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RESEARCH ARTICLE

Effect of APOE4 Allele and Gender on the Rate of Atrophy in the Hippocampus, Entorhinal Cortex, and Fusiform Gyrus in Alzheimer's Disease

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Abstract: ***Background*:** The hippocampus, entorhinal cortex, and fusiform gyrus are brain areas that deteriorate during early-stage Alzheimer's disease (AD). The ApoE4 allele has been identified as a risk factor for AD development, is linked to an increase in the aggregation of amyloid β (Aβ) plaques in the brain, and is responsible for atrophy of the hippocampal area. However, to our knowledge, the rate of deterioration over time in individuals with AD, with or without the ApoE4 allele, has not been investigated.

***Methods*:** In this study, we, for the first time, analyze atrophy in these brain structures in AD patients with and without the ApoE4 using the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset.

***Results*:** It was found that the rate of decrease in the volume of these brain areas over 12 months was related to the presence of ApoE4. Further, we found that neural atrophy was not different for female and male patients, unlike prior studies, suggesting that the presence of ApoE4 is not linked to the gender difference in AD.

***Conclusion*:** Our results confirm and extend previous findings, showing that the ApoE4 allele gradually impacts brain regions impacted by AD.

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1. INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia and is marked by neurodegeneration, formation of extracellular amyloid β (Aβ) plaque and intracellular neurofibrillary tangles containing aggregated *tau* [1-5]. The medial temporal lobe is involved with the formation of episodic memory and spatial cognition and includes numerous substructures that are responsible for various cognitive and emotional functions [6-11]. The medial temporal lobe includes the hippocampus and its adjacent cortical areas, such as the parahippocampal cortex, the entorhinal cortex, the fusiform gyrus, and the perirhinal cortex, among other regions [12, 13]. These brain structures play a role in different memory processes [14-16], and are also impacted by AD [16-19]. Importantly, as we show below, these brain structure deteriorates at different temporal rates in AD.

The hippocampus is a brain structure deep in the temporal lobe. It plays a crucial role in decision-making, associative learning, memory processing and consolidation [20-23]. In addition, the hippocampus is also involved in learning and retrieving past experiences [21] and provides the neural basis for cognitive mapping [24, 25]. The hippocampus is one of the regions in the brain which undergoes atrophy during early AD [21, 26, 27]. Vijayakumar and Vijayakumar [28] found that the hippocampal volume and ratio were reduced by 25% in patients with AD.

Along with the hippocampus, the entorhinal cortex also undergoes atrophy during early AD [29-33]. In AD, atrophy progresses gradually, starting from the entorhinal cortex and

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the hippocampus [29]. It then encompasses the lateral temporal, the medial parietal, and the frontal region and finally affects all the areas of the cerebral cortex [34-36].

The entorhinal cortex is located in the medial temporal lobe and is considered a portal for information entering the hippocampus [37]. Importantly, the entorhinal cortex provides most of the cortical input to the hippocampus [38]. The transentorhinal region has been recognized as the key region that undergoes atrophy during the early stages of AD [39]. It has been argued that, subsequently, the damage spreads to the entorhinal cortex, the hippocampus, and various limbic structures [30].

The fusiform gyrus is located on the basal surface of the occipital and temporal lobes. The fusiform gyrus has been linked to cognitive deficits for individuals with AD and mild cognitive impairment and is a promising area of investigation for the early detection and progression of AD [40]. However, in the context of AD, relative to other areas of the brain (*e.g.,* the hippocampus, temporal lobe, and the prefrontal cortex), the fusiform gyrus remains understudied [40, 41], especially regarding the expression of genes in the fusiform gyrus that is linked to the progression of AD (*e.g.,* Apolipoprotein E).

