

BRIEF COMMUNICATION

Episodic Memory and Hippocampal Volume Predict 5-Year Mild Cognitive Impairment Conversion in Healthy Apolipoprotein $\epsilon 4$ Carriers

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(RECEIVED May 8, 2019; FINAL REVISION November 26, 2019; ACCEPTED January 22, 2020; FIRST PUBLISHED ONLINE March 5, 2020)

Abstract

Objective: The Apolipoprotein (APOE) $\epsilon 4$ allele increases the risk for mild cognitive impairment (MCI) and dementia, but not all carriers develop MCI/dementia. The purpose of this exploratory study was to determine if early and subtle preclinical signs of cognitive dysfunction and medial temporal lobe atrophy are observed in cognitively intact $\epsilon 4$ carriers who subsequently develop MCI. **Methods:** Twenty-nine healthy, cognitively intact $\epsilon 4$ carriers ($\epsilon 3/\epsilon 4$ heterozygotes; ages 65–85) underwent neuropsychological testing and MRI-based measurements of medial temporal volumes over a 5-year follow-up interval; data were converted to z -scores based on a non-carrier group consisting of 17 $\epsilon 3/\epsilon 3$ homozygotes. **Results:** At follow-up, 11 $\epsilon 4$ carriers (38%) converted to a diagnosis of MCI. At study entry, the MCI converters had significantly lower scores on the Mini-Mental State Examination, Rey Auditory Verbal Learning Test (RAVLT) Trials 1–5, and RAVLT Immediate Recall compared to non-converters. MCI converters also had smaller MRI volumes in the left subiculum than non-converters. Follow-up logistic regressions revealed that left subiculum volumes and RAVLT Trials 1–5 scores were significant predictors of MCI conversion. **Conclusions:** Results from this exploratory study suggest that $\epsilon 4$ carriers who convert to MCI exhibit subtle cognitive and volumetric differences years prior to diagnosis. (*JINS*, 2020, 00, 1–6)

Keywords: Mild cognitive impairment, Alzheimer disease, Risk factors, MRI, Hippocampus, Longitudinal studies

INTRODUCTION

Healthy elders with an Apolipoprotein (APOE) $\epsilon 4$ allele are at increased risk for conversion to mild cognitive impairment (MCI) and dementia compared to non-carriers (Corder et al., 1993). During the preclinical stage, some studies have demonstrated subtle cognitive and structural brain differences between $\epsilon 4$ carriers and non-carriers, but others have not reported such differences (O'Donoghue, Murphy, Zamboni, Nobre, & Mackay, 2018; Fouquet, Besson, Gonneaud,

La Joie, & Chételat, 2014). O'Donoghue and colleagues (2018) attribute the mixed findings to several factors, such as age of the samples when examined, sensitivity of the cognitive measures employed, and limited longitudinal follow-up.

Another key factor is the individual variability associated with the penetrance of the $\epsilon 4$ allele. Most studies treat $\epsilon 4$ carriers as a homogenous group, yet epidemiological studies indicate that the lifetime cumulative incidence of MCI and dementia is approximately 21–26% for heterozygotes ($\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$) and 37–47% for homozygotes ($\epsilon 4/\epsilon 4$), whereas the non-carrier incidence rate is 12–16% (Qian et al., 2017). Factors that may influence the $\epsilon 4$ conversion rate include medical comorbidities and lifestyle habits (Baumgart et al., 2015).

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We previously reported the results of a longitudinal study of $\epsilon 4$ carriers and non-carriers (Rao et al., 2015). All participants were healthy and cognitively intact at study entry. Over the course of a 5-year follow-up interval, 11 of 29 $\epsilon 4$ carriers (37.9%) converted to MCI; by comparison, only 1 of 18 non-carriers (5.6%) converted. The purpose of this exploratory study was to determine if there are early and subtle preclinical signs of cognitive dysfunction and medial temporal lobe atrophy in the 11 $\epsilon 4$ carriers who subsequently developed MCI compared to the 18 carriers who did not convert.

