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APOE ε4 associated with preserved executive function performance and maintenance of temporal and cingulate brain volumes in younger adults

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Abstract

The *APOE* ε4 allele is associated with cognitive deficits and brain atrophy in older adults, but studies in younger adults are mixed. We examined *APOE* genotype effects on cognition and brain structure in younger adults and whether genotype effects differed by age and with presence of depression. 157 adults (32% ε4 carriers, 46% depressed) between 20–50 years of age completed neuropsychological testing, 131 of which also completed 3T cranial MRI. We did not observe a direct effect of *APOE* genotype on cognitive performance or structural MRI measures. A significant genotype by age interaction was observed for executive function, where age had less of an effect on executive function in ε4 carriers. Similar interactions were observed for the entorhinal cortex, rostral and caudal anterior cingulate cortex and parahippocampal gyrus, where the effect of age on regional volumes was reduced in ε4 carriers. There were no significant interactions between *APOE* genotype and depression diagnosis. The ε4 allele benefits younger adults by

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Disclosures

All authors (including Dr. Taylor, Mr. Boyd, Ms. Turner, Mr. McQuoid, Dr. Ashley-Koch, Dr. MacFall, Dr. Saleh, and Dr. Potter) declare they have no conflict of interest.

Informed Consent Statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

Preliminary data were previously presented at the 53rd Annual Meeting of the American College of Neuropsychopharmacology.

allowing them to maintain executive function performance and volumes of cingulate and temporal cortex regions with aging, at least through age fifty years.

Keywords

Aging; depression; cognition; MRI; APOE

Background

There is a need to identify early biomarkers indicative of Alzheimer's disease risk as the presentation of clinically evident symptoms lag behind the development of neuropathology (Jack, et al. 2013, Risacher and Saykin 2013). Supporting this goal, it is important to understand how genetic differences that increase Alzheimer's disease risk may influence cognitive performance and brain structure in pre-clinical populations. This is particularly relevant to younger adult populations who could benefit from preventive strategies. When considering genotypic effects, it is important to test not only for direct relationships but also whether genetic influences alter the effect of age on clinical or imaging measures. Similarly, it is important to examine interactive effects of common conditions that are themselves associated with an increased risk of dementia, such as depression (Byers, et al. 2012).

Apolipoprotein E (apoE) is a very-low-density lipoprotein involved in transporting cholesterol from the blood. In the central nervous system, the apoE lipoprotein is involved in mobilization of cholesterol and fatty acids, aids in recovery from injury and promotes synaptic plasticity (Mahley and Huang 2012, Nathan, et al. 1994). The human *APOE* gene coding for this protein is located on chromosome 19 and has 3 allelic variants: ε2, ε3, and ε4. A large body of work demonstrates that the *APOE* ε4 allele is the primary genetic risk factor for the development of Alzheimer's disease in later life (Corder, et al. 1993, Strittmatter, et al. 1993) and, compared with non-carriers, even healthy older ε4 carriers exhibit differences on cognitive testing (Caselli, et al. 2004). Similarly, healthy older ε4 carriers exhibit smaller volumes and greater rates of atrophy in multiple cortical and subcortical regions (Donix, et al. 2010, Honea, et al. 2009, Risacher, et al. 2010, Taylor, et al. 2014, Wishart, et al. 2006). In contrast, the *APOE* ε2 allele may have protective effects, as it is associated with reduced age-related cognitive decline and lower risk for developing Alzheimer's disease (Suri, et al. 2013).

Studies investigating the *APOE* ε4 allele's effects on cognition in younger adult carriers are less consistent. Compared with noncarriers, several reports found that younger adult ε4 carriers exhibited better cognitive performance (Schultz, et al. 2008, Yu, et al. 2000) on tasks of attention (Rusted, et al. 2013), verbal memory (delayed recall) (Mondadori, et al. 2007), verbal fluency (Alexander, et al. 2007, Marchant, et al. 2010), and prospective memory (Evans, et al. 2014, Marchant, et al. 2010). In context with observations in geriatric populations, these findings support a theory that *APOE* ε4 exhibits antagonistic pleiotropy, or different effects on cognition at different ages (Han and Bondi 2008). However, other studies failed to observe differences on cognitive performance based on *APOE* genotype (Bunce, et al. 2011, Ihle, et al. 2012, Jorm, et al. 2007, Matura, et al. 2014, Richter-

Schmidinger, et al. 2011), raising questions about this theory and whether *APOE* genotype has any effect on cognition in younger adults.

