)	10 (25.6%)	9 (22.5%)	
Married/living with partner	23 (29.1%)	15 (38.5%)	8 (20.0%)	
Widowed	9 (11.4%)	5 (12.8%)	4 (10.0%)	
Employment				$X^2=0.6$, $p=0.734$
Working	29 (36.7%)	16 (41.0%)	12 (32.5%)	
Retired	37 (46.8%)	17 (43.6%)	20 (50.0%)	
Unemployed/Disabled	13 (16.5%)	6 (15.4%)	7 (17.5%)	
ADAS-Cog Total	14.3 (5.4)	12.0 (4.5)	16.6 (5.3)	$t=-4.2$, $p<0.001$
HAM-D	23.0 (5.1)	23.2 (5.5)	22.9 (4.8)	$t=0.3$, $p=0.776$
Family History of Depression				$X^2=0.3$, $p=0.573$
No	39 (49.4%)	18 (46.2%)	21 (52.5%)	
Yes	40 (50.6%)	21 (53.8%)	19 (47.5%)	
Family History of Dementia				$X^2=0.1$, $p=0.757$
No	43 (54.4%)	22 (56.4%)	21 (52.5%)	
Yes	36 (45.6%)	17 (43.6%)	19 (47.5%)	
Family History of Alzheimer's				$X^2=0.7$, $p=0.390$
No	66 (83.5%)	34 (87.2%)	32 (80.0%)	
Yes	13 (16.5%)	5 (12.8%)	8 (20.0%)	

Demographic Variable	All Patients (n=79)	EMCI (n=39)	LMCI (n=40)	T-test/Chi Square
CIRS Total	7.4 (4.2)	8.1 (4.3)	6.7 (4.0)	t=1.6, p=0.120
Vascular Problems				X ² =1.8, p=0.184
No	51 (64.6%)	28 (71.8%)	23 (57.5%)	
Yes	28 (35.4%)	11 (28.2%)	17 (42.5%)	
FAQ Patient	4.0 (3.5)	3.9 (3.8)	4.1 (3.2)	t=-0.3, p=0.775
FAQ Informant	3.1 (4.0)	2.7 (4.2)	3.6 (3.9)	t=-1.0, p=0.326
ApoE genotype				X ² =0.01, p=0.924
ApoE allele not present	51 (64.6%)	25 (69.4%)	26 (68.4%)	
ApoE allele present	23 (29.1%)	11 (30.6%)	12 (31.6%)	

Comparison of EMCI and LMCI groups at baseline on clinical and demographic variables. The LMCI group had significantly higher (worse) ADAS-Cog Total scores than the EMCI group. No other significant group differences were found. All values are expressed as mean (SD) or n (%).

Table 2

ANCOVA of neuropsychological measures

Instrument	All Patients (n=79)	EMCI (n=39)	LMCI (n=40)	F-Ratio	P-value	Effect Size
Folstein MMSE	27.9 (2.0)	28.5 (1.7)	27.3 (2.1)	F(1,73)=8.7	p=0.004	$\eta_p^2=0.106$
WAIS-III Block Design	31.2 (11.3)	34.1 (11.3)	28.3 (10.7)	F(1,73)=5.4	p=0.024	$\eta_p^2=0.069$
WAIS-R Digit Symbol	42.0 (12.2)	45.0 (12.5)	39.1 (10.1)	F(1,73)=3.5	p=0.065	$\eta_p^2=0.046$
CFL Letter Total	40.3 (12.4)	42.8 (11.0)	38.0 (13.4)	F(1,73)=3.4	p=0.069	$\eta_p^2=0.045$
CFL Animal Total	17.5 (4.6)	19.0 (4.7)	16.0 (4.2)	F(1,73)=8.1	p=0.006	$\eta_p^2=0.100$
Stroop Interference	-2.3 (8.5)	-1.4 (6.7)	-3.3 (10.0)	F(1,73)=1.1	p=0.290	$\eta_p^2=0.015$
WMS-R Visual Rep I	32.1 (5.8)	32.9 (6.0)	31.2 (5.6)	F(1,73)=1.7	p=0.198	$\eta_p^2=0.023$
WMS-R Visual Rep II	23.7 (11.1)	27.2 (10.2)	20.3 (10.9)	F(1,73)=8.0	p=0.006	$\eta_p^2=0.099$
Trails A	46.6 (20.1)	44.6 (21.9)	48.7 (18.3)	F(1,73)=0.1	p=0.710	$\eta_p^2=0.002$
Trails B	130.0 (64.5)	120.9 (63.3)	138.8 (65.2)	F(1,73)=0.7	p=0.418	$\eta_p^2=0.009$
BNT Total Correct	14.5 (1.1)	14.6 (1.1)	14.4 (1.1)	F(1,73)=0.5	p=0.484	$\eta_p^2=0.007$
UPSIT	29.4 (7.7)	31.6 (7.7)	27.2 (7.3)	F(1,73)=3.9	p=0.051	$\eta_p^2=0.052$

