Journal of Alzheimer's Disease 76 (2020) 591–600
DOI 10.3233/JAD-191312
IOS Press

Genetic Risk for Alzheimer's Disease Moderates the Association Between Medial Temporal Lobe Volume and Episodic Memory Performance Among Older Adults

Sarah Prieto[a,*], Kate E. Valerio[a], Jena N. Moody[a], Scott M. Hayes[a,b] and Jasmeet P. Hayes[a,b] for the Alzheimer's Disease Neuroimaging Initiative[1]
[a]*Department of Psychology, The Ohio State University, Columbus, OH, USA*
[b]*Chronic Brain Injury Initiative, The Ohio State University, Columbus, OH, USA*

Handling Associate Editor: Ralph Buchert

Accepted 29 April 2020

Abstract.
Background: A complex set of interactions between biological, genetic, and environmental factors likely underlies the development of Alzheimer's disease (AD). Identifying which of these factors is most associated with AD is important for early diagnosis and treatment.
Objective: We sought to examine genetic risk and structural brain volume on episodic memory in a sample of older adults ranging from cognitively normal to those diagnosed with AD.
Methods: 686 adults (55–91 years old) completed a 3T MRI scan, baseline cognitive assessments, and biospecimen collection through the Alzheimer's Disease Neuroimaging Initiative. Hierarchical linear regression analyses examined main and interaction effects of medial temporal lobe (MTL) volume and polygenic hazard score (PHS), indicating genetic risk for AD, on a validated episodic memory composite score.
Results: Genetic risk moderated the relationship between MTL volume and memory, such that individuals with high PHS and lower hippocampal and entorhinal volume had lower memory composite scores [$\Delta F\,(1,677) = 4.057$, $p = 0.044$, $\Delta R^2 = 0.002$]. Further analyses showed this effect was driven by the left hippocampus [$\Delta F(1,677) = 5.256$, $p = 0.022$, $\Delta R^2 = 0.003$] and right entorhinal cortex [$\Delta F\,(1,677) = 6.078$, $p = 0.014$, $\Delta R^2 = 0.003$].
Conclusions: Among those with high genetic risk for AD, lower volume was associated with poorer memory. Results suggest that the interaction between AD genetic risk and MTL volume increases the likelihood for memory impairment among older adults. Results from this study suggest that genetic risk and brain volume should be considered key factors in tracking cognitive decline.

Keywords: Alzheimer's disease, atrophy, entorhinal cortex, episodic memory, hippocampus, medial temporal lobe, polygenic risk

*Correspondence to: Sarah Prieto, Department of Psychology, The Ohio State University, Columbus, OH, USA. Tel.: +1 614 292 3300; E-mail: prieto.39@buckeyemail.osu.edu.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://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

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive cognitive decline. AD is the sixth leading cause of death in the United States with approximately 5.8 million individuals currently living with this condition [1]. The frequency of AD diagnoses is expected to double by year 2040 [2], placing an increasing burden on family caregivers, the healthcare system, and the economy. A better understanding of the factors associated with dementia, including brain and genetic markers, will inform early intervention strategies to attenuate cognitive decline. Here, we examine the synergistic relationship between AD-related genetic and brain markers to determine associations with episodic memory impairment, which is the defining clinical feature of AD.

Previous work has demonstrated that biological markers of AD, such as brain atrophy, accumulation of amyloid deposits, and neurofibrillary tangles, can be detected years before the onset of clinical AD symptoms [3–5]. The medial temporal lobe, including the hippocampus and entorhinal cortex, shows the earliest signs of atrophy and tau accumulation [6, 7]. These regions have also been consistently associated with memory impairment in mild cognitive impairment [8, 9], suggesting that they are critical for understanding memory in AD, as well as in healthy older adults.

Genetic factors are also thought to play a role in the development of AD. It is estimated that genetic factors contribute 58–79% to AD risk [10]. The $\varepsilon 4$ allele of *apolipoprotein E* (*APOE*) is the strongest and most well-known contributor to AD [11–13]. However, recent work has demonstrated that polygenic approaches, which integrate the influence of multiple genes on a trait [14], add predictive value in the AD phenotype compared to when *APOE* is considered alone [15]. Nevertheless, the vast majority of studies have focused on the risk associated with a single candidate gene, such as *APOE* [16] which may contribute to smaller effect sizes and non-significant findings. Furthermore, a limitation in many studies is that only a single biomarker (e.g., genetics or neuroimaging) is examined in relation to AD, providing only a partial picture of the complex AD phenotype.

