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Apolipoprotein $\epsilon 2$ and Functional Decline in Amnestic Mild Cognitive Impairment and Alzheimer's Disease

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Abstract

Background—Recent work has demonstrated the potentially protective effects of the apolipoprotein (APOE) $\epsilon 2$ allele on cognitive functioning in individuals at risk for developing Alzheimer's disease (AD). However, little is known regarding the effect of $\epsilon 2$ genotype on rate of change in daily functioning over time. The aim of the current study was to examine the relationship between APOE genotype and change over time in ability to perform daily activities.

Methods—We examined the relationship between APOE genotype and change in the ability to perform activities of daily living at 12- and 24-month intervals in 225 healthy comparison subjects, 381 individuals with amnestic mild cognitive impairment (MCI), and 189 individuals with AD who were enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. Neuropsychological measures were also collected at each follow-up.

Results—Overall, individuals with at least one APOE- $\epsilon 2$ allele showed less functional decline over time and better performance on neuropsychological measures than those without an $\epsilon 2$ allele, even after controlling for potential confounders. When diagnostic groups were examined individually, presence of the $\epsilon 2$ allele continued to be associated with slower functional decline, although the relationship was no longer statistically significant in most cases, likely due to reduced statistical power.

Conclusions—Our findings suggest that the APOE- $\epsilon 2$ allele provides a buffer against significant changes in daily functioning over time and is associated with better neuropsychological performance across a number of measures.

Keywords

APOE; Alzheimer's disease; mild cognitive impairment; neuropsychology; functional decline

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Objective

The likelihood of developing Alzheimer's disease (AD) has been linked to the presence of one or more copies of the $\epsilon 4$ allele on the apolipoprotein E (APOE) gene, such that individuals with the $\epsilon 4$ allele have been shown to be at higher risk for developing AD (1). There is also evidence of a link between the presence of the APOE- $\epsilon 4$ allele and cognitive impairment (2–5), including impairments in episodic memory and executive functioning (3). Higher rates of functional decline have also been found among $\epsilon 4$ individuals (6), and functional deficits have been identified in $\epsilon 4$ carriers who were cognitively intact at the time of evaluation (7), although alternative findings have also been published (8).

In contrast, the APOE- $\epsilon 2$ allele appears to confer cognitive benefits (1–3, 9, 10–14). For example, presence of the APOE- $\epsilon 2$ allele has been associated with improvement in episodic memory over time (12) and reduced risk of cognitive decline (4) among older adults. Individuals with APOE- $\epsilon 2$ genotype have also been reported to be cognitively intact despite the presence of significant AD neuropathology (14–15), suggesting a protective mechanism. Although the link between $\epsilon 2$ and cognition is well established, we are not aware of research examining the longitudinal relationship between APOE- $\epsilon 2$ genotype and change in daily functioning over time. Specifically, it is unknown whether the possession of one or more APOE- $\epsilon 2$ alleles is associated with a slower rate of functional decline in older adults, which may have clinical significance in terms of likely course of the disease and treatment planning. Research into this question may also indicate factors that predict maintenance of daily living skills and independence in older adults.

The current study investigated the association between APOE- $\epsilon 2$ genotype and functional outcome at 12- and 24-month follow-ups in a sample of individuals with normal cognition, amnesic mild cognitive impairment (MCI), and probable AD. We compared rate of functional decline in individuals with at least one $\epsilon 2$ allele to those without an $\epsilon 2$ allele. We also examined between-group differences in neuropsychological performance as a function of APOE genotype. We hypothesized that individuals with an APOE- $\epsilon 2$ allele would show a slower rate of functional decline over time than individuals without an $\epsilon 2$ allele. Consistent with previous findings, we also predicted that the presence of one or more $\epsilon 2$ alleles would be associated with relatively better cognitive functioning.

Methods

The Alzheimer's Disease Neuroimaging Initiative (ADNI)

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a \$60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The principal investigator of this initiative is Michael W. Weiner, M.D., VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal

of ADNI was to recruit 800 adults, ages 55–90, to participate in the research – approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. For additional information, see www.adni-info.org.

Participants

Participants were enrolled in ADNI and consisted of 228 healthy comparison participants, 391 individuals diagnosed with amnesic MCI, and 193 individuals diagnosed with AD, for a total sample size of 812. Seventeen participants were excluded from data analysis (see below), bringing the total to 795.

