GeroScience (2024) 46:563–572
https://doi.org/10.1007/s11357-023-00943-x

ORIGINAL ARTICLE

Sex difference in brain functional connectivity of hippocampus in Alzheimer's disease

Jordan Williamson · Shirley A. James · Peter Mukli · Andriy Yabluchanskiy · Dee H. Wu · William Sonntag · Alzheimer's Disease Neuroimaging Initiative Consortium · Yuan Yang

Received: 5 May 2023 / Accepted: 11 September 2023 / Published online: 25 September 2023

Abstract Alzheimer's disease (AD), affecting nearly 6.5 million people, is the fifth leading cause of death in individuals 65 years or older in the USA. Prior research has shown 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 has linked these sex differences to neuroimaging markers of brain pathology, such as hippocampal volumes. Specifically, research from our lab found that functional connectivity from the hippocampus to the precuneus cortex and brain stem was significantly stronger in males than in females with mild cognitive impairment. The aim of this study was to extend our understanding to individuals with AD and to determine if these potential

J. Williamson · Y. Yang (✉)
Department of Bioengineering, University of Illinois Urbana-Champaign, Urbana, IL, USA
e-mail: yuany@illinois.edu

J. Williamson
e-mail: jordan36@illinois.edu

S. A. James
Department of Public Health, Health Science Center, University of Oklahoma, Oklahoma City, OK, USA
e-mail: Shirley-james@ouhsc.edu

P. Mukli · A. Yabluchanskiy · W. Sonntag
Vascular Cognitive Impairment and Neurodegeneration Program, Oklahoma Center for Geroscience and Healthy Brain Aging, Department of Neurosurgery, Health Sciences Center, University of Oklahoma, Oklahoma City, OK, USA
e-mail: peter-mukli@ouhsc.edu

A. Yabluchanskiy
e-mail: andriy-yabluchanskiy@ouhsc.edu

W. Sonntag
e-mail: William-Sonntag@ouhsc.edu

D. H. Wu
Department of Radiological Science and Medical Physics, Health Science Center, University of Oklahoma, Oklahoma City, OK, USA
e-mail: dee-wu@ouhsc.edu

D. H. Wu · Y. Yang
Data Institute for Societal Challenges, University of Oklahoma, Norman, OK, USA

D. H. Wu · Y. Yang
Beckman Institute for Advanced Science and Technology, University of Illinois Urbana-Champaign, Urbana, IL, USA

Y. Yang
Department of Rehabilitation Sciences, Health Science Center, University of Oklahoma, Oklahoma City, OK, USA

Y. Yang
SFCRI Clinical Imaging Research Center, Carle Foundation Hospital, Urbana, IL, USA

Y. Yang
Department of Physical Therapy and Human Movement Sciences, Northwestern University, Chicago, IL, USA

sex-specific functional connectivity biomarkers extend through different disease stages. The resting state fMRI and T2 MRI of cognitively normal individuals ($n = 32$, female = 16) and individuals with AD ($n = 32$, female = 16) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were analyzed using the Functional Connectivity Toolbox (CONN). Our results demonstrate that males had a significantly stronger interhemispheric functional connectivity between the left and right hippocampus compared to females. These results improve our current understanding of the role of the hippocampus in sex differences in AD. Understanding the contribution of impaired functional connectivity sex differences may aid in the development of sex-specific precision medicine for improved AD treatment.

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

Introduction

The National Institute of Health estimates the prevalence of Alzheimer's disease dementia (AD) in individuals 65 years or older in the USA is approximately 6.5 million, and this number is projected to increase to 13.8 million by the year 2060. AD is the most common form of dementia and, in addition to behavioral changes, significantly deteriorates individuals' cognitive abilities including impaired memory retrieval. AD is currently the fifth leading cause of death for those older than 65 years living in the USA [1, 2]. The study of AD is critically important, not only because the disease causes a significant loss of function but also because the cost of caring for an individual diagnosed with AD during the last 5 years of life has been estimated at $287,000 [3]. People with AD experience a duality of brain lesions; plaque deposits between the neuronal cells in the brain that are composed of amyloid beta (Aβ) and aggregated tau proteins forming neurofibrillary tangles (NFT) nested inside neurons [1, 2]. Importantly, disrupted connection between neuronal populations fundamental for higher order cognitive processing and memory have been implicated. Network studies have shown that AD has global brain connectivity differences, and this pathology is not equally distributed, but preferentially affects specific hub areas [4, 5]. Specifically, selective disruption has been found in the posterior and parietal hubs, left temporal centrality, and the hippocampus [6, 7]