In the current study, we examined the influence of both genetic and brain imaging markers on episodic memory performance using a heterogeneous sample of older adults that included individuals characterized as having normal cognition (NC), mild cognitive impairment (MCI), and AD from the Alzheimer's Diseases Neuroimaging Initiative (ADNI) database. ADNI is a longitudinal, multisite study aimed at helping researchers investigate the clinical, imaging, genetic, and biomarkers involved in AD to improve early detection and treatment. Genetic risk for AD was determined using a polygenic hazard score (PHS) that integrated 31 AD-associated single nucleotide polymorphisms (SNPs) plus two *APOE* variants. Because medial temporal lobe (MTL) regions are among the first to atrophy in AD, we focused our analyses on hippocampal and entorhinal cortex volume with episodic memory performance as our outcome variable. Episodic memory refers to the recollection of an event defined by a unique spatial and temporal context [17, 18]. This domain of memory has been implicated in both MCI and AD, and is considered one of the earliest hallmarks of AD progression [19, 20]. Episodic memory performance was quantified using a composite score derived from weighted episodic memory data collected as part of the ADNI neuropsychological battery. This composite score was created to aid researchers in predicting decline and conversion to AD and has been shown to be as or more effective at predicting conversion than any single score comprising the battery [21]. In the present study, we hypothesized that individuals with high polygenic risk for AD and smaller MTL volumes would show reduced episodic memory performance.

MATERIALS AND METHODS

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). 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 MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see http://www.adni-info.org. Data used in this manuscript were downloaded from the ADNI database (http://adni.loni.usc.edu) on February 13, 2020 from the following four datasheets: ADNIMERGE.csv, DESIKANLAB.csv, UCSFFSX51_11_08_19.csv, and UWNPSYCHSUM_03_07_19.csv.

Participants

As described in greater detail in the ADNI protocol (http://www.adni-info.org), participants were between the ages of 55 and 91 years, had completed at least six years of education, and were willing and able to perform all test procedures described in the protocol. The 686 participants in this sample were originally recruited to be part of the ADNI 2 or ADNI GO phase of the study. The full list of inclusion and exclusion criteria can be accessed on the online ADNI protocol (http://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/clinical/ADNI-2_Protocol.pdf). Non-Hispanic White individuals with a non-accelerated T1 MRI screening scan and baseline visit information were included for analyses. Written informed consent was obtained from all participants, and all data were deidentified.

The cognitively normal group was defined as having a Mini-Mental State Examination (MMSE) score between 24 and 30 and a global Clinical Dementia Rating (CDR) of zero [22]. Diagnostic criteria for MCI included an MMSE score between 24 and 30, a global CDR of 0.5, a subjective memory concern reported, and an objective memory impairment on the Wechsler Memory Scale Logical Memory II [23]. Diagnostic criteria for AD included MMSE scores between 20 and 26 and global CDR of 0.5 or 1.0 at baseline.

MRI analyses

All participants in ADNI 2 and ADNI GO received a 3T MRI scan that underwent quality control and preprocessing at the Mayo Clinic. Cortical reconstruction and volumetric segmentation were performed by the University of California San Francisco with FreeSurfer image analysis suite (version 5.1). The scans were processed cross-sectionally using the 2010 Desikan-Killiany atlas. Regions-of-interest (ROI) were registered to each individual subject's cortical representation via surface-based registration and subcortical volume was extracted for each subject. Cortical volume values of the entorhinal cortex and hippocampus were extracted for the left and right hemisphere, as well as bilaterally. All volumes were adjusted for intracranial volume using the covariance formula ($Brainvolume\_adj = Brainvolume\_nat - b(TIV_{nat} - Mean\ TIV_{nat})$ where TIV is the total intracranial volume and b is the slope of the regression of the region of interest on TIV [24]. Since both the entorhinal cortex and hippocampus have been associated with AD, bilateral entorhinal cortex and hippocampal volume were combined to create a single ROI for AD (AD ROI).

Polygenic hazard score

PHS was composed of 31 AD-associated single nucleotide polymorphisms and two *APOE* variants that were identified using genotype data from the International Genomics of Alzheimer's Project and the Alzheimer's Disease Genetics Consortium as described elsewhere [25]. Supplementary Table 1 details the specific AD risk variants used in that study. 1,854 AD-associated SNPs (at $p < 10^{-5}$) were identified using genome-wide association study data from 17,008 individuals with AD and 37,154 controls in the International Genomics of Alzheimer's Project [25, 26]. In a stepwise procedure, genotype data from 6,409 AD patients and 9,386 controls in Phase 1 of the Alzheimer's Disease Genetics Consortium were used to identify the top AD-associated SNPs and develop a survival model using a Cox proportional hazard model for PHS. In each step, the SNP that most improved model prediction after controlling for the effects of sex and *APOE* variant was added, and this process continued until residuals did not improve with the addition of another SNP. In the final model, two *APOE* variants, the $\varepsilon 2$ and $\varepsilon 4$ alleles, and 31 AD-associated SNPs were integrated into a single PHS that reflects an individual's risk for developing AD based their age and genotype. The final continuous-measure score was used as a measure of genetic risk for AD in the current study. This PHS was tested in independent samples and found that it strongly predicted AD age of onset and progression to AD [25].