There is less work in younger adults examining the effects of *APOE* genotype on brain structure. Studies examining small samples report that young adult and midlife ε4 carriers exhibit smaller hippocampal volumes (Lind, et al. 2006, O'Dwyer, et al. 2012) while others report that younger adult carriers exhibit increased entorhinal cortex volumes (DiBattista, et al. 2014). Analyses utilizing voxel-based approaches are mixed: some find no difference in cortical gray matter volume (Dowell, et al. 2013, Matura, et al. 2014) while others report thinner cortex in frontal regions (Fennema-Notestine, et al. 2011). Such differences may be reconciled by observations that the ε4 allele may be associated with regionally different effects, as a study examining gray matter networks in younger carriers found the ε4 allele was associated with gray matter reductions in frontal and cingulate regions, but relative increases in other regions including the hippocampus (Alexander, et al. 2012).

Just as aging is a risk factor for developing Alzheimer's disease, so is depression (Byers, et al. 2012, Diniz, et al. 2013). Depression increases the risk of dementia even occurring over a decade before dementia onset, although the effect of earlier life depression is primarily in *APOE* ε4 carriers (Karlsson, et al. 2015). Early work concluded that *APOE* genotype is not a risk factor for depression (Steffens, et al. 2003), but recent longitudinal population-based studies found that the ε4 allele was associated with prospectively identified depressive symptoms (Skoog, et al. 2015). Studies in depressed older populations report that ε4 carriers exhibit greater depression severity, poorer cognitive performance, and smaller frontotemporal volumes (Corsentino, et al. 2009, Kim, et al. 2002, Lavretsky, et al. 2003, Niti, et al. 2009, Qiu, et al. 2009, Rajan, et al. 2014, Yuan, et al. 2010). This work suggests there is an interactive or additive effect of depression and *APOE* genotype on cognitive decline, brain atrophy and risk of dementia (Rajan, et al. 2014). It is unclear if such relationships exist in younger adult populations where depression is associated with structural alterations in frontal, temporal, and cingulate regions (Kempton, et al. 2011, Pizzagalli 2011) and neurocognitive differences (McClintock, et al. 2010). Given the overlap in depressive and cognitive symptoms in older adults, it is important to examine if depression and *APOE* genotype may have interactive effects in younger adults.

The purpose of the study was to examine influences of *APOE* genotype on cognition and gray matter structure in a young to midlife adult sample. Given the nature of the relationships between *APOE* ε4 genotype and pathological aging, we hypothesized we would observe an interactive effect between *APOE* genotype and age on cognition and brain structure. We also sought to determine whether *APOE* genotype's effects on cognition and brain structure differs in individuals with current major depressive disorder.

Methods

Participants

Participants between the ages of 20 and 50 years were enrolled at Duke University and Vanderbilt University. Depressed participants had a DSM-IV diagnosis of recurrent MDD, as assessed by the Mini-International Neuropsychiatric Interview (MINI, version 5.0)

(Sheehan, et al. 1998) and interview with a study psychiatrist. Additional entry criteria included onset of first depressive episode before age 35 years and a Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) of 15 or greater. Entry criteria specified no antidepressant use in the last month; however, most subjects reported no antidepressant use for at least three months or longer. Eligible control subjects had neither any lifetime history of psychiatric disorders nor any history of psychotropic medication use.

Exclusion criteria included other lifetime DSM-IV Axis I disorders including substance abuse or dependence. Subjects were excluded for Axis II disorders determined by the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (First, et al. 1997). Additional exclusion criteria included: history of psychosis, acute suicidality, use of illicit substances in the last month, ECT in the last 6 months, a family history of bipolar disorder, any unstable medical condition, any history of neurological illness or head injury, or MRI contraindications.

Both the Duke University Medical Center Institutional Review Board and the Vanderbilt University Institutional Review Board approved this study. All study participants provided informed consent.

Neuropsychological Testing

Participants completed a battery of neuropsychological tests that covered cognitive domains relevant to depression. A trained psychometric technician supervised by a licensed clinical psychologist administered neuropsychological testing.

Similar to our past approach in late-life depression (Sheline, et al. 2010), we created rationally constructed composite domain variables from a broad test battery. To combine tasks, we created Z-scores for each measure based on the performance of all participants and averaged the Z-scores for all tests within each domain for each individual. Internal consistency for each domain was assessed using Cronbach's coefficient alpha (CoA). This resulted in four composite neuropsychological measures: a) episodic memory (Logical Memory 1 and 2; Benton Visual Retention Test, number correct; Rey's Verbal Learning Test, total I-V and total VII, CoA = 0.87); b) executive function (Controlled Oral Word Association [COWA] test (total score); Trails B time (reverse scored time to completion); verbal fluency (total phonological and semantic); Stroop Color-Word interference condition (number completed); CoA = 0.75); c) processing speed (Symbol-Digit Modality (number completed); Trails A (reverse scored time to completion); Stroop color naming condition (number completed); CoA = 0.70); and d) working memory (Digit span forward (number of trials correctly completed); digit span backward (number of trials correctly completed); CoA = 0.75).

