Published in final edited form as:

Am J Geriatr Psychiatry. 2011 January ; 19(1): 23–32.

The moderating effect of the APOE ϵ 4 allele on the relationship between hippocampal volume and cognitive decline in older depressed patients

Nataie Sachs-Ericsson, Ph.D., Kathryn Sawyer, M.A., Elizabeth Corsentino, B.A., and Nicole Collins, B.A.

Department of Psychology, Florida State University

David C. Steffens, M.D., M.H.S.

Department of Psychiatry and Behavioral Sciences, Duke University Medical Center

Abstract

Objectives—The Apolipoprotein E epsilon-4 (APOE ϵ 4) allele and depression are independently associated with increased risk for cognitive decline (CD). We have reported that depressed elders with an APOE ϵ 4 allele had greater CD compared with those depressed elders without the allele. Depression affects the hippocampus, and reduced hippocampal volume has been associated with CD. The current study sought to examine in depressed patients the relationships between hippocampal volume, the APOE ϵ 4 allele, and their interaction on CD. Analyses were performed to examine the influence of baseline hippocampal volume, the APOE ϵ 4 allele, and their interactions on change in cognitive functioning overtime.

Design—Secondary data analysis using linear regression analyses.

Setting—Clinical Research Center for the Study of Depression in Later Life conducted at Duke University.

Participants—Depressed older patients (N=61) followed over 4 years.

Measures—At baseline, cognitive functioning (assessed by the MMSE), left and right hippocampal volume (assessed by MRI), and APOE genotype were obtained. At four-year follow-up cognitive functioning was re-assessed.

Results—The APOE ϵ 4 allele and left hippocampal volume, but not right hippocampal volume, were independently associated with CD. Importantly, we found the APOE ϵ 4 allele to moderate the effects of left hippocampal volume on CD. The APOE ϵ 4 allele appeared to have little effect among those with larger left hippocampal volumes, whereas the allele influenced CD among those with smaller hippocampal volumes.

Conclusion—Future studies of cognitive impairment and decline should examine both individual and conjoint effects of putative risk factors.

Please address all correspondence to: Natalie Sachs-Ericsson, Ph.D. Department of Psychology Florida State University 850 644-4576
sachs@psy.fsu.edu.

The authors report no competing interests.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

cognitive decline; hippocampus; APOE ϵ 4; depression

Cognitive decline (CD) is likely the result of complex interactions of genetic and environmental influences. CD occurring later in life is associated with the Apolipoprotein E epsilon-4 (APOE ϵ 4) allele and depressive symptoms. APOE ϵ 4 is considered the most widely recognized genetic risk factor for late-onset Alzheimer's disease (AD), the most common form of dementia (1-3). It is associated with earlier onset and higher relative risk for developing AD. For example, evidence of the presence and magnitude of ϵ 4-related cognitive deficits was examined with a meta-analysis of the available literature. Thirty-eight studies were included, and cognitive performance was collapsed into 8 domains. Results indicated significant APOE- ϵ 4 group differences for global cognitive functioning, episodic memory, and executive functioning, in favor of non- ϵ 4 carriers (4). Although the mechanisms by which the APOE ϵ 4 allele confers risk for AD is still not altogether clear, the APOE ϵ 4 is thought to increase the deposition of amyloid beta ($A\beta$) protein and impair its clearance in the brain, which leads to the formation of amyloid plaques, a hallmark feature of AD. APOE ϵ 4 may also contribute to higher levels of tangle formations, which are also associated with AD (5).

Additionally, there is mounting evidence that depression is associated with increased CD later in life. Longitudinal evidence has provided growing support for this idea. For instance, a history of depressive symptoms was associated with the AD, even when the onset of depressive symptoms preceded the onset of AD by more than 25 years (6). Sachs-Ericsson and colleagues (7) found, in a large sample of community-dwelling older adults, depressive symptoms were associated with increased cognitive errors three years later. Moreover, results from a meta-analysis of case-control and prospective studies determined that a history of depression approximately doubles the risk for developing dementia (8). It should also be noted that a study based on the Neurocognitive Outcomes of Depression in the Elderly (NCODE) data (9), a sample from which the depressed participants examined in the current study were obtained, demonstrated that a diagnosis of Major Depressive Disorder at baseline significantly increases the odds of subsequent dementia relative to a control group of healthy elders (10). Nonetheless, some studies have failed to find an association between prior depressive symptoms and the onset of CD (11-13).

Sapolsky and colleagues (14) have proposed a glucocorticoid cascade hypothesis in which depression or chronic stressors lead to chronic, prolonged activation of the Hypothalamic-Pituitary-Adrenal axis (HPA axis). The HPA axis involves the hypothalamus, as well as the pituitary and adrenal glands. In response to stress, the hypothalamus releases vasopressin and corticotrophin-releasing hormone (15). These hormones, in turn, stimulate the pituitary gland to release adrenocorticotrophic hormone (ACTH). ACTH then stimulates the adrenal gland to release corticosteroids, such as cortisol (16). Prolonged and repeated cortisol release may cause hippocampal damage and neuronal death, which in turn places depressed individuals at greater risk for developing dementia. Among some depressed persons, an abnormal HPA response has been found to persist even after the depression has remitted (17).