AD disproportionately affects females, as the prevalence of AD is two-thirds higher in women than men [1, 2]. Additionally, compared to males with AD, females perform worse on a variety of neuropsychological tasks and have greater total brain atrophy and temporal lobe degeneration [8–10]. This difference has been attributed to a variety of sex-specific factors including genetics (such as the presence of the "X" chromosome [11]), hormonal differences and menopause, and hypertensive disorders of pregnancy [12–15]. This disproportionate risk of AD in females has also been linked to sex differences in known risk factors, such as age, depression, education level, sleep differences, and genetics (such as apolipoprotein E4 [16]) [14, 17]. These sex differences can be observed throughout AD disease stages, including the pre-clinical phase of AD. It has been shown that cognitively normal females with elevated amyloid beta had higher cognitive decline compared to males with the same level of amyloid beta [18]. Additionally cognitively normal females have a higher degradation in fractal motor activity regulation, which is correlated with preclinical AD amyloid and tau biomarkers [19]. Recently, research has revealed that brain imaging markers may also be a contributing factor in sex differences, specifically related to the hippocampus [20]. The damage demonstrated in the AD brain initially occurs in the entorhinal cortex and hippocampus, areas of the brain largely impacting cognition, particularly memory. Individuals diagnosed with early AD or mild cognitive impairment (MCI) have a reduction in their hippocampal volume, combined with microhemorrhage [21, 22]. Additionally, hippocampal atrophy has been found to be significantly faster and affects the progression of AD only in females [23, 24]. Researchers have also suggested males have a higher degree of brain resilience because of higher anterior cingulate cortex amyloid load and glucose hypometabolism in the precuneus, posterior cingulate, and inferior parietal cortex [25].

These findings led researchers in this laboratory to study sex differences in the functional connectivity of the hippocampus to the rest of the brain in individuals with MCI. We previously demonstrated that connectivity from the hippocampus to the precuneus

cortex and brain stem was significantly stronger in males than in females [26]. The aim of this study was to extend this to individuals with AD, to determine if these potential sex-specific functional connectivity biomarkers extend through different disease stages. Using a similar protocol to our previous research [26], the purpose of our current study is to investigate what differences exist in the functional connectivity of the hippocampus to the rest of the brain in individuals with Alzheimer's disease.

Methods

Data source

The data for this study were extracted from the ADNI [27], 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 http://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 3.0-T T2 magnetic resonance imaging. To maximize the sample size, participants were selected from any visit of ADNI-1, ADNI-GO, ADNI-2, and ADNI-3. A similar search methodology was applied for cognitively normal (CN) participants. The screening resulted in a total of 19 AD females, 16 AD males, 33 CN females, and 25 CN males. To balance the number of participants in each group, 16 of each group were randomly selected for the study. Demographics of AD participants are provided in Table 1; some participants did not have all demographics in the database.

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 [28]. CONN utilizes SPM12 (Wellcome 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/) [29–31] and the Automated Anatomical Labeling (AAL) atlas [32].

The images were processed through the default functional and structural preprocessing pipeline as detailed by Nieto-Castanon [33]. 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) and at the voxels. Next, the images were denoized to remove confounding effects from the BOLD signal through linear regression and band-pass filtering. A quality assurance check was made after the denoizing 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 timeseries, S is the BOLD timeseries 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.