Analysis of covariance comparing EMCI and LMCI groups on neuropsychological test performance. The LMCI group had significantly worse MMSE, Block Design, Animal fluency, Visual Reproduction II, and UPSIT performance than the EMCI group. Note: all values are expressed as mean (SD). All models are adjusted for age, sex, HAM-D, and years of education.

Table 3

ANCOVA and logistic regression of MRI lesions and brain tissue volumes

Measurement	MRI Patients (n=55)	EMCI (n=24)	LMCI (n=31)	F-ratio/Wald test	P-value	Effect Size
Fazekas hyperintensity rating						
Deep white matter						
Low (0-1)	46 (83.6%)	20 (83.3%)	26 (83.9%)	Wald=0.2	p=0.656	OR=0.647
High (2-3)	9 (16.4%)	4 (16.7%)	5 (16.1%)			
Periventricular						
Low (0-1)	30 (54.5%)	16 (66.7%)	14 (45.2%)	Wald=1.4	p=0.244	OR=2.103
High (2-3)	25 (45.5%)	8 (33.3%)	17 (54.8%)			
Hyperintensity volume(cc)						
Deep white volume	5.6 (11.7)	3.8 (11.4)	7.0 (12.0)	F(1,49)=0.9	p=0.338	$\eta_p^2=0.019$
Periventricular volume	28.5 (45.0)	24.2 (43.5)	31.8 (46.6)	F(1,49)=0.7	p=0.797	$\eta_p^2=0.001$
Brain volume(cc)						
Total hippocampus	4.9 (0.7)	5.1 (0.6)	4.8 (0.7)	F(1,49)=2.1	p=0.157	$\eta_p^2=0.040$
Right hippocampus	1.9 (0.3)	2.0 (0.3)	1.9 (0.2)	F(1,49)=4.6	p=0.037	$\eta_p^2=0.085$
Left hippocampus	3.0 (0.4)	3.1 (0.4)	2.9 (0.5)	F(1,49)=0.8	p=0.380	$\eta_p^2=0.015$
Right parahippocampal gyrus	2.0 (0.4)	2.1 (0.3)	1.9 (0.4)	F(1,49)=2.0	p=0.164	$\eta_p^2=0.038$
Left parahippocampal gyrus	3.1 (0.5)	3.2 (0.4)	3.0 (0.5)	F(1,49)=1.3	p=0.260	$\eta_p^2=0.025$
Right entorhinal cortex	0.2 (0.03)	0.2 (0.04)	0.1 (0.03)	F(1,49)=0.5	p=0.464	$\eta_p^2=0.004$
Left entorhinal cortex	0.2 (0.03)	0.2 (0.04)	0.2 (0.03)	F(1,49)=0.1	p=0.864	$\eta_p^2=0.001$

Analysis of covariance comparing EMCI and LMCI groups on radiological characteristics. The LMCI group had significantly smaller right hippocampus volume than the EMCI group. No other significant group differences were observed for Fazekas hyperintensity ratings, hyperintensity volumes, or other temporal lobe structures. Note: all values are expressed as mean (SD) or n (%). All models are adjusted for age, sex, HAM-D, and years of education.