Given the association between depression and hypercortisolemia, some have suggested a depression-as-stress model to explain the relationship of depression and changes in left and right hippocampal volume seen on magnetic resonance imaging (MRI) brain scans (18). A 2004 meta-analysis found an overall decrease among depressed patients of 8% of hippocampal volume on the left side and 10% on the right side (19). A recent report also

used meta-analytic techniques to examine data from 32 MRI studies of hippocampal volume in patients with major depression, confirming a difference in left and right hippocampal volume between depressed and healthy controls (20). Thus, we might expect depression to influence hippocampal volumes.

Severity of depression may influence the extent to which hippocampal damage or CD occurs. For example, in one study longer duration of depression predicted smaller hippocampal volume (18). Shah and colleagues (21) compared hippocampal volumes of participants with chronic depression, defined as depression lasting for greater than two years, to healthy controls and participants recovered from a (non-chronic) major depressive episode. In the study, chronically depressed participants, but not participants recovered from a (non-chronic) major depressive episode, had reduced left hippocampal volumes and a trend toward reduced right hippocampal volumes. Thus, depression severity (chronic or non-chronic) may influence the extent of hippocampal change.

Smaller hippocampal volume has been associated with diminished cognitive functioning. One study found that depressed patients, compared with controls, had smaller hippocampal volumes and scored lower in verbal memory, a neuropsychological measure of hippocampal function (18). In other studies, left hippocampal volumes were associated with verbal memory function in normal aging (22) and small left hippocampal volume was significantly associated with later dementia (23). Thus, we might expect hippocampal volume to predict changes in cognitive functioning over time.

We recently reported that depressed elders with an APOE $\epsilon 4$ allele had greater CD compared with those depressed elders without the $\epsilon 4$ allele (24). In light of previous findings, in the current study of depressed older patients, we hypothesized that those with smaller left or right hippocampal volumes at baseline would show more CD over time. Secondly, we hypothesized consistent with prior reports, that the APOE $\epsilon 4$ allele would be associated with CD. Third, we hypothesized that the APOE $\epsilon 4$ allele would have a greater affect on CD among those with smaller left or right hippocampal volumes compared with those with larger hippocampal volumes.

Methods

This study used previously collected data from the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study, a longitudinal study of geriatric depression supported by the National Institutes of Mental Health (9).

Informed Consent

All participants provided written informed consent to participate, and the research protocol is reviewed and approved annually by the Duke University Internal Review Board

Recruitment

Participant recruitment began in 1994 and continues to the present.

Depressed participants—Non-demented adults over age 60 who presented for inpatient or outpatient psychiatry services at Duke University Medical Center or at the Duke General Internal Medicine Clinic in Durham, North Carolina and met DSM-IV criteria for a current episode of Major Depression were recruited into the study. Participants were excluded from the NCODE study if they met criteria for another major psychiatric illness (schizophrenia, schizoaffective disorder, bipolar disorder, lifetime alcohol or substance dependence, and dementia).

NCODE Sample of Depressed Participants—There were 248 depressed inpatient and outpatient participants who met the NCODE criteria and were included in the NCODE study. Of these 248 participants, some failed to complete scheduled assessments or left the study; thus, there was some missing data due to attrition. For the current study, we identified a subset of patients who had all of the data required for the planned analyses needed to test the study's hypotheses. Participants were only excluded in the current study if they were missing data necessary for the current study's analysis.

Missing Data

Among the 248 depressed inpatient and outpatients participants for whom baseline data were obtained, there were 112 depressed participants followed for at least 4 years. That is, we had a year 4 assessment of cognitive functioning on 112 participants from the NCODE data set. Unfortunately, many participants were excluded from the current data analyses because they were missing baseline MRI data. Among these 112 participants, only 83 had baseline MRI data on hippocampal volume. Among these 83, some participants were missing other data necessary for the regression analyses (e.g., APOE status, etc.), leaving us with a sample of 61 depressed patients for whom we had all data required for the regression analyses performed in the current study. Data was missing due to patient attrition, missed appointments, or an inability to complete an MRI at baseline.

Measures

Baseline demographic and depression assessment—Trained interviewers administered the Duke Depression Evaluation Schedule (DDES) to all patients to determine if the patient met the criteria of major depression. The DDES is a structured interview that includes sections on demographic information, current life stress and social support. The DDES also included the Diagnostic Interview Survey (DIS) (25) which allows for an assessment of DSM-IV current and lifetime Major Depression. Items on the DIS paralleled symptom criteria for DSM-IV diagnosis of depression. It fully specified all questions and probes to be used, its symptom scoring system indicated not only whether a symptom met criteria, but why it failed to, and it was accompanied by a set of computer programs that made diagnoses on the basis of analysis of symptom scores. In addition to diagnostic results, the DIS also provides a total symptom count across diagnoses and a count of the number of criteria met for each diagnosis, and whether or not that diagnosis is positive. The DIS has been used in a set of epidemiological studies sponsored by the National Institute of Mental Health Center for Epidemiological Studies. Its accuracy has been evaluated in a test-retest design comparing independent administrations by psychiatrists and lay interviewers with inpatients, outpatients, ex-patients, and non-patients (25). It has been found to have good validity and reliability for participants of all ages (25). It is widely used in research in aging populations (see, for example: (26-29). Additionally, in making the diagnosis of clinical depression, other assessments described below were conducted by a geriatric psychiatrist.