Table 1 AD participant demographics

ID	Sex	Age	ApoE genotype	MMSE	GD Scale	CDR	FAQ	NPI-Q
S001	F	71.9	ε3 ε4	–	–	–	–	–
S002	F	74.4	ε3 ε3	–	–	–	–	–
S003	F	68.9	ε3 ε4	18.0	1.0	1.0	19.0	2.0
S004	F	60.7	ε3 ε3	–	–	–	–	–
S005	F	75.5	ε3 ε4	24.0	–	1.0	15.0	7.0
S006	F	73.7	ε3 ε4	15.0	1.0	1.0	26.0	3.0
S007	F	58.8	ε4 ε4	18.0	7.0	1.0	25.0	10.0
S008	F	81.8	ε3 ε4	23.0	1.0	1.0	21.0	4.0
S009	F	77.8	ε3 ε4	22.0	2.0	0.5	14.0	9.0
S010	F	74.2	ε4 ε4	26.0	0.0	0.5	6.0	5.0
S011	F	75.9	ε4 ε4	23.0	2.0	1.0	20.0	2.0
S012	F	56.5	ε3 ε4	26.0	1.0	1.0	16.0	2.0
S013	F	87.2	ε3 ε4	19.0	0.0	1.0	28.0	2.0
S014	F	62.8	ε3 ε3	–	–	–	–	–
S015	F	74.9	–	–	–	–	–	–
S016	F	73.6	ε3 ε4	16.0	0.0	1.0	20.0	5.0
S017	M	60.7	ε3 ε3	–	–	–	–	–
S018	M	72.8	ε3 ε4	16.0	2.0	1.0	20.0	7.0
S019	M	77.1	ε3 ε4	25.0	3.0	1.0	20.0	2.0
S020	M	74.3	ε3 ε3	–	–	–	–	–
S021	M	68.8	ε2 ε3	–	–	–	–	–
S022	M	71.9	ε3 ε3	22.0	3.0	1.0	23.0	7.0
S023	M	76.9	ε4 ε4	25.0	1.0	0.5	2.0	0.0
S024	M	79.6	ε2 ε3	21.0	2.0	0.5	9.0	1.0
S025	M	75.9	ε3 ε4	21.0	1.0	1.0	26.0	4.0
S026	M	76.6	ε4 ε4	21.0	4.0	1.0	20.0	14.0
S027	M	66.6	–	–	–	–	–	–
S028	M	75.1	ε4 ε4	23.0	1.0	2.0	22.0	12.0
S029	M	71.6	ε3 ε4	24.0	3.0	1.0	14.0	2.0
S030	M	83.0	ε3 ε4	22.0	1.0	0.5	6.0	1.0
S031	M	80.0	ε3 ε4	23.0	1.0	0.5	9.0	1.0
S032	M	73.9	ε4 ε4	24.0	2.0	1.0	18.0	3.0
Female $\mu \pm$ SD		**72.8 ± 9.4**	**–**	**20.6 ± 3.9**	**1.5 ± 2.1**	**0.9 ± 0.21**	**19.5 ± 6.4**	**4.4 ± 3.0**
Male $\mu \pm$ SD		**76.2 ± 3.5**	**–**	**22.3 ± 2.5**	**2.0 ± 1.0**	**0.9 ± 0.42**	**15.7 ± 7.8**	**4.5 ± 4.6**
Between sex *t*-tests		**$P = 0.372$**	**–**	**$P = 0.329$**	**$P = 0.085$**	**$P = 0.740$**	**$P = 0.265$**	**$P = 0.418$**

Statistical analysis

IBM SPSS (IBM Corp., Armonk, NY, USA) was used to run independent t-tests on the available AD 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 SBC maps were compared to female CN SBC maps; this was repeated for the male participants.Female

Table 2 Functional connectivity differences within the hippocampus

Groups	ROI	Brain area (atlas)	% atlas covered	# of voxels
FAD vs. FCN	Right hippocampus	Right hippocampus*	47%	331
		Left hippocampus	0%	0
	Left hippocampus	Left hippocampus*	53%	524
		Right hippocampus	2%	13
MAD vs. MCN	Right hippocampus	Right hippocampus*	76%	527
		Left hippocampus*	20%	155
	Left hippocampus	Left hippocampus*	68%	514
		Right hippocampus*	31%	216
FAD vs. MAD	Right hippocampus	Right hippocampus*	70%	489
		Left hippocampus*	14%	105
	Left hippocampus	Left hippocampus*	67%	507
		Right hippocampus*	20%	140
FCN vs. MCN	Right hippocampus	Right hippocampus*	80%	557
		Left hippocampus	12%	90
	Left hippocampus	Left hippocampus*	75%	571
		Right hippocampus*	19%	132

*Indicates that the area is large enough to be statistically significant

AD versus male AD maps and female CN versus male CN were also compared. For a cortical area to be considered significantly different between SBC maps, 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 [35]. 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) to be considered significant. These regions of statistical difference from SBC maps were then highlighted on a template brain.

Results

Table 1 displays AD participant demographics with statistical analysis to ensure there were no significant differences in covariates.

The left and right hippocampi atlases were the only brain regions identified to be significantly different between all comparisons. Table 2 displays the amount of area of the atlas that was different when the right and left hippocampus were selected as the ROI with stars on areas that were large enough to be considered statistically significant. For visualization for each sex between AD and CN, this data is additionally displayed in Fig. 1.