Full participant inclusion and exclusion criteria are available at <http://www.adni-info.org>. All enrolled participants were required to be between the ages of 55–90 (inclusive), have a study partner capable of providing an independent assessment of functioning, and willing to undergo all procedures. Comparison participants were required to have a Mini Mental Status Examination (MMSE) score between 24–30 (inclusive), a Clinical Dementia Rating Scale (CDR) score of 0, and be non-depressed, non-MCI, and non-demented. MCI participants were required to have a MMSE score between 24–30 (inclusive), a memory complaint, objective memory loss as measured by education-adjusted scores on the Logical Memory II subtest of the Wechsler Memory Scale-Revised, a CDR score of 0.5, absence of significant levels of impairment in other cognitive domains, essentially intact activities of daily living, and no dementia. AD participants were required to have MMSE scores between 20–26 (inclusive), CDR of 0.5 or 1, and were required to meet NINCDS/ADRDA criteria for probable AD.

Participants underwent serial evaluations of functional and clinical status at various intervals. Neuropsychological data were collected at each evaluation as well, although only neuropsychological data from the baseline evaluation were used in this study. The current study used data collected at the baseline, 12-month, and 24-month evaluations.

Apolipoprotein (APOE) genotyping

APOE genotyping was conducted for all ADNI study candidates using blood samples collected at the screening visit. Lumbar puncture was performed with a 20- or 24-gauge spinal needle as described in the ADNI procedures manual (<http://www.adni-info.org/>). Cerebrospinal fluid was collected into collection tubes provided to each site, then transferred into polypropylene transfer tubes followed by freezing on dry ice within one hour after collection, and shipped overnight to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center on dry ice. TaqMan quantitative polymerase chain reaction assays were used for genotyping APOE nucleotides 334 T/C and 472 CT with an ABI 7900 real-time thermocycler (Applied Biosystems, Foster City, CA) using DNA freshly prepared from whole blood.

Functional and Clinical Measures

Ability to perform activities of daily living was assessed using the Functional Activities Questionnaire (FAQ) (16). The FAQ is an informant-based measure of instrumental activities of daily living (IADLs) that inquires into an older adult's ability to independently carry out various activities, including manage finances, prepare a balanced meal, and remember appointments. Ratings range from normal (0) to dependent (3) on ten subscales for a total of 30 points, with higher scores indicating worse functional status. The Clinical Dementia Rating (CDR) scale (17) was used to rate the severity of dementia symptoms in all patients.

Neuropsychological Measures

Neuropsychological data used in the current study were collected from each participant at the baseline evaluation. We selected the following measures from the ADNI cognitive battery: Mini Mental Status Examination (MMSE; 18); American National Adult Reading Test (ANART; 19); Delayed Recall measure from the Logical Memory subtest of the Wechsler Memory Scale, 3rd Edition (WMS-III; 20); Delayed Recall measure from Rey's Auditory Verbal Learning Test (21); Digit Span subtest of the WMS-III; Clock Drawing Test; Verbal Fluency Test (animals, vegetables); Trail Making Test, Parts A and B (total time).

An executive functioning composite variable was calculated using the following measures: Clock Drawing (total score), Trail Making Test (Part B; time to completion in seconds), Digit Span Backwards (total score), and Verbal Fluency (Animals and Vegetables; total correct words produced). Performance on these measures was standardized by calculating z-scores for performance on each test, which were then summed to create a composite score. Scores were standardized across the entire sample as well as within each diagnostic group, and the appropriate standardized variables were used in each analysis. A long-term memory composite variable was calculated using the Logical Memory (Delayed Recall) and RAVLT (Delayed Recall) measures, and procedures for creating the standardized scores and composite variable were similar to those described above.

Data Analysis

We compared $\epsilon 2$ patients to non- $\epsilon 2$ patients on measures of daily functioning and neuropsychological performance. Individuals with at least one APOE- $\epsilon 2$ allele ($\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$) were included in the $\epsilon 2$ group. Individuals without an $\epsilon 2$ allele ($\epsilon 3/\epsilon 3$, $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$) were included in the non- $\epsilon 2$ group. Individuals possessing both an $\epsilon 2$ and $\epsilon 4$ allele ($N = 17$) were excluded from the analyses, consistent with data analysis practices in the literature in this area (12, 14), in order to examine the independent contribution of $\epsilon 2$ allele to functional change over time. This exclusion left us with an effective sample size of 795 (225 healthy subjects, 381 MCI, and 189 AD cases) for the analyses described below. Of these participants, 33 comparison subjects, 15 individuals with MCI, and 5 AD participants possessed at least one $\epsilon 2$ allele.