Baseline assessment of severity of depression—A geriatric psychiatrist completed a Montgomery Asberg Depression Rating Scale (MADRS)(30) to determine severity of depression at baseline. The MADRS has been used to assess depression in geriatric populations (31,32). The psychiatrist used a structured interview to assess the following: apparent sadness, sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, difficulty in getting started or slowness in initiating and performing everyday activities, inability to feel, pessimistic thoughts and suicide. Each item had a 6 point response scale. For example, "Apparent sadness" was rated using a six point scale ranging from ("No sadness" to "Looks miserable all the time and extremely despondent").

All ten items had good to excellent interrater reliability (33). The intraclass correlation for raters using the SIGMA was found to be $r=.93$, $p<.0001$. We had baseline MADRS score for all participants in the current study. For some participants in the study, we also had an assessment on the MADRS around the time that the year 4 Mini Mental State Examination (MMSE) was assessed.

Baseline cognitive screening—At baseline, a geriatric psychiatrist examined each participant, reviewed the participant's medical records, and consulted with the participant's referring physician to determine whether the participant had dementia. Additionally, all participants were administered the Mini Mental Status Examination (MMSE). Participants with MMSE scores of 25 or higher, and no indications of dementia, were enrolled.

Clinical assessment of depression—At baseline, a geriatric psychiatrist interviewed each potential participant and completed standardized clinical assessments for depression, including the MADRS and the Clinical Global Impression scale. Based on the patient's reported symptoms, the results of the DIS, and the clinical interview, the presence or absence of major clinical depression was determined.

Mini Mental State Examination (MMSE)—The MMSE (34) assesses cognitive functioning in five areas: orientation, registration, attention and calculation, recall, and language; and provides an objective measure of global cognitive functioning. Scores range from 0 to 30, with higher scores indicative of better cognitive functioning; a score below 25 is generally indicative of cognitive impairment. The MMSE has been used extensively in epidemiologic research of older adults. In the current study, reliability is acceptable ($\alpha = .70$).

Assessment of genotype—APOE genotype was determined using previously described methods (35). APOE genotype was determined by DNA extraction and polymerase chain reaction. High-molecular-weight deoxyribonucleic acid (DNA) was obtained from whole blood, and crude DNA extract was obtained from buccal cheek swabs. Genomic DNA was amplified by polymerase chain reaction (PCR). An initial denaturization was followed by 35 cycles of annealing in the final extension. After amplification, 5U of HhaI was directly added to each well, and the plates were incubated for at least 3 hours at 37°C. Type III Stop dye was added to each well, and 3 μ l of each reaction was loaded on a 6% nondenaturing polyacrylamide gel and electrophoresed for 1 hour under constant current (45mA). After electrophoresis, the DNA was visualized by staining with SyberGold (FMC) (Whitaker Biproducts, CT) followed by fluorography. Each fluorogram was read independently by two observers.

MRI—Participants underwent structural MRI of the brain at baseline. The methodology of hippocampal measurement has been reported previously by Steffens et al (2002). Briefly, as described by Steffens, participants were imaged using a 1.5-tesla whole-body MRI system (Signa, GE Medical Systems, Milwaukee, WI). Two sets of dual-echo fast spin-echo (FSE) acquisitions were obtained, one in the axial plane for morphometry of most cerebral structures, and a second in a coronal oblique plane for segmentation of the hippocampus. The pulse sequence parameters were repetition time (TR)=4,000 msec, and echo time (TE)=30, 135 msec, with 32 KHz (± 16 KHz) full imaging bandwidth; echo train length=16, a 256×256 matrix, 3-mm section thickness, 1 Nex and a 20-cm FOV (field of view). The images were acquired in two separate acquisitions, with a 3-mm gap between sections for each acquisition. The second acquisition was offset by 3 mm from the first, so that the resulting data set consisted of contiguous sections. For the near coronal acquisition, the localizer scan was used to identify the anterior commissure–posterior commissure (AC–PC)

line. Oblique, near-coronal images were prescribed perpendicular to this line, covering the entire brain from just anterior of the temporal lobe to a plane posterior to the lateral ventricles. Images were archived as normal procedure on magneto-optical disks in the MR Imaging Center. The MRI images were then transferred to the Neuropsychiatric Imaging Research Laboratory (NIRL), located at Duke University Medical Center, for processing on SUN workstations, and secondary archive. Thin-slice, dual-echo FSE images, consisting of proton-density and T2-weighted images, were used for all processing. Hippocampal measurements used an oblique/coronal series of slices, and all other measures were done with axial images. Two computer programs were used to make volume measurements. Left and right hippocampal volumes were determined with the GRID Program, which was developed at NIRL. Technicians computing hippocampal volume using the GRID program demonstrated acceptable interrater reliability (left hippocampus intraclass correlation coefficient = 0.8)(23). The hippocampus units are presented in Milliliters (mL).