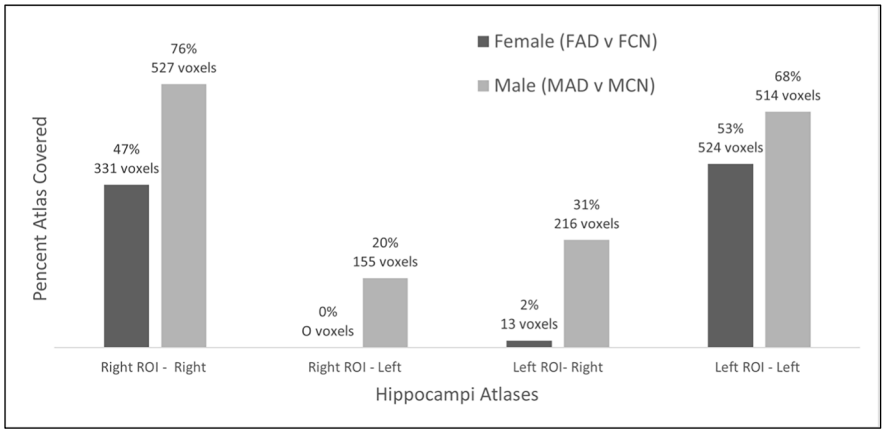

Fig. 1 Functional connectivity differences within the hippocampus in AD for each sex

Between sex, in the diseased state (FAD vs. MAD) and the controls (FCN vs. MCN), and between healthy and diseased for each sex (FAD vs. FCN and MAD vs. MCN) when the right and left hippocampus were selected as the ROI, the functional connectivity throughout the right and left hippocampus, respectively, had a significant between-group difference. Additionally, there was a significant sex difference within the disease (Fig. 2), and for the controls (Fig. 3) to the right hippocampus when the left hippocampus was selected as the ROI.

The regions that had a sex-specific difference between healthy and diseased were the left and right hippocampus when the right and left hippocampus were selected as ROI, respectively. In AD, males showed significantly stronger connectivity between the right and left hippocampus. This difference is shown visually by comparing boxes A and D in Figs. 4 and 5.

Discussion

This study supports the hypothesis that there are sex differences in cortical pathophysiological biomarkers in AD. Specifically, it expands the current understanding of hippocampal communication, demonstrating that there is a sex difference in interhemispheric functional connectivity between the left and right hippocampus.

Previous comprehensive studies have demonstrated disconnection deficits of interhemispheric cortical pathways are associated with AD [36–39]. In particular, these studies have found that functional interhemispheric hippocampal connectivity is decreased in Alzheimer's compared to controls [40, 41]. This difference may be a direct decrease or there may also be in compensatory pathways between the two hippocampi. As research has shown that there is a generation of maladaptive compensatory mechanisms associated with AD [42, 43]. However, the differences found in previous studies have not, to our knowledge, been extended to sex-specific differences. This finding may in part be a contributory factor in the observed worse neuropsychological task performance seen in females.

Unlike our previous study with MCI subjects [26], the functional connectivity between the hippocampus and precuneus cortex or the brain stem did not appear to be different between sex in AD. The precuneus

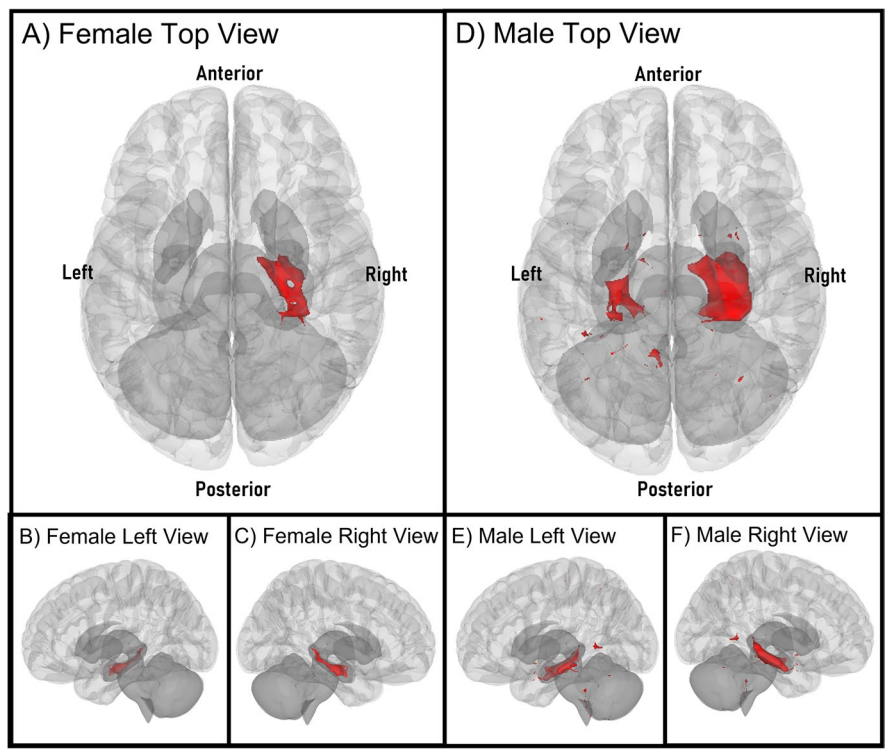

Fig. 2 Sex-differences in Alzheimer's disease in the hippocampus. Highlighted display the statistically significant cortical regions between female Alzheimer's disease (AD) and male AD ($p < 0.001$). **A–C** Results with the right hippocampus selected as ROI. **D–F** Results with the left hippocampus selected as ROI