Memory composite score

A previously validated composite episodic memory score was used to assess memory function [21]. This composite score was calculated from elements of the Rey Auditory Verbal Learning Test, Alzheimer's Disease Assessment Scale-Cognitive, MMSE, and the Logical Memory subtest of the Wechsler Memory Test-Revised. Cognitive data from 803 ADNI participants were used in a single factor model to develop a composite score. To test the validity and performance of the composite score, the ability of the score to detect change in each diagnostic group over time was assessed. Next, the score's ability to predict

Table 1
Demographic and clinical characteristics

Variable	NC Mean (SD)	MCI Mean (SD)	AD Mean (SD)	*p*
Age in years	73.2 (5.8)[ab]	71.6 (7.3)[ab,bc]	74.7 (8.1)[bc]	<0.001
N (# of female)	203 (110)	376 (162)	107 (42)	0.013
Education in years	16.7 (2.6)[ac]	16.3 (2.7)	15.7 (2.6)[ac]	<0.001
Polygenic Hazard Score (PHS)	0.053 (0.63)[ac,ab]	0.404 (0.79)[ab,bc]	0.793 (0.83)[ac,bc]	<0.001
Adjusted AD ROI volume	5734 (526)[ac,ab]	5317 (820)[ab,bc]	4384 (646)[ab,bc]	<0.001
Episodic memory composite score	1.09 (0.57)[ac,ab]	0.32 (0.67)[ab,bc]	–0.93 (0.51)[ab,bc]	<0.001

AD, Alzheimer's disease; AD ROI, AD single region of interest; NC, normal cognition; MCI, mild cognitive impairment. [a]NC, [b]MCI, [c]AD, [ab]significant difference between NC and MCI, [ac]significant difference between NC and AD, [bc]significant difference between MCI and AD. Superscripts indicate that the pairwise groups have statistical significance using the Tukey HSD.

conversion from MCI to AD was measured and the strength of the relationship with memory-associated MRI-derived parameters was calculated. Findings indicated that the performance of the composite score was equivalent or superior to the individual memory indicators.

Statistical approach

All data were analyzed using IBM SPSS Statistics for Macintosh, version 26. Demographic and participant characteristic analyses were conducted to compare participants with NC, MCI, and AD using either chi-square tests for categorical variables or analysis of variance (ANOVA) for continuous variables.

Hierarchical linear regression models were conducted to analyze the interactive effects of PHS and brain volume on composite episodic memory scores. Covariates included in the first step of the linear regression model were: sex, age, education, cerebrospinal fluid amyloid-β (Aβ), and diagnosis. Cerebrospinal fluid (CSF) $A\beta_{1-42}$ was analyzed using the fully automated Roche Elecsys immunoassay at the UPenn/ADNI Biomarker laboratory. Values outside of the measuring range of the assay (200–1700 pg/mL) were truncated to the technical limits. The second step of the model assessed for main effects of PHS and AD ROI volume. The third step of the model added the interaction between genetic risk and brain volume. If significant interaction effects were observed, follow-up partial correlation analyses were conducted to determine the direction of the interaction effects using the same covariates. Additional follow-up analyses were conducted to determine which specific MTL regions were driving the interaction (left hippocampus, right hippocampus, left entorhinal cortex, right entorhinal cortex). If significant MTL regions were identified, diagnosis-stratified analyses were conducted to establish if the effects were more prominent in a particular diagnostic group (NC, MCI, AD).

RESULTS

Sample characteristics

Participant demographic and clinical characteristics as a function of diagnostic group are shown in Table 1. Individuals in the MCI group were significantly younger than the other two groups. Participants in the AD group had fewer years of education than individuals with NC. There were significant differences in episodic memory composite score, PHS, and adjusted AD ROI volume among the three groups.

Genetic risk for AD moderates the relationship between AD ROI volume and episodic memory

PHS moderated the relationship between AD ROI volume and memory, such that individuals with high PHS and lower AD ROI volume had lower episodic memory composite scores [ΔF (1,677) = 4.057, $p = 0.044$, $\Delta R^2 = 0.002$] (see Table 2 model 3 and Fig. 1A]. To parse the interaction effect, partial correlations were used to examine the relationship between AD ROI volume and episodic memory for low and high PHS (using a median split). Adjusting for all covariates, results revealed that among individuals with high genetic risk for AD, lower AD ROI volume was associated with lower episodic memory composite score (high: $pr = 0.398$, $p < 0.001$). The relationship between AD ROI volume and episodic memory was also present in the low genetic risk for AD group (low: $pr = 0.241$, $p < 0.001$). To determine whether there was a significant difference among the correlations for high and low genetic risk groups, the Fisher Z statistic was calculated using a two-

Table 2
Summary of regression analysis for association with MTL volume

	Model 1				Model 2				Model 3			
Variable	*B*	*SE(B)*	β	*p*	*B*	*SE(B)*	β	*p*	*B*	*SE(B)*	β	*p*
Education	0.037	0.009	0.110	<0.001	0.038	0.008	0.113	<0.001	0.038	0.008	0.113	<0.001
Age	–0.017	0.003	–0.135	<0.001	–0.007	0.003	–0.054	<0.043	–0.007	0.003	–0.055	0.039
Sex	–0.240	0.046	–0.133	<0.001	–0.304	0.044	–0.169	<0.001	–0.303	0.044	–0.168	<0.001
Diagnosis	–0.820	0.037	–0.601	<0.001	–0.648	0.039	–0.475	<0.001	–0.645	0.039	–0.473	<0.001
Aβ	0.000	0.000	0.197	<0.001	0.000	0.000	0.131	<0.001	–0.000	0.000	0.131	<0.001
PHS					–0.065	0.031	–0.057	<0.036	–0.404	0.171	–0.355	0.018
AD ROI					0.000	0.000	0.270	<0.001	0.000	0.000	0.248	<0.001
PHSxAD ROI									6.4706E-5	0.000	0.297	0.044
R^2	0.594				0.642				0.644			
Model F	199.3				173.5				153.0			

PHS, polygenic hazard score; AD ROI, AD single region of interest; MTL, medial temporal lobe; Aβ, amyloid-β.

