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An Investigation of PreMCI: Subtypes and Longitudinal Outcomes

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Abstract

Background/Aims—To investigate the clinical features and rates of progression of conditions that are not considered to be normal, but do not fulfill criteria for mild cognitive impairment (MCI).

Methods—We longitudinally evaluated 269 elderly subjects who did not meet formal criteria for MCI at baseline but had: 1) a clinical history suggesting MCI without neuropsychological deficits (PreMCI-Clinical); or 2) neuropsychological deficits on one or more memory measures in conjunction with a negative clinical examination (amnestic PreMCI-NP) or were normal on both neuropsychological and clinical examination.

Results—The rates of progression to MCI or dementia over an average 2 to 3 year period was 3.7% for NCI subjects, whereas it was significantly greater for all PreMCI subtypes (22.0% for PreMCI-Clinical, 38.9% for amnestic PreMCI-NP subjects with two or more memory impairments). Among PreMCI subjects as a whole, lower baseline scores on object memory and category fluency tests were the best predictors of progression to MCI or dementia. Cardiovascular risk factors, Parkinsonian symptoms and hippocampal atrophy were not associated with progression.

Conclusion—Distinct PreMCI subtypes defined on the basis of clinical and neuropsychological evaluations were found to have distinct charateristics, but both subtypes demonstrated elevated risk for progression to MCI or dementia. Despite the lack of evidence of clinical impairment,

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subjects with neuropsychological deficits in two memory domains were particularly at increased risk for progression of their deficits.

Keywords

PreMCI; Mild Cognitive Impairment; amnestic MCI; Alzheimer's disease; MRI; Neuropsychological Tests; Memory Impairment; Hippocampal Volumes

INTRODUCTION

Amnestic mild cognitive impairment (aMCI) is considered to be an intermediate state between normal aging and dementia,[1,2] even though the neuropathology of aMCI and Alzheimer's disease (AD) patients is frequently indistinguishable.[3] In a non-demented patient, the diagnosis of aMCI typically involves a history of cognitive impairment, provided by the patient and/or a knowlegable informant and confirmation of cognitive deficits by neuropsychological testing.[4,5] Among cognitively normal elderly individuals, several risk factors increase the risk for progression to MCI or AD, including subjective memory complaints, biomarkers linked to increased risk for developing AD, such as elevated amyloid deposition, medial temporal atrophy on MRI scans and regional hypometabolism on PET scans,[6] elevated tau/aβ CSF ratios,[7] abnormal fMRI activation patterns,[8] maternal family history of AD,[9] and ApoE4 genotype.[10]

Nevertheless, normal subjects with abnormal biomarkers do not always progress to MCI or AD, whereas those with normal biomarkers may evidence progression to MCI or dementia[11]. For these reasons there may be reluctance to initiate treatment at a very early stage of AD without the additional presence of clinical symptoms, a Clinical Dementia Rating (CDR) score of 0.5, or evidence of objective cognitive impairment, as individuals with such symptoms are more likely to progress to dementia and demonstrate AD pathology at autopsy.[12, 13,14] Thus, it is important to develop formal criteria for an intermediate state between normal cognition and aMCI, (i.e., a PreMCI stage), that is likely to be progressive over time and may represent the earliest clinically definable stage of AD.

We report here on the results of a longitudinal study of elderly subjects who had either: a) isolated amnestic impairments shown on neuropsychological tests, without clinical history and examination suggesting MCI; or b) a normal neuropsychological profile with a clinical history and examination suggesting MCI. We also report on the rates of progression to a formal diagnosis of MCI or dementia in these different PreMCI subtypes, as well as the clinical, neuropsychological and neuroimaging features at baseline that predict progression of cognitive and functional impairment over time.

METHODS

Subject Recruitment

The current sample was recruited from a group of 937 subjects who were enrolled in the Florida Alzheimer's Disease Research Center Clinical Core (FADRC-CC) in Miami Beach and Tampa, FL between 2005 and 2009. The study was approved by the Institutional Review Board at Mount Sinai Medical Center, Miami Beach, and the University of South Florida, Tampa. All subjects or a legal representative provided informed consent.