MRI Acquisition

To simplify data analyses across two sites using different MRI scanners by different manufacturers, only subjects with MRI data acquired at Duke University was included in these analyses. Cranial MRI was performed using the eight-channel parallel imaging head coil on a whole-body MRI system (Trio, Siemens Medical Systems, Malvern, PA). Parallel imaging was employed with an acceleration factor of 2. Duplicate T1-weighted image sets

were acquired during the scan session using a sagittal MPRAGE sequence with TR/TE = 2300/3.46 msec, a 240 Hz/pixel bandwidth, a 256 x 256 matrix, a 240 mm diameter field-of-view, 160 slices with a 1.2 mm slice thickness, yielding an image with voxel sizes of 0.9 x 0.9 x 1.2mm.

Analyses of Volumetric and Cortical Thickness MRI Data

All volumetric measures were calculated using FreeSurfer (version 5.1) software running in a high-performance Linux cluster environment. The FreeSurfer methods used to derive cortical and subcortical brain volumes have been previously described.(Dale, et al. 1999, Fischl, et al. 2002, Fischl, et al. 2004a, Fischl, et al. 2004b) Cortical parcellation used the Desikan-Killiany Atlas;(Desikan, et al. 2006) in each hemisphere, this method identified 33 cortical and 7 subcortical gray matter regions (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus). Intracranial volume was assessed using the method implemented in FreeSurfer. We visually inspected the data by overlaying the surfaces and subcortical segmentations over the T1 data. Individual slices in each orientation were assessed for errors. No manual corrections were needed.

We also tested for differences in cortical thickness using Freesurfer's QDEC module. This was an atheoretical approach to test for differences not captured in atlas-based comparisons. In this method, cortical thickness is computed as the shortest distance between any point on the pial surface and the gray/white boundary and vice-versa; these two values are averaged (Fischl and Dale 2000). Maps were smoothed using the standard Gaussian kernel of 10mm. We used a general linear model (GLM) to test for differences in cortical thickness while correcting for multiple comparisons using the Monte Carlo simulation method. Data were tested against an empirical null distribution of maximum cluster size by running 10,000 synthesized Gaussian noise simulations with an initial threshold of $p < 0.01$. Right and left hemispheres were tested separately.

Selection of *a priori* regions of interest

Selection of a priori volumetric regions for primary analyses was based on work that identified *APOE* genotype effects on regional volumes. These included: the amygdala, hippocampus, entorhinal cortex, parahippocampal gyrus, precuneus, and cingulate cortex (Donix, et al. 2010, Honea, et al. 2009, Hostage, et al. 2014, O'Dwyer, et al. 2012, Reinvang, et al. 2013, Risacher, et al. 2010, Taylor, et al. 2014). For the cingulate cortex, we examined anterior divisions due to its implication in depression (Pizzagalli 2011) and posterior divisions due to *APOE* genotype's influence on metabolism in midlife populations (Protas, et al. 2013).

Genotyping

Genotyping was conducted on blood samples. *APOE* alleles (corresponding to allele combinations at single nucleotide polymorphism (SNP) +3937/rs429358 and SNP+4075/rs7412) were genotyped using the ABI 7900 Taqman (Applied Biosystems, Foster City, California, USA) system. The two *APOE* single nucleotide polymorphisms exist at amino acid 112 and 158, which are targeted by the Taqman probes. The individual genotypes at the two sites are then combined to create a single standard *APOE* genotype.

Analytic Plan

Our *a priori* hypotheses involved interactive effects between *APOE* ε4 genotype, age, and depression diagnosis, so we took a stepwise approach. All analyses were conducted with SAS 9.4 (Cary, NC) using PROC MIXED. Our primary analyses included all participants regardless of *APOE* genotype, however as the *APOE* ε2 allele may have protective effects (Suri, et al. 2013) we also conducted follow-up analyses where ε2 carriers were excluded.

First, we created initial models that did not include interaction terms but instead tested for a direct effect of *APOE* ε4 genotype. In these models, either cognitive domain z-scores or MRI measures were the dependent variable, with *APOE* ε4 genotype (presence or absence of an ε4 allele), diagnosis (depressed / never depressed), age, sex, and race (white or minority). Analyses of cognitive data included the additional covariate of years of education, while analyses of imaging data included total intracranial volume and hemisphere. After testing for initial effects, we subsequently created additional models that included either an *APOE* by age interaction term or an *APOE* by diagnosis interaction term. Final models tested for a three-way age by *APOE* by depression diagnosis interaction.

For analyses of cognition, we focused on our *a priori* plan of examining the z-transformed summary measures of processing speed, working memory, episodic memory, and executive function. For domains with a statistically significant genotype effect or interaction term, we planned for subsequent analyses that would examine the individual z-transformed tests within those domains.

