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ORIGINAL ARTICLE

Sex differences in interacting genetic and functional connectivity biomarkers in Alzheimer's disease

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Abstract As of 2023, it is estimated that 6.7 million individuals in the United States live with Alzheimer's disease (AD). Prior research indicates that AD disproportionality affects females; females have a greater incidence rate, perform worse on a variety of neuropsychological tasks, and have greater total brain atrophy. Recent research shows that hippocampal functional connectivity differs by sex and may be related to the observed sex differences in AD, and apolipoprotein E (ApoE) ε4 carriers have reduced hippocampal functional connectivity. The purpose of this study was to determine if the ApoE genotype plays a role in the observed sex differences in hippocampal functional connectivity in Alzheimer's disease. The resting state fMRI and T2 MRI of individuals with AD ($n=30$, female = 15) and cognitively normal individuals ($n=30$, female = 15) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were analyzed using the functional connectivity toolbox (CONN). Our results demonstrated intrahippocampal functional connectivity differed between those without an ε4 allele and those with at least one ε4 allele in each group. Additionally, intrahippocampal functional connectivity differed only by sex when Alzheimer's participants had at least one ε4 allele. These results improve our current understanding of the role of the interacting relationship between sex, ApoE genotype, and hippocampal function in AD. Understanding these biomarkers may aid

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in the development of sex-specific interventions for improved AD treatment.

Keywords Alzheimer's disease (AD) · Sex difference · Apolipoprotein E · Functional connectivity

Introduction

The 2023 estimate of Americans over the age of 65 living with Alzheimer's disease (AD) is 6.7 million [1]. AD is currently the fifth leading cause of death for those older than 65 years living in the United States [2, 3]. Alzheimer's disease disrupts communication, metabolism, and repair of neurons and their networks [4]. It is characterized by abnormal levels of amyloid plaques, neurofibrillary tangles, chronic inflammation, and vascular dysfunction [4, 5]. Individuals with AD develop memory impairments that severely impact daily life. AD disproportionately affects females, as the prevalence of AD is two-thirds higher in women than men [2, 3]. Additionally, compared to males with AD, females perform poorer on a variety of neuropsychological tasks and have greater total brain atrophy and temporal lobe degeneration [6–8]. Theories for the sex-biased differences in AD include sex-specific developmental factors such as hormonal differences and menopause and hypertensive disorders of pregnancy [9–12]. Additionally, differences have been linked to sex differences in known risk factors, such as age, depression, education level, and sleep [11, 13]. The independent contributions of cognitive and genetic risk factors for AD have received considerable attention; however, their interactions are less known.

Previous work has shown a possible interaction between sex and a known genetic risk factor for AD, the apolipoprotein E ε4 allele (ApoE-4). In humans, ApoE exists in three different isoforms, ε2, ε3, and ε4. The expression of ApoE isoforms and AD is multifactorial; a recent finding showed that an ε2 allele robustly decreases late-onset AD, whereas the expression of one ε4 allele increases the risk of developing AD, and the expression of two ε4 alleles increases the risk 9–15-fold [14–16]. The ApoE-4 is expressed in more than half of AD patients [17]. The presence of the ApoE-4 is known to cause numerous structural and functional brain changes associated with AD, including amyloid-β mechanisms, synaptic plasticity, cholesterol homeostasis, neurovascular function, and neuroinflammation [18–20]. Functional connectivity (FC) studies using electroencephalography (EEG) have shown that ApoE-4 is associated with functional network disruptions [21, 22]. However, the ApoE-4 role in the sex differences of AD is still being debated as the current results are inconsistent [18, 23–25].

Recently, research has revealed that hippocampal FC may be a biomarker and contributing factor in sex differences. Hippocampal atrophy has been found to be significantly faster and affect the progression of AD only in females [26, 27]. Additionally, previous studies have shown that females with AD have overall weaker hippocampal FC compared to males [28–31]. Further, previous work by Heise et. al has shown that in cognitively normal (CN)

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females, ApoE-4 carriers have reduced hippocampal FC to the precuneus and posterior cingulate cortex [32]. The purpose of this study was to build upon this prior research and determine if the ApoE genotype plays a role in the observed sex differences in functional connectivity of the hippocampus.