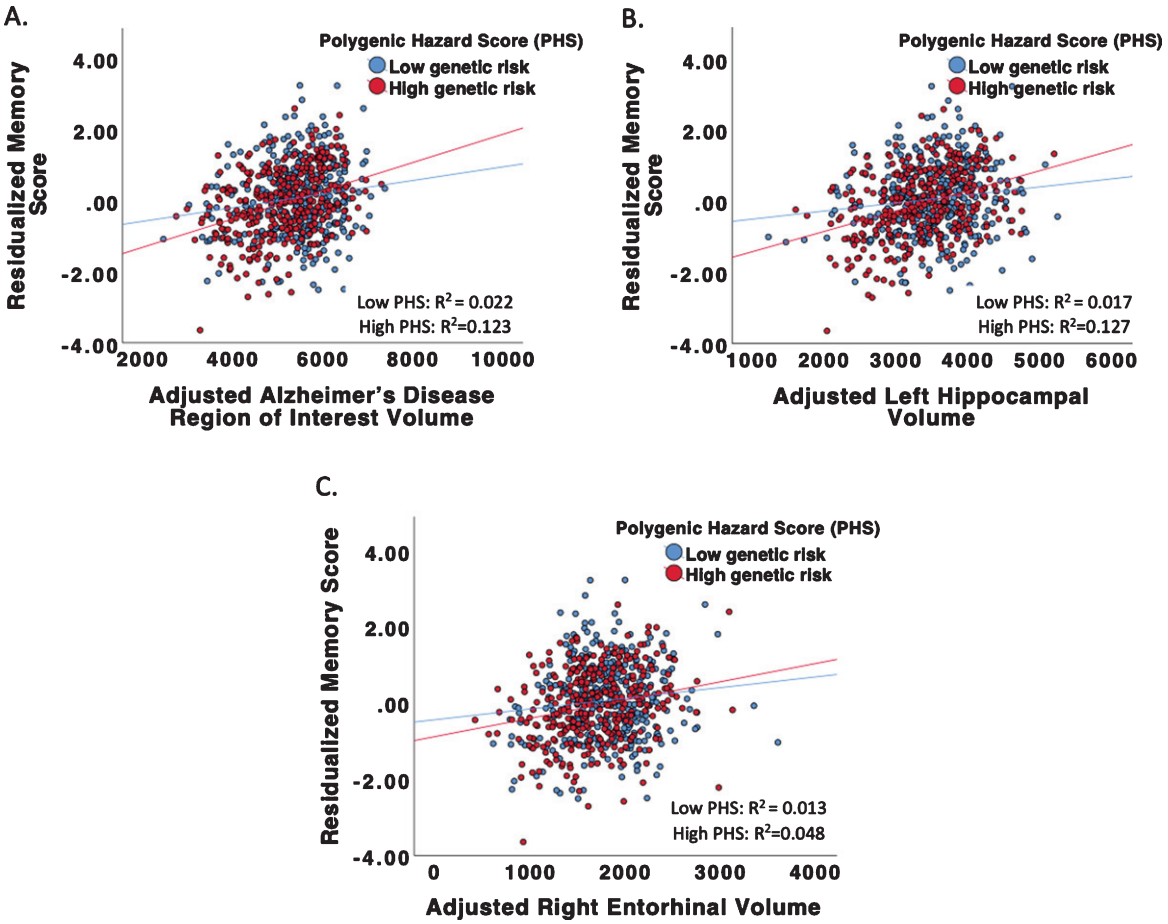

Fig. 1. A) The interaction of PHS and bilateral AD ROI volume. Among individuals with high genetic risk for AD, lower brain volume was associated with lower episodic memory composite scores. Values on the x-axis represent combined bilateral entorhinal cortex and hippocampal volume. B) The interaction of PHS and left hippocampal volume. Individuals with high genetic risk and low volume had lower episodic memory scores. C) The interaction of PHS and right entorhinal cortex volume. Individuals with high genetic risk for AD and smaller volume had lower scores on the episodic memory composite. All regional volumes were adjusted for intracranial volume. Values on the y-axis represent standardized residuals of episodic memory performance (accounting for sex, age, education, diagnosis, and Aβ). AD, Alzheimer's disease; ROI, regions-of-interest; PHS, polygenic hazard score; Aβ, amyloid-β.

tailed test. Results revealed a significant difference ($p = 0.022$), suggesting that the relationship between AD ROI volume and episodic memory was stronger among individuals with high genetic risk for AD compared to those with low genetic risk.