An a priori decision was made to analyze both the entire (pooled) sample and each diagnostic group separately. Change scores on the FAQ were calculated from baseline to 12 and 24 months to indicate 12- and 24-month functional change, respectively. Mixed design analysis of variance (ANOVA) was conducted to compare $\epsilon 2$ and non- $\epsilon 2$ individuals on 12- and 24-month functional change. Independent samples t-tests were used to compare $\epsilon 2$ and non- $\epsilon 2$ individuals on baseline neuropsychological performance. Due to subject attrition, analyses were based on different sample sizes, depending on how many participants were studied at a particular follow-up. Only participants with complete datasets at a given time point were used in analyses at that time point, while participants with missing data were excluded, and missing data were not imputed.

Results

Demographic and Clinical Data

Demographic and clinical data for participants in each diagnostic group are presented in Table 1. 132 MCI participants (34.6%) converted to AD and 9 comparison participants converted to MCI over 24 months. Additionally, 12 MCI participants reverted to a healthy comparison diagnosis, and 2 AD participants reverted to MCI. Of the individuals who converted from MCI to AD, 88 had a $\epsilon 3/\epsilon 4$ or $\epsilon 4/\epsilon 4$ genotype, 43 had a $\epsilon 3/\epsilon 3$ genotype,

and 1 had a $\epsilon 2/\epsilon 3$ genotype. Of the individuals who converted from comparison to MCI, 6 had a $\epsilon 3/\epsilon 4$ or $\epsilon 4/\epsilon 4$ genotype and 3 had a $\epsilon 3/\epsilon 3$ genotype. Of the individuals who reverted from MCI to comparison, 3 had a $\epsilon 3/\epsilon 4$ or $\epsilon 4/\epsilon 4$ genotype, 8 had a $\epsilon 3/\epsilon 3$ genotype, and 1 had a $\epsilon 2/\epsilon 3$ genotype. Both of the individuals who reverted from AD to MCI had a $\epsilon 3/\epsilon 4$ genotype.

We then compared APOE- $\epsilon 2$ patients to non- $\epsilon 2$ patients on demographic and clinical variables (Table 1). Chi-square analysis revealed significant between-group differences in gender ($\chi^2 = 6.54$, $p < .02$), such that the $\epsilon 2$ group had a higher percentage of females (58.5%), whereas the non- $\epsilon 2$ group had a higher percentage of males (59.4%). We also found significant differences in APOE- $\epsilon 2$ distribution among diagnostic groups. Overall, the highest percentage of $\epsilon 2$ subjects was found in the comparison group (14.7%), while MCI patients (3.9%) and AD patients (2.6%) had significantly fewer individuals with an $\epsilon 2$ allele. The groups did not differ in age [$t(793) = 0.98$, $p = .33$], years of education [$t(793) = 0.09$, $p = .93$], or racial distribution ($\chi^2 = 7.07$, $p = .13$).

Longitudinal Changes in Daily Functioning

Using the pooled sample, we compared APOE- $\epsilon 2$ individuals to non- $\epsilon 2$ individuals on change in total FAQ score from baseline to 12 months using repeated measures ANOVA, with Genotype ($\epsilon 2$, non- $\epsilon 2$) as the between subjects variable and Time (Baseline, 12 months) as the within subjects variable. To adjust for possible effects of gender on functional decline, Gender was also included as a between-subjects variable. The main effects of Time [$F(1,700) = 26.94$, $p < .001$] and Genotype [$F(1,700) = 7.80$, $p < .01$] remained significant, while the main effect of Gender was not significant [$F(1,700) = 0.20$, $p > .65$]. Additionally, the 3-way interaction (Time \times Genotype \times Gender) was significant [$F(1,700) = 4.24$, $p < .05$], such that $\epsilon 2$ females showed the least change over 12 months (mean change = 0.10 points) relative to $\epsilon 2$ males (mean change = 2.0 points), non- $\epsilon 2$ males (mean change = 1.83 points), and non- $\epsilon 2$ females (mean change = 2.48 points). The Time \times Gender [$F(1,700) = 1.02$, $p > .31$] and Genotype \times Gender [$F(1,700) = 0.05$, $p > .82$] interactions were not significant. Lastly, we compared changes in individual subscales of the FAQ over time in each group. Subscales included ability to play games of skill, prepare a balanced meal, and travel outside of one's neighborhood. To do this, we compared $\epsilon 2$ to non- $\epsilon 2$ individuals on 12-month change on each subscale using independent samples t-tests. None of the comparisons was reached significance.

