APOE ε4 Gene Dose and Sex Effects on Alzheimer’s Disease MRI Biomarkers in Older Adults with Mild Cognitive Impairment

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Handling Associate Editor: Liqin Zhao

Accepted 11 July 2019

Abstract

Background: APOE ε4 and sex have been linked to increased risk for conversion to Alzheimer’s disease (AD). However, the relationship between APOE ε4 gene dose, sex, and AD biomarkers remains understudied.

Objective: To investigate the effect of APOE ε4 dose on AD biomarkers in a sample of older adults with mild cognitive impairment (MCI), and to examine whether APOE ε4 dose modifies AD risk differently in MCI women and men.

Methods: We examined cross-sectional AD biomarkers for participants with MCI (n = 930, 55–96 years old) from three large aging cohorts. Region of interest MRI volumes, global cognition, and episodic memory were analyzed by number of APOE ε4 alleles and stratified by sex.

Results: Across all participants, number of APOE ε4 alleles was associated with smaller hippocampal and amygdala volumes and poorer cognition. When stratified by sex, women showed an APOE ε4 dose effect for bilateral hippocampal and left amygdala volumes and cognition. In contrast, men showed an APOE ε4 dose effect for hippocampal volumes with a trend in amygdala, but cognition did not differ between men with 1 and 2 APOE ε4 alleles. Women with 2 APOE ε4 alleles had poorer memory between 65–69 and poorer global cognition between 70–74 compared to men with 2 APOE ε4 alleles.

Conclusion: APOE ε4 confers a dose effect on AD biomarkers in patients with MCI, and the number of APOE ε4 alleles has a greater detrimental impact in women than men, which may be specific to a critical time window.

Keywords: Alzheimer’s disease, APOE, genetics, hippocampus, memory, mild cognitive impairment, MRI, sex effects

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²Data used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.
³Data used in the preparation of this article was obtained from the Australian Imaging Biomarkers and Lifestyle flagship study of ageing (AIBL) funded by the Commonwealth Scientific and Industrial Research Organisation (CSIRO) which was made available at the ADNI database (http://www.loni.usc.edu/ADNI). The AIBL researchers contributed data but did not participate in analysis or writing of this report. AIBL researchers are listed at http://www.aibl.csiro.au.

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INTRODUCTION

Alzheimer’s disease (AD) is the most common form of dementia. Currently, there are no effective treatments for AD, creating a critical public health concern [1]. Because it is likely that effective therapies will require early intervention, understanding the role of AD risk factors, such as apolipoprotein E e4 (APOE e4) and sex, is critical for identifying individuals who are at greatest risk [2].

The greatest known genetic risk factor for late-onset sporadic AD is the APOE e4 allele [3]. APOE e4 is more prevalent in people with AD compared to cognitively normal individuals [4, 5], and extensive research has demonstrated that relative to APOE e3, APOE e4 significantly increases the risk of developing mild cognitive impairment (MCI) [6] and AD [7, 8]. One APOE e4 allele increases risk by 2- to 3-fold, and 2 alleles increase risk by 10-fold [5, 9]. While a number of studies have shown that AD risk increases as the number of APOE e4 alleles increases [5, 10], few have examined the effect of APOE e4 dose on specific biomarkers for AD. Evidence for an APOE e4 dose effect on cognitive and MRI biomarkers is needed.

Female sex is another major risk factor for AD [11]. Studies that have examined the interaction between APOE e4 and sex suggest that women may be more adversely affected. Indeed, 1 APOE e4 allele has been shown to increase lifetime AD risk in women, whereas 2 APOE e4 alleles increased lifetime risk in men [5]. Similar APOE e4 by sex effects have been observed for hippocampal volumes [12]. A recent meta-analysis of approximately 58,000 subjects reported a critical time window starting at 65 years old in which women with APOE e4 are at greater risk of conversion than men with APOE e4 [13]. Another recent paper examined the longitudinal differences between men and women and the effect of APOE e4 status across the AD spectrum on hippocampal volume, cognition, and association with cerebrospinal fluid (CSF) biomarkers of tau and amyloid [14]. The findings from this study suggest pronounced sex differences exist within the MCI stage, motivating additional explicit examination of this phase of disease progression.