MATERIALS AND METHODS

Participants

Participants included 29 $\epsilon 4$ carriers and 17 non-carriers (excluded one non-carrier who subsequently converted to MCI). The non-carrier group ($N = 17$) served as a reference for the cognitive and MRI outcome variables. Community-dwelling, cognitively intact, healthy older adults, ages 65–85 years, were recruited from newspaper advertisements and screened *via* telephone to determine eligibility; details of the inclusion/exclusion criteria are provided in our earlier publications (Rao et al., 2015; Seidenberg et al., 2009). Briefly, potential participants were excluded if they self-reported a diagnosis of MCI/AD, other neurological disease (e.g., multiple sclerosis), head trauma (e.g., loss of consciousness >30 min), chronic medical diseases (e.g., type 1 diabetes, congestive heart failure), a history or evidence of substance abuse, major psychiatric disturbance (e.g., schizophrenia, bipolar disorder, major depression, or generalized anxiety disorder) based on DSM-IV Axis-I criteria, self-reported current depression symptoms [Geriatric Depression Scale (Yesavage et al., 1982) score > 11], impaired activities of daily living [Lawton Instrumental Activities of Daily Living (IADL; Lawton & Brody, 1969) score < 5 (5 indicates intact IADL)], and contraindications to MRI scanning (e.g., physical size limitations, ferrous objects within the body, and claustrophobia).

APOE genotyping was based on a polymerase chain reaction method. DNA was isolated with Gentra Systems Autopure LS for Large Sample Nucleic Acid Purification. All 29 carriers had the $\epsilon 3/\epsilon 4$ genotype and all 17 non-carriers had the $\epsilon 3/\epsilon 3$ genotype.

Neuropsychological testing and MRI scanning were conducted on the same day at study entry, at 18 months, and 5 years after entry. Participants were asked to refrain from alcohol use for 24 h and caffeine use for 12 h prior to testing. The neuropsychological test battery consisted of the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), Mattis Dementia Rating Scale 2 (DRS-2; Jurica, Leitten, & Mattis, 2001), and Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958). To minimize practice effects, alternate, equivalent test forms were used at each session (Schmidt, 1996, 2004).

Written informed consent was obtained from all participants and they were financially compensated for participation.

All procedures were approved by the Institutional Review Board of the Medical College of Wisconsin.

Definition of MCI Conversion

Participants were evaluated for the presence of MCI or dementia at the 5-year follow-up session. The diagnosis was based on a multidisciplinary consensus that involved review of medical and social history, cognitive test results, and activities of daily living (Rao et al., 2015). A participant was classified as MCI if one or more subscales on the RAVLT Trials 1–5, and RAVLT Delayed Recall, and DRS-2 Total score were at least 1.5 *SD* below sex-corrected means based on local norms calculated using an independent sample of 91 healthy controls from Milwaukee. The sex correction was utilized because there was a significant difference in RAVLT performance between men and women. There were no age decade group differences, and education was not significantly correlated with RAVLT indices. Therefore, age decade and education were not used in establishing cutoff scores. The performance advantage of females compared to males on verbal memory tests is well-established (Sundermann et al., 2019). Additional classification of MCI included preserved IADL function Lawton and Brody (1969) summary score equal to 5; to meet criteria for dementia, a participant would meet criteria for MCI and have a score <5 on this index.

None of the 29 $\epsilon 4$ carriers met criteria for MCI/dementia at the 18-month follow-up. At the 5-year follow-up, 11 $\epsilon 4$ carriers (37.9%) were diagnosed with MCI and none with dementia. Thus, the 29 $\epsilon 4$ carriers were divided into two groups: 11 *MCI converters* and 18 *non-converters*. No group differences were observed in the time interval between study entry and the 5-year follow-up testing (MCI converters = 4.8 years, *SD* = .4; non-converters = 4.8 years, *SD* = .5; $p = .75$, $d = .001$, 95% CI: $-.74$ to $.76$).