Methods

Data source

The data for this study were extracted from the ADNI [33], which is a publicly accessible dataset available at http://adni.loni.usc.edu. Launched in 2003, ADNI is a longitudinal, multi-site, cohort study, led by Principal Investigator Michael W. Weiner, MD. The original study, ADNI-1, has been extended three times, and the database contains subject data from ADNI-1, ADNI-GO, ADNI-2, and ADNI-3. The overall goal of the studies was to evaluate 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). For up-to-date information, see www.adni-info.org.

Participant selection

The data were filtered for participants with AD. Participant selection was limited to those with data collected from resting-state functional magnetic resonance imaging (rs-fMRI) and 3-Tesla T2 magnetic resonance imaging. Additionally, the data had to include the ApoE genotype. To maximize the sample size, participants were selected from any visit to ADNI-GO, ADNI-2, and ADNI-3. These cohorts used the same protocol to collect resting state data. A Philips system was used to collect straight axial rs-fMRI; the participants had their eyes open for the entire scan with their heads positioned on the mid-sagittal slice from the tri-planar scout. This process was repeated for cognitively normal (CN) individuals. Filtering the data resulted in a total of 17 AD females, 15 AD males, 28 CN females, and 22 CN males. To balance the number in each group, 15 of each group were computer randomly selected. Averages and standard deviation of available participant demographics of participants are provided in Table 1.

Table 1 Participant genotypes (*AD*, Alzheimer's disease; *CN*, cognitively normal)

Genotype	ε2ε3	ε2ε4	ε3ε3	ε3ε4	ε4ε4
AD female	0	0	3	9	3
AD male	2	0	3	6	4
CN female	2	1	6	5	1
CN male	1	0	9	5	0

Analysis of functional connectivity

The participant's original rs-fMRI and MRI images (NiFTI format) were imported into the NITRC Functional Connectivity Toolbox (CONN) version 20b [34]. CONN utilizes SPM12 (Welcome Department of Cognitive Neurology, UK) and MATLAB R2020a (MathWorks, Natick, MA, USA) in its processes and by default a combination of the Harvard–Oxford atlas (HOA distributed with FSL http://www.fmrib.ox.ac.uk/fsl/) [35–37] and the Automated Anatomical Labeling (AAL) atlas [38].

The images were processed through the default functional and structural preprocessing pipeline as detailed by Nieto-Castanon [39]. This included realignment, slice timing correction, coregistration/normalization, segmentation, outlier detection, and smoothing. Additionally, this step extracted the blood-oxygen-level dependent (BOLD) time series from the regions of interest (ROIs) (using the Harvard–Oxford cortical regions) and at the voxels. Next, the images were denoised to remove confounding effects from the BOLD signal through linear regression and band-pass filtering. This removes unwanted motion, physiological, and other artifactual effects from the BOLD signal before computed connectivity measures. The system used a combination of aCompCor (White and CSF ROIs, five components each), scrubbing (as many

regressors as identified invalid scans), motion regression (12 regressors: 6 motion parameters + 6 first-order temporal derivatives), and filtering. A quality assurance check was made after the denoising to ensure normalization and that there were no visible artifacts in the data.

A seed-to-voxel analysis was conducted for each participant. This analysis created a seed-based connectivity (SBC) map between the ROI (left or right hippocampus) to every voxel of the brain. The SBC map is computed as the Fisher-transformed bivariant correlation coefficients between the ROI BOLD time series and each individual voxel BOLD time series [34]. The mathematical relationship to construct the SBC is:

$$r(x) = \frac{\int S(x,t)R(t)dt}{\left(\int R^2(t)dt \int S^2(x,t)dt\right)^{1/2}}$$
$$Z(x) = tanh^{-1}(r(x))$$

where R is the average ROI BOLD time series in the hippocampus, S is the BOLD time series at each voxel, r is the spatial map of Pearson correlation coefficients, and Z is the SBC map of the Fisher-transformed correlation coefficients for the ROI.

Statistical analysis

IBM SPSS (IBM Corp. Armonk, NY, USA) was used to run independent *t*-tests on the available participant data to ensure there was not a statistically significant sex difference in age, the Mini Mental State Examination (MMSE), the Geriatric Depression (GD) Scale, the Global Clinical Dementia Rating (CDR), the Functional Activities Questionnaire (FAQ), and the Neuropsychiatric Inventory Questionnaire (NPI-Q) ($p > 0.05$). If normal distribution could not be assumed based on the Shapiro–Wilk test, a non-parametric Mann–Whitney test was performed.