For purposes of this investigation, we selected cases diagnosed with PreMCI (n=208) or no cognitive impairment (NCI) (n= 253), as described below. Of these 461 cases, 269 subjects, who had complete baseline data and at least one annual longitudinal follow-up evaluation at the time of data analysis, were included in this study. No difference in age, educational

attainment or MMSE scores were found among NCI and PreMCI subjects who had or did not have longitudinal follow-up.

Evaluations—The following were completed on all subjects: (1) full clinical history, obtained from the participant and corroborated by a reliable informant; (2) neurological evaluation; (3) psychiatric evaluation, including administration of the Geriatric Depression Scale (GDS)[15] and the Neuropsychiatric Inventory [16]; (4) Clinical Dementia Rating scale (CDR)[17]; (5) Mini-Mental State Evaluation (MMSE) [18]; (6) a neuropsychological test battery, as outlined in NACC[19] protocol, as well as additional tests, which included the Three-Trial Fuld Object Memory Evaluation (OME)[20] and Hopkins Verbal Learning Test-Revised (HVLT-R)[21].

Cardiovascular Risk (CVR) Score was calculated as the sum of 10 independent risk factors selected from the NACC/UDS assessment protocol (Form A5: Subject Health History).[19] These factors were rated as present or absent and included: (1) heart attack/cardiac arrest; (2) atrial fibrillation; (3) angioplasty/endarterectomy/coronary artery bypass surgery; (4) congestive heart failure; (5) stroke/TIA; (6) hypertension; (7) hypercholesterolemia; (8) diabetes; (9) smoked cigarettes in the last 30 days; (10) smoked more than 100 cigarettes in his/her life.

Unified Parkinson Disease Rating Scale (UPDRS)[22] (motor section) was utilized as a sensitive tool for quantifying motor dysfunction and parkinsonism in patients with various forms of MCI and dementia.

Diagnostic Procedures

(a) Physician's Baseline Cognitive Diagnosis: The physician assigned a cognitive diagnosis of NCI, MCI or Dementia, using the subject's entire clinical history and an assessment of cognitive and functional decline. The historical information was derived from an extensive interview with the participant and the informant and an informant-based, validated, detailed structured interview (the mCDR)[23], which is designed specifically to assess cognitive and functional impairment in the earliest stages of cognitive impairment. While the physician also took into consideration the suggestion of cognitive deficits (insight, comprehension and recall) during the physical and neurological examination, the clinician was blinded to objective neuropsychological testing, other than the score on the MMSE. Factors that were taken into consideration in making the cognitive diagnosis were a detailed subject clinical history, present medical and psychiatric conditions, the subject's educational and cultural background, sensory (especially visual and hearing) and motor deficits, language and speech disorders, and the perceived reliability of the informant.

(b) Neuropsychological Classification: The neuropsychological classification at baseline was made blind to the clinical examination. Because a single memory measure may not tap all aspects of early amnestic cognitive impairment, we selected subtests from three different memory measures (the Fuld Object Memory Evaluation, Wechsler Memory Scale Logical Memory delayed recall (WMS LM-D), and the Hopkins Verbal Learning Test-Revised delayed recall (HVLTR-D) that have been shown to be sensitive to early cognitive impairment in the elderly and for which we had co-normed data for individuals at different levels of age and educational attainment. The Modified Fuld Object Memory Evaluation (Fuld OME) requires the recall of ten visually presented household objects across three trials with selective reminding cues and with distractor trials that interfere with the learning of the to-be-remembered targets. The total score of the Fuld OME has been found to have high sensitivity and specificity in differentiating mildly demented and MCI subjects from normal elderly community-dwelling elderly[24,25]. The WMS LM-D (delayed paragraph recall) is

used in the NACC battery and in the Alzheimer's Disease Neuorimaging Initiative (ADNI)[19,26]. Finally, in the HVLTR-D, delayed recall of a list of 12 to-be-remembered targets is sensitive to rate of forgetting associated with medial temporal lobe deficits[27].