Data Analytical Plan

First, we described the demographics of the depressed patients in the current study. We described means and standard deviations of the variables used in the analyses. Among the participants in the current study, we also described the correlations among relevant variables. We then performed a series of linear regression analyses in which the MMSE score, obtained approximately four years after baseline, was the dependent measure. In the first regression analysis, the APOE allele and left hippocampal volume and their interactions were the predictor variables of interest. We also controlled for age, gender, years of education, severity of depression using the MADRS, and baseline MMSE. We entered the variables in a planned order. First we included variables that may predict CD but also may be correlated with hippocampal volume or APOE status. By including age, gender, years of education, and baseline severity of depressive symptoms in the first step of the analyses, we controlled for these variables' influence on CD. Thus, controlling for these variables first, allowed us to examine the specific impact of the APOE allele and hippocampal volume on the next step. It should be noted by controlling for the baseline MMSE in the first step, this allowed us to examine changes in cognitive functioning between baseline to year four. Therefore, on the second step we examined the main effects of the APOE allele and left hippocampal volume. On the final step we examined the interaction of the APOE allele and left hippocampal volume on cognitive functioning. It is important to enter the main effects first and place the interaction on a separate step so that the main effects of the APOE allele or the hippocampus (determined in the second step) are interpretable.

A second regression analyses was performed. It was identical to the regression analysis described above, except we examined the main effects of the right hippocampal volume on cognitive functioning and its interaction with the APOE ϵ 4 allele in predicting CD. Finally, based on a subset of participants for whom we had data on severity of depression at time 4, we repeated the two regression analyses, but this time controlled for the severity of depressive symptoms at time 4, which could have influenced CD.

Results

Demographics and Descriptive Statistics

Table 1 describes the demographics of the current sample (N=61) who were followed to year 4. However, data needed for the current study's analyses were missing for some participants who were followed to year 4 (specifically 51 participants). Most data was missing for baseline MRI. Analyses comparing those participants in the current study to those who were not included (due to missing data) showed few differences between groups. These comparisons included demographic data, indices of depression (e.g., age of onset,

number of lifetime episodes) and APOE genotype. However, there was one significant difference. Participants who were excluded had higher severity of depression as measured by the MADRS, $M = 29.33$ ($SD = 8.9$) vs. $M = 26.08$ ($SD = 6.3$), $F(1, 111) = 5.128$, $p = .025$.

The participants included in the survey had an average age of 67.9 years ($SD = 6.1$), were 61.1% female, and had an average of 14.6 ($SD = 2.5$) years of education. Ethnicity was as follows: African American 9.1%, Asian 1.5%, Caucasian 81.8%, Iranian 1.5%, Mixed Race 4.5%, and Native American 1.5%. Overall, this was a sample of highly educated, predominately white participants. This should be taken into consideration when interpreting the results. Indices of depression severity suggested that these participants had a relatively severe course of depression. Age of onset was 43.0 years of age ($SD = 19.7$). Over a third had been hospitalized in the past for their depression (35.9%). The vast majority had taken antidepressant medication (83.6%). The participants reported that on average they had had 7.7 ($SD = 16.6$) depressive episodes. Removing two outliers, the number of life time episodes was 5.6 ($SD = 6.5$) episodes. Thus, this was a rather homogenous group in regard to depression severity.

A repeated measures (paired-samples) t-test showed there was no significant difference between the baseline MMSE, 28.4 ($SD = 1.8$), and Year 4 MMSE, 27.8 ($SD = 1.7$), $F(1, 60) = 1.9$, $p < .17$. Additionally, a paired-samples t-test showed that the right hippocampal volume, 3.1 ($SD = .4$) mL was larger than left hippocampal volume, 3.0 ($SD = .4$) mL, $t(1, 65) = 3.3$, $p < .01$. Thus, as other studies have found, the right hippocampus was larger at baseline than the left hippocampus.

Relationship of Indices of Depression Severity to Hippocampal Volume, MMSE Scores, and APOE Genotype

Baseline hippocampal volume (both left and right) was unrelated to the baseline MMSE. The APOE $\epsilon 4$ allele was not associated with MMSE scores at baseline, and there was no relationship between APOE genotype and baseline left or right hippocampal volume. Among these depressed participants, most indices of depression severity were unrelated to MMSE scores or hippocampal volume. However, earlier age of onset was related to baseline MMSE ($r(61) = 2.9$, $p < .01$) such that the earlier the onset, the fewer correct the participant scored on the MMSE. However, age of onset was related to years of education ($r(61) = 3.5$, $p < .01$). Once years of education were controlled for, age of onset was no longer related to the MMSE. It should be noted that the homogeneous nature of the sample (e.g., severely depressed) may have obscured relationships among variables.

APOE Allele

There was 26.2% of the sample who had at least one APOE $\epsilon 4$ allele. The distributions of alleles were as follows: For APOE $\epsilon 2$ allele 89.2% had none, 7.7% had one, and 3.1% had two. For APOE $\epsilon 3$ allele 10.8% had none, 24.6% had one, and 64.6% had two. For APOE $\epsilon 4$ allele 73.8% had none, 20% had one, and 6.2% had two.