In the present study, we examined the effects of APOE e4, sex, and their interaction on MRI brain volumes and cognition in a sample of older adults with MCI [15] via within-sex and between-sex analyses.

METHODS

Study design

De-identified and coded data from 930 participants with MCI between 55–96 years old were acquired with permission from three aging cohorts: The Alzheimer’s Disease Neuroimaging Initiative (ADNI), the National Alzheimer’s Coordinating Center (NACC), and the Australian Imaging, Biomarker & Lifestyle Study (AIBL). This study was approved by our local institutional review board as non-human subjects research. Subjects with a baseline diagnosis of MCI with a probable etiology of AD were included. APOE e4 carriers who may have conferred protection from AD [16] were excluded from the analysis to include only those who were APOE e3/e3, APOE e3/e4, and APOE e4/e4. Participants with no available diagnosis, genetic information for APOE, imaging and cognitive data, less than 6 years of education, or possible co-enrollment across cohorts were excluded. Variables were harmonized across datasets. For example, education was binned into 4 groups to enable comparison with the AIBL dataset: 6 to 8 years, 9 to 12 years, 13 to 15 years, and 15 + years.

Datasets

Data from the ADNI (n = 723), NACC (n = 121), and AIBL (n = 86) cohorts were aggregated to create the final dataset for analysis (n = 930). ADNI was launched in 2003 as a public-private partnership with the primary goal of testing whether serial collection of imaging, biomarker, clinical, and neuropsychological data can be combined to measure the progression of MCI and early AD [17]. AIBL is an ADNI collaboratory study established in the Australian cities Melbourne and Perth in 2006 in order to assemble a cohort of individuals who could be assessed at regular intervals for AD [18]. NACC was established by the National Institute on Aging in 1999 to support collaborative research in AD from participants at 34 past and present NIH-funded Alzheimer’s Disease Centers (ADCs) [19].

All three cohorts collect imaging, genetics, cognitive, and biological biomarker data, and evaluate enrolled participants approximately every 12–18 months with a comprehensive cognitive battery and clinical assessment. Diagnostic classification for study participants in the ADNI and AIBL cohorts are determined by a clinician or physician, and diagnoses are monitored by a clinical review committee.
to ensure uniform application of the diagnostic criteria across sites. NACC aggregates data from multiple ADC’s, and diagnoses are made either by a physician or by a consensus committee, according to each ADC’s protocol. A detailed description of how MCI is determined for each cohort is included in the Supplemental Materials. ADNI, AIBL, and NACC data collected between August 2005 and October 2014 were included in this study.

Brain imaging and quality control

Baseline T1-weighted MPRAGE MRI images from both 1.5T and 3T scanners were downloaded with authorization from ADNI, AIBL, and NACC databases and processed using FreeSurfer software version 5.3.0 (http://surfer.nmr.mgh.harvard.edu, Boston, MA) [20]. Hippocampal volumes were selected a priori as the region of interest based on its relevance to cognition and AD. Exploratory MRI analyses included total gray matter brain volume and five additional brain regions in medial and lateral temporal lobes that have shown sex and APOE differences [51] that are affected in early AD [21–23]. All hippocampal output volumes were visually inspected and scored by two experienced raters using ITK-SNAP software version 3.4.0 (http://www.itksnap.org) for accuracy [24]. Segmentation failed if a substantial segmentation error was identified, defined as an unambiguous mislabeling of a substantial portion of the total volume. 131 (14.1%) subjects were excluded from the analysis for poor segmentation accuracy. Subjects who failed quality control or had more than 12 months between cognitive and MRI acquisition were excluded from hippocampal analyses but included in the cognition analyses.

Cognitive tests

Baseline scores from the Mini-Mental State Examination (MMSE) [25, 26] and Immediate Recall and Delayed Recall from the Wechsler Memory Scale - Revised (WMS-R) [27] Logical Memory tests were examined as measures of global cognition and episodic memory, respectively. These were the common cognitive tests available across the cohorts.