F-tests were conducted between the SBC maps to compare differences between groups. Female AD participants with at least one ε4 allele SBC maps were compared to Male AD participants with at least one ε4 allele SBC maps. This was repeated for female and male AD participants with no ε4 allele. Additionally, female AD with at least one ε4 allele were compared to females without a ε4 allele, and this was repeated with males. Finally, similar comparisons were made with CN participants. For a cortical area to be considered significant, the toolbox used the Gaussian random field theory parametric statistics, with a cluster threshold $p < 0.05$ (FDR-corrected) and voxel threshold $p < 0.001$ (uncorrected) to control the type I error in multiple comparisons [40]. Due to the small size of the voxel, to reduce differences attributed to noise, the area must be over 100 voxels large or cover more than 80% of a given atlas (specific brain area). These regions of statistical difference

Table 2 Participant demographics (*AD*, Alzheimer's disease; *CN*, cognitively normal; *MMSE*, Mini Mental State Examination; *GD Scale*, Geriatric Depression Scale; *CDR*, Global Clinical Dementia Rating; *FAQ*, Functional Activities Questionnaire; *NPI-Q*, Neuropsychiatric Inventory Questionnaire)

Group	Statistic	Age	MMSE	GD Scale	CDR	FAQ	NPI-Q
AD female	μ ± SD	71.6 ± 8.6	20.9 ± 3.9	1.5 ± 2.1	0.91 ± 0.20	19.1 ± 6.3	4.6 ± 2.9
	% missing	0	26	33	26	26	26
AD male	μ ± SD	74.5 ± 5.2	22.3 ± 2.5	2.0 ± 1.0	0.91 ± 0.42	15.8 ± 7.6	4.5 ± 4.9
	% missing	0	20	20	20	20	20
AD between sex *t*-tests		$p = 0.267$	$p = 0.341$	$p = 0.500$	$p = 0.956$	$p = 0.261$	$p = 0.932$
CN female	μ ± SD	71.5 ± 4.2	29.47 ± 0.8	0.93 ± 1.2	0.04 ± 0.13	0.0 ± 0	0.64 ± 1.4
	% missing	0	0	0	6	6	6
CN male	μ ± SD	75.9 ± 6.7	28.2 ± 2.0	0.6 ± 0.83	0.07 ± 0.18	0.33 ± 1.1	0.73 ± 1.4
	% missing	0	0	0	0	0	0
CN between sex *t*-tests		$p = 0.060$	$p = 0.080$	$p = 0.370$	$p = 0.600$	$p = 0.240$	$p = 0.860$