We next examined change in FAQ over 24 months using the analytic strategy described above. We found significant main effects of Genotype [$F(1,590) = 7.82$, $p < .01$] and Time [$F(1,590) = 20.11$, $p < .001$], indicating lower FAQ scores among $\epsilon 2$ individuals than non- $\epsilon 2$ individuals and higher FAQ scores at the 24-month follow-up than at baseline, respectively. We also found a significant Genotype \times Time interaction [$F(1,590) = 16.24$, $p < .001$], such that $\epsilon 2$ individuals (mean change = 0.46 points) showed a significantly slower change in FAQ over 24 months than did non- $\epsilon 2$ individuals (mean change = 3.53 points; see Table 2). The main effect of Gender was non-significant [$F(1,590) = 0.50$, $p = .48$], as were the Time \times Gender [$F(1,590) = 1.27$, $p = .26$], Genotype \times Gender [$F(1,590) = 0.34$, $p = .56$], and Time \times Genotype \times Gender [$F(1,590) = 1.88$, $p = .17$] interactions. We also compared changes in individual subscales of the FAQ over 24 months in each group. Results indicated significant between-group differences on the following subscales: shopping alone for necessities [$t(552) = 2.46$, $p < .02$], playing games of skill/working on a hobby [$t(552) = 2.76$, $p < .01$], preparing a balanced meal [$t(552) = 2.41$, $p < .02$], keeping track of current events [$t(552) = 2.17$, $p < .05$], paying attention to and understanding a television program/book/magazine [$t(552) = 2.40$, $p < .02$], and traveling outside of the neighborhood [$t(552) = 3.60$, $p < .001$]. In all cases, $\epsilon 2$ participants showed significantly slower rates of decline in these areas than non- $\epsilon 2$ participants.

Next, using the pooled sample, we examined changes in FAQ across time as a function of diagnostic group and genotype. To do this, we used a repeated measures ANOVA, with Diagnosis (control, MCI, AD) and Genotype ($\epsilon 2$, non- $\epsilon 2$) as the between-subjects variables and Time (Baseline, 12 months, 24 months) as the within-subjects variable. Results indicated significant main effects of Time [$F(2,1158) = 9.35, p < .001$] and Diagnosis [$F(2,579) = 84.52, p < .001$], while the main effect of Genotype did not reach significance [$F(1,579) = 2.19, p = .14$]. The Time \times Diagnosis [$F(4,1158) = 4.03, p < .005$] and Time \times Genotype [$F(2,1158) = 8.46, p < .001$] interactions were also significant, while the Genotype \times Diagnosis interaction did not reach significance [$F(2,579) = 1.21, p = .30$]. Lastly, the 3-way interaction (Time \times Diagnosis \times Genotype) was significant [$F(4,1158) = 3.93, p < .005$].

Given the significant 3-way interaction, we next examined changes in FAQ within each diagnostic group as a function of APOE genotype, using a similar analytic strategy as described above. Results are presented in Table 3. We first examined changes over 12 months. For comparison participants, none of the effects (Genotype, Time, Genotype \times Time) reached significance (all p 's $> .19$). Among the amnesic MCI patients, we found a significant main effect of Time, such that FAQ scores were worse at the 12-month follow-up than at baseline. However, neither the main effect of Genotype [$F(1,337) = 0.44, p = .51$] nor the Genotype \times Time interaction [$F(1,337) = 1.06, p = .72$] reached significance. For the AD group, we again found a significant main effect of Time, indicating that FAQ scores were worse at the 12-month follow-up than at baseline. Neither the main effect of Genotype [$F(1,156) = 1.04, p = .31$] nor the Genotype \times Time interaction [$F(1,156) = 0.51, p = .48$] reached significance.