Apolipoprotein E (ApoE) is a 299 amino acid protein with roles within specific tissues, including lipid metabolism, primary lipid transporter (in cells in the central nervous system to achieve optimal lipid homeostasis), and is found in large numbers in the brain [42, 43]. ApoE also plays a crucial role in neuronal maintenance and repair, with each polymorphic form having a distinct function [44]. The three primary polymorphic forms (ApoE2, ApoE3, and ApoE4) [43] encode different protein isomers and have different effect on lipid and neuronal homeostasis [42]. Among the various isomeric forms, ApoE4 is associated with an increase in the aggregation of Aβ [45-48], followed by ApoE3 and ApoE2. Several studies have found that the ApoE4 allele is a genetic risk for the development of AD [49, 50], among other genes [51]. Specifically, the ApoE4 allele has been linked to an increase in amyloid deposition and neurofibrillary tangles in the brain [52, 53] as well as a loss of choline acetyltransferase in the frontal and temporal cortex [30, 54-56]. The loss of choline acetyltransferase was reported to vary among male and female patients with AD [57, 58]. Notably, Wisniewski and Drummond [45] reported that the interaction between ApoE and Aβ modulates the aggregation and clearance of Aβ and thus has an impact on the development of amyloid plaques and neurofibrillary tangles. In addition, it was also shown that ApoE4 promoted the oligomerization and fibrillization of Aβ, which is related to the early onset of AD [45, 59]. Importantly, a recent study reported that ApoE4 is associated with a rapid cognitive decline and is the second strongest risk factor for the development of AD following age [60].

2. THE CURRENT STUDY

The current study aims to use publicly available data to, for the first time, analyse the rate of atrophy in the hippocampus and the entorhinal cortex in AD patients with and without the ApoE4 allele over a period of 6 and 12 months as well as to analyse the effect of the ApoE4 allele on the connectivity patterns between the entorhinal cortex and hippocampus. Specifically, in this article, we will investigate if the presence of the ApoE4 allele affects the rate of decrease in the volume of the entorhinal cortex and the hippocampus. The ApoE4 allele appears to contribute to atrophy in various medial temporal lobe regions. In addition, we will also investigate gender differences in neural atrophy in AD. The investigation of gender differences in AD is important as it is related to response to cholinesterase inhibitor treatment, as found in some clinical trials [57, 58, 61-64].

3. MATERIALS AND METHODS

Data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), as in prior studies [65-70]. The ADNI was launched in 2003 as a public-private partnership led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

The decrease in the hippocampus and entorhinal cortex volume in 6 and 12 months compared to the baseline was calculated for both male and female patients with and without the ApoE4 allele. A t-test was conducted to determine statistical significance. The level of significance was set at $p < 0.05$.

4. RESULTS

We present our results on the hippocampus, the entorhinal cortex, and the fusiform gyrus, respectively.

4.1. Hippocampus

Mixed linear models were conducted to identify if hippocampal volume decreased with the presence of ApoE4 alleles across time (*i.e.,* the period of 0, 6, and 12 months) while controlling for age and gender (and their interaction) and the interaction between time and ApoE4, and with a random intercept for participant ID.

The hypothesised model showed significant improvement compared to the empty model. Table **1** shows that female participants had significantly smaller hippocampal volume than male participants, and hippocampal volume decreased as age increased. There was also a significant effect of time, whereby hippocampal volume decreased significantly from baseline through to 12 months. Notably, there was a significant interaction between APoE4 and time. This suggests that the decrease in hippocampal volume from baseline to 12 months depended on the presence of ApoE4 alleles. Specifically, those with two ApoE4 alleles showed significantly more reduced hippocampal volume than those with no ApoE4 alleles. However, there was no age by gender interaction, this suggests that the reduced hippocampal volume for females compared to males was not dependent on their age. The significant random intercept indicates that participants differed significantly at their baseline measurements indicating significant variation in hippocampal volume between

Table 1. Mixed linear model predicting Hippocampal volume.

Variable-	Estimate	SE	df	t	*p*	95% CI	
						Lower	Upper
Intercept	11623.64	368.21	1642.99	31.57	<.001	10901.43	12345.85
Female	-194.03	538.21	1639.05	-0.36	.719	-1249.68	861.62
APOE4 (0 Alleles)	1015.6	90.00	1679.05	11.29	<.001	839.08	1192.12
APOE4 (1 Allele)	536.16	92.47	1679.69	5.80	<.001	354.80	717.52
APOE4 (2 Alleles)	-	-	-	-	-	-	-
Age	-73.08	4.91	1641.06	-14.89	<.001	-82.71	-63.45
Time	-18.07	1.81	2931.25	-9.98	<.001	-21.62	-14.52
Gender * Age	-3.82	7.30	1639.33	-0.52	.601	-18.13	10.49
APOE4 (1 Allele) ×Time	8.03	1.98	2931.82	4.06	<.001	4.15	11.91
APOE4 (1 Allele) × Time	1.32	2.04	2931.81	0.65	.517	-2.68	5.33
APOE4 (2 Alleles)× Time	-	-	-	-	-	-	-
Random effects	-	-	-	Wald Z	-	-	-
Residual	28717.97	751.77	-	38.20	<.001	27281.68	30229.87
Intercept | ID	1071029.10	37851.95	-	28.30	<.001	999351.82	1147847.40

participants. However, there was consistency in the measurement of hippocampal volume (ICC = .97).