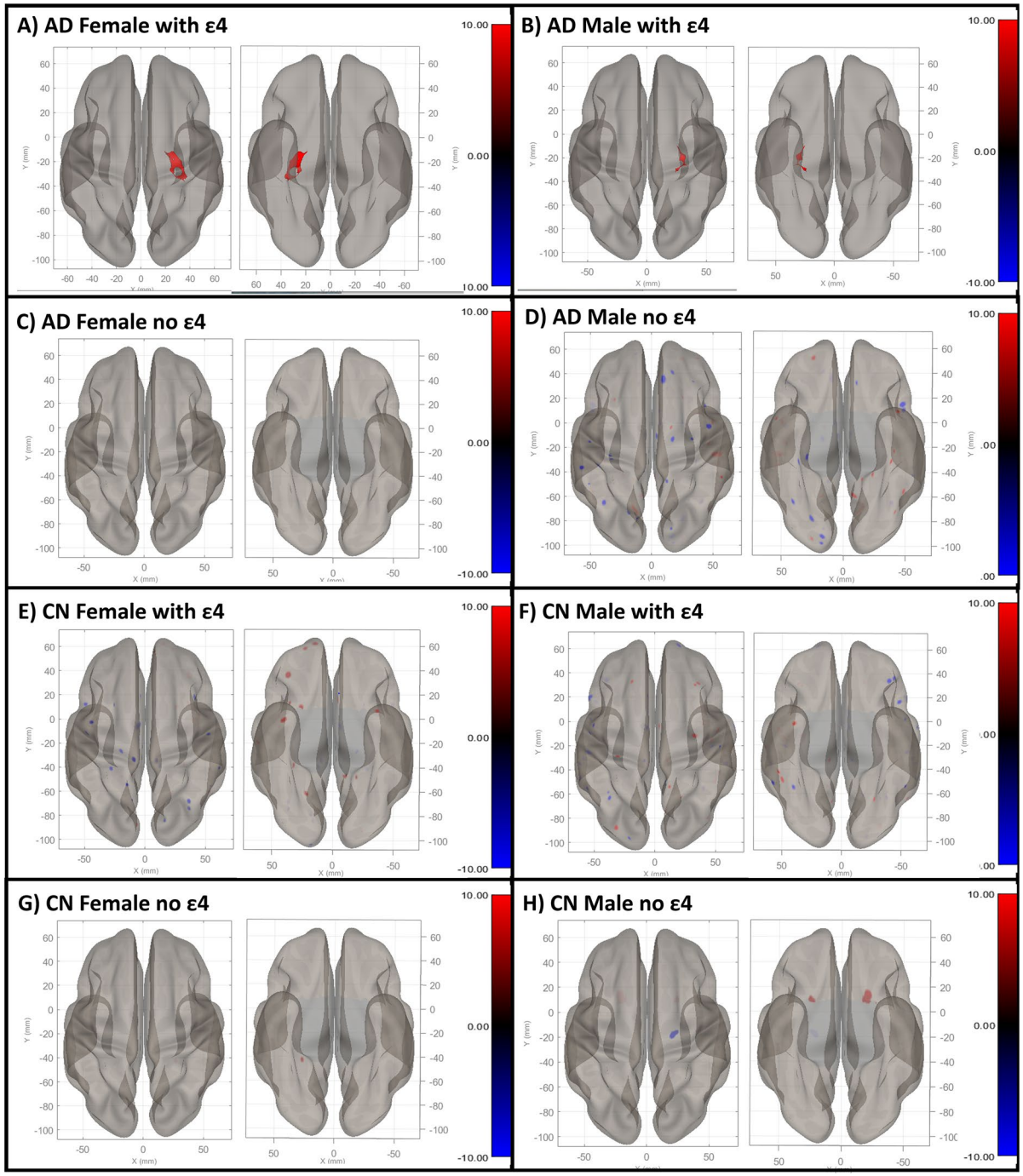

Fig. 1 Seed-based functional connectivity map where functional connectivity differs from zero with the right hippocampus selected as ROI

between SBC maps were then highlighted on a template brain.

Results

Table 1 displays the number of each genotype per group. Table 2 displays participant demographics with statistical analysis to ensure there were no significant sex differences in covariates. The SBC maps for each group with the right hippocampus selected as the ROI are displayed in Fig. 1, this depicts areas of the brain where the functional connectivity differs from zero, with positive in red and negative in blue. Figure 1 demonstrates that there is connectivity within the data before performing statistical analysis between SBC maps.

For each group (female AD, male AD, female CN, and male CN), when the right and left hippocampi were selected as the ROI, the functional connectivity within the right and left hippocampus, respectively, had a significant difference between individuals who have a least one ε4 compared to those who did not have a ε4 allele with those with no ε4 allele having higher functional connectivity (Table 3). This can be visualized for the right hippocampus ROI in Fig. 2.

With regard to sex in the AD and CN groups, the only difference found was between females and male with AD who have at least one ε4 allele (Table 4). There were no significant sex differences for those with no ε4 allele or between cognitively normal individuals. When the right and left hippocampus were selected as the ROIs (for those with AD that have at least one ε4 allele), the functional connectivity within the right and left hippocampus, respectively, has a significant between-sex group difference with males having higher functional connectivity. This is visualized in Fig. 3. For the right hippocampus ROI, males averaged a connectivity within the right hippocampus of 0.434; the female average was 0.387. For the left hippocampus ROI, males averaged a connectivity within the left hippocampus of 0.543; the female average was 0.353. The functional connectivity values for AD subjects with at least one ε4 allele are provided in Fig. 4.