For analyses of volumetric MRI data, we initially focused on our *a priori* regions as described above. Subsequent analyses also considered other brain regions not specified in our a priori hypotheses but quantified by our image analysis method. Given the large number of regions identified, for analyses of regions not included in our *a priori* hypotheses we corrected for multiple comparisons using the false discovery rate (FDR) method. When testing for differences in cortical thickness using FreeSurfer's QDEC module, we used a general linear model (GLM) to test for differences between genotype groups, including age as an additional independent variable. This allowed us to examine the direct effects of *APOE* genotype on cortical thickness as well as test for statistical interactions between genotype and age.

To elucidate the relationship between cognition and structure, we examined cognitive domains and brain regions identified as exhibiting statistically significant relationship in the above planned analyses. In these analyses, we examined the z-transformed cognitive domain score as the dependent variable. Independent variables included age, sex, diagnosis, race, and education. We also included brain regions as independent variables, utilizing the mean volume across the hemispheres, normalized for total intracranial volume.

Results

APOE Genotype Effects on Cognitive Performance

The sample for cognitive analyses included participants recruited at both the Duke and Vanderbilt sites. This consisted of 107 *APOE* ε4 negative individual (48% depressed, N=51)

and 50 *APOE* ε4 positive individuals (42% depressed, N = 21; Table 1). There was no significant difference in *APOE* ε4 frequency between diagnostic groups ($\chi^2 = 0.44$, p = 0.5070). The complete genotypic breakdown consisted of: 2/2, N=2; 2/3, N=14; 2/4, N=4; 3/3, N=87; 3/4, N=45; 4/4, N=5). The depressed cohort was significantly older and exhibited greater severity of depressive symptoms by MADRS than the nondepressed cohort, but there was no significant difference in age or MADRS score within each diagnostic cohort between those who were and were not ε4 carriers. After controlling for demographic covariates, we did not observe any statistically significant differences in the z-transformed cognitive domain scores between individuals identified by both genotype and diagnosis (Table 1).

In primary models without interaction terms, we did not find direct effects of either *APOE* genotype or diagnosis on any cognitive domain score. We also did not observe any statistically significant interactions between depression diagnosis and genotype on cognitive domain scores. Similarly, we did not find statistically significant three-way interactions between *APOE* genotype, age, and depression.

On testing for an interaction between age and *APOE* genotype, we found a significant interaction for executive function ($F_{1,149} = 4.23$, p = 0.0415) and a trend for episodic memory ($F_{1,149} = 3.16$, p = 0.0779) but no difference for other domains (working memory: $F_{1,149} = 1.90$, p = 0.1707; processing speed: $F_{1,149} = 0.01$, p = 0.9038). In analysis of executive function, *APOE* ε4 noncarriers exhibited worse executive function with increasing age than did the ε4 carriers (Figure 1). In other words, presence of the *APOE* ε4 allele reduced the effect of age on executive function.

We conducted additional analyses for the executive function and episodic memory domains, examining the z-transformed individual test items included in the composite domain scores. Controlling for the same covariates as in primary models, for the executive function domain we found significant interactions between age and genotype for Trails B (time to completion; $F_{1,149} = 4.39$, p = 0.0378) and COWA total score ($F_{1,149} = 8.97$, p = 0.0032), but not verbal fluency ($F_{1,149} = 0.48$, p = 0.4880) or Stroop color-word interference ($F_{1,149} = 0.08$, p = 0.7722). For the episodic memory domain, there was a significant interaction only for the Benton Visual Retention Test (number correct; $F_{1,149} = 7.00$, p = 0.0090). The interactions were similar to those observed with the executive function composite score, where ε4 carriers exhibited less reduction in performance with age (Figure 1). In the absence of the age by genotype interaction term, *APOE* genotype did not have a direct effect on test measures.

Secondary analyses where we excluded the twenty ε2 carriers were largely concordant with the results described above. We continued to observe a significant interaction between age and genotype for executive function ($F_{1,129} = 5.36$, p = 0.0222), but there was no support for a trend with episodic memory ($F_{1,129} = 2.63$, p = 0.1074). Analyses of specific cognitive tests resulted in findings similar to those reported above, aside from Trails B time to completion that no longer achieved statistical significance ($F_{1,129} = 3.84$, p = 0.0523). Again, ε4 carriers exhibited less reduction in performance with age and in the absence of the age by genotype interaction term, *APOE* genotype did not have a direct effect on any test measure.