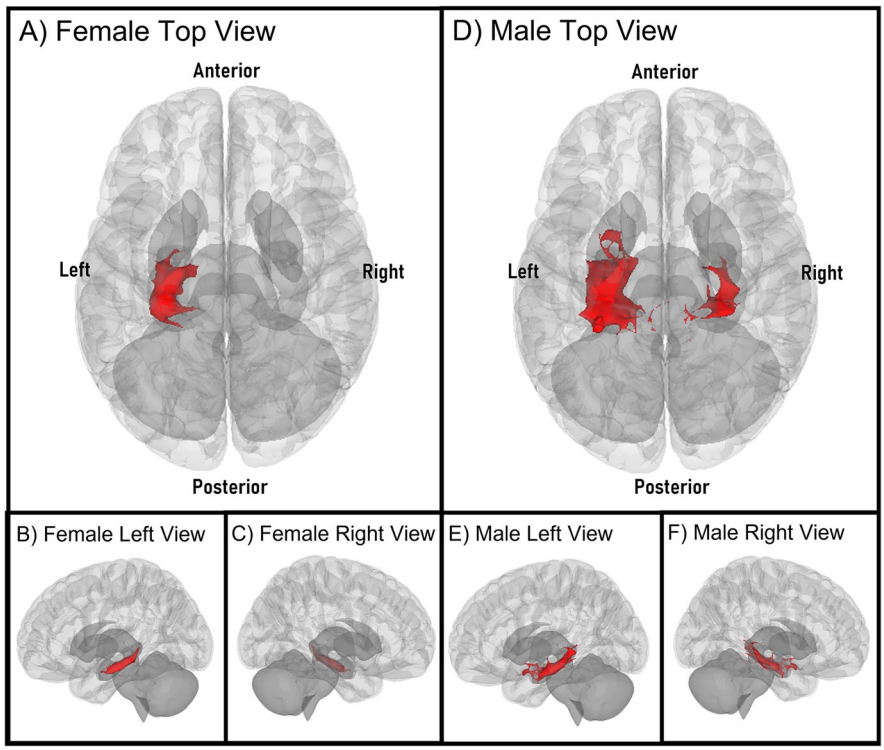

Fig. 3 Sex-differences in controls in the hippocampus. Highlighted display the statistically significant cortical regions between female cognitively normal (CN) and male CN ($p < 0.001$). **A**–**C** Results with the right hippocampus selected as ROI. **D**–**F** Results with the left hippocampus selected as ROI

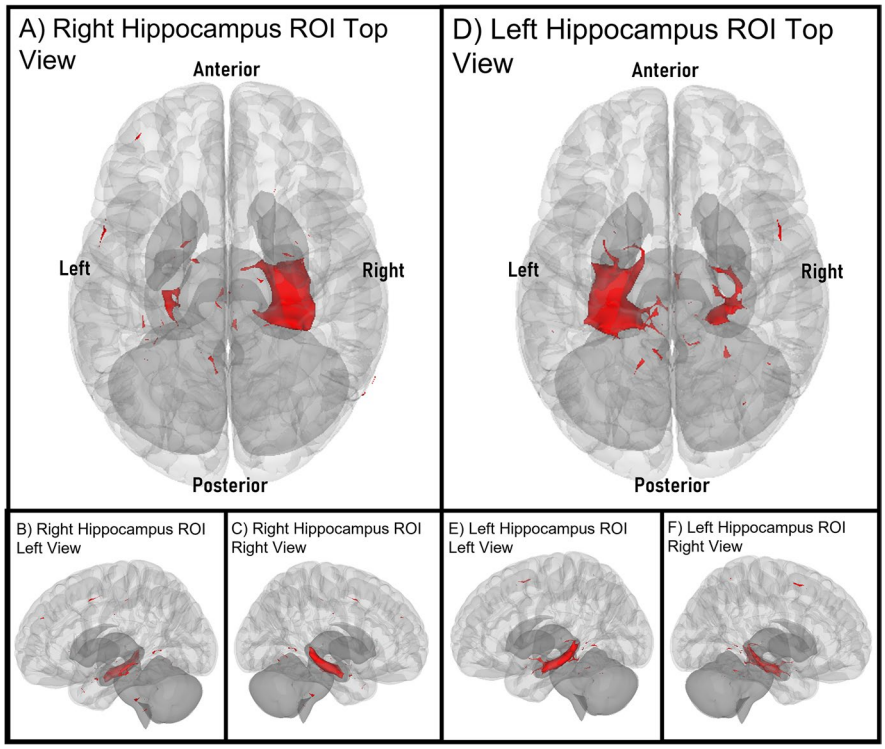

Fig. 4 Sex-specific pathological features with right hippocampus as ROI. Highlighted display the statistically significant cortical regions between Alzheimer's disease (AD) and cognitively normal (CN) ($p < 0.001$). **A**–**C** FAD vs. FCN; **D**–**F** MAD vs. MCN