4.2. Entorhinal Cortex

Mixed linear models were conducted to identify if Entorhinal cortex volume decreased with the presence of ApoE4 alleles across time (*i.e.,* the period of 0, 6, and 12 months) while controlling for age and gender (and their interaction) and the interaction between time and ApoE4, and with a random intercept for participant ID. The hypothesised model showed significant improvement compared to the empty model. See Table **2** for results.

There was a significant time effect, whereby the volume of the entorhinal cortex decreased significantly from baseline to 12 months. There was also a significant effect of APoE4 on Entorhinal cortex volume. Participants who presented with zero or one APOE4 alleles had significantly larger Entorhinal cortex volume than those with two APOE4 alleles. Further, age was negatively associated with Entorhinal cortex volume. There was no significant difference in the Entorhinal cortex volume between females and males and no significant APoE4 × Time interaction. This suggests that a decrease in Entorhinal cortex volume was due to the presence of APoE4 but was not dependent on time. There was also no age by gender interaction, suggesting the effect of age on Entorhinal cortex volume was not dependent on gender. Further, the significant random intercept indicates that participants differed significantly at their baseline measurements indicating significant variation in Entorhinal cortex volume between participants. However, there was consistency in the measurement of Entorhinal cortex volume across participants (ICC = .87).

4.3. Fusiform Gyrus

Mixed linear models were conducted to identify if Fusiform Gyrus volume decreased with the presence of ApoE4 alleles across time (*i.e.,* the period of 0, 6, and 12 months) while controlling for age and gender (and their interaction) and the interaction between time and ApoE4, and with a random intercept for participant ID. The hypothesised model showed significant improvement compared to the empty model.

Table **3** shows a significant time effect, whereby the volume of the fusiform gyrus decreased significantly from baseline to 12 months. Entorhinal cortex volume significantly decreased, and there was a significant effect of APoE4 on the volume of the entorhinal cortex. Participants who presented with zero or one APOE4 alleles had significantly larger Fusiform Gyrus volume compared to those with 2 APOE4 alleles. However, there was also a significant APoE4 × Time interaction. This suggests that a decrease in Fusiform Gyrus volume across time was dependent on the presence of APoE4 alleles. There was no significant difference in the Fusiform Gyrus volume between females and males, and there was no significant age by gender interaction, suggesting the effect of age on Fusiform Gyrus volume was not dependent on gender. Further, the significant random intercept indicates that participants differed significantly at their baseline measurements indicating significant variation in Fusiform Gyrus volume between participants. However, there was consistency in the measurement of Fusiform Gyrus volume across participants (ICC = .0.94).

Table 2. Mixed linear model predicting Entorhinal cortex volume.

Variable	Estimate	SE	df	t	*p*	95% CI	
						Lower	Upper
Fixed effects	-	-	-	-	-	-	-
Intercept	5508.02	254.46	1607.80	21.65	<.001	5008.91	6007.14
Female	-517.74	369.12	1590.27	-1.40	.161	-1241.76	206.28
APOE4 (0 Alleles)	543.40	63.08	1779.95	8.62	<.001	419.68	667.11
APOE4 (1 Allele)	241.24	64.85	1783.87	3.72	<.001	114.05	368.44
APOE4 (2 Alleles)	-	-	-	-	-	-	-
Age	-30.51	3.40	1600.06	-8.97	<.001	-37.17	-23.84
Time	-10.07	2.91	2854.31	-3.46	.001	-15.78	-4.36
Gender * Age	1.75	5.01	1592.49	0.35	.727	-8.08	11.59
APOE4 (0 Alleles) ×Time	3.83	3.18	2857.95	1.20	.229	-2.41	10.07
APOE4 (1 Allele) × Time	1.61	3.29	2859.06	0.49	.625	-4.84	8.05
APOE4 (2 Alleles) × Time	-	-	-	-	-	-	-
Random effects	-	-	-	Wald Z	-	-	-
Residual	71781.81	1919.81	-	37.39	<.001	68116.00	75644.93
Intercept | ID	465730.30	17631.69	-	26.41	<.001	432424.00	501602.20

Table 3. Mixed linear model predicting Fusiform Gyrus volume.