APOE Genotype Effects on Regional Brain Volumes

To simplify analyses of MRI data across sites with different MRI manufacturers, we only included MRI data from the Duke site. Notably, 9 participants recruited at Duke either could not complete MRI or had MRI data of poor quality and so could not be included in analyses. The sample with MRI and *APOE* genotype data thus included 58 individuals with MDD and 73 never-depressed comparison subjects. There was no difference in *APOE* ε4 frequency between depressed and nondepressed groups in the MRI sample (ε4 −, MDD N=41; ε4 −, no MDD N=47; ε4 +, MDD N=17; ε4 +, no MDD N=26; $\chi^2 = 0.58$, p = 0.4452). Other demographic comparisons were comparable to the larger sample (Supplemental Table 1).

In primary models examining *a priori* defined regional brain volumes, we did not find direct effects of either *APOE* genotype or depression diagnosis on any region. We also did not observe any statistically significant interactions between depression diagnosis and genotype on regional volumes. Similarly, we did not find statistically significant three-way interactions between *APOE* genotype, age, and depression.

In analyses of our *a priori* defined regions, we observed statistically significant interactions between *APOE* genotype and age for the entorhinal cortex, rostral and caudal cingulate cortex (Table 2). Similar to what is observed in the cognitive analyses, the *APOE* ε4 allele reduced the effect of age on regional volumes (Figure 2). In other words, the relationship between age and volume exhibits a more negative slope in *APOE* ε4 noncarriers compared with ε4 carriers. These findings persisted when removing the seventeen *APOE* ε2 allele carriers, and we additionally observed an interaction between age and genotype for the parahippocampal gyrus.

Additional analyses examined other regions measured by FreeSurfer that were not part of our *a priori* hypotheses, where we again created similar models testing for direct and interactive effects of *APOE* genotype. After FDR correction for multiple comparisons, we observed neither statistically significant primary effects nor interactive effects of *APOE* genotype.

APOE Genotype Effects on Cortical Thickness

We found no statistically significant effects where *APOE* genotype was directly associated with differences in cortical thickness. When examining age by genotype interactions, we did not observe any regions where the effect of age on cortical thickness differed significantly between the *APOE* genotype groups. Similarly, we observed no differences when testing for different effects of genotype between depressed and nondepressed participants.

Relationship between Cognitive Domains and Regional Brain Volumes

Finally we sought to examine the relationship between cognitive domains and regional volumes identified in the above analyses. These analyses focused on the z-transformed executive function domain score, examining the entorhinal cortex, parahippocampal gyrus, and caudal and rostral anterior cingulate cortex volumes. After controlling for demographic differences, normalized parahippocamapal gyrus ($F_{1,124} = 7.66$, p = 0.0065) and rostral anterior cingulate cortex volumes ($F_{1,124} = 6.18$, p = 0.0143) were significantly associated

with executive function. There was also a trend for the caudal anterior cingulate cortex volume ($F_{1,124} = 3.86$, $p = 0.0518$) but no relationship with entorhinal cortex volume ($F_{1,124} = 2.06$, $p = 0.1536$).

Discussion

Our major finding is that in a younger adult population, the *APOE* ε4 allele reduces the effect of aging on executive function and regional brain volumes in temporal and anterior cingulate regions. Overall *APOE* ε4 carriers exhibited less reduction in executive function and regional volumes with age than did *APOE* ε4 noncarriers. We did not observe a direct effect of *APOE* genotype on cognition or brain morphology. We also did not find evidence to support that depression diagnosis interacted with *APOE* genotype to result in greater deficits in cognition or altered brain morphology. These findings were persistent across the entire sample, then also when we limited the sample to individuals who did not carry the ε2 allele.

Integration with aging literature

Our analyses of *APOE* genotype's effect in younger adults are concordant with and extend past work. These findings support the theory of antagonistic pleiotropy (Han and Bondi 2008), or that the ε4 allele has different effects on cognition at different ages. This may represent superior compensatory function during midlife. Had our sample's age extended past age 50 years, we anticipate that we would observe a downward curve in the age-cognition relationship in older ε4 carriers. Recent work suggests this more rapid rate of cognitive decline in ε4 carriers occurs around age 70 years (Jack, et al. 2015), well beyond our current sample.

There is still uncertainty about what cognitive domains may be differentially affected by *APOE* genotype. We found that genotype influenced the effect of age in our executive function domain (specifically performance on the Trails B and COWA) and visual memory measured with the BVRT. These findings are supported by past studies (Marchant, et al. 2010), although *APOE* effects on attention (Rusted, et al. 2013) may also be influencing performance on our executive function tests.

Our neuroimaging findings follow a pattern similar to our cognitive findings. These results are discrepant with a previous study that did not observe interactive effects of *APOE* genotype and age on structural measures (Filippini, et al. 2011). However, that study examined a smaller sample with two distinct age populations rather than a young to midlife adult sample with a continuous age range.