The use of multiple measures in each cognitive domain may result in spurious classification of impairment among subjects who are in fact normal. Therefore, impairment in the total recall on the Fuld OME, WMS LM-D, or HVLTR-D score was defined as the 7th percentile or lower, corresponding to approximately 1.5 standard deviations below expected levels, based on age- and education-relevant normative data. c) MRI Scans were acquired using a proprietary 3-D volumetric protocol on a GE or Siemens 1.5 Tesla machine. Volumetric analysis of brain MRIs utilized a modification of a commonly-used volumetric program (the International Brain Atlases using Statistical Parametric Mapping or IBASPM) [28].

Diagnostic Classification: Subjects diagnosed with aMCI or non-amnestic MCI (naMCI) in the FADRC-CC were judged to have met Petersen's criteria for MCI[5] as well as criteria for a diagnosis of Cognitive Impairment without Dementia (CIND)[32]. Subjects judged to meet criteria for Dementia were impaired on neuropsychological testing and judged by the clinician to have sufficient memory, or other cognitive and functional impairment to meet criteria for dementia by DSM-IV criteria[33].

For the purposes of this investigation, the following PreMCI diagnostic classifications were also made:

Amnestic PreMCI-NP: These subjects were judged to have normal cognition based on clinical evaluation by the physician but had impairment at 1.5 SD or more, relative to expected levels, on one of the three memory measures.

Amnestic PreMCI-NP+: These subjects were judged to have normal cognition based on the clinical evaluation by the physician but had impairment at 1.5 SD or more, relative *to* expected levels, on two or more of the three memory measures.

PreMCI-Clinical: These subjects were diagnosed as MCI by the physician on the basis of an informant history of cognitive impairment, with subtle functional decline, as well as by observations made during the physical, psychiatric and neurological examination. However, scores on all memory and non-memory measures, including Trails B[29], Category Fluency[30], and Block Design[31] were not lower than 1.0 SD below expected levels.

No Cognitive Impairment (NCI): These subjects were judged to be cognitively normal by the physician, and on neuropsychological testing and scores on all memory and non-memory measures were not lower than 1.0 SD below expected levels.

Progression over Time: Progression from a normal or PreMCI state to aMCI or naMCI required a diagnosis of MCI by clinical evaluation of the physician with confirmation of cognitive deficits by the neuropsychologist who used a threshold of 1.5 SD or below expected levels of performance on one or more memory measures, with or without non-memory impairment (aMCI)) or one or more non- memory measures (naMCI). While the follow-up diagnosis by the physician and the neuropsychologist were made independently, they were not blind to the previous or baseline diagnoses, as is the case with most longiudinal studies. These clinicians were directed to adhere to as strictly as possible to guidelines or rules in making the consensus diagnosis at baseline and all follow-up evalutions.

The designation of aMCI versus naMCI (which was assessed by Category Fluency, Trails B and Block-Design) was determined by the neuropsychological findings. Subjects were considered to have progressed to dementia if in the physician's judgment, social and occupational function was sufficiently impaired to fulfill DSM-IV criteria for a dementia syndrome[33] and the patient had deficits on memory testing equal to or greater than 2.0 SD below expected levels.

Statistical Analysis: Comparison of group means was conducted using a series of one-way analyses of variance (ANOVA) with the criteria for significance set at $p<.05$. For group contrasts, tatistical power exceeded .80 for an ANOVA with four groups and 269 subjects with an alpha level set at .05. Post-hoc tests of means were performed using the Scheffe's procedure with the criteria for significance set at $p\leq.05$. The application of different diagnostic criteria was compared to the NCI group for the purpose of identifying progressors versus non-progressors and was examined using receiver operator curve (ROC) analyses. Differences in proportions between groups were examined using chi-square analyes with the criteria for significance set at $p<.05$. Because of censoring of outcomes and unequal follow-up times, Cox regression procedures were employed to determine the extent to which baseline predictors among all categories of PreMCI subjects were associated with progression to either aMCI or dementia over time. We then calculated odds ratios associated with prediction of outcome and determined whether a combination of predictors could enhance prediction of outcome with the criteria for significance set at $p<.05$.

RESULTS

There were significant group differences with regards to age [$F(3,262)=3.92$; $p<.01$] and MMSE scores [$F(3,263=6.63$; $p<.001$]. The PreMCI-Clinical group was older than the amnestic PreMCI-NP group but there was no age difference between these groups and the NCI or PreMCI-NP+ groups. NCI subjects had higher MMSE scores and a greater percentage were females relative to the Pre-MCI-Clinical group but there were no further group differences in MMSE scores or gender distribution. As indicated in Table 1, there were no statistically significant differences between means with regards to educational attainment, primary language and average length of follow-up.