We next examined change in FAQ within each diagnostic group over 24 months (see Table 3). Among comparison subjects, neither the main effect of Time [$F(1,190) = 0.85, p = .36$] nor the Genotype \times Time interaction [$F(1,190) = 0.46, p = .23$] was significant. The main effect of Genotype was somewhat stronger but did not reach statistical significance [$F(1,190) = 3.72, p = .055$]. For the amnesic MCI group, we found a significant main effect of Time, such that FAQ scores were lower at baseline than at 24 months. Neither the main effect of Genotype [$F(1,269) = 0.57, p = .45$] nor the Genotype \times Time interaction [$F(1,269) = 1.85, p = .17$] reached significance. Among AD patients, neither the main effect of Time [$F(1,129) = 3.12, p = .08$] nor the main effect of Genotype reached statistical significance [$F(1,129) = 1.02, p = .31$]. The Genotype \times Time interaction was significant, indicating significantly slower FAQ change among $\epsilon 2$ individuals (mean change = 2.5 points) relative to non- $\epsilon 2$ individuals (mean change = 7.1 points; see Table 3).

Neuropsychological Performance

In the pooled sample, we compared APOE- $\epsilon 2$ individuals to non- $\epsilon 2$ individuals on neuropsychological measures. For memory and executive functioning, only composite measures were analyzed. Results are displayed in Table 4. Overall, the $\epsilon 2$ group had higher scores than the non- $\epsilon 2$ group on the MMSE, executive composite, and memory composite. The groups' performance did not differ on ANART, Digit Span-Forward, or Trail Making Test Part A (see Table 4).

We next examined neuropsychological performance in each diagnostic group as a function of APOE genotype. Among comparison participants, non- $\epsilon 2$ individuals (mean = 29.2) had higher MMSE scores than $\epsilon 2$ individuals [mean = 28.8; $t(223) = 2.42, p < .02$], while $\epsilon 2$ individuals (mean = 8.7) performed better than non- $\epsilon 2$ individuals (mean = 7.2) on RAVLT-Delayed Recall [$t(222) = 2.19, p < .05$]. No other differences in neuropsychological performance were found. In the amnesic MCI group, no significant group differences were found in the primary analyses (global cognition, attention, memory composite, executive

composite). However, when performance on individual memory and executive functioning measures was examined, $\epsilon 2$ patients (mean = 5.6) showed significantly better performance relative to non- $\epsilon 2$ patients (mean = 3.7) on Logical Memory-Delayed Recall [$t(379) = 2.71$, $p < .01$]. The $\epsilon 2$ patients (mean = 5.5) also performed better than the non- $\epsilon 2$ patients (mean = 2.7) in the MCI group on RAVLT-Delayed Recall [$t(379) = 3.26$, $p < .005$]. Among AD patients, no differences were found.

Lastly, given the documented relationship between MCI-amnesic type and development of AD, we selected MCI patients who were greater than 1.5 SDs *below* the MCI group mean on the memory composite score ($n = 88$) and MCI patients who were greater than 1.5 SDs *above* the MCI group mean on the memory composite score ($n = 71$), and we compared frequency of $\epsilon 2$ alleles across groups. Results are displayed in Table 5. We found that MCI patients with relatively poorer memory performance were less likely to have an $\epsilon 2$ allele (1.1%) relative to MCI patients with relatively better memory performance (9.9%). Furthermore, a higher percentage of MCI patients with relatively poorer memory performance (70.5%) had at least one $\epsilon 4$ allele, relative to MCI patients with relatively better memory performance (36.6%). We also compared these groups on rate of functional decline over time. As expected, MCI patients with poorer memory performance showed significantly more decline over 12 and 24 months compared to MCI patients with better memory performance (see Table 5).

Conclusions

In the present study, we found that individuals with at least one copy of the APOE- $\epsilon 2$ allele showed significantly less functional decline over time and performed significantly better on many neuropsychological measures, relative to individuals without an $\epsilon 2$ allele. When the data were examined within each diagnostic group, results were similar and largely in the same direction. However, most findings in the individual groups did not reach statistical significance. We discuss each of these points in more detail below.