This work supports that aging is associated with poorer cognitive performance and smaller brain volumes, even in young to midlife adults. Our observations occur before ages where significant increases in amyloidosis occur (Jack, et al. 2015) and such aging effects are reduced in *APOE* ε4 carriers. Brain aging in younger adults may be due to multiple causes, including vascular risk factors, early tauopathy (Crary, et al. 2014, Jack, et al. 2013), or occur in the absence of any specific pathology (Jagust 2013). Further work is needed to better understand what processes are modified in *APOE* ε4 allele carriers and how that

benefit to cognition and brain structure is obtained prior to later amyloid deposition and cognitive decline.

Integration with depression literature

It is clear that neuropathology related to cognitive decline can occur decades before the onset of clinical symptoms (Jack, et al. 2013) and that earlier-life onset is associated with increased dementia risk (Byers, et al. 2012). However, there are few studies examining the relationship between depression and risk factors for Alzheimer's disease in younger adult populations. We observed neither differential effects of *APOE* genotype nor different genotype by age interactions between depressed and nondepressed individuals. This does not support a theory that cognitive or morphological differences related to *APOE* genotype may adversely affect neural circuitry in such a way that it would increase a predisposition to depression. Overall this suggests that the ultimate pathways by which depression increases dementia risk does not occur through apolipoprotein E mediated mechanisms in younger adults. However, the underlying nature of the relationship between depression and dementia remains an important question and alternative pathways should be considered, such as the relationship between depression and proinflammatory processes.

Study strengths and limitations

The study has several strengths, including a large sample size and comprehensive neuropsychological testing battery. Moreover image analyses utilized a combination of hypothesis-testing and hypothesis-generating approaches. These methods are complementary, as we found no relationship between study measures and cortical thickness, but did find volumetric differences in cingulate cortex regions and subcortical structures. Finally, in post-hoc analyses, we demonstrated a relationship between the identified cognitive domain (executive function) and identified brain regions (parahippocampal gyrus and rostral anterior cingulate cortex).

The study also has limitations. Although we have a broad cognitive battery, specific domains such as attention (Rusted, et al. 2013) were not assessed. Additionally, this was a well-educated sample and it is unclear if these results would generalize to populations with lower education. Moreover, although we examine age effects, this remains a cross-sectional study. Ultimately longitudinal studies are necessary to examine change in such measures and aging trajectories. Finally, there are notable limitations related to the sample, including a lower number of *APOE* ε4 allele carriers than ε4 noncarriers, although this limitation applies to much of the existent literature. The age difference between the diagnostic cohorts is also important. The strong effect of age on both cognitive and brain aging may have negatively affected our ability to detect a diagnosis by genotype interaction.

It should be emphasized that despite examining a relatively large sample, we made numerous statistical comparisons. For our *a priori* hypotheses, we did not control for multiple comparisons, thus increasing the risk for a type 1 error. Given the significance levels observed, correcting for multiple comparisons would have resulted in null findings. Thus while our findings fit within past literature, they should be viewed cautiously.

Despite these limitations, this study advances our understanding of the aging process by demonstrating that the *APOE* ε4 allele mitigates the effect of age on cognitive processes and brain structure in early- to midlife-adulthood. This occurs prior to significant increases in amyloid deposition as detected by PET scanning (Jack, et al. 2015), suggesting that the ε4 allele may modify other processes influencing brain aging. More work is needed to determine what those processes are, but also to determine how depression may increase risk of dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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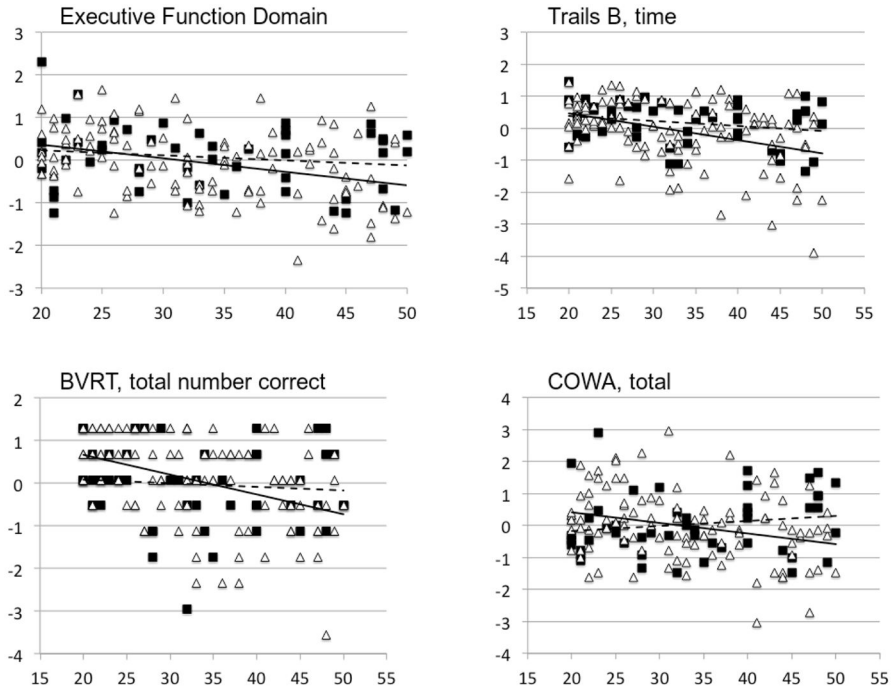

Figure 1.