APOE e4 gene dose

APOE e4 dose was defined as the number of APOE e4 alleles (0, 1, or 2) carried by a participant. An APOE e4 dose effect was defined as a significant difference that corresponded with the number of APOE e4 alleles, in which the effect was significant between 0 versus 1 allele, and 1 versus 2 alleles. By this definition, each APOE e4 allele had a significant, measurable effect on the biomarker and thus may have increased AD risk.

Statistical analysis

Analysis of covariance (ANCOVA) was used to assess the effect of number of APOE e4 alleles on MRI brain volumes and cognition using SPSS version 25. Main effects of APOE e4 dose and sex in the entire sample was assessed, along with main effects of APOE e4 dose when stratified by sex and 5-year age bins. Cohort, baseline age, and education were included as covariates. Total intracranial volume and scanner field strength were also included as covariates when analyzing brain volumes. Post-hoc pairwise comparisons were used to examine group differences based on the number of APOE e4 alleles. Because of our a priori hypothesis that APOE e4 effects may differ by sex, brain volumes, and cognition were examined separately for women and men. Post-hoc pairwise comparisons of brain volumes and cognition by APOE group were tested via within-sex and between-sex analyses. Additionally, APOE e4 effects across the aging spectrum were examined at each 5-year period, separately for women and men, and predicted values for cognition were derived from models with factors for age, APOE e4, cohort, and education. Sex and APOE e4 dose-dependent effects are expected to be subtle, especially given the low prevalence of e4/e4 carriers, therefore results were not corrected for multiple comparisons.

RESULTS

Participant demographics

Demographic data for the study population by APOE e4 genotype are summarized in Table 1. Participants were predominately white (84%). The ratio of women:men did not differ significantly by APOE e4 group (p = 0.75). Average years of education did not differ by APOE e4 group (p = 0.79); however, the average years of education was significantly higher for men than for women (p = 0.001). Age differed significantly by APOE e4 genotype (p < 0.001). Participants with 1 APOE e4 allele were younger than those with 0 APOE e4 alleles (p = 0.026) and
those with 2 APOE ε4 alleles were younger than those with 1 APOE ε4 allele (p = 0.001). Participant demographics are also shown separated by cohort in Supplementary Table 1.

**Biomarkers across all participants**

**Hippocampus**

There was a main effect of APOE ε4 dose for left and right hippocampal volumes, our a priori ROI (left & right, ps < 0.001). Post-hoc tests showed smaller left and right hippocampal volume with each APOE ε4 allele in a dose-dependent manner (0 > 1 > 2, all ps < 0.001) (Fig. 1).

Among the exploratory MRI volumes, a main effect of APOE ε4 was also seen bilaterally in the amygdala (p < 0.0001) (Fig. 2, Supplementary Table 2). Post-hoc tests showed a dose-dependent response in the left (0 > 1 > 2, p ≤ 0.001) and right (0 > 1 > 2, p < 0.05) hemispheres. No dose dependent differences were seen in the other brain regions (Fig. 2). Effect size, standard error (SE), and significance are reported in Supplementary Table 2 for all ROIs.

**Cognition**

For cognition, there was a significant main effect of APOE ε4 dose on MMSE, Immediate Recall, and Delayed Recall across all participants (all ps < 0.001) (Fig. 1). Post-hoc comparisons showed that worse performance on MMSE and Delayed Recall was associated with each APOE ε4 allele in a dose-dependent manner (0 > 1 > 2). Participants with 1 APOE ε4 allele had significantly worse cognitive performance on all tests than non-carriers (all ps < 0.001), and participants with 2 APOE ε4 alleles had significantly worse performance than those with one allele on MMSE and Delayed Recall (all ps < 0.05).

**APOE ε4 dose effects**

**Between-sex analyses**

For age, between-sex analyses showed there was no difference between women and men with no APOE ε4 alleles (p = 0.57). However, women with 1 APOE ε4 allele were younger than men with 1 APOE ε4 allele (p < 0.001). Similarly, women with 2 APOE ε4 alleles were younger than men with 2 APOE ε4 alleles (p = 0.03).