Variable	Estimate	SE	*df*	t	*p*	95% CI	
						Lower	Upper
Fixed effects	-	-	-	-	-	-	-
Intercept	26275.92	888.81	1628.32	29.56	<.001	24532.58	28019.25
Female	-2336.28	1295.65	1622.70	-1.80	.072	-4877.61	205.05
APOE4 (0 Alleles)	873.61	216.53	1658.36	4.04	<.001	448.91	1298.31
APOE4 (1 Allele)	143.10	222.41	1659.12	0.64	.520	-293.12	579.33
APOE4 (2 Alleles)	-	-	-	-	-	-	-
Age	-118.17	11.89	1627.04	-9.94	<.001	-141.49	-94.86
Time	-30.24	2.19	4899.31	-13.79	<.001	-34.54	-25.94
Gender × Age	5.35	17.59	1623.61	0.30	.761	-29.15	39.84
APOE4 (0 Alleles) × Time	-	-	-	-	-	-	-
APOE4 (1 Allele) × Time	21.74	2.29	4898.34	9.48	<.001	17.24	26.24
APOE4 (2 Alleles) × Time	6.48	2.37	4897.10	2.73	.006	1.83	11.12
Random effects	-	-	-	Wald Z	-	-	-
Residual	390369.72	7947.84	-	49.12	<.001	375,098.95	406262.17
Intercept | ID	6,065,886.94	217,875.21	-	27.84	<.001	5,653,543.76	6,508,304.51

5. DISCUSSION

AD is a neurodegenerative disorder mainly characterized by deterioration in cognitive function and loss of memory [43, 71, 72]. AD is associated with an aggregation of amyloid β (Aβ) into extracellular plaques in the brain and the presence of neurofibrillary tangles and neuropil threads formed by *tau* [45, 73]. The later stages of AD include severe memory loss, language impairment, difficulty speaking and disorientation [43]. In the current study, we have examined the rate of atrophy in the hippocampus, entorhinal cortex, and fusiform gyrus within a period of 0 to 12 months in the presence and absence of the ApoE4 allele.

The protein ApoE plays a role in controlling cholesterol levels in peripheral circulation. It also plays a significant role in neural processes, regulating the exchange of metabolites between the glial cells and neurons. This process is essential for keeping brain tissues healthy [74, 75]. ApoE4, a polymorphic form of the protein ApoE, increases the aggregation of Aβ and is a risk factor for AD development. Many studies have shown that the presence of the ApoE4 allele results in atrophy in various brain areas [76-78].

One of the main findings of the present study is that the rate of decrease in the hippocampal and Fusiform Gyrus volume from 0 to 12 months was dependent on the presence of one or more ApoE4 alleles. Specifically, when two ApoE4 alleles were present, there was a significant decrease in the volume of the hippocampus and Fusiform Gyrus from baseline measurements and the 12-month follow-up. These findings indicate that the reduction in volume in the hippocampus and the Entorhinal cortex across time depended on the presence of ApoE4 alleles within the ADNI sample. However, this interaction effect was not found in the Entorhinal cortex, but ApoE4 alleles were a significant bio-marker for a reduction in volume in the Entorhinal cortex (independent of time).

Our results showed that there was a reduction in entorhinal cortex volume over 12 months, and this decrease is associated with APOE4. However, the decrease over time was not dependent on the presence of APOE4, as observed in the hippocampus and fusiform gyrus. This may support previous literature suggesting that the entorhinal cortex is one of the first brain structures to undergo atrophy, which is in agreement with prior results [79-83]. Because it is one of the earlier areas to be affected, the deterioration might begin before the presence of APOE4. Therefore, this suggests measuring the volume of the entorhinal cortex as a diagnostic tool for detecting AD [30]. In addition, Juottonen and colleagues [30] found that a decrease in the volume of the entorhinal cortex was more significant in the left than in the right hemisphere in patients with AD carrying the ApoE4 allele compared to patients without the allele [84]. Furthermore, Lehtovirta *et al.* [85] found that a decrease in hippocampal volume was greater in AD patients with the ApoE4 allele.