There were statistically significant differences with regards to the CDR sum of boxes (CDR-sb) [$F(3,234)=23.87$; $p<.001$] and UPDRS scores[$F(3,226)=4.45$; $p\leq.004$]. Post-hoc tests of means indicated that PreMCI-Clinical subjects had higher CDR-sb scores than the other study groups but there were no mean differences between groups with regards to UPDRS scores. No significant group differences between groups was observed with regards to the CVR score [$F(3,217)=2.00$; p=ns].

Study groups differed with regards to performance on all memory measures, namely the Fuld OME [$F(3,258)=16.78$; $p<.001$], WMS LM-D [$F(3,265)=67.63$; $p<.001$] and HVLTR-D [$F(3,275)=67.63$; $p<.001$]. Amnestic PreMCI-NP subjects evidenced lower scores than NCI subjects on the WMS LM-D and HVLTR-D, while the amnestic PreMCI-NP+ subjects scored lower on all three memory measures, relative to NCI subjects. In contrast, PreMCI-Clinical subjects had memory scores equivalent to those of NCI subjects.

There were also group differences on non-memory measures, including the category fluency [$F(3,65)=12.83$; $p<.001$]; Trails B [$F(3,259)=6.08$; $p\leq.001$] and Block Design [$F(3,254)=4.09$ $p<.01$]. Post-hoc tests of means indicated that the amnestic PreMCI-NP+ subjects evidenced lower category fluency scores than the other study groups but there were no other group mean differences on the other non-amnestic measures.

Although there were statistically significant F-values on ANOVAs conducted for right hippocampal volumes [F(3,204)=4.37; p <.006] and left hippocampal volumes [F(3,204)=3.04; p <.04, post-hoc test of means did not indicate statistically significant mean differences.

It should be noted that because of modest differences in age and other demographic between groups, we entered these variables into covariate models, but obtained no differences in the results reported above.

Subjects with NCI and PreMCI were followed for 10.4 to 54.1 months, with an average of 26.2 months (SD=10.7 months), and were considered to have met a clinical endpoint once they progressed to a formal diagnosis of aMCI, naMCI or Dementia. For purposes of chi-square analyses, the possible categories were: no progression, progression to naMCI, aMCI or dementia. A 4 × 4 (Diagnosis by Outcome) chi-square analysis revealed a significant difference between diagnostic groups with regards to outcome [X^2 (df=9)=48.79; p<.001]. In addition, individual chi-square analyses confimed that each PreMCI group had greater progression to a more impaired state relative to the NCI group. As depicted in Table 2, only 3.1% of NCI subjects progressed to a formal diagnosis of aMCI at follow-up compared to 12.5% of amnestic PreMCI-NP, 27.8% of amnestic PreMCI-NP+ and 7.3% of PreMCI-Clinical subjects. PreMCI-Clinical and PreMCI-NP subjects progressed to a formal diagnosis of naMCI at a rate of 9.8% and 4.2% respectively, compared to a rate of approximately .6% or less for the other groups. Only subjects in the amnestic PreMCI-NP + (11.1%) and PreMCI-Clinical groups (4.9%) progressed to dementia over the follow-up period. Among all PreMCI-Clinical subjects, the total number of those who completely reverted to normal was 58.5% while the reversion rate to normal among PreMCI-NP subjects was 60.4%. In contrast, only 27.8% of PreMCI-NP+ subjects reverted to a normal state. Finally, the total number of NCI subjects progressing to MCI or dementia was 3.7% compared to rates ranging from 16.74% to 38.9% for the two amnestic PreMCI-NP groups.

To compare the likelihood of progression to a more impaired state among PreMCI and NCI groups the area under the ROC curves (aROC) was examined. As presented in Table 3, the aROC was .68 (p<.01) for the PreMCI-NP group, .74 (p<.002) for the PreMCI-NP+ group; and .70 (p<.005) for the PreMCI Clinical group, indicating that all PreMCI groups were at increased risk for progression to a more impaired state. While the sensitivities were equivalent between the three PreMCI groups (53.9%–57.1%), the highest degree of specificity was obtained for the PreMCI-NP+ group (93.4%).