For between-sex analyses of hippocampal volume, left hippocampal volumes were significantly smaller for women than men with 1 APOE ε4 allele, while right hippocampal volume was significantly smaller for women than men with 0, 1, or 2 APOE ε4 alleles (all ps < 0.05). Sex-differences were also observed in the left and right amygdala for women with 0, 1, and 2 APOE ε4 alleles relative to men (all ps < 0.002). No dose dependent effects (0 versus 1 versus 2) were observed in other ROIs (Fig. 2, Supplementary Table 2).

For cognition, delayed recall differed by sex, such that women with 2 APOE ε4 alleles had lower delayed recall scores than men with 2 APOE ε4 alleles (p = 0.005). A trend for the same pattern was observed for men and women with 1 APOE ε4 allele (p = 0.078). There were no sex-specific differences on MMSE or immediate recall.
Fig. 1. Hippocampal volume and cognitive performance by number APOE ε4 alleles. A) Hippocampal volume (HCV) and cognitive performance on the Mini-Mental State Examination (MMSE) (B), Wechsler Memory Scale-Revised Immediate Recall (C) and Delayed Recall (D) stratified by number of APOE ε4 alleles. *p < 0.05; **p < 0.001.

Fig. 2. Significance heatmaps for brain regions of interest. Region of interest p-value heatmaps showing significant APOE ε4 effects for All Participants, sex-stratified effects, and the main effects of sex by APOE ε4 allele.
Sex-stratified analyses

Sex-stratified analyses showed an APOE e4 dose effect of age for women with 1 or 2 APOE e4 alleles compared to women with 0 APOE e4 alleles (all ps < 0.0001), but no age difference between women with 1 and 2 APOE e4 alleles (p = 0.19). Men were only of a younger age if they had 2 alleles when compared to men with 1 APOE e4 allele (p < 0.005).

When stratified by sex, the APOE e4 dose effect on hippocampal volumes remained significant for both women and men, separately (all ps ≤ 0.05). No differences were observed between left and right hippocampal volumes, so analyses combined left and right hippocampi. In women, post-hoc analyses showed that those with 1 APOE e4 allele had smaller hippocampal volumes than those with 0 APOE e4 alleles, and those with 2 APOE e4 alleles had smaller hippocampal volumes than those with 1 APOE e4 allele (all ps < 0.05). Men showed a similar pattern, such those with 1 APOE e4 allele had smaller hippocampal volumes than those with 0 APOE e4 alleles, and those with 2 APOE e4 alleles had smaller hippocampal volumes than those with 1 APOE e4 allele (all ps < 0.05) (Fig. 3). The above analyses were repeated using a residual normalization method for the left and right hippocampi against intracranial volume, and the significance of the results remained unchanged.

In women, an APOE e4 dose dependent volumetric difference was observed in the left amygdala, such that women with 1 APOE e4 allele had smaller volumes than women with 0 APOE e4 alleles (p = 0.016) and women with 2 APOE e4 alleles smaller than women with only 1 APOE e4 allele (p = 0.019). For women with 1 APOE e4 allele compared to women with 0 APOE e4 alleles, smaller volumes were observed in the right amygdala, left and right inferior parietal cortex, the right middle temporal lobe, and in total brain volume (all ps ≤ 0.05; Fig. 2; Supplementary Table 2). In men, the left and right amygdala were smaller for men with 1 APOE e4 allele than men with 0 APOE e4 alleles (all ps < 0.05; Fig. 2; Supplementary Table 2). No other APOE e4 dose differences in the other brain regions were observed for men.

Sex-stratified analyses showed that women had a significant APOE e4 dose effect, with lower scores with each APOE e4 allele for all cognitive tests (all ps, p < 0.05). In contrast, men showed lower scores for those with 1 APOE e4 allele compared to those with 0 APOE e4 alleles for all cognitive tests (MMSE: p = 0.011, Immediate Recall: p = 0.015,

Delayed Recall: p = 0.004); however, there was no difference in cognition between men with 1 or 2 APOE e4 alleles (Fig. 4).