Linear Regression Analysis of Left Hippocampal Volume

As described in Table 2, after controlling for baseline MMSE scores, education, age, gender, and baseline severity of depressive symptoms, we found both smaller hippocampal volume and the APOE $\epsilon 4$ allele to predict decrease in cognitive functioning over the four years. On the last step of the analysis we found a significant interaction of the APOE $\epsilon 4$ allele and left hippocampal volume on change in MMSE scores. The APOE $\epsilon 4$ allele had a greater effect on CD among those with smaller hippocampal volumes compared to those with larger volumes. In a subsequent analysis in which we had data for only 54 participants, we controlled for severity of depressive symptoms at the year four follow-up. Depression

severity at follow-up was unrelated to CD. Moreover, the results did not change the findings described above.

Linear Regression Analysis of Right Hippocampal Volume

As shown in Table 3, analyses were conducted for right hippocampal volume. As before, the control variables were entered on the first step. The right hippocampal volume and APOE status were included on the second step. On the second step there was no relationship between the right hippocampus and CD. As expected, APOE $\epsilon 4$ allele predicted CD. The interaction of the APOE $\epsilon 4$ allele and right hippocampal volume was not statistically significant ($p = .09$); though the pattern of results for the interaction was consistent with those found for the left hippocampus. We repeated the analysis with 54 participants who had been assessed for depression severity at follow-up. Again, follow-up depression severity was unrelated to CD, and the interaction between the right hippocampus and the APOE $\epsilon 4$ allele was not statistically significant ($p = .06$).

Discussion

In the current study we examined a population of older depressed patients. We found the APOE $\epsilon 4$ allele and the left hippocampal volume to each predict cognitive decline (CD) over a four-year period. Importantly, we found the APOE $\epsilon 4$ allele moderated the relationship of hippocampal volume on CD. Specifically, the APOE $\epsilon 4$ allele had little effect on cognitive functioning among those with larger left hippocampal volumes; however, the APOE $\epsilon 4$ allele influenced those with smaller hippocampal volumes, such that those with the allele showed greater decrease in cognitive functioning than those without the allele. The right hippocampal volume did not predict CD. The interaction of the APOE $\epsilon 4$ allele and the right hippocampal volume was not significant ($p = .09$); though the pattern of results for the interaction was consistent with those found for the left hippocampus.

In our previous research we found the prospective influence of depressive symptoms on CD was greater for individuals with the APOE $\epsilon 4$ allele compared to those without the allele (24). Other recent studies have found similar findings (36). We speculated that the mechanism underlying our previous finding (e.g., a significant interaction between depression and APOE $\epsilon 4$) was related to the APOE $\epsilon 4$ allele having greater effect on those depressed participants with the greatest damage to the hippocampus (e.g., smaller hippocampal volume) (24). In the current study we attempted to explicate the mechanism by which depression moderated the effects of the APOE $\epsilon 4$ allele on CD.

Indeed, we found the APOE $\epsilon 4$ allele to have greater effect on CD among those depressed participants with smaller left hippocampal volume (assessed at baseline). The effect of the APOE $\epsilon 4$ allele on reduced hippocampal volume may be a result of the inability of the brain to compensate for this combined assault. Smaller hippocampal volume and the APOE $\epsilon 4$ allele may act synergistically in a greater disruption of neurological functioning, which may in turn lower an individual's cognitive reserve capacity; the individual's ability to successfully contend with increasing pathology (37).

This study's results offer one important explanation as to why the APOE $\epsilon 4$ allele is associated with CD in some but not all individuals with the allele. There likely are other factors that influence the relationship between the APOE $\epsilon 4$ allele and CD. Similarly, there likely are factors other than depression that influence hippocampal volume. Identifying factors that enhance known risk factors is an important area of future research.

It is also important to note that there may be a relationship between the APOE $\epsilon 4$ allele and hippocampal volume. Some studies have shown individuals with the $\epsilon 4$ allele have a greater

rate of hippocampal volume loss over time compared to individuals without an $\epsilon 4$ allele (e.g., (38). In one study, the APOE $\epsilon 4$ allele appeared to significantly impact rate of volume loss over time in the hippocampus in nondemented older adults (39). The potential relationship between the APOE $\epsilon 4$ allele and hippocampal volume may augment the interaction between hippocampal volume loss and the APOE $\epsilon 4$ allele on CD.

We found significant results for the left, but not the right, hippocampus. The hippocampus is a reliably asymmetrical structure in normal adults, with larger right hippocampal volumes (40). In the current study, we also found the right hippocampus to be larger than the left hippocampus. This difference could be related to our having found a significant effect for the left but not the right hippocampus. In this regard, Jak and colleagues (39) examined longitudinal change in bilateral hippocampal volumes, and the percent change bilaterally was greater in those positive for the APOE $\epsilon 4$ allele, and the effect was greater for the left than the right hippocampus. Because of this asymmetry, it may take a longer time (e.g., increasing age) for the detrimental effects of depression and the APOE $\epsilon 4$ allele to affect cognitive processes due to damage of the right hippocampus. This is an important area of research to pursue.

This study's results suggest that over time the APOE $\epsilon 4$ allele most likely affects those who are already compromised by a smaller hippocampus, which may (or may not) be due to depression. The patient may be compromised by other unmeasured 3rd variables". Chronic ongoing stress, as described above, would also influence hippocampal volume. Thus, there may be an array of factors associated with stress that affect hippocampal volume and may in turn interact with the APOE $\epsilon 4$ allele in predicting CD. It would also be important to consider if there was an interaction of the APOE $\epsilon 4$ allele and hippocampal volume on CD in non depressed persons. Indeed, as previous research has already shown, this depressed sample is at a higher risk for dementia relative to healthy controls (10). Thus, examining these findings in healthy adults is an important area of further study.