Table 3 Hippocampal functional connectivity differences between genotypes

Comparison	*N*	ROI	Brain areas (atlas) of significant difference	% atlas covered	# of voxels
Female (F): Alzheimer's disease (AD) ε4 vs. no ε4	F ε4 = 12	Right hippocampus	Right hippocampus[a]	29%	205
			Left hippocampus	0%	0
Female (FMCI vs. FCN)	F no ε4 = 3	Left hippocampus	Left hippocampus[a]	18%	138
			Right hippocampus	0%	0
Male (M): AD ε4 vs. no ε4	M ε4 = 10	Right hippocampus	Right hippocampus[a]	25%	172
			Left hippocampus	3%	22
	M no ε4 = 5	Left hippocampus	Left hippocampus[a]	22%	168
			Right hippocampus	3%	20
F: cognitively normal (CN) ε4 vs. no ε4	F ε4 = 7	Right hippocampus	Right hippocampus[a]	17%	122
			Left hippocampus	0%	0
Female (FMCI vs. FCN)	F no ε4 = 8	Left hippocampus	Left hippocampus[a]	28%	215
			Right hippocampus	0%	0
M: CN ε4 vs. no ε4	M ε4 = 5	Right hippocampus	Right hippocampus[a]	19%	131
			Left hippocampus	1%	10
	M no ε4 = 10	Left hippocampus	Left hippocampus[a]	18%	140
			Right hippocampus	2%	12

[a]The area is large enough to be statistically significant

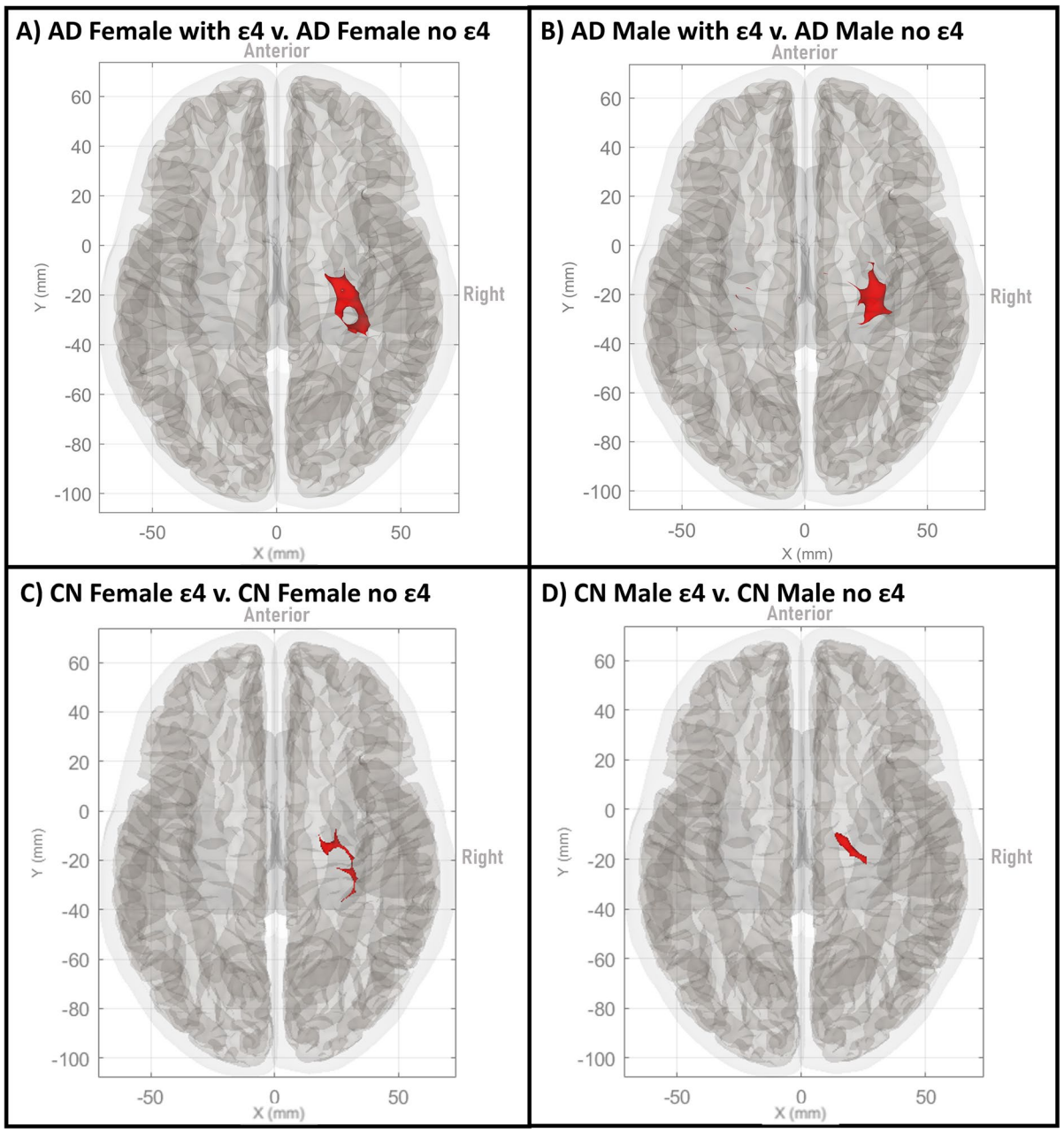

Fig. 2 Hippocampal functional connectivity difference between individuals with an ε4 allele versus those without ε4 allele with right hippocampus as ROI. Highlighted display the statistically significant cortical regions ($p < 0.001$)