Age-specific effects

Based on our recent work demonstrating a relationship between APOE e4 status, sex, and age [13], we examined the effect of age and APOE e4 on our biomarkers. There was no significant age by APOE e4 interaction on the AD biomarkers (all ps > 0.14). In age-stratified analyses of 5-year bins, there was a trend for an APOE e4 by sex interaction on delayed memory in those 65–69 years of age (p = 0.09). Additionally, there was a trend for an APOE e4 by sex interaction on the MMSE for those 70–74 years of age (p = 0.06). Post-hoc analyses in this age group showed that women with 2 APOE e4 alleles performed worse than men with 2 APOE e4 alleles on delayed memory (65–69 years p = 0.047) and MMSE (70–74 years, p = 0.004) (Fig. 5). There were no significant differences at the other 5-year age bins.

DISCUSSION

Understanding the contribution of number of APOE e4 alleles and how these effects are modified by sex and age is important for determining AD risk [28, 29]. In the present study, we showed an association between number of APOE e4 alleles and the AD biomarkers for hippocampal and amygdala volume and cognition in older adults with MCI, providing insight into those at risk for AD. Importantly, we demonstrated that the effect of APOE e4 dose on cognition differs by sex and preliminary, exploratory analyses suggest that cognitive
differences for women compared to men exist between 65–69 for episodic memory and between 70–74 for global cognition. While APOE e4 dose is associated with smaller hippocampal volume in both sexes, 2 APOE e4 alleles may have a greater impact on cognition in women than in men.

Across all participants, those with 2 APOE e4 alleles were significantly younger than those with 1 APOE e4 allele who were younger than those with 0 APOE e4 alleles, suggesting that APOE e4 may shift risk of AD earlier. However, this effect was modified by sex, showing men with 2 APOE e4 alleles were younger than men with 0 or 1 APOE e4 allele, while women with 1 or 2 APOE e4 alleles were significantly younger than women with 0 APOE e4 alleles.

Previous research has demonstrated an APOE e4 dose effect of increased AD risk and undesirable changes to a variety of AD biomarkers in participants with MCI. APOE e4 carriers with MCI are at increased risk of converting to AD [30], have poorer cognitive function [12, 31, 32], smaller hippocampal volumes [12, 31, 33, 34], lower CSF amyloid-β, higher CSF hyperphosphorylated tau [35] and higher total tau [14]. Our study expands this work to examine how APOE e4 dose and sex modify risk based on AD biomarkers.

Our general finding of a significant APOE e4 dose effect on hippocampal and amygdala volumes in this sample of individuals with MCI suggests that each APOE e4 allele has a measurable effect on regional brain structure. While not all studies have found this [36], our result is supported by previous research which found reduced hippocampal volume [33] and cognition [31] with each APOE e4 allele and reduced amygdala volume for APOE e4 carriers versus non-carriers [36, 37] in individuals with MCI. Furthermore, our results show that, while there was a significant APOE e4 dose effect on hippocampal and amygdala volume for both men and women, the same was not true for cognition. In our analysis of cognitive performance, women had worse performance with each APOE e4 allele, while men with 1 and 2 APOE e4 alleles did not differ, suggesting a differential impact of APOE e4 allele between the sexes on cognition. Importantly, at 1 and 2 APOE e4 alleles performance on delayed memory was significantly worse for women than men, even though women were also significantly younger.
To date, the effects of APOE e4 dose on brain structure and cognition, two important AD biomarkers, have not been demonstrated conclusively in women and men. The research predominantly informing current views on the interaction between APOE e4 and sex reports differences in AD risk. These studies reported that APOE e4 confers greater AD risk to women than men. Specifically, it has been reported in a number of studies that one copy of the e4 allele is sufficient to increase AD risk in women, whereas two copies but not one, increase risk in men [5, 7, 9, 38, 39]. A similar finding was demonstrated by Fleisher et al., who reported an APOE e4 by sex interaction in the hippocampal volume of MCI subjects [12]. Recent studies reported that women with higher amyloid burden were at greater risk of cognitive decline than men and that this effect was even stronger in women who were APOE e4 carriers [14, 40]. Additionally, women who were APOE e4 carriers had greater tau burden than men who were APOE e4 carriers [14], especially in those who had significant amyloid burden [41]. New genetic targets associated with amyloid and tau pathology have been implicated in women’s risk for AD, suggesting that the sex differences may extend beyond APOE e4 [42].