As in all studies, there are limitations that must be considered in interpreting the study's result. Our use of the MMSE to measure cognition may not have been as sensitive to change as would a more complete cognitive battery. It may be that the MMSE is not the best measure for detecting the relationship between hippocampal volume and cognition in this sample due to the participants' high level of educational attainment, which may create a ceiling effect in the population. Secondly, in the current study we only examine change in cognitive functioning based on two time points.

Another limitation is that the study was not a representative sample of depressed persons. Indeed, it was comprised of predominately white, well-educated depressed participants. Lack of variability among the participants may have limited our ability to examine the relationships among variables.

Importantly, the results were based on a relatively small sample. We cannot rule out the possibility that results were due to Type I or Type II error. The fact that we did not find a relationship between the right hippocampus and CD, and its interaction with the APOE allele (e.g., $p = .09$) may have resulted from not having sufficient power to detect a true association. Indeed, power analyses showed we could only detect large effects. Moreover, we specified a regression model with seven covariates and only 61 participants, raising the further possibility that the model could be unstable.

A number of participants followed over the four years were excluded, for the most part, because we did not have a baseline MRI for the participant. As other studies have consistently found, data is often not missing at random (41). Indeed, those with missing data had higher levels of depressive symptoms at baseline. If these individuals had been included

in the study, it is not clear if we would have found the same results identified in the current study.

Moreover, though we found the APOE $\epsilon 4$ allele to moderate the effects of left hippocampal volume on CD, other potential third variables may have been operating and may account for this relationship. These variables may be genetic, environmental, or both. The reasons why some individuals but not others who have identified risk factors for dementia do not develop dementia is an area that certainly warrants further investigation.

In sum, this study adds to the literature on the complex relationships among late-life depression, the APOE $\epsilon 4$ allele and CD. In the current study of depressed patients followed over 4 years, we found that the APOE $\epsilon 4$ allele and reduced left hippocampal volume were associated with CD. Importantly, we found that left hippocampal volume moderated the effects of the APOE $\epsilon 4$ allele on CD. That is, the APOE $\epsilon 4$ allele appeared to have little effect on change in cognitive functioning among those with larger left hippocampal volumes, whereas the APOE $\epsilon 4$ allele influenced those with smaller volumes such that those with the allele showed greater decreases in cognitive functioning than those without the allele.

Acknowledgments

Support: This research was supported by NIMH grants K01 MH066380, K24 MH70027, R01 MH54846 and P50 MH 60451.

References

1. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene Dose of Apolipoprotein E Type 4 Allele and the Risk of Alzheimer's Disease in Late Onset Families. *Science* 1993;261(5123):921. [PubMed: 8346443]
2. Saunders AM, Strittmatter WJ, Schmechel D, St. GeorgeHyslop PH, PericakVance MA, Joo SH, Rosi BL, Gusella JF, CrapperMacLachlan DR, Alberts MJ, Hulette C, Crain B, Goldgaber D, Roses AD. Association of apolipoprotein E allele [epsilon]4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993;43(8):1467. [PubMed: 8350998]
3. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD. Apolipoprotein E: High-Avidity Binding to {beta}-Amyloid and Increased Frequency of Type 4 Allele in Late-Onset Familial Alzheimer Disease. *Proceedings of the National Academy of Sciences* 1993;90(5):1977.
4. Small BJ, Rosnick CB, Fratiglioni L, Bäckman L. Apolipoprotein E and Cognitive Performance: A Meta-Analysis. *Psychology and Aging* 19(4):592–600. [PubMed: 15584785] *Psychology and Aging* 2004;19(4):592–600. [PubMed: 15584785]
5. Ohm TG, Kirca M, Bohl J, Scharnagl H, Gro W, Marz W. Apolipoprotein E polymorphism influences not only cerebral senile plaque load but also Alzheimer-type neurofibrillary tangle formation. *Neuroscience* 1995;66(3):583. [PubMed: 7644022]
6. Green RC, Cupples LA, Kurz A, Auerbach S, Go R, Sadovnick D, Duara R, Kukulll WA, Chui J, Edeki T, Griffith PA, Friedland RP, Bachman D, Farrer L. depression as a risk factor for alzheimer disease. *Archives of Neurology* 2003;60:753. [PubMed: 12756140]
7. Sachs-Ericsson N, Joiner T, Plant EA, Blazer DG. The Influence of Depression on Cognitive Decline in Community-Dwelling Elderly Persons. *Am. J. Geriatr. Psychiatry* 2005;13(5):402–408. [PubMed: 15879589]
8. Jorm AF. Is Depression a Risk Factor for Dementia or Cognitive Decline?A Review. *Gerontology* 2000;46(219):227.
9. Steffens DC, McQuoid DR, Potter GG. Outcomes of Older Cognitively Impaired Individuals With Current and Past Depression in the NCODE Study. *J Geriatr Psychiatry Neurol* 2009;22(1):52–61. [PubMed: 19196631]