Longitudinal Changes in Daily Functioning – Pooled Sample

Of primary interest in the present study was the relationship between APOE genotype and rate of functional change over time. Overall, we found significantly less functional decline over 24 months among individuals with at least one APOE- $\epsilon 2$ allele, regardless of diagnosis, including significant group differences on 6 out of 10 FAQ subscales. Although the link between APOE- $\epsilon 2$ genotype and preserved cognition has been well established (3, 11–14), to our knowledge ours is the first study to demonstrate that the APOE- $\epsilon 2$ allele is associated with a slower rate of decline in IADLs. Furthermore, the differences in rate of functional decline are not attributable to between group differences in education or estimated premorbid IQ, as the groups were similar on these factors. These findings provide additional evidence to suggest that possession of an APOE- $\epsilon 2$ allele may be related to slower decline, in contrast to APOE- $\epsilon 4$, which has been associated with elevated rates of functional decline (6). The presence of one or more APOE- $\epsilon 2$ alleles may potentially contribute to one's cognitive reserve (22), allowing individuals to function independently for a longer period.

Additional analyses also identified a significant Time \times Genotype \times Gender interaction at 12 months, such that the least decline was found for females with at least one $\epsilon 2$ allele, relative to $\epsilon 2$ males or non- $\epsilon 2$ individuals. This result indicates that gender influences the relationship between APOE genotype and functional decline to some degree at 12 months. However, the effect is no longer significant at 24 months. The mechanisms underlying this finding are unclear. Further research is needed to better address the interaction between gender, APOE status, and functional decline.

Longitudinal Changes in Daily Functioning – Individual Diagnostic Groups

When the diagnostic groups were examined individually, results remained similar to those found in the pooled sample, although they did not always reach statistical significance. Within the AD group, $\epsilon 2$ individuals showed significantly slower functional decline over 24 months than non- $\epsilon 2$ AD patients. This finding further suggests a role for $\epsilon 2$ in longitudinal maintenance of IADLs, even among individuals who have already converted to mild AD. Additionally, the largest percentage of $\epsilon 2$ individuals by far was found in the healthy comparison group (14.7%), with far less in amnesic MCI (3.9%) and the least in AD (2.6%). Thus, the $\epsilon 2$ variant is most common among individuals who have remained functionally and cognitively intact to this point, which is in line with research demonstrating a decreased risk for dementia among $\epsilon 2$ carriers (7).

Despite these significant findings, however, the majority of analyses conducted within individual diagnostic groups did not yield statistically significant results. One potential explanation is that lower statistical power contributed to the null findings in this case. Certainly, sample sizes were significantly reduced when participants were divided into diagnostic groups and further split into genotype groups, which may have resulted in analyses that were underpowered. Future research endeavors should aim to address this question using larger sample sizes to achieve better statistical power.

Potential Clinical Applications

In light of the known relationship between amnesic MCI and likelihood of conversion to AD (10, 23), we conducted post-hoc analyses comparing MCI patients with better vs. worse memory performance on rate of functional change. We found that MCI patients with relatively poorer memory showed significantly more functional decline over 12 and 24 months than MCI patients with relatively better memory, further supporting the hypothesis that memory performance among MCI patients is highly predictive of conversion to AD (24). We also found a greater representation of $\epsilon 4$ alleles and a reduced representation of $\epsilon 2$ alleles among MCI patients with poorer memory performance, relative to those with better memory performance, consistent with previous research (7) and suggesting that APOE genotypes confer varying effects on cognition and everyday function in individuals with MCI.

Neuropsychological Performance

APOE- $\epsilon 2$ patients showed significantly better performance than non- $\epsilon 2$ patients on a number of neuropsychological measures in the pooled sample, including significantly higher scores on the memory and executive functioning composite measures. Our data support previous findings that have found a positive effect of $\epsilon 2$ on cognition (13), including longitudinal studies in which patients are followed over a number of years (4, 12). Not surprisingly, performance on measures of executive functioning (25–26) and memory (27) is highly related to degree of functional impairment among older adults. Future research may further address the relationship between genotype, cognition, and longitudinal changes in daily functioning.