MRI Acquisition and Processing

High-resolution, three-dimensional spoiled gradient-recalled at steady-state (SPGR) anatomic images were acquired on a General Electric (Waukesha, WI) Signa Excite 3.0 Tesla short bore scanner equipped with a quad split quadrature transmit/receive head coil ($TE = 3.9$ ms; $TR = 9.5$ ms; inversion recovery (IR) preparation time = 450 ms; flip angle = 12° ; number of excitations (NEX) = 1; slice thickness = 1.0 mm; FOV = 24 cm; resolution = 256×224). Whole brain and regional volumes were derived from T1-weighted SPGR images using Freesurfer v.6.0 software hippocampal subfields algorithm (Iglesias et al., 2015). Intracranial volume (ICV) was corrected using the Freesurfer estimate of TIV (%TIV). Hippocampal measures as defined by Freesurfer 6.0 subfield segmentation were selected *a priori* to assess differences in volumes between $\epsilon 4 +$ MCI converters and $\epsilon 4 +$ non-converters (bilateral whole hippocampus and subiculum).

Table 1. Means (*SD*) of demographic characteristics

	$\epsilon 4-$ [Reference] (<i>n</i> = 17)	$\epsilon 4+$ Non-Converters (<i>n</i> = 18)	$\epsilon 4+$ MCI Converters (<i>n</i> = 11)	<i>p</i> -value
Age (years)	72.0 (5.2)	71.1 (4.0)	73.3 (5.1)	.50
Range	65–80	65–77	67–81	
Education (years)	13.8 (2.0) ^a	16.1 (2.8) ^a	14.8 (1.8)	.03
Range	11–17	12–20	12–16	
Sex (F, %)	15 (88%)	14 (78%)	8 (73%)	.56
GDS	2.2 (2.6)	1.6 (2.0)	1.9 (2.0)	.67

Note. GDS = Geriatric Depression Scale.

^a Denotes significant group difference.

STATISTICAL ANALYSIS

Using the 17 $\epsilon 4$ non-carriers as a reference group, *z*-scores based on means and standard deviations were computed for all variables. A one-way ANOVA was utilized to examine demographic characteristics between the three groups.

The focus of this study was to examine differences between the $\epsilon 4+$ MCI converters and $\epsilon 4+$ non-converters on cognitive and MRI variables obtained at study entry. To correct for unequal variances between groups, *t*-test results using the Welch–Satterthwaite approximation were used for group comparisons. Effect size (Cohen's *d*) and 95% confidence intervals were calculated for each variable. MRI structural volumes were corrected for ICV. *Post-hoc* logistic regression analyses examined the ability of neuropsychological testing and medial temporal lobe brain volumes to predict MCI conversion.

RESULTS

Table 1 summarizes demographic characteristics of the MCI converters, $\epsilon 4$ non-converters, and non-carriers. No significant ($p < .05$) group differences were observed with regard to age and sex. A significant difference ($p = .03$) was observed between the three groups on education, but there was no significant group difference between the $\epsilon 4$ converters and $\epsilon 4$ non-converters. The non-carrier group had significantly fewer years of education compared to the $\epsilon 4$ non-converters ($p = .01$, $d = -.91$, 95% CI: -1.64 – $-.24$), but there was no significant difference between non-carriers and the $\epsilon 4$ converters. The two $\epsilon 4$ groups did not differ in self-reported family history of dementia [MCI converters: 6 (55%); non-converters: 13 (72%); $p = .33$]. The non-carrier group was defined by the absence of any self-reported family history. The three groups did not differ in depression scores (converters = 1.9, $SD = 2.0$; non-converters = 1.6, $SD = 2.0$; non-carriers = 2.2, $SD = 2.6$; $p = .67$; $\eta^2 = .02$).

Table 2 summarizes results of comparisons of cognitive measures and medial temporal lobe volumes obtained at study entry between converters and non-converters. Converters showed poorer performance on the MMSE, RAVLT Trials 1–5, and RAVLT Immediate Recall compared to non-converters at study entry, even though all participants

performed within normal limits (i.e., above 1.5 SDs below the sex-corrected means on the RAVLT and DRS-2 Total Score greater than 121). There were no group differences at study entry on any DRS-2 Total or subscales. Converters showed significantly smaller volumes in the left subiculum and total subiculum volume compared to the non-converters. Although there were no group differences observed in total hippocampal volume, the scores trended in the same direction.