Because of censoring of outcomes and unequal follow-up times, Cox regression procedures were employed and odds ratios were calculated to determine the extent to which baseline predictors among all categories of PreMCI subjects were associated with progression to either aMCI or dementia over the period of follow-up (Table 4). Lower baseline scores on the Fuld OME, HVLTR-D, Category Fluency and Trails B were all predictors of progression to a more impaired cognitive state, with the Fuld OME score being the most strongly associated with outcome. Demographic variables such as age, gender and other demographic variables did not enter as significant preditors of outcome in these models. When all statistically significant univariate predictor variables were entered into the step-wise Cox regression model, only the 3-Trial Fuld-OME (B=−.190; SE= .09 Wald= 5.06; p<.025) and Category Fluency Test (B=−.067; SE= .028 Wald= 5.74; p<.018). remained as predictors.

DISCUSSION

In this study we examined a group of subjects who were intermediate between normal and MCI states, because they were not cognitively normal, did not meet formal criteria for MCI

and were discordant with regards to impairment in clinical versus neuropsychological domains. Other studies of PreMCI [12,14] have also used similar criteria to those that we have employed with regard to categorizing PreMCI-Clinical subjects. However, in contrast to this study, these other investigations applied diagnostic criteria retrospectively, employed a very limited number of memory measures and used dementia, and not MCI, as the clinical end point. In this study, MCI and PreMCI diagnoses were made prospectively using multiple memory and non-memory measures. This is also the first investigation to examine progression of PreMCI to both MCI and dementia among two subgroups of PreMCI subjects (one neuropsychologically derived and the other clinically derived).

As might be expected from the diagnostic criteria that were used, the PreMCI-Clinical group was characterized by having greater functional impairment, as determined by CDR-sb scores, whereas the amnestic PreMCI-NP subjects had impairment on memory measures as well as on the category fluency test. Nevertheless, groups were not differentiated from each other with regards to cardiovascular risk factors, UPDRS scores or MRI measures of hippocampal atrophy.

All three PreMCI subtypes were at elevated risk for progression to more impaired states (16.7% to 38.9%), in comparison to the NCI group (3.7%) over an average follow-up period of 26 months, with the highest rates of progression and lowest rate of reversion to normal in the PreMCI-NP+ group. PreMCI-Clinical and PreMCI-NP+ subtypes had rates of progression to aMCI or dementia that were six- to ten-fold greater than that of NCI subjects. Nearly 40% of PreMCI–NP+ subjects showed cognitive deterioration to either an anmestic MCI, naMCI or dementia state. Therefore, even in the absence of clinical evidence of impairment at baseline, those with neuropsychological deficits on two memory tests who are subthreshold for a formal diagnosis of MCI are at an elevated risk for progression of their deficits. The best predictors of progression to MCI and dementia included scores on an episodic memory test (the Fuld-OME) and on the category fluency test. The odds ratio for the Fuld-OME test, which has a range of 0 to 30 points, indicated that a one point increase was associated with 23% reduction in risk of progression to MCI or dementia.

The term PreMCI has been used to describe both a preclinical stage of dementing disease (i.e., normal cognitive function in conjunction with abnormal biomarkers)[6–7] or a very early clinical stage (i.e., a CDR score of 0.5, but without neuropsychological deficits).[12,14] In this study we have defined PreMCI as a very early stage of impairment, which we have further subdivided according to the presence of either only clinical or only neuropsychological deficits. Among all PreMCI subtypes, the presence of amnestic deficits in the absence of clinical symptoms and of hippocampal atrophy, but with an elevated rate of progression to aMCI or dementia, suggests the possibility that these PreMCI subjects may be in the very early neurodegenerative stage of AD, or even in the purely amyloid stage of this disorder. However, it is likely that some PreMCI subjects have either no identifiable pathology or a non-AD pathology, such as vascular cognitve impairment of Lewy Body Disease. Continued follow-up of the amnestic PreMCI-NP groups will be important in providing greater insights into its future disease progression and clarification of etiologies associated with further worsening.