Discussion

This study supports that there are sex differences in cortical pathophysiological biomarkers in AD. Specifically, this research expands the current understanding of intrahippocampal communication, demonstrating that the ApoE ε4 allele may play a role in the observed sex differences in hippocampal functional connectivity in AD.

Our finding that resting-state FC differs between those with an ε4 allele versus those without an ε4 allele is consistent with previous research. Several

Table 4 Hippocampal functional connectivity differences between sexes

Comparison	*N*	ROI	Brain areas (atlas) of significant difference	% atlas covered	# of voxels
Alzheimer's disease (AD) ε4: female (F) vs. male (M) (FMCI vs. FCN)	F = 12	Right hippocampus	Right hippocampus[a]	33%	228
			Left hippocampus	0%	0
	M = 10	Left hippocampus	Left hippocampus[a]	39%	250
			Right hippocampus	1%	5
AD ε3: F vs. M	F = 3	Right hippocampus	Right hippocampus	1%	5
			Left hippocampus	0%	0
	M = 5	Left hippocampus	Left hippocampus	1%	3
			Right hippocampus	0%	0
Cognitively normal (CN) ε4: F vs. M (FMCI vs. FCN)	F = 7	Right hippocampus	Right hippocampus	2%	11
			Left hippocampus	0%	0
	M = 5	Left hippocampus	Left hippocampus	3%	30
			Right hippocampus	1%	4
CN ε3: F vs. M	F = 8	Right hippocampus	Right hippocampus	5%	38
			Left hippocampus	0%	0
	M = 10	Left hippocampus	Left hippocampus	6%	48
			Right hippocampus	0%	0

[a]The area is large enough to be statistically significant

studies have reported that the ApoE ε4 allele is associated with decreased FC in cognitively normal adults as well as in mouse models [41–45]. In AD, the ApoE ε4 allele is shown to change both structural and functional characteristics, specifically within the hippocampus [46, 47]. It is also known that intrahippocampal functional hippocampal connectivity is decreased in Alzheimer's compared to controls [48, 49]. This has also been demonstrated in 3xTg mouse models [48]. This difference may be a direct decrease, or there may also be in compensatory pathways of the hippocampus. Research has shown that there is a generation of maladaptive compensatory mechanisms associated with AD [50, 51]. Further, this difference in hippocampal communication may also differ between females and males with AD [28, 29]. However, the novel finding of this research is the possibility that this sex difference may be linked to an interacting genetic factor, ApoE.

The sex difference in hippocampal FC was only observed between participants that had AD and had at least one ApoE ε4 allele. Comprehensive studies have shown that ApoE ε4 carriers have atrophic hippocampal volumes and that the sex modulates the ApoE-related decrease in both gray and white matter activity [52, 53]. However, how ApoE is related to the difference in hippocampal FC between males and females remains unknown. ApoE ε4 has been shown to modulate neurodegeneration in a sex-specific manner, with females having a stronger association between ApoE and tau levels and amyloid-β, particularly in the presence of amyloidosis [54, 55]. Therefore, one hypothesis may be that ApoE affects tau protein aggregates or amyloidogenic processes differently, which is then playing a role in disconnecting the hippocampus from specific memory systems resulting in worse neuropsychological task performance seen in females [8, 56]. Another hypothesis is related to the female endocrine and reproductive history. It could be that the observed sex differences in functional connectivity are the result of the activation effects of cycling hormones in women prior to menopause. It is known that across the menstrual cycle, there is gray matter plasticity in the hippocampal, the amygdala, and the