Logistic regression was used to examine the effect of left subiculum volume and RAVLT Trials 1–5 on the likelihood of conversion to MCI after 5 years. Left subiculum volume was a statistically significant predictor of MCI conversion (odds ratio = .49; 95% CI: .25–.97; $SE = .35$; $p = .04$; $AUC = .75$), suggesting that as left subiculum volume decreases, the odds of MCI conversion increases. RAVLT Trials 1–5 was also a statistically significant predictor of MCI conversion (odds ratio = .36; 95% CI: .15–.87; $SE = .46$; $p = .02$; $AUC = .74$), suggesting that as RAVLT Trials 1–5 score decreases, the odds of MCI conversion increases.

DISCUSSION

This study demonstrated that *APOE* $\epsilon 4$ carriers who subsequently convert to MCI exhibit subtle cognitive deficits and medial temporal lobe atrophy up to 5 years prior to diagnosis. Despite scoring within the normal range on all neuropsychological tests at study entry, converters exhibited lower baseline cognitive test scores on the MMSE, RAVLT Trials 1–5, and RAVLT Immediate Recall relative to non-converters. In addition, converters had smaller baseline brain volumes in the hippocampal subfield of the subiculum compared to non-converters. Left subiculum volume and RAVLT Trials 1–5 were statistically significant predictors of MCI conversion. These findings suggest that cognitive and structural brain imaging have the potential to identify $\epsilon 4$ carriers who are in the preclinical stage of AD. It is important to emphasize that none of the $\epsilon 4$ carriers met criteria for MCI at study entry.

Two previous longitudinal studies (Haller et al., 2017; Stonnington et al., 2018) have examined possible baseline differences in cognitive performance between $\epsilon 4$ carriers

Table 2. Comparison of $\epsilon 4$ + converters and $\epsilon 4$ + non-converters at study entry

	MCI Converters (<i>n</i> = 11)	Non-Converters (<i>n</i> = 18)	<i>t</i>	<i>p</i> -value	Cohen's <i>d</i>	Cohen's <i>d</i> 95% CI
Neuropsychological measures						
MMSE	-1.27 (1.41)^a	-.17 (1.13)	2.19	.04	.86	.03–1.63
RAVLT Trials 1–5	-.76 (1.17)	.23 (.82)	2.46	.03	.98	.11–1.75
RAVLT Immediate Recall	-.99 (1.01)	-.04 (1.18)	2.31	.03	.87	.09–1.67
RAVLT Delayed Recall	-.97 (1.74)	.00 (1.61)	1.50	.15	.58	-.20–1.34
DRS Total	-1.61 (2.92)	-.07 (.86)	1.70	.12	.71	-.16–1.44
Structural MRI Volumes						
Left						
Hippocampus	-1.59 (2.05)	.01 (2.59)	1.84	.08	.68	-.08–1.47
Subiculum	-1.47 (1.29)	.06 (1.87)	2.61	.02	.95	.19–1.79
Right						
Hippocampus	-.92 (1.06)	-.06 (1.40)	1.81	.08	.67	-.09–1.46
Subiculum	-.85 (1.08)	-.08 (1.24)	1.76	.09	.66	-.11–1.44
Total						
Hippocampus	-2.51 (3.07)	-.05 (4.00)	1.86	.07	.69	-.07–1.48
Subiculum	-2.32 (2.19)	-.02 (2.94)	2.40	.02	.89	.12–1.70

Notes. CI = confidence interval; MMSE = Mini-Mental State Examination; DRS = Dementia Rating Scale; RAVLT = Rey Auditory Verbal Learning Test. ^a *z*-scores derived from means and standard deviations from the $\epsilon 4$ - group. **Bold** text indicates confidence intervals that do not overlap with zero. Hippocampal volume is derived through Freesurfer 6.0 and includes CA1–CA4, dentate gyrus, and hippocampal tail; volumes are ICV corrected.