Further analyses were conducted to examine laterality (left, right hemisphere) and individual ROI (hippocampus, entorhinal cortex) effects. A significant interaction of the left hippocampus and genetic risk emerged, such that individuals with high genetic risk and low volume had the lowest episodic memory scores [$\Delta F(1,677) = 5.256$, $p = 0.022$, $\Delta R^2 = 0.003$] (Fig. 1B). Partial correlations revealed that among individuals with both high and low PHS, left hippocampal volume was associated with the memory composite score (high: $pr = 0.399$, $p < 0.001$; low: $pr = 0.209$, $p < 0.001$). To further clarify this relationship, the Fisher Z statistic was calculated using a two-tailed test. Results revealed a significant difference ($p = 0.0061$), indicating a stronger association between left hippocampal volume and episodic memory among individuals with high genetic risk for AD compared to those with low genetic risk. In the right hippocampus, there were no significant interactions. However, main effects of PHS ($p < 0.001$) and right hippocampal volume ($p < 0.001$) emerged, such that greater genetic risk and smaller volume were independently associated with worse episodic memory performance.

A significant interaction was observed between PHS and right entorhinal cortex volume [$\Delta F(1,677) = 6.078$, $p = 0.014$, $\Delta R^2 = 0.003$] (Fig. 1C). This was significant for participants with both low and high PHS (low: $pr = 0.173$, $p = 0.001$; high: $pr = .202$, $p < 0.001$). A Fisher Z statistic was calculated using a two-tailed test, and the results indicated no significant differences between individuals with high genetic risk for AD compared to those with low genetic risk for AD ($p = 0.697$). No significant interactions in the left entorhinal cortex were observed. However, there were main effects of PHS and left entorhinal cortex volume, such that higher genetic risk and low volume were each individually associated with lower memory scores (ps < 0.001).

Association between genetic risk for AD and brain volume in diagnosis-stratified sample

Diagnosis-stratified analyses were conducted for the regions with a significant PHS x ROI interaction on episodic memory (i.e., left hippocampus and right entorhinal cortex). There was a significant interaction between left hippocampal volume and PHS among individuals with MCI [$\Delta F(1,368) = 4.169$, $p = 0.042$, $\Delta R^2 = 0.008$] (Fig. 2). Within the MCI diagnostic category, this association was significant for participants with both low and high PHS (low: $pr = 0.256$, $p = 0.001$; high: $pr = 0.416$, $p < 0.001$). Using a two-tailed Fisher Z statistic, there was a nonsignificant trend for individuals with high genetic risk to have a stronger relationship between left hippocampal volume and episodic memory ($p = 0.0819$). No interactions were present in NC or AD individuals, but significant main effects of left hippocampal volume ($p < 0.001$) and PHS ($p = 0.005$) were observed in the AD group.

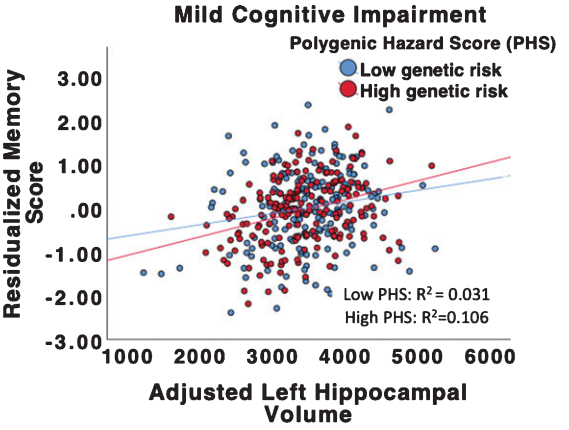

Fig. 2. The interaction of PHS and left hippocampal volume among individuals with MCI. Among individuals with MCI, high genetic risk for AD and lower brain volume was associated with lower episodic memory composite scores. Values on the x-axis represent left hippocampal volume adjusted for intracranial volume. Values on the y-axis represent standardized residuals of episodic memory performance (accounting for sex, age, education, and Aβ). PHS, polygenic hazard score; MCI, mild cognitive impairment; Aβ, amyloid-β.

A significant interaction emerged between right entorhinal cortex volume and PHS among individuals with AD [$\Delta F(1,99) = 4.967$, $p = 0.028$, $\Delta R^2 = 0.038$] (Fig. 3). This relationship was only significant for individuals with high PHS ($pr = 0.365$, $p < 0.001$). There were also main effects of right entorhinal cortex volume ($p < 0.001$) and PHS ($p = 0.001$) in the MCI group, such that lower volume and higher genetic risk were independently associated with lower episodic memory scores

DISCUSSION

The purpose of the current study was to examine neurobiological markers that influence cognitive

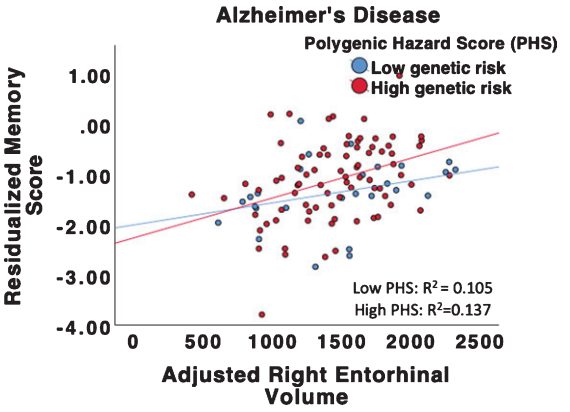

Fig. 3. The interaction of PHS and right entorhinal cortex volume among individuals with AD. Among individuals with AD, high genetic risk and lower brain volume was associated with lower episodic memory composite scores. Values on the x-axis represent left hippocampal volume adjusted for intracranial volume. Values on the y-axis represent standardized residuals of episodic memory performance (accounting for sex, age, education, and Aβ). AD, Alzheimer's disease; PHS, polygenic hazard score; Aβ, amyloid-β.