Moreover, the lack of statistical significance in the change of hippocampal, fusiform gyrus, and entorhinal cortex volume between female and male patients for the 12-month period is intriguing as this has not been reported in prior studies. Our findings are not in line with prior findings showing that the presence of APOE4 increases the risk of developing AD in females more than in males [86]. Some prior studies have shown that male and female with AD show differences in cholinergic system and activity [57]. Further research is required to explain this result and whether it holds on for a longer duration. It is possible that we did not find a significant decrease in the hippocampal volume as 12 months is a short period. However, it is unclear why male patients showed a decrease in hippocampal volume during this time compared to female patients.

There are multiple studies on the impact of gender on Alzheimer's disease. Most studies report that AD is more common in female than in male patients [87-96]. Some studies argue that gender differences in the prevalence of AD could be related to differences in cognitive reserve [97], estrogen levels [98] or stress [23, 99]. Other studies found that male and female patients with AD may respond differently to cholinesterase inhibitor medications [57, 58]. In other words, Giacobini and colleagues [58] suggested that cholinesterase inhibitor medications may be more effective at managing dementia symptoms in female than in male AD patients. For example, one study found that females progress faster to AD than males [100]. Our findings are different from Juottonen *et al.* [30] and Sampedro *et al.* [101]. For example, [30] found that the effect of the APoE allele on the entorhinal cortex volume was prominent in female patients with AD. It is unclear why the rate of atrophy differs in our male and female groups. However, various studies have evaluated estrogen's effect on cognitive decline. Further, in AD, the protective effect of estrogen against cognitive decline has been suggested, and it has been theorised that estrogen-based hormone therapy close to menopause might reduce the risk of AD [73, 102]. In addition, ApoE is important in transporting lipids across plasma membranes and is also involved in the exchange of metabolites between glial cells and neurons, which is essential for ensuring healthy brain tissue [74]. Reilly *et al.* [103] found that gender affects the action of ApoE on the allocation of plasma lipids which may affect the efficiency of ApoE4 in maintaining healthy brain tissue. Importantly, our findings align with those of a recent study [104]. In this study, female patients showed better memory performance and less hippocampal damage than male patients with AD [105-107]. One limitation of the [104] study was that they did not look at temporal differences in neural atrophy or investigate changes in other brain areas, such as the entorhinal cortex.

It is important to note that some studies, however, did not find any gender differences in Alzheimer's disease, which is in agreement with our findings. For example, Edland and colleagues did not find any sex differences in a sample of AD patients [108]. Edland and colleagues argue that gender differences in the prevalence of AD could be related to geographreical location and age group of the patients. The patients in the Edland and colleagues study are from the USA, which is similar to ADNI data we used here.

ApoE4 has been recognized as a risk factor in AD and is known to affect the age of onset of AD and impair the functioning of other brain regions, including the entorhinal cortex, fusiform gyrus, and hippocampus. However, the mechanism causing this damage is unclear [30]. Entorhinal cortex and hippocampus atrophy may be due to failed neuronal re-

generation. This process is important for structures in the medial temporal lobe as it is the area where the integral process of synaptogenesis predominantly occurs [30, 109]. The inability to compensate for the harm caused by the ApoE4 allele may lead to neuronal degeneration and, thus, atrophy in medial temporal lobe structures, including the entorhinal cortex and the hippocampus. Another potential related mechanism underlying AD is synaptic pruning, which is the process of eliminating synapses [110]. Several studies suggest that cognitive decline and memory impairment in aging and AD is related to synaptic pruning [111-113].