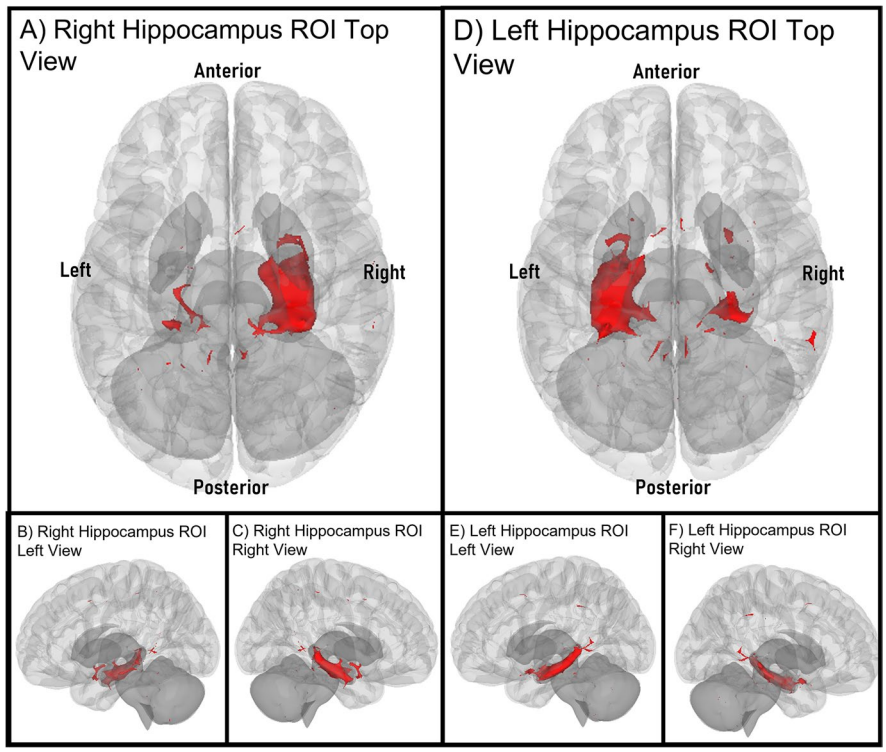

Fig. 5 Sex-specific pathological features with left hippocampus as ROI. Highlighted display the statistically significant cortical regions between Alzheimer's disease (AD) and cognitively normal (CN) ($p < 0.001$). **A**–**C** FAD vs. FCN; **D**–**F** MAD vs. MCN

cortex, specifically, has been shown to be related to the prodromal stages of AD [44, 45]. The precuneus cortex is known to exhibit early brain atrophy and is considered a vulnerable region for the transitional stage between MCI and dementia [46]. Therefore, it may be that the hippocampus-precuneus cortex functional connectivity is only a biomarker of MCI. This finding may provide rational for the use of the precuneus cortex as good target for tailored sex-specific intervention, such as non-invasive brain stimulation (NIBS) [47, 48], to decrease the progression of MCI to AD.

While this research provides preliminary findings on sex differences in functional connectivity of the hippocampus in AD, the small sample size ($n = 64$) is a limitation. Therefore, future work includes increasing sample size in a larger database. While the dataset uses clinical measures to define AD, the dataset lacks biological markers to confirm the pathology. Additionally, the communication of the left and right hippocampus is facilitated by the dorsal hippocampal commissure (DHC). The DHC is a white matter tract crossing the midline beneath the corpus callosum, providing interhemispheric connection between temporal lobe regions [49]. This tract has been suggested to play a key role in memory, particularly recognition memory [50]. Therefore, a future work could explore if there is sex difference in the integrity of this tract in AD. Furthermore, studies such as these could be enhanced by expanding functional connectivity from other regions of interest for AD in addition to the hippocampus and combining aforementioned risk factors such as cognitive reserve or genetic differences to explore potential connections.

Acknowledgements Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals

Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. This work was also partially supported by the American Heart Association (AHA834339) and the National Institute on Aging of National Institutes of Health (R01AG075834) awards. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Author contribution J.W. conducted the study. J.W and S.J. drafted the manuscript. Y.Y. contributed to conceptualization, problem solving, and guidance during the conduction of the study. A.Y., P.M., D.W., W.S., and Y.Y. participated in editing the manuscript.