performance related to AD. In this study, we investigated the associations between regions of the medial temporal lobe, genetic risk for AD, and a previously validated episodic memory composite score. There were three main findings. First, among individuals with high genetic risk for AD, smaller medial temporal lobe volume was associated with lower episodic memory scores. Second, the moderating effect of genetic risk for AD was primarily observed in the left hippocampus and right entorhinal cortex. Finally, after conducting diagnosis-specific analyses within these regions, two different patterns of results emerged. The interaction between left hippocampal volume and genetic risk was observed in the MCI group whereas the association between right entorhinal cortex volume and genetic risk for AD was significant in the AD group. Together, these findings suggest that medial temporal lobe volume and polygenic risk for AD represent important markers of episodic memory performance, even when taking into account other important biological markers such as CSF Aβ levels.

The present study demonstrates the power of using a polygenic approach over a candidate gene approach to studying complex phenotypes. A previous study using the *APOE* gene as a measure of genetic risk in the ADNI sample failed to find an association between genetic risk, hippocampal volume, and cognitive performance across control, MCI, and AD participants [16]. The ε4 variant of *APOE* has been frequently studied because it is the strongest known contributor to AD [12, 27]. However, even potent candidate genes such as *APOE* account provide an incomplete picture of the variance associated with neurodegenerative disease [27]. Polygenic approaches, by contrast, aggregate weightings across multiple SNPs that account for more variance in diseases such as AD [28]. Successful polygenic approaches have been used in various conditions, including multiple sclerosis, rheumatoid arthritis, and schizophrenia. Recently, research investigating AD has used PHS to combine particular genetic variants that can provide a more comprehensive measure for AD risk [29]. Importantly, in line with this direction of research, the current study used a PHS calculation that was derived from genotyping over 70,000 individuals and aggregating 31 AD-associated SNPs and two *APOE* variants [25]. The improved predictive capabilities of PHS may have contributed to our finding of genetics moderating the relationship between the AD ROI and episodic memory.

Further analyses were conducted to examine the effects of individual ROIs (hippocampus, entorhinal cortex) and laterality (left, right hemisphere). In the hippocampus, the association between genetic risk for AD and brain volume on episodic memory performance was significant in the left hemisphere. This is consistent with previous research which has found that hippocampal volume is associated with memory recall performance in older adults with age-related cognitive decline, individuals with MCI, and those diagnosed with AD [30]. The left hippocampus appears to be more vulnerable to neurodegeneration than the right, although the mechanisms contributing to this effect are unknown [30, 31]. Another possible interpretation of this finding is that results may be driven through the use of a primarily verbal outcome variable. Previous research has noted that verbal episodic memory tests are more strongly associated with left hippocampal volume, whereas visuospatial memory tests are more strongly associated with right hippocampal volume [32].

Diagnostic-specific results revealed that hippocampal volume and genetic risk for AD were associated with lower episodic memory scores in both the MCI and AD groups. However, the interaction of these risk factors explained more variance in episodic memory only in the MCI group. It is possible that by the time individuals progress to AD, the combination of these two variables can no longer explain significantly more variance in episodic memory per-

formance because these individuals are further along a cognitive decline trajectory.

In addition to the hippocampal findings on episodic memory in the present study, genetic risk for AD also moderated the relationship between the right entorhinal cortex and episodic memory in the entire sample. Follow-up diagnostic-specific tests revealed that this finding was specific to the AD group. There is some consensus that the entorhinal cortex is uniquely indicative of neurodegeneration that does not occur in normal age-related decline [37]. Neuropathological staging of AD conducted at the time of autopsy suggests that stages 1 and 2 are comprised of accumulating neurofibrillary tangles specifically in the entorhinal cortex [33]. *In vivo* detection of tau via PET imaging has led to converging evidence that largely parallels previous autopsy findings [34]. As such, the current results which indicate that among individuals with MCI there are meaningful differences in the hippocampus, while entorhinal cortex differences were driven by the AD group are consistent with prior work. The current findings extend the literature of episodic memory by suggesting that moderating effects of genetics may be particularly meaningful in the hippocampus among individuals with MCI, but within the entorhinal cortex among those already diagnosed with AD.

Several limitations of the current study warrant comment. This study examined associations between anatomical regions of the MTL and genetic risk for AD; however, causal relationships cannot be drawn as the analyses conducted were cross-sectional. By only studying one time point, we are limited in understanding the temporal relationship between our variables of interest (genetic risk and brain volume). Additionally, only White, non-Hispanic individuals were included, minimizing the generalizability of findings. As more diverse individuals are included in genetic datasets, polygenic hazard score should be validated for individuals from different ethnic backgrounds, allowing similar analyses to be done on a larger and more diverse population.