The strengths of this study include the well-defined, prospective and replicable criteria we have developed for PreMCI subtypes, which distinguish them from NCI subjects in terms of baseline characteristics and longitudinal outcome. The limitations include the relatively modest numbers of subjects in the amnestic PreMCI-NP+ group and the small number of subjects who progressed to dementia during the follow-up period. Further, in contrast, to the PreMCI-NP+, which had significantly greater progression than remission rates during the follow-up period, other PreMCI subgroups had greater remission than progression rates.

Given the finding of significant fluctuations in cognitive status between baseline and follow-up, a longer follow-up should improve understanding of the relation between PreMCI impairments and progression to MCI and dementia. Although beyond the scope of the current study, further work could also investigate non-amnestic PreMCI impairments as they relate to outcome.

The influence of base rates should be considered when interpreting the results of our study. Many of our PreMCI and NCI subjects were either relatives of subjects attending our memory disorder clinics or our free community memory screening programs. Although they were recruited initially as elderly normal subjects, some of them were ultimately classified as PreMCI, naMCI or aMCI, after more detailed evaluation. It may be expected that the frequency of cognitive impairment among these subjects, either at baseline or follow-up, represents the base rates of underlying brain diseases, such as AD, in this age group. The frequency of PreMCI at baseline and its rate of progression in our study should only be compared to similar statistics from other studies after consideration is given to the setting and manner by which subjects were recruited (e.g., memory disorder clinics, primary care settings or epidemiological studies).

The results of this study suggest that subjects who have subtle declines in function based on history and clinical examination (PreMCI-Clinical) or isolated deficits on memory tests (amnestic PreMCI-NP), but who do not meet formal criteria for any form of MCI, may have potentially progressive conditions, possibly of neurodegenerative or vascular etiology. The importance of identifying these PreMCI subtypes early is that a more favorable response to lifestyle or pharmacological interventions is likely in this disease stage.

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Table 1

Baseline Demographic, Clinical and Neuropsychological Variables

	NCI (n=162)	Pre-MCI amnestic (NP) (n=48)	Pre-MCI amnestic (NP)+ (n=18)	Pre-MCI Clin (n=41)	F-value
Age	71.78[ab] (SD= 5.6)	70.56[a] (SD= 7.1)	72.56[ab] (SD= 5.8)	74.71[b] (SD= 5.7)	3.92**
Education	14.57 (SD= 3.6)	14.71 (SD=2.4)	13.78 (SD=3.1)	14.10 (SD=3.1)	.55
Gender	71.78%	63.0%	64.0%	57.7%	X^2=8.08
% English- Speaking	83.6%	75.0%	77.8%	78.0%	X^2=2.18
MMSE	29.14[a] (SD=1.2)	28.58[ab] (SD=1.4)	28.17[ab] (SD=2.1)	28.34[b] (SD=1.4)	6.63***
CDR Sum of Boxes	.18[a] (SD=.33)	.37[a] (SD=.45)	.310[a] (SD=.44)	.95[b] (SD=.91)	23.87***
UPDRS Score	1.40 (SD=2.8)	3.19 (SD=4.8)	1.81 (SD=3.1)	3.33 (SD= 4.4)	4.45**
Months Follow-up	26.69 (SD=10.9)	23.69 (SD=9.6)	22.76 (SD=11.0)	29.39 (SD=10.6)	2.74*
3-Trial Fuld OME	26.06[a] (SD=2.1)	24.65[a] (SD=2.6)	22.47[b] (SD=2.7)	25.38[a] (SD=1.9)	16.78***
Story Passage Delay	12.49[a] (SD=3.2)	7.13[b] (SD=2.5)	4.00[c] (SD=2.4)	12.29[a] (SD=3.2)	72.84***
HVLT- Delay	9.73[a] (SD=1.6)	7.33[b] (SD=2.8)	3.89[c] (SD=1.2)	9.05[a] (SD=1.4)	67.63***
Category Fluency	49.74[a] (SD=11.1)	44.92[a] (SD=7.9)	36.11[b] (SD=9.8)	43.61[a] (SD=8.6)	12.83***
Trails B	81.70 (SD=29.7)	103.27 (SD=45.5)	100.19 (59.4)	101.90 (47.5)	6.08***
Block Design	33.58 (SD=8.7)	29.23 (SD=8.9)	33.76 (SD=8.8)	29.75 SD=9.8)	4.09**
CVR Score	2.32 (SD=1.6)	2.13 (SD=1.7)	2.63 (SD=1.5)	2.95 (SD=1.6)	2.00
Hippocampal Volume Right	.00250 (SD=.0003)	.00248 (SD=.0003)	.00236 (SD=.002)	.00229 (SD=.003)	4.37**
Hippocampal Volume Left	.00263[a] (SD=.003)	.00261 (SD=.003)	.00244 (SD=.003)	.00249 (SD=.003)	3.04***