10. Steffens DC, Welsh-Bohmer KA, Burke JR, Plassman BL, Beyer JL, Gersing KR, Potter GG. Methodology and Preliminary Results From the Neurocognitive Outcomes of Depression in the Elderly Study. *J Geriatr Psychiatry Neurol* 2004;17(4):202–211. [PubMed: 15533991]
11. Dufoil C, Fuhrer R, Dartigues J, Alperovitch A. Longitudinal analysis of the association between depressive symptomatology and cognitive deterioration. *American Journal of Epidemiology* 1996;144(7):634. [PubMed: 8823058]
12. Chen P, Ganguli M, Mulsant BH, Dekosky ST. The temporal relationship between depressive symptoms and dementia. *Archives of General Psychiatry* 1999;56(261):266.
13. Bassuk SS, Berkman LF, Wypij D. Depressive symptomatology and incident cognitive decline in an elderly community sample. *Archives of General Psychiatry* 1998;55:1073. [PubMed: 9862549]
14. Sapolsky R. Why stress is bad for your brain. *Science* 1996;273:749–750. [PubMed: 8701325]
15. Ma X-M, Lightman SL, Aguilera G. Vasopressin and Corticotropin-Releasing Hormone Gene Responses to Novel Stress in Rats Adapted to Repeated Restraint. *Endocrinology* 1999;140(8):3623–3632. [PubMed: 10433220]
16. Salak-Johnson JL. Adaptation and Stress: Neuroendocrine, Physiological, and Behavioral Responses. *Encyclopedia of Animal Science* 2004:5–8.
17. Beluche I, Chaudieu I, Norton J, Carriere I, Boulenger JP, Ritchie K, Ancelin ML. Persistence of abnormal cortisol levels in elderly persons after recovery from major depression. *J Psychiatr Res* 2009;43(8):777–83. [PubMed: 19054531]
18. Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression Duration But Not Age Predicts Hippocampal Volume Loss in Medically Healthy Women with Recurrent Major Depression. *J. Neurosci* 1999;19(12):5034–5043. [PubMed: 10366636]
19. Videbech P, Ravnkilde B. Hippocampal Volume and Depression: A Meta-Analysis of MRI Studies. *Am J Psychiatry* 2004;161(11):1957–1966. [PubMed: 15514393]
20. McKinnon MC, Yucel K, Nazarov A, GM. M. A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *J Psychiatry Neuroscience* 2009;34(1):41–54.
21. Shah PJ, Ebmeier KP, Glabus MF, Goodwin GM. Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. *British Journal of Psychiatry* 1998;527–32. [PubMed: 9828995]
22. Ystad MA, Lundervold AJ, Wehling E, Espeseth T, Rootwelt H, Westlye LT, Andersson M, Adolfsdottir S, Geitung JT, Fjell AM, Reinvang I, Lundervold A. Hippocampal volumes are important predictors for memory function in elderly women. *BMC Med Imaging* 2009;10:9–17.
23. Steffens D, Payne M, Greenberg D, Byrum C, Welsh-Bohmer K, Wagner H, MacFall J. Hippocampal volume and incident dementia in geriatric depression. *American Journal of Geriatric Psychiatry* 2002;10:62–71. [PubMed: 11790636]
24. Corsentino EA, Sawyer K, Sachs-Ericsson N, Blazer DG. Depressive symptoms moderate the influence of the apolipoprotein epsilon4 allele on cognitive decline in a sample of community dwelling older adults. *Am J Geriatr Psychiatry* 2009;17(2):155–65. [PubMed: 19155747]
25. Robins LN, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health Diagnostic Interview Schedule: Its History, Characteristics, and Validity. *Arch Gen Psychiatry* 1981;38(4):381–389. [PubMed: 6260053]
26. Beekman ATF, de Beurs E, van Balkom AJLM, Deeg DJH, van Dyck R, van Tilburg W. Anxiety and Depression in Later Life: Co-Occurrence and Communalities of Risk Factors. *Am J Psychiatry* 2000;157(1):89–95. [PubMed: 10618018]
27. Koenig H, Larson D, Hays J, McCullough M, George L, Branch P, Meador K, Kuchibhatla M. Religion and survival of 1010 male veterans hospitalized with medical illness. *Journal of Religion and Health* 1998;37:15–29.
28. Farrell KR, Ganzini L. Misdiagnosing Delirium as Depression in Medically Ill Elderly Patients. *Archives of Internal Medicine* 1995;155:2459–2464. [PubMed: 7503605]
29. Cole MG, McCusker J, Elie M, Dendukuri N, Latimer E, Bel E. Systematic detection and multidisciplinary care of depression in older medical inpatients: a randomized trial. *Canadian Medical Association Journal* 2006;174(1):38–44. [PubMed: 16330624]

30. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry* 1979;134(4):382–389. [PubMed: 444788]
31. Baudic S, Tzortzis C, Barba GD, Traykov L. Executive Deficits in Elderly Patients With Major Unipolar Depression. *J Geriatr Psychiatry Neurol* 2004;17(4):195–201. [PubMed: 15533990]
32. Parker RD, Elizabeth PF, Hayden BB, Carl FP, David CS. A three-factor analytic model of the MADRS in geriatric depression. *International Journal of Geriatric Psychiatry* 2003;18(1):73–77. [PubMed: 12497559]
33. Williams JBW, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Asberg Depression Rating Scale (SIGMA). *The British Journal of Psychiatry* 2008;192(1):52–58. [PubMed: 18174510]
34. Folstein M, Folstein S, McHugh P. Mini-Mental state: a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;12:189–198. [PubMed: 1202204]
35. Saunders AM, Strittmatter WJ, Schmechel D, St. George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ, Hulette C, Crain B, Goldgaber D, Roses AD. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993;43:1467–1472. [PubMed: 8350998]
36. Niti M, Yap K-B, Kua E-H, Ng T-P. APOE- $\{\epsilon\}$ 4, Depressive Symptoms, and Cognitive Decline in Chinese Older Adults: Singapore Longitudinal Aging Studies. *J Gerontol A Biol Sci Med Sci* 2009;64A(2):306–311. [PubMed: 19181718]
37. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc* 2002;8:448–460. [PubMed: 11939702]
38. Cohen RM, Small C, Lalonde F, Friz J, Sunderland T. Effect of apolipoprotein E genotype on hippocampal volume loss in aging healthy women. *Neurology* 2001;57(12):2223–2228. [PubMed: 11756601]
39. Jak AJ, Houston WS, Nagel BJ, Corey-Bloom J, Bondi MW. Differential Cross-Sectional and Longitudinal Impact of APOE Genotype on Hippocampal Volumes in Nondemented Older Adults. *Dementia and Geriatric Cognitive Disorders* 2007;23(6):382. [PubMed: 17389798]
40. Pedraza O, Bowers D, Gilmore R. Asymmetry of the hippocampus and amygdala in MRI volumetric measurements of normal adults. *Journal of the International Neuropsychological Society* 2004;10(05):664–678. [PubMed: 15327714]
41. Graham, JW.; Cumsille, PE.; Elek-Fisk, E. *Handbook of psychology: Research methods in psychology*. Vol. Vol. 2. John Wiley & Sons Inc; Hoboken, NJ, US: 2003. Methods for handling missing data; p. 87

Table 1

Sample Demographics

	<i>M (SD) or %</i>	Range
Race		
White	82%	--
Non-white	18%	
Sex		
Female	61%	--
Age	67.9 (6.1)	60-83
Education in Years	14.6 (2.5)	5-17
APOE Status		
ε4 Carrier	26%	--
ε4 Non-carrier	74%	
Baseline MMSE score	28.4(1.8)	22-30
Follow-up MMSE score ^a	27.8 (1.7)	5-30
Age of first depressive episode	43.0 (19.7)	7-78
Lifetime number of depressive episodes	7.7 (16.6)	1-95
Baseline MADRS score	26.1 (6.3)	11-47
Follow-up MADRS score	9.4 (8.6)	0-36
Left Hippocampal volume	3(.4) mL	2.12-3.72
Right Hippocampal volume	3.1(.4) mL	2.24-4.04

Table 2

Linear regression analysis of the left hippocampal volume and the APOE allele and their interaction on cognitive decline.

	Variable	Beta (Unstandardized)	Standard Error	F	Df	p value
	Constant	17.1	10.58	2.61		.112
Step 1 Adj R^2 = .23	MMSE Baseline	.36	.30	1.43	1,56	.237
	Sex	-.10	1.1	.009	1,56	.924
	Age	-.10	.08	1.65	1,56	.205
	Years of education	.65	.22	8.99	1,56	.004
	MADRS	-.07	.08	.67	1,56	.416
Step 2 Adj R^2 = .33	APOE Carrier	-2.51	1.04	5.84	1,54	.02
	Left Hippocampal Volume	2.83	1.34	4.44	1,54	.04
	Interaction of the APOE Carrier and the Left Hippocampal Volume	1.08	.54	4.05	1,53	.049

APOE Carrier represents whether or not the individual has 1 or more APOE $\epsilon 4$ alleles.

MADRS is Montgomery Asberg Depression Rating Scale. The MADRS may range from 0 to 60.

The MMSE is the Mini Mental State Exam. The MMSE may range from 0 to 30.

Linear regression analysis of the right hippocampal volume and the APOE allele and their interaction on cognitive decline.

Table 3

	Variable	Beta (Unstandardized)	Standard Error	F	Df	p value
	Constant	17.1	10.58	2.61		.112
Step 1	MMSE Baseline	.36	.30	1.43	1,56	.237
Adj $R^2 =$.23	Sex	-.10	1.1	.009	1,56	.924
	Age	-.10	.08	1.65	1,56	.205
	Years of education	.65	.22	8.99	1,56	.004
	MADRS	-.07	.08	.67	1,56	.416
Step 2	APOE Carrier	-2.51	1.04	5.84	1,54	.02
Adj $R^2 =$.29	Right Hippocampal Volume	1.84	1.4	183	1,54	.19
Step 3	Interaction of the APOE Carrier and Right Hippocampal Volume	.942	.54	.29	1,53	.09
Adj $R^2 =$.32						

APOE Carrier represents whether or not the individual has 1 or more APOE $\epsilon 4$ alleles.
MADRS is Montgomery Asberg Depression Rating Scale. The MADRS may range from 0 to 60.
The MMSE is the Mini Mental State Exam. The MMSE may range from 0 to 30.