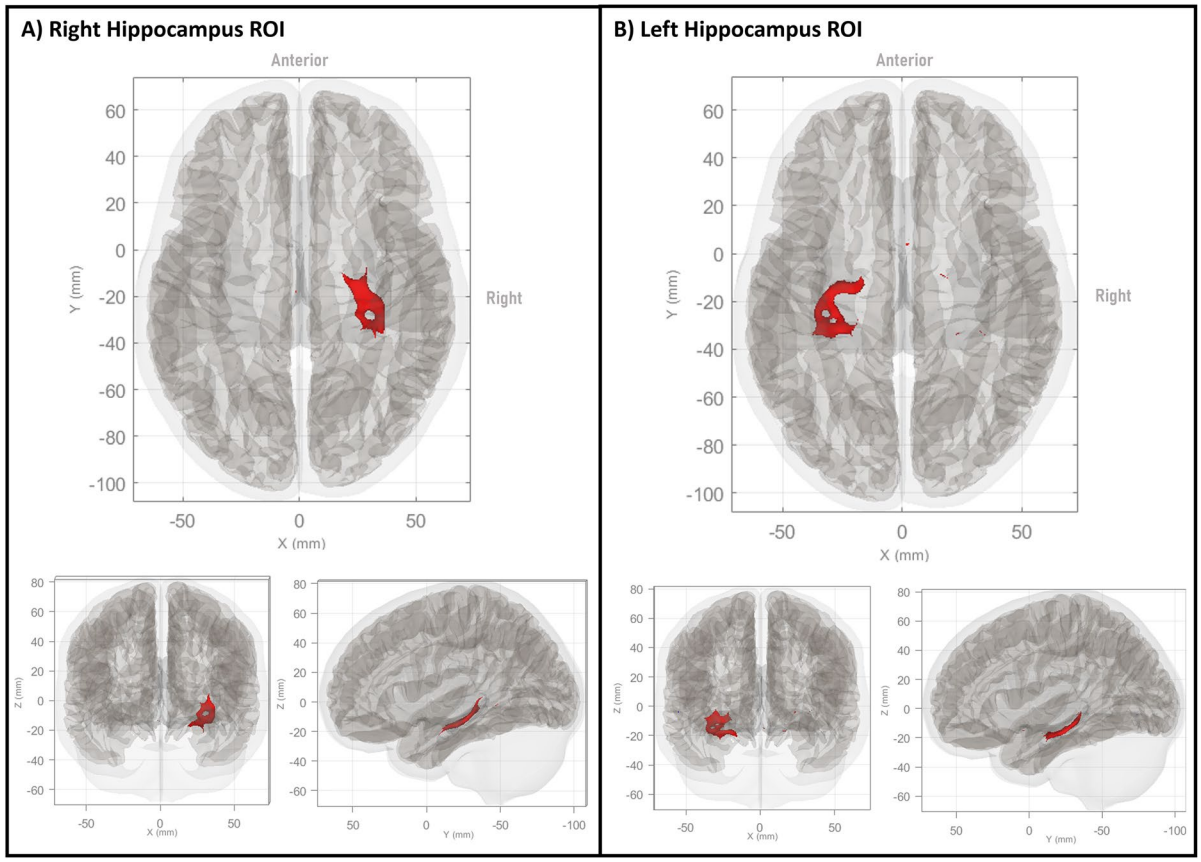

Fig. 3 Hippocampal functional connectivity difference between females and males with AD who have an ε4 allele. Highlighted display the statistically significant cortical regions ($p < 0.001$)

temporal and parietal regions of the brain [57]. One could observe if functional connectivity in women who had hysterectomies or hormone therapy is more similar or different from men.

Further, there are other biological and gender considerations regarding ApoE and aging. The ApoE ε4 allele has been shown to have a large impact on stress response–related processes, including a strong interconnection between mitochondrial function, endoplasmic reticulum stress, synaptic integrity, and the immune response [58, 59]. In addition to AD, the ApoE genotype is related to the severity of other proteinopathies and neurodegenerative diseases characterized by overt neuroinflammation [60]. These include multiple sclerosis, Parkinson's, dementia with Lewy bodies, and amyotrophic lateral sclerosis. These conditions also have reported sex differences in both development and progression [61]. The study of sex differences in these different neurological conditions, including AD, is significant as it could lead to an understanding of the molecular underpinning of ApoE and further the advancement of precise treatment based on sex.