NCI= no cognitive impairment; Pre-MCI amnestic (NP)= objective impairment on one memory measure but clinically normal; Pre-MCI amnestic (NP)+ = objective impairment on two or more memory measure but clinically normal; PreMCI Clin= Clinical history suggestive of mild cognitive impairment but WNL neuropsychological test performance.

Note:

* p<.05;

** p ≤ .01;

*** p ≤ .001. Following a statistically significant F-Value at p<.05, means compared horizontally with different alphabetic superscripts are statistically significant by the Scheffe' procedure.

Table 2

Pre-MCI and MCI subgroups and progression to more severe cognitive states over time

	No Significant Change	Progress to Na- MCI	Progress to aMCI	Progress to Dementia	Total Progressing to MCI or Dementia
Pre-MCI- amnestic+ (NP) (n= 18)	18 (61.1%)	0 (0.0%)	5 (27.8%)	2 (11.1%)	38.9%
Pre-MCI- amnestic (NP) (n= 48)	40 (83.3%)	2 (4.2%)	6 (12.5%)	0 (0.0%)	16.7%
Pre-MCI Clinical Only (n=41)	32 (78.0%)	4 (9.8%)	3 (7.3%)	2 (4.9%)	22.0%
No Cognitive Impairment (n=162)	156 (96.3%)	1 (.6%)	5 (3.1%)	0 (0.0%)	3.7%

Note: 5 subjects in the Pre-MCI amnestic+ (NP) group, 29 subjects in the Pre-MCI amnestic (NP) group and 24 subjects in the Pre-MCI clinical group reverted to a normal state upon longitudinal follow-up

Table 3

ROC analyses examining the relative Predictive Powers of Different Sets of PreMCI Diagnostic Criteria Versus NCI subjects used to Predict Progression to MCI or Dementia

Diagnostic Group	Sensitivity	Specificity	AUC and SE	Asymptotic Significance	95% CI
Pre-MCI- amnestic (NP)	57.1%	79.59%	.684 (.07)	.009	.616–.746
Pre-MCI- amnestic+ (NP)	53.9%	93.41%	.736 (.07)	.001	.666–.799
Pre-MCI Clinical Only	57.1%	82.98%	.701(.07)	.004	.632–.763

TABLE 4

Baseline Predictors of Progression to amnestic MCI or Dementia

	B	SE B	Wald	Significance	Odds Ratio
Age	*.051*	*.034*	*2.16*	*.142*	***ns***
3-Trial Fuld Object Memory Evaluation	*−.267*	*.08*	*11.7*	***≤.001***	***.766 (CI= .657– .892)***
Delay Story Passage	*−.083*	*.05*	*2.80*	*.094*	*ns*
HVLT-Delay	*−.132*	*.07*	*4.02*	***.045***	***.876 (CI=.770–.997)***
Category Fluency	*−.086*	*.03*	*11.86*	***.001***	***.917 (CI=.873–.963)***
Trails B	*.007*	*.003*	*4.16*	***.041***	***1.007 (CI=1.000–1.014)***
Block Design	*−.013*	*.02*	*.29*	*.589*	*ns*
Hippocampal Volume Right	*−344.50*	*681.01*	*.16*	*.693*	*ns*
Hippocampal Volume Left	*−1437.09*	*969.46*	*2.2*	*.138*	***ns***
CDR sum of Boxes	*−.191*	*.31*	*.39*	*.534*	*ns*
UPDRS	*−.012*	*.05*	*.06*	*.806*	*ns*