Summary

The goal of the current study was to examine associations between genetic risk for AD and brain volume to aid our understanding of cognitive functioning in healthy and pathological aging. We used a polygenic risk score for AD in combination with volume measurements in two regions of the MTL and found that among older adults, genetic risk for AD and MTL volume appear to have synergistic effects on episodic memory. Furthermore, results in the hippocampus were particularly driven by individuals with MCI, whereas results in the entorhinal cortex were driven by individuals with AD. These findings highlight the importance of incorporating multiple modalities to understand risk for cognitive decline in aging to better inform prevention and treatment approaches for AD. In addition, these findings suggest that genetic risk and brain volume should be included as key variables in models tracking progression of cognitive decline.

ACKNOWLEDGMENTS

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 supported by the National Institute on Aging (NIA) of the National Institutes of Health (NIH) R01AG058822 (awarded to JPH), R21AG056921 (awarded to SMH), and The Ohio State University Discovery Themes Chronic Brain Injury Initiative (SMH and JPH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-1312r1).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-191312.

REFERENCES

[1] Alzheimer's Association (2019) 2019 Alzheimer's disease facts and figures. *Alzheimers Dement* **15**, 321-387.

[2] Mayeux R, Stern Y (2012) Epidemiology of Alzheimer disease. *Cold Spring Harb Perspect Med* **2**, a006239.

[3] Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ (2013) Update on hypothetical model of Alzheimer's disease biomarkers. *Lancet Neurol* **12**, 207-216.

[4] Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, Szoeke C, Macaulay SL, Martins R, Maruff P, Ames D, Rowe CC, Masters CL (2013) Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. *Lancet Neurol* **12**, 357-367.

[5] Braak H, Braak E (1995) Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging* **16**, 271-278; discussion 278-284.

[6] Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* **9**, 119-128.

[7] Xie L, Wisse LEM, Pluta J, Flores R de, Piskin V, Manjón JV, Wang H, Das SR, Ding S-L, Wolk DA, Yushkevich PA (2019) Automated segmentation of medial temporal lobe subregions on *in vivo* T1-weighted MRI in early stages of Alzheimer's disease. *Hum Brain Mapp* **40**, 3431-3451.

[8] Jack CR, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, Tangalos EG, Kokmen E (1998) Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. *Neurology* **51**, 993-999.

[9] Raslau FD, Mark IT, Klein AP, Ulmer JL, Mathews V, Mark LP (2015) Memory Part 2: The role of the medial temporal lobe. *Am J Neuroradiol* **36**, 846-849.

[10] Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S, Fiske A, Pedersen NL (2006) Role of genes and environments for explaining Alzheimer disease. *Arch Gen Psychiatry* **63**, 168-174.

[11] Bettens K, Sleegers K, Van Broeckhoven C (2013) Genetic insights in Alzheimer's disease. *Lancet Neurol* **12**, 92-104.

[12] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**, 921-923.

[13] Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD (1993) Apolipoprotein E: High-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A* **90**, 1977-1981.

[14] Lewis CM, Vassos E (2017) Prospects for using risk scores in polygenic medicine. *Genome Med* **9**, 96.

[15] Ridge PG, Mukherjee S, Crane PK, Kauwe JSK, Alzheimer's Disease Genetics Consortium (2013) Alzheimer's disease: Analyzing the missing heritability. *PLoS One* **8**, e79771.

[16] Wang X, Zhou W, Ye T, Lin X, Zhang J (2019) The relationship between hippocampal volumes and delayed recall is modified by APOE ε4 in mild cognitive impairment. *Front Aging Neurosci* **11**, 36.

[17] Tulving E (1972) Episodic and semantic memory. In *Organization of memory*, Academic Press, Oxford, England, pp. xiii, 423–xiii, 423.

[18] Tulving E (1985) Memory and consciousness. *Can Psychol Can* **26**, 1-12.

[19] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 270-279.

[20] Gold CA, Budson AE (2008) Memory loss in Alzheimer's disease: Implications for development of therapeutics. *Expert Rev Neurother* **8**, 1879-1891.

[21] Crane PK, Carle A, Gibbons LE, Insel P, Mackin RS, Gross A, Jones RN, Mukherjee S, Curtis SM, Harvey D, Weiner M, Mungas D (2012) Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Brain Imaging Behav* **6**, 502-516.

[22] Morris JC (1993) The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology* **43**, 2412-2414.

[23] Elwood RW (1991) The Wechsler Memory Scale—Revised: Psychometric characteristics and clinical application. *Neuropsychol Rev* **2**, 179-201.

[24] Buckner RL, Head D, Parker J, Fotenos AF, Marcus D, Morris JC, Snyder AZ (2004) A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: Reliability and validation against manual measurement of total intracranial volume. *Neuroimage* **23**, 724-738.