In the individual diagnostic groups, we found that amnesic MCI patients with at least one APOE- $\epsilon 2$ allele performed significantly better than non- $\epsilon 2$ amnesic MCI patients on episodic memory measures, with fewer differences seen in comparison participants and no differences in AD participants. This finding raises the possibility that the buffer effect of $\epsilon 2$ on cognition is most optimal at the MCI stage, prior to the onset of AD. Notably, these differences were also found without associated differences in functional decline between $\epsilon 2$ and non- $\epsilon 2$ MCI participants. It is possible that declines in cognition (i.e., memory) represent a precursor to declines in daily functioning among individuals with MCI, and $\epsilon 2$

provides a buffer against such declines at the MCI level. The opposite pattern was found in AD participants: $\epsilon 2$ individuals showed less decline over 24 months than non- $\epsilon 2$ participants but did not show differences on any neuropsychological measures. In this case, the presence of $\epsilon 2$ may continue to provide some degree of protection against functional decline, despite cognitive functioning that is non-distinguishable from that of non- $\epsilon 2$ individuals. Overall, however, and in contrast to the pooled sample findings, the association between $\epsilon 2$ and neuropsychological functioning in the individual diagnostic groups was much less robust.

Limitations

Limitations of the current study include reduced statistical power for analyses within individual diagnostic groups. As described previously, many of the analyses within individual groups were conducted using smaller sample sizes. A more sufficiently powered study may have yielded more significant findings in each of the diagnostic groups. Secondly, the sample was largely Caucasian and highly educated, reducing demographic variance and potentially limiting the generalizability of our findings to other settings and populations. Lastly, only individuals with amnesic MCI were used in the current study. While this population is of interest due to the relationship between amnesic MCI and risk for development of AD, findings may not generalize to individuals with non-amnesic MCI.

Summary

The current study examined the longitudinal association between APOE- $\epsilon 2$ genotype and functional changes and performance on neuropsychological measures among individuals with amnesic MCI, probable AD, and comparison participants. Overall, we found that individuals with at least one APOE- $\epsilon 2$ allele showed significantly less functional decline over 24 months compared to individuals without an $\epsilon 2$ allele. Possession of an $\epsilon 2$ allele was also associated with better neuropsychological performance across a number of cognitive measures. To our knowledge, we provide the first demonstration of a slower rate of functional decline among individuals with an APOE- $\epsilon 2$ allele. Our findings also support the positive influence of $\epsilon 2$ on neurocognition.

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Table 1

Demographic and Clinical Data

	Control (n = 225)	MCI (n = 381)	AD (n = 189)	p-value* for ANOVA/ χ^2
Age (years)	75.9 (5.0)	74.8 (7.4)	75.3 (7.5)	.13 ¹
Education (years)	16.0 (2.9)	15.7 (3.0)	14.7 (3.1)	< .001 ¹
Gender (% male/female)	51.8/48.2	64.7/35.3	52.8/47.2	.002 ²
Race (% Caucasian)	91.7	93.4	93.8	.33 ³
APOE Genotype (% ϵ 2)	14.7	3.9	2.6	< .001 ²

	ϵ 2	non- ϵ 2	p-value*
Age (years)	76.1 (6.2)	75.2 (6.9)	.33 ⁴
Education (years)	15.6 (3.2)	15.5 (3.1)	.93 ⁴
Gender (% male/female)	41.5/58.5	59.4/40.6	< .02 ⁵
Race (% Caucasian)	84.9	93.5	.13 ⁶

-Standard deviations are presented in parentheses

-APOE: apolipoprotein E gene

* Represents p-value for statistical comparison of the groups on the variable

¹ Results of ANOVA (between group df = 2, within group df = 809)

² Results of χ^2 (df = 2)

³ Results of χ^2 (df = 8)

⁴ Results of t-test (df= 793)

⁵ Results of χ^2 (df = 1)

⁶ Results of χ^2 (df = 4)

Table 2FAQ values for $\epsilon 2$ and non- $\epsilon 2$ groups at Baseline, 12-month, and 24-month evaluations

	$\epsilon 2$ M (SD)	non- $\epsilon 2$ M (SD)
Baseline	2.83 (6.4)	5.13 (6.6)
12 Months ^{1,2}	3.53 (6.7)	6.90 (8.2)
24 Months ^{3,4,5}	3.29 (6.8)	8.66 (9.5)