It should be noted that the sample size of this study was small, and the cross-sectional design further constrains conclusions about the nature of change in hippocampal activity over time. Future work should include longitudinal designs to track these changes in larger samples to provide more

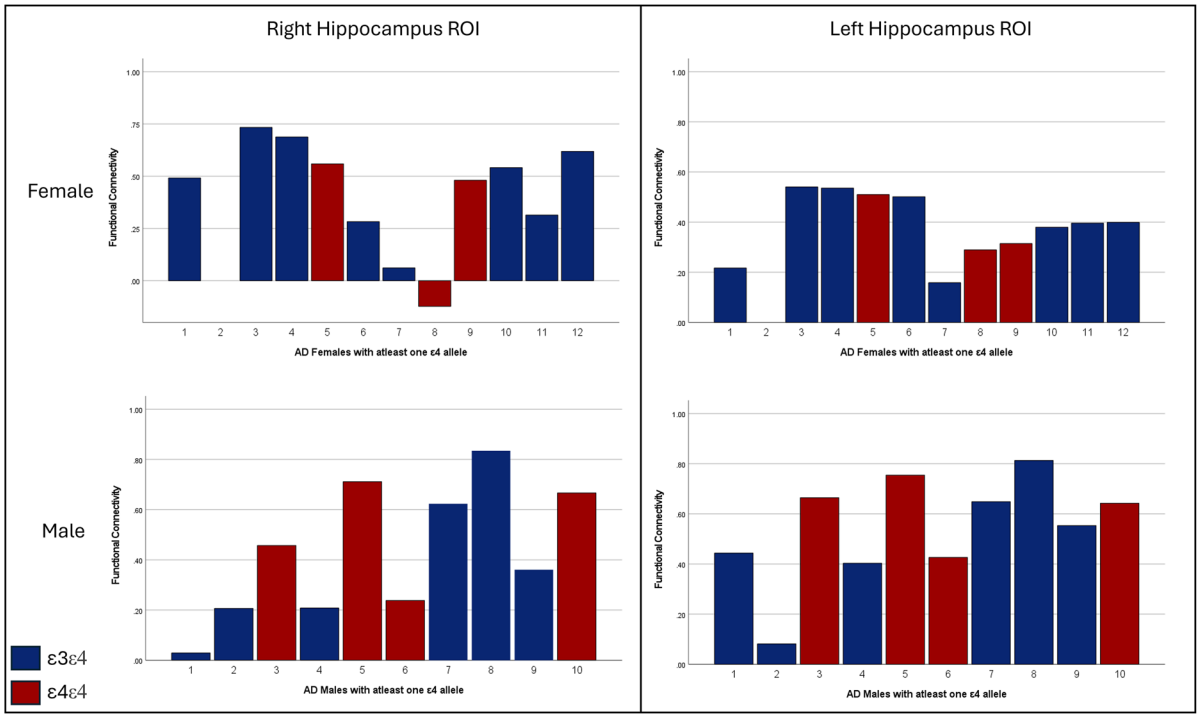

Fig. 4 Functional connectivity of right hippocampus ROI to the right hippocampus and left hippocampus ROI to the left hippocampus in AD participants with at least one ε4 allele

robust statistical power and a more representative spectrum of the AD population. The sample size (that was limited by fMRIs available on the ADNI database) also did not allow for separating the genotypes further, for example, observing the differences between homozygous and heterozygous ApoE ε4 carriers or exploring the differences that may emerge with ApoE ε2. Further, our analysis included the uneven distribution of heterozygotes and homozygotes across sexes, most significantly within the AD group with at least one ApoE ε4 allele. With an increased number of participants, the number in each group would be equalized to ensure this is not a confounding variable. With an increased number of participants to allow for larger groups, this future work would strengthen the study of sex, ApoE, and functional connectivity of the hippocampus. Additionally, exploring the molecular underpinning of ApoE including a study with tau or amyloid-β levels would provide an indication of their role in changes to connectivity. Another important future work would be focusing on the effects of the female reproductive cycle. Nevertheless, the current finding supports accounting for sex and ApoE genotype in neuroimaging biomarkers, diagnostics, and treatments. Additionally, it furthers the rationale for the development of sex-specific interventions using the emerging cortical pathophysiological biomarkers, such as non-invasive brain stimulation (NIBS) to optimize therapeutic outcomes [62, 63]. The prospect of sex-specific interventions also calls for a deeper examination of the socio-cultural dimensions of AD. Gender roles and environmental factors may exacerbate or mitigate expressions of genetic risk, which warrants consideration in research and clinical settings.

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Data availability All data derived from the ADNI and that specific to this study are available to researchers by request as outlined in the ADNI access policy (adni.loni.usc.edu).

Declarations

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