In this study, we also analysed the effect of the ApoE4 allele on the connectivity between the hippocampus, fusiform gyrus, and entorhinal cortex. Studies have revealed that the entorhinal cortex contributes to hippocampal formation [29]. Damage to this structure, caused by the presence of the ApoE4 allele, may help develop AD. While the hippocampus is responsible for major AD symptoms, early AD symptoms result from damage to the entorhinal cortex [114]. In individuals carrying the ApoE4 allele, neurofibrillary tangles have been detected in their 30s, with greater frequency representing the effect of this allele early in life [114]. In addition, the presence of ApoE4 has been linked with the degeneration of pyramidal neurons in the entorhinal cortex in early AD [114-116]. Nuriel *et al.* [75] showed that the presence of the ApoE4 allele is linked with hypermetabolism in the entorhinal cortex. Lastly, we have identified that the presence of APOE4 alleles contributes to the significant deterioration of the volume of the fusiform gyrus. These findings have supported recent evidence suggesting the fusiform gyrus is implicated in the early onset and progression towards AD. We have extended these findings by identifying that the expression of APOE4 alleles contributes to the reduction in the volume of the fusiform gyrus and is an essential biomarker for the progression of AD.

Moreover, the hippocampal and parahippocampal cortices consist of various cell types. Place cells have a unique spatial firing arrangement [38]. However, these neural activities were not reported within the hippocampus but in the entorhinal cortex. The entorhinal cortex provides most of the cortical input to the hippocampus [38]. The medial entorhinal cortex has the following cell types: grid, border and head direction cells [117, 118]. The interactions between place cells in the hippocampus and other cell groups in the entorhinal cortex have been studied [38]. The grid cells are responsible for controlling spatial navigation [119]. Border cells provide direct input to the hippocampus among these hippocampus-projecting entorhinal neurons. Border cells are neurons that fire signals in response to the environmental boundary, producing a signal in local hippocampal cells [38]. However, to our knowledge, the effect of the ApoE4 allele on border cells has not yet been investigated. Research conducted on grid cells has found that their function, which includes spatial navigation, was prominently impaired in young people with the ApoE4 allele. In addition, it was also found that grid cells are responsible for maintaining place cells [119]. In other words, the decrease in the function of grid cells leading to poor maintenance in place cells could be responsible for a decreased connectivity between the entorhinal cortex and the hippocampus due to the ApoE4 allele. In addition, a damage to grid cells is responsible for navigation impairment observed in AD [119].

Building on prior work [22, 120-123], future work should investigate whether ApoE4 affects the connection between the place cell in the hippocampus and cell types such as grid cells, border cells and head direction cells in the entorhinal cortex. Importantly, computational modelling work should understand how the interaction between the hippocampus and entorhinal cortex (including cells in these brain regions) relates to memory performance and the development of different symptoms in AD.

6. LIMITATIONS

This study was not without limitations. For instance, the ADNI data does not include "age of AD onset" but only the age at which participants completed their baseline assessment. This contributed to several limitations that prevented further exploration of our findings. For example, without age of onset data, we could not control for how long participants had the disease. As such, our interpretation of the rate of atrophy in the hippocampus and the entorhinal cortex due to ApoE4 allele should be interpreted with some caution. For instance, we found that the participants differed significantly at their baseline measurements (*i.e.,* random intercept) for the volume of the fusiform gyrus, entorhinal cortex, and hippocampus. The differences between participants at baseline could be explained by their age of onset. That is, we do not know how long participants have had symptoms of AD or how long they have been diagnosed with AD. Therefore, we are unable to estimate or control for the rate of atrophy that might have already occurred before baseline measurements. We strongly advise future ADNI projects and studies to consider the impact of the age of AD onset. This will give us a deeper understanding of the disease progression and help us determine the stage of atrophy in the hippocampus, entorhinal cortex, and fusiform gyrus in AD patients with and without the ApoE4 allele.

CONCLUSION

This study provided information on the rate of atrophy in the hippocampus, fusiform gyrus, and the entorhinal cortex in AD patients with and without the ApoE4 allele. In the near future, data analysis could be improved by analysing data for a longer time frame (for example, up to 36-48 months) to gain more information on the rate of atrophy of different brain areas, including the cortex. In this study, individuals having one and two ApoE4 alleles were included. Strictly selecting individuals with only one or two alleles can lead to understanding the effect of alleles in greater detail. Furthermore, analysing atrophy in subregions within the hippocampal, fusiform gyrus, and entorhinal cortex would provide greater insight into understanding the mechanism of the spread of AD.

LIST OF ABBREVIATIONS

AD = Alzheimer's Disease

Aβ = Amyloid β

ADNI = Alzheimer's Disease Neuroimaging Initiative

ApoE = Apolipoprotein E

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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