Funding This research is supported by a seed grant from the Vice President for Research and Partnerships of the University of Oklahoma and the Data Institute for Societal Challenges. This work was also supported by the NIH/NICHD R01HD109157, NSF 2236459, American Heart Association (nos. 932980 and 966924), Oklahoma Shared Clinical and Translational Resources (U54GM104938) with an Institutional Development Award from National Institute of General Medical Sciences, NIA-supported Geroscience Training Program in Oklahoma (T32AG052363), Oklahoma Nathan Shock Center (P30AG050911), and Cellular and Molecular GeroScience CoBRE (P20GM125528).

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

Ethics approval and consent to participate The institutional review boards of all participating ADNI sites reviewed and approved the data collection protocols provided by ADNI.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

References

1. National Institutes of Health. Alzheimer's Disease, In: Accelerating Medicines Partnership (AMP). 2021. https://www.nih.gov/research-training/accelerating-medicines-partnership-amp/alzheimers-disease#:~:text=It%20is%20the%20most%20common,to%2013.8%20million%20by%202050.
2. Gaugler J, et al. 2022 Alzheimer's disease facts and figures. Alzheimer's Dement. 2022;18(4):700–89.
3. Kelley AS, et al. The burden of health care costs for patients with dementia in the last 5 years of life. Ann Intern Med. 2015;163(10):729–36.
4. van den Heuvel MP, Sporns O. Network hubs in the human brain. Trends Cogn Sci. 2013;17(12):683–96.
5. Stam CJ. Modern network science of neurological disorders. Nat Rev Neurosci. 2014;15(10):683–95.
6. Yu M, et al. Selective impairment of hippocampus and posterior hub areas in Alzheimer's disease: an MEG-based multiplex network study. Brain. 2017;140(5):1466–85.
7. de Haan W, et al. Disruption of functional brain networks in Alzheimer's disease: what can we learn from graph spectral analysis of resting-state magnetoencephalography? Brain Connect. 2012;2(2):45–55.
8. Chapman RM, et al. Women have farther to fall: gender differences between normal elderly and Alzheimer's disease in verbal memory engender better detection of Alzheimer's disease in women. J Int Neuropsychol Soc. 2011;17(4):654–62.
9. Gumus M, et al. Progression of neuropsychiatric symptoms in young-onset versus late-onset Alzheimer's disease. Geroscience. 2021;43:213–23.
10. Henderson VW, Buckwalter JG. Cognitive deficits of men and women with Alzheimer's disease. Neurology. 1994;44(1):90–6.
11. Davis EJ, et al. A second X chromosome contributes to resilience in a mouse model of Alzheimer's disease. Sci Transl Med. 2020;12(558):eaaz5677.
12. Andrew MK, Tierney MC. The puzzle of sex, gender and Alzheimer's disease: why are women more often affected than men? Womens Health. 2018;14:1745506518817995.
13. Mielke MM. Sex and gender differences in Alzheimer's disease dementia. Psychiatr Times. 2018;35(11):14–7.
14. Mielke MM, et al. Consideration of sex and gender in Alzheimer's disease and related disorders from a global perspective. Alzheimer's Dement. 2022;18(12):2707–2724.
15. Pearce EE, et al. Telomere length and epigenetic clocks as markers of cellular aging: a comparative study. Geroscience. 2022;44(3):1861–9.
16. Sienski G, et al. APOE4 disrupts intracellular lipid homeostasis in human iPSC-derived glia. Sci Transl Med. 2021;13(583):eaaz4564.
17. Guerreiro R, Bras J. The age factor in Alzheimer's disease. Genome Med. 2015;7(1):1–3.
18. Buckley RF, et al. Sex, amyloid, and APOE ε4 and risk of cognitive decline in preclinical Alzheimer's disease: findings from three well-characterized cohorts. Alzheimer's Dement. 2018;14(9):1193–203.