Differential effect of age between *APOE* ε4 carriers and noncarriers on z-transformed cognitive performance

Data presented are the domain and tests exhibiting statistically significant age by genotype interactive effects on performance, after controlling for depression diagnosis, sex, race, and education. The executive function domain is the averaged z-score over multiple neuropsychological tests, including Trails Part B, COWA, verbal fluency and the Stroop color-word condition. The individual tests presented are those with statistically significant interactions between genotype and age, and included BVRT from the episodic memory domain. *APOE* ε4 noncarriers are triangles / solid line, *APOE* ε4 carriers are squares / dashed line. Z-transformed test performance score on the y-axis, age in years on x-axis.

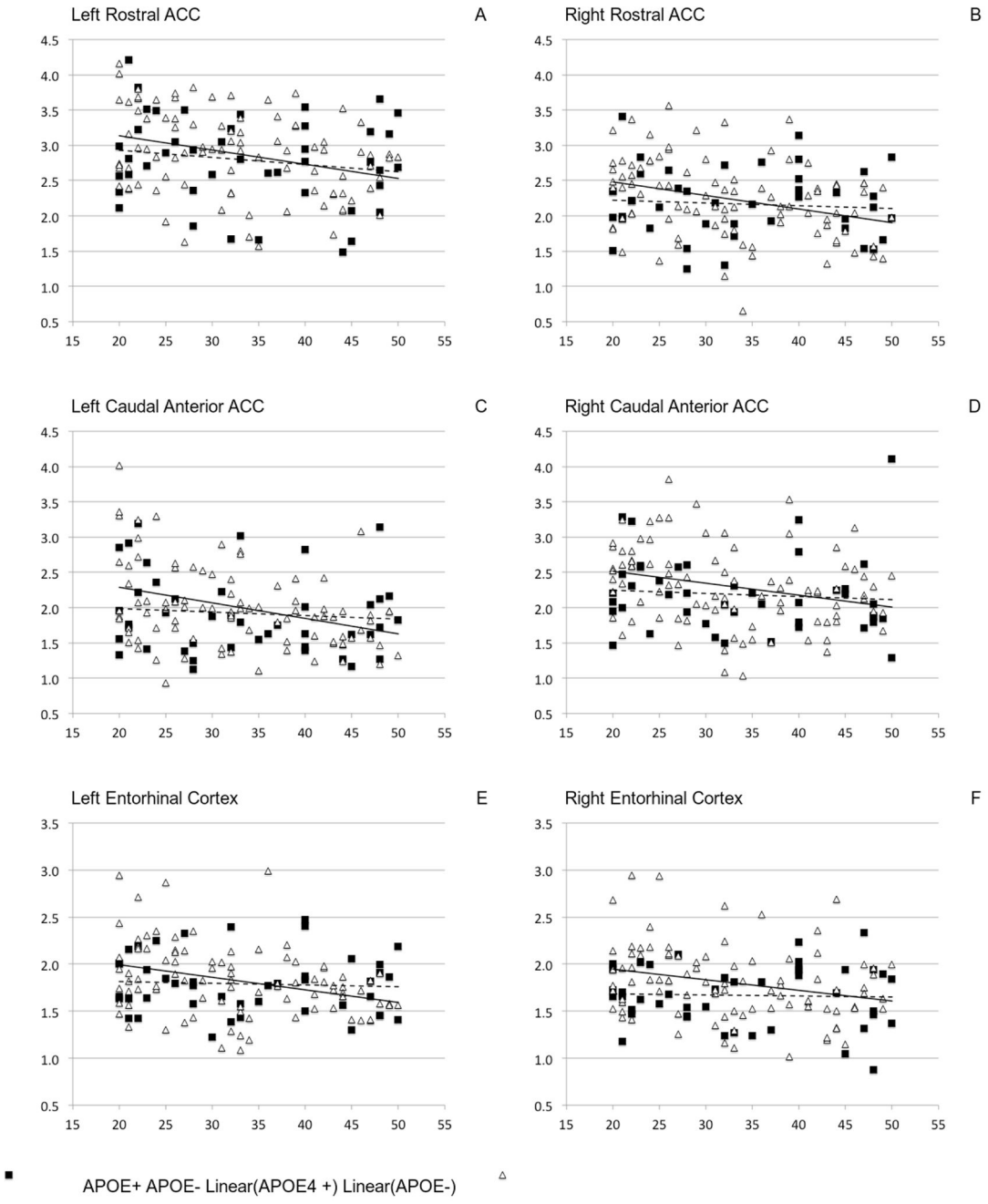

Figure 2.