While previous research suggests that APOE e4 relates to AD risk differently for women and men, a recent meta-analysis by our group reported that...
women and men had nearly the same risk of developing MCI or AD between 55–85 years of age [13]. However, a critical period of risk for APOE ε4 women to convert to MCI was found between 55–70 years of age whereas APOE ε4 women to convert to AD were at elevated risk between 65–75 years of age. This study, which aggregated data for nearly 58,000 participants, suggests that the sex-specific effect of APOE ε4 may not differ, but that sex differences are evident at critical time periods. Although preliminary and exploratory in nature, the trends in our current findings support this critical period in women with 2 APOE ε4 alleles compared to men with 2 APOE ε4 alleles between 65–69 years of age in delayed memory performance. Additionally, this same relationship was identified for global cognition, but for those 5 years older, between 70–74 years of age, positing a temporal relationship of differences in memory preceding differences in global cognition, although this cannot be directly assessed in our cross-sectional analysis.

Potential mechanistic explanations for the consistent sex and APOE ε4 differences may be related to hormonal changes experienced by women during menopause, which has cascading effects in the subsequent aging process. Higher levels of estradiol are associated with better cognitive performance [43] and estrogen has been shown to reduce vulnerability to cell death in the hippocampus in the presence of amyloid-β [44], which may be exacerbated APOE ε4 carriers because of higher amyloid-β burden [45, 46].

A primary strength of our study is the direct, intentional analysis of sex differences in AD by utilizing large, retrospective datasets to examine subtle and understudied effects. Obtaining and harmonizing large datasets to increase the sample of participants with 2 APOE ε4 alleles was a necessary task to examine APOE ε4 dose effects stratified by sex and age; although the study was underpowered for multiple comparison correction likely due to subtle sex and APOE ε4 dose effects. However, there are limitations to conducting retrospective analyses. Many aging cohorts have only a limited number of cognitive tests available for analysis. There is some variability in how MCI is defined (see Supplementary Materials). Other risk factors that may differ between women and men, such as smoking, alcohol use, and cardiovascular disease [47], were not available in all the datasets and therefore, not included in our models. Other sex-specific considerations may also be contributing to this, such higher rates of mortality due to cardiovascular disease and stroke in men that might lead to a surviving population of older adult men who are healthier than their female counterparts [48]. Additionally, ascertainment bias poses several problems for population-based studies. For example, our cohort is enriched for APOE ε4 carriers beyond what is observed in the general population. Individuals with a family history of AD may be more likely to participate [49], and importantly, these studies may oversample healthier individuals due to the difficulty for sick participants to participate in follow-up data collection [50]. Lastly, the combination of 1.5T and 3T MRI scans is less favorable than MRI scans from the same scanner and/or MRI field strength.

Our findings, taken together with previous literature, support the hypothesis that detrimental effects conferred by APOE ε4 are dose-dependent and sex-specific in the MCI stage. While the importance of APOE ε4 is key to understanding AD risk, sex as a biological factor may additionally modify level of risk at critical time periods.

**ACKNOWLEDGMENTS**

This project is supported by the National Institutes of Health (R01-AG054617, R01-AG046928, P41-EB015922, U54-EB020406), Big Data Discovery Science (BDDS), and the Global Alzheimer’s Association Interactive Network (GAAIN 14-244631). The NACC database is funded by NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIA funded ADCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Steven Ferris, PhD), P30 AG013854 (PI M. Marsel Mesulam, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG016570 (PI Marie-Francoise Cheselet, MD, PhD), P50 AG005131 (PI Douglas Galasko, MD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30...
AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P50 AG005136 (PI Thomas Monteine, MD, PhD), P50 AG033514 (PI Sanjana Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), and P50 AG047270 (PI Stephen Strittmatter, MD, PhD).

Data collection and sharing for this project was funded by the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer’s Association; Alzheimer’s Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Mesoc Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org).

The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer’s Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Authors’ disclosures available online (https://www.j-alz.com/manuscript-disclosures/18-0859r1).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-180859.

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