[25] Desikan RS, Fan CC, Wang Y, Schork AJ, Cabral HJ, Cupples LA, Thompson WK, Besser L, Kukull WA, Holland D, Chen C-H, Brewer JB, Karow DS, Kauppi K, Witoelar A, Karch CM, Bonham LW, Yokoyama JS, Rosen HJ, Miller BL, Dillon WP, Wilson DM, Hess CP, Pericak-Vance M, Haines JL, Farrer LA, Mayeux R, Hardy J, Goate AM, Hyman BT, Schellenberg GD, McEvoy LK, Andreassen OA, Dale AM (2017) Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score. *PLoS Med* **14**, e1002258.

[26] Lambert J-C, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, Jun G, DeStefano AL, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thornton-Wells TA, Jones N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin C-F, Gerrish A, Schmidt H, Kunkle B, Dunstan ML, Ruiz A, Bihoreau M-T, Choi S-H, Reitz C, Pasquier F, Hollingworth P, Ramirez A, Hanon O, Fitzpatrick AL, Buxbaum JD, Campion D, Crane PK, Baldwin C, Becker T, Gudnason V, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S, Letenneur L, Morón FJ, Rubinsztein DC, Eiriksdottir G, Sleegers K, Goate AM, Fiévet N, Huentelman MJ, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuinness B, Larson EB, Green R, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, St George-Hyslop P, Clarimon J, Lleo A, Bayer A, Tsuang DW, Yu L, Tsolaki M, Bossù P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Sanchez-Garcia F, Fox NC, Hardy J, Deniz Naranjo MC, Bosco P, Clarke R, Brayne C, Galimberti D, Mancuso M, Matthews F, Moebus S, Mecocci P, Zompo MD, Maier W, Hampel H, Pilotto A, Bullido M, Panza F, Caffarra P, Nacmias B, Gilbert JR, Mayhaus M, Lannfelt L, Hakonarson H, Pichler S, Carrasquillo MM, Ingelsson M, Beekly D, Alvarez V, Zou F, Valladares O, Younkin SG, Coto E, Hamilton-Nelson KL, Gu W, Razquin C, Pastor P, Mateo I, Owen MJ, Faber KM, Jonsson PV, Combarros O, O'Donovan MC, Cantwell LB, Soininen H, Blacker D, Mead S, Mosley TH, Bennett DA, Harris TB, Fratiglioni L, Holmes C, de Bruijn RFAG, Passmore P, Montine TJ, Bettens K, Rotter JI, Brice A, Morgan K, Foroud TM, Kukull WA, Hannequin D, Powell JF, Nalls MA, Ritchie K, Lunetta KL, Kauwe JSK, Boerwinkle E, Riemenschneider M, Boada M, Hiltunen M, Martin ER, Schmidt R, Rujescu D, Wang L, Dartigues J-F, Mayeux R, Tzourio C, Hofman A, Nöthen MM, Graff C, Psaty BM, Jones L, Haines JL, Holmans PA, Lathrop M, Pericak-Vance MA, Launer LJ, Farrer LA, van Duijn CM, Van Broeckhoven C, Moskvina V, Seshadri S, Williams J, Schellenberg GD, Amouyel P (2013) Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet* **45**, 1452-1458.

[27] Harrison TM, Bookheimer SY (2016) Neuroimaging genetic risk for Alzheimer's disease in preclinical individuals: From candidate genes to polygenic approaches. *Biol Psychiatry Cogn Neurosci Neuroimaging* **1**, 14-23.

[28] Dudbridge F (2013) Power and predictive accuracy of polygenic risk scores. *PLoS Genet* **9**, e1003348.

[29] Raghavan N, Tosto G (2017) Genetics of Alzheimer's disease: The importance of polygenic and epistatic components. *Curr Neurol Neurosci Rep* **17**, 78.

[30] Maruszak A, Thuret S (2014) Why looking at the whole hippocampus is not enough—a critical role for anteroposterior axis, subfield and activation analyses to enhance predictive value of hippocampal changes for Alzheimer's disease diagnosis. *Front Cell Neurosci* **8**, 95.

[31] Moon SW, Lee B, Choi YC (2018) Changes in the hippocampal volume and shape in early-onset mild cognitive impairment. *Psychiatry Investig* **15**, 531-537.

[32] Steffens DC, Payne ME, Greenberg DL, Byrum CE, Welsh-Bohmer KA, Wagner HR, MacFall JR (2002) Hippocampal volume and incident dementia in geriatric depression. *Am J Geriatr Psychiatry* **10**, 62–71.

[33] Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol (Berl)* **82**, 239–259.

[34] Schöll M, Maass A, Mattsson N, Ashton NJ, Blennow K, Zetterberg H, Jagust W (2019) Biomarkers for tau pathology. *Mol Cell Neurosci* **97**, 18–33.

[35] Ridha BH, Barnes J, Bartlett JW, Godbolt A, Pepple T, Rossor MN, Fox NC (2006) Tracking atrophy progression in familial Alzheimer's disease: A serial MRI study. *Lancet Neurol* **5**, 828-834.

[36] Kaup AR, Mirzakhanian H, Jeste DV, Eyler LT (2011) A review of the brain structure correlates of successful cognitive aging. *J Neuropsychiatry Clin Neurosci* **23**, 6-15.

[37] Gallagher M, Koh MT (2011) Episodic memory on the path to Alzheimer's disease. *Curr Opin Neurobiol* **21**, 929-934.