Differences in age effects on regional brain volumes between APOE ε4 positive and negative individuals

Data presented are those regions exhibiting statistically significant age by genotype interactive effects on regional volumes, after controlling for depression diagnosis, sex, race, intracranial volume and hemisphere. Similar findings were observed unilaterally for the hippocampus, parahippocampus, and amygdala (figures not shown). *APOE* ε4 noncarriers are triangles / solid line, *APOE* ε4 carriers are squares / dashed line. Z-transformed test

performance score on the y-axis, age in years on x-axis. Regional volume in milliliters on the y-axis, age in years on x-axis.

Table 1

Demographic and cognitive domain score differences by *APOE* genotype and diagnostic group

	APOE ε4 **− Depressed (N = 51)**	***APOE ε4*** **− Nondepressed (N = 56)**	***APOE ε4*** **+ Depressed (N = 21)**	***APOE ε4*** **+ Nondepressed (N = 29)**	**Test Statistic**	**p value**
Age (y)	36.5 (8.8)	29.2 (8.2)	36.8 (8.8)	31.4 (10.1)	F = 7.69	p < 0.0001
Sex (% female)	66.7% (34)	58.9% (33)	76.2% (16)	68.9% (20)	χ^2 = 2.32	p = 0.5088
Race (% Caucasian)	64.7% (33)	51.8% (29)	61.9% (13)	51.7% (15)	χ^2 = 2.39	p = 0.4955
Education (y)	15.5 (2.5)	15.8 (1.9)	14.7 (2.1)	16.1 (2.4)	F = 1.83	p = 0.1434
MADRS	23.9 (4.2)	0.6 (0.9)	24.4 (5.2)	1.31 (1.4)	F = 692.83	p < 0.0001
Episodic Memory	−0.76 (4.16)	0.92 (4.02)	−1.35 (4.22)	0.62 (3.40)	F = 0.38	p = 0.7675
Executive Function	−0.95 (3.07)	0.49 (3.12)	0.13 (2.97)	0.40 (3.06)	F = 1.67	p = 0.1762
Processing Speed	−0.76 (2.35)	0.57 (2.39)	−0.28 (1.89)	0.30 (2.46)	F = 1.21	p = 0.3094
Working Memory	−0.28 (1.68)	0.48 (1.75)	−0.10 (1.68)	−0.15 (1.72)	F = 1.13	p = 0.3383

Continuous measures presented as mean (standard deviation). Group differences in demographic variables (age, education, MADRS score) tested using analysis of variance (ANOVA) where the model had a total 156 degrees of freedom. Categorical variables presented as percentage (number), differences tested using chi-square with 3 degrees of freedom. Cognitive domain data presented as z-transformed scores, mean (SD). These cognitive domain models tested for 4-way group differences and included 147 degrees of freedom, controlling for age, sex, education, and race.

Table 2

Interactive effects of *APOE* genotype and age on *a priori* brain region volumes

	All MRI Subjects (N= 131)		*APOE* ε3 and ε4 carriers only (N= 114)	
Region	**F value**	**p value**	**F value**	**p value**
Amygdala	F = 3.37	p = 0.0685	F = 2.09	p = 0.1514
Cingulate, Caudal Anterior	F = 5.94	p = 0.0161	F = 4.18	p = 0.0434
Cingulate, Rostral Anterior	F = 5.08	p = 0.0260	F = 3.94	p = 0.0496
Cingulate, Isthmus	F = 0.14	p = 0.7057	F = 0.62	p = 0.4338
Cingulate, Posterior	F = 0.86	p = 0.3565	F = 1.16	p = 0.2838
Entorhinal cortex	F = 6.64	p = 0.0111	F = 5.35	p = 0.0226
Hippocampus	F = 3.10	p = 0.0808	F = 2.71	p = 0.1025
Parahippocampal gyrus	F = 3.06	p = 0.0828	F = 3.92	p = 0.0503
Precuneus	F = 0.45	p = 0.5028	F = 0.15	p = 0.7009

Variables for the entire sample analyses had 1,129 df. Variables in analyses where ε2 carriers were excluded had 1,112 df. Mixed models included the independent variables of *APOE* ε4 genotype, diagnosis (depressed / never depressed), age, sex, race, intracranial volume, and hemisphere.