who subsequently experience a deterioration in cognition and those that do not. Like our study, Stonnington et al. (2018) found poorer baseline performance on episodic memory measures in their MCI converters relative to non-converters. This study is remarkable because nearly half of their sample converted from cognitively normal to MCI/dementia after a relatively brief 2-year follow-up interval. However, most of their carriers were homozygotes ($\epsilon 4/\epsilon 4$). In contrast, none of our carriers, who were exclusively heterozygotes ($\epsilon 3/\epsilon 4$), converted to MCI at 18 months, emphasizing the need for a lengthier follow-up interval in carriers with a single $\epsilon 4$ allele. In contrast, no baseline differences in cognitive performance were observed by Haller et al. (2017). Unlike our study and that of Stonnington et al. (2018), the criterion for change in Haller et al. (2017) was not MCI conversion but cognitive decline on neuropsychological test performance. Like our study, the majority of their carriers were heterozygotes.

Recent studies have also found subtle baseline structural brain differences in cognitively intact $\epsilon 4$ carriers who later experienced cognitive decline. Lower gray matter density in the posterior cingulate and parietal lobe was observed in $\epsilon 4$ carriers who declined cognitively over an 18-month follow-up interval (Haller et al., 2017). Hippocampal gray matter volume was shown to be the best predictor of MCI progression over a 2-year follow-up (Stonnington et al., 2018). We extended these findings by focusing our analyses on hippocampus and subiculum, finding that smaller baseline volume is present in the subiculum in $\epsilon 4$ + converters compared to $\epsilon 4$ + non-converters at study entry. Our findings are consistent with literature suggesting that atrophy of the subiculum may be one of the earliest neuroanatomical markers of AD (Carlesimo et al., 2015). In a general population of older participants, the volume of the subiculum has been

useful in the prediction of MCI conversion (Hanseeuw et al., 2011). Another study found that smaller subiculum volumes were associated with increased risk of developing dementia over a 5-year follow-up interval in older adults who were cognitively intact at study entry (Evans et al., 2018). The current study suggests that the volume of the subiculum may identify those $\epsilon 4$ carriers who are at greatest risk for developing MCI within 5 years.

This exploratory study has several limitations. Although the statistical analyses were uncorrected for multiple comparisons, the significant group differences had medium to strong effect sizes despite a relatively small sample size. We also did not correct for age and education because the two groups of interest were not significantly different, and these variables were not significantly related with the outcome variables. The small battery of neuropsychological tests used for diagnosis of MCI makes it difficult to identify a clear distinction between single-domain and multiple-domain amnesic MCI, so it is possible that our sample may represent a combination of the two. We did not measure AD-specific biomarkers (e.g., amyloid or tau pathology) with CSF or PET. Only heterozygotes ($\epsilon 3/\epsilon 4$) were included in the current study, so we were unable to determine the impact of allele dose. The $\epsilon 4$ non-carrier group had significantly fewer years of education compared to the $\epsilon 4$ + non-converter group. However, when analyzed further, there were no significant Kendall's tau correlations between education and any neuropsychological measures (r 's = -.10 to .25) or structural MRI volumes (r 's = .06–.15). Importantly, there were no educational differences between the converter and non-converter groups, the key comparison for this study. For this reason, education was not included as a variable in the logistic regression analyses.

Accurate detection of elders in the preclinical stage has strong therapeutic implications for altering the AD disease

course. Given evidence that neuropathological changes associated with late onset AD develop at least a decade prior to a diagnosis of MCI/AD (Price & Morris, 1999; Jack et al., 2010), interventions administered during the preclinical stage may have greater success in delaying or preventing the onset of MCI/AD. In addition, this information may be useful in selecting high-risk individuals for clinical trials. Results from this exploratory study suggest that APOE genotyping, coupled with cognitive testing and medial temporal lobe volumes, may constitute a relatively low-cost method for detecting elders in the preclinical stage. Future research conducted with larger samples, combined with specific biomarkers for AD pathology, and examination of cognitive domains in addition to episodic memory are needed to examine the utility of subtle cognitive and structural brain differences in predicting which $\epsilon 4$ carriers develop MCI.

ACKNOWLEDGEMENTS

This work was supported by the National Institutes of Health Grants R01AG022304 and M01RR00058. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Aging or the National Institutes of Health.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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