Note: Higher scores reflect poorer functioning

¹Main effect of Time, $F(1,702) = 24.13$, $p < .001$

²Main effect of Genotype, $F(1,702) = 7.60$, $p < .01$

³Main effect of Time, $F(1,592) = 19.96$, $p < .001$

⁴Main effect of Genotype, $F(1,592) = 7.80$, $p < .01$

⁵Time \times Genotype, $F(1,702) = 16.11$, $p < .001$

Table 3

Mean FAQ values for $\epsilon 2$ and non- $\epsilon 2$ individuals within each diagnostic group at Baseline, 12-month, and 24-month evaluations

	Control ¹		MCI ^{2,3}		AD ^{4,5}	
	$\epsilon 2$	non- $\epsilon 2$	$\epsilon 2$	non- $\epsilon 2$	$\epsilon 2$	non- $\epsilon 2$
Baseline	0.03 (0.2)	0.16 (0.6)	4.3 (6.2)	3.9 (4.5)	16.8 (8.9)	12.9 (6.8)
12 Months	0.09 (0.4)	0.29 (1.1)	6.6 (6.9)	5.6 (5.9)	19.5 (2.4)	17.2 (7.1)
24 Months	0.00 (0.0)	0.46 (1.3)	8.4 (7.0)	8.3 (7.6)	19.3 (7.0)	20.0 (7.3)

¹Controls: No significant effects at 12 or 24 months

²MCI: Main effect of Time (12 months), $F(1,337) = 15.01$, $p < .001$

³MCI: Main effect of Time (24 months), $F(1,269) = 8.41$, $p < .005$

⁴AD: Main effect of Time (12 months), $F(1,156) = 7.08$, $p < .001$

⁵AD: Time \times Genotype (24 months), $F(1,129) = 6.42$, $p < .02$

-Standard deviations are presented in parentheses

Table 4

Mean values on neuropsychological measures for ε2 and non-ε2 individuals

	APOE genotype		t-value	df	p-value
	ε2 M (SD)	Non-ε2 M (SD)			
Global/Premorbid					
MMSE	27.7 (2.4)	26.7 (2.7)	2.75	793	.006
ANART*	11.8 (9.9)	13.2 (10.0)	1.00	789	.32
Memory					
Composite	1.56	-0.11	6.59	792	< .001
LM – Delay	9.6 (5.8)	5.5 (5.3)			
RAVLT – Delay	7.0 (4.3)	3.4 (3.9)			
Attention					
Digit Span - Forward	8.2 (2.3)	8.2 (2.0)	0.05	793	.96
TMT A (secs)	44.1 (22.7)	48.2 (27.7)	1.07	791	.29
Executive Function					
Composite	1.21	0.003	2.38	776	.02
Clock Drawing	4.4 (0.9)	4.1 (1.1)			
VF – Vegetables	12.8 (4.4)	11.0 (4.4)			
VF – Animals	17.3 (6.0)	16.1 (5.8)			
Digit Span - Backward	6.7 (2.2)	6.1 (2.2)			
TMT B (secs)	120.1 (70)	135.8 (80.7)			

* total number of errors

MMSE = Mini-Mental State Examination; ANART = American National Adult Reading Test; LM = Logical Memory; RAVLT = Rey’s Auditory Verbal Learning Test; VF = Verbal Fluency; TMT A = Trail Making Test, Part A; TMT B = Trail Making Test, Part B.

Frequency of $\epsilon 2$ and $\epsilon 4$ alleles and rate of functional decline among MCI patients as a function of memory performance

Table 5

Genotype	MCI Memory Subgroup		df	p-value
	>1.5 SDs	<1.5 SDs		
% $\epsilon 2$ allele	9.9	1.1	1	.01
% $\epsilon 4$ allele	36.6	70.5	1	<.001
Functional decline				
12 months	0.70 (3.5)	2.83 (4.7)	142	.003
24 months	1.26 (4.7)	6.46 (6.2)	112	<.001

-Subgroups were composed of MCI patients who were greater than 1.5 SDs below the MCI group mean on the memory composite score (n = 88) and MCI patients who were greater than 1.5 SDs above the MCI group mean on the memory composite score (n = 71)

-% $\epsilon 2$ allele = percentage of individuals with at least one $\epsilon 2$ allele

-% $\epsilon 4$ allele = percentage of individuals with at least one $\epsilon 4$ allele

-Standard deviations are presented in parentheses