19. Gao L, et al. Fractal motor activity regulation and sex differences in preclinical Alzheimer's disease pathology. Alzheimer's Dement. 2021;13(1):e12211.
20. Heise V, et al. Apolipoprotein E genotype, gender and age modulate connectivity of the hippocampus in healthy adults. Neuroimage. 2014;98:23–30.
21. Ferretti MT, et al. Sex differences in Alzheimer disease - the gateway to precision medicine. Nat Rev Neurol. 2018;14(8):457–69.
22. Jiang J, et al. Glucose metabolism patterns: a potential index to characterize brain ageing and predict high conversion risk into cognitive impairment. GeroScience. 2022;44(4):2319–36.
23. Burke SL, et al. Sex differences in the development of mild cognitive impairment and probable Alzheimer's disease as predicted by hippocampal volume or white matter hyperintensities. J Women Aging. 2019;31(2):140–64.
24. Ardekani BA, Convit A, Bachman AH. Analysis of the MIRIAD data shows sex differences in hippocampal atrophy progression. Journal of Alzheimer's Disease. 2016;50:847–57.
25. Cavedo E, et al. Sex differences in functional and molecular neuroimaging biomarkers of Alzheimer's disease in cognitively normal older adults with subjective memory complaints. Alzheimer's & Dementia. 2018;14(9):1204–15.
26. Williamson J, et al. Sex differences in brain functional connectivity of hippocampus in mild cognitive impairment. Front Aging Neurosci. 2022;14:959394.
27. Mueller SG, et al. The Alzheimer's disease neuroimaging initiative. Neuroimaging Clinics. 2005;15(4):869–77.
28 Whitfield-Gabriel S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2012;2(3):125–41.
29 Jenkinson M, et al. Fsl. Neuroimage. 2012;62(2):782–90.
30. Smith SM, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004;23:S208–19.
31. Woolrich MW, et al. Bayesian analysis of neuroimaging data in FSL. Neuroimage. 2009;45(1 Suppl):S173–86.
32. Tzourio-Mazoyer N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 2002;15(1):273–89.
33. Nieto-Castanon A. Handbook of functional connectivity magnetic resonance imaging methods in CONN. 1st ed. Boston: Hilbert Press; 2020.
34. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2012;2(3):125–41.
35. Worsley KJ, et al. A unified statistical approach for determining significant signals in images of cerebral activation. Hum Brain Mapp. 1996;4(1):58–73.
36. Rose SE, et al. Loss of connectivity in Alzheimer's disease: an evaluation of white matter tract integrity with colour coded MR diffusion tensor imaging. J Neurol Neurosurg Psychiatry. 2000;69(4):528–30.
37. Delbeuck X, Van der Linden M, Collette F. Alzheimer' disease as a disconnection syndrome? Neuropsychol Rev. 2003;13:79–92.
38. Morrison J, et al. The laminar and regional distribution of somatostatin and neuritic disconnection syndrome. In: Scheibel AB, Wechsler AF, editors. The biological substrates of Alzheimer's disease. Orlando: Academic; 1986. pp 115–131.
39. Reuter-Lorenz PA, Mikels JA. A split-brain model of Alzheimer's disease?: Behavioral evidence for comparable intra and interhemispheric decline. Neuropsychologia. 2005;43(9):1307–17.
40. Manno FA, et al. Early stage alterations in white matter and decreased functional interhemispheric hippocampal connectivity in the 3xTg mouse model of Alzheimer's disease. Front Aging Neurosci. 2019;11:39.
41. Wang Z, et al. Interhemispheric functional and structural disconnection in Alzheimer's disease: a combined resting-state fMRI and DTI study. PLoS One. 2015;10(5):e0126310.
42. Aganj I, et al. Compensatory brain connection discovery in alzheimer's disease. Proc IEEE Int Symp Biomed Imaging. 2020;2020:283–7.
43. Gardini S, et al. Increased functional connectivity in the default mode network in mild cognitive impairment: a maladaptive compensatory mechanism associated with poor semantic memory performance. J Alzheimer's Dis. 2015;45:457–70.
44. Franzmeier N, et al. Left frontal cortex connectivity underlies cognitive reserve in prodromal Alzheimer disease. Neurology. 2017;88(11):1054–61.
45. Rami L, et al. Distinct functional activity of the precuneus and posterior cingulate cortex during encoding in the preclinical stage of Alzheimer's disease. J Alzheimer's Dis. 2012;31:517–26.
46. Canter RG, Penney J, Tsai L-H. The road to restoring neural circuits for the treatment of Alzheimer's disease. Nature. 2016;539(7628):187–96.
47. Casula EP, et al. Regional precuneus cortical hyperexcitability in Alzheimer's disease patients. Ann Neurol. 2022;93(2):371–83.
48. Koch G, et al. Transcranial magnetic stimulation of the precuneus enhances memory and neural activity in prodromal Alzheimer's disease. Neuroimage. 2018;169:302–11.
49. Nasa A, et al. The human dorsal hippocampal commissure: delineating connections across the midline using multi-modal neuroimaging in major depressive disorder. Neuroimage: Rep. 2021;1(4):100062.
50. Postans M, et al. Uncovering a role for the dorsal hippocampal commissure in recognition memory. Cereb Cortex. 2019;30(3):1001–15.