Sex differences in the genetic architecture of cognitive resilience to Alzheimer's disease

Jaclyn M. Eissman,[1,2] Logan Dumitrescu,[1,2] Emily R. Mahoney,[1,2] Alexandra N. Smith,[1,2] Shubhabrata Mukherjee,[3] Michael L. Lee,[3] Phoebe Scollard,[3] Seo-Eun Choi,[3] William S. Bush,[4] Corinne D. Engelman,[5] Qiongshi Lu,[6,7] David W. Fardo,[8,9] Emily H. Trittschuh,[10,11] Jesse Mez,[12] Catherine C. Kaczorowski,[13] Hector Hernandez Saucedo,[14] Keith F. Widaman,[15] Rachel F. Buckley,[16,17,18] Michael J. Properzi,[16] Elizabeth C. Mormino,[19] Hyun-Sik Yang,[16,17] Theresa M. Harrison,[20] Trey Hedden,[21] Kwangsik Nho,[22,23] Shea J. Andrews,[21] Douglas Tommet,[24] Niran Hadad,[13] R. Elizabeth Sanders,[3] Douglas M. Ruderfer,[2] Katherine A. Gifford,[1] Xiaoyuan Zhong,[6,7] Neha S. Raghavan,[25,26,27] Badri N. Vardarajan,[25,26,27] Alzheimer's Disease Neuroimaging Initiative (ADNI), Alzheimer's Disease Genetics Consortium (ADGC), A4 Study Team, Margaret A. Pericak-Vance,[28] Lindsay A. Farrer,[12,29,30] Li-San Wang,[31] Carlos Cruchaga,[32] Gerard D. Schellenberg,[31] Nancy J. Cox,[2] Jonathan L. Haines,[4] C. Dirk Keene,[33] Andrew J. Saykin,[34] Eric B. Larson,[3,35] Reisa A. Sperling,[16] Richard Mayeux,[25,26,27] Michael L. Cuccaro,[28] David A. Bennett,[36] Julie A. Schneider,[36] Paul K. Crane,[3] Angela L. Jefferson[1] and Timothy J. Hohman[1,2]

1 Vanderbilt Memory and Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN, USA.

2 Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA.

3 Department of Medicine, University of Washington, Seattle, WA, USA.

4 Cleveland Institute for Computational Biology, Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH, USA.

5 Department of Population Health Sciences, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA.

6 Department of Statistics, University of Wisconsin-Madison, Madison, WI, USA.

7 Department of Biostatistics and Medical Informatics, University of Wisconsin-Madison, Madison, WI, USA.

8 Department of Biostatistics, College of Public Health, University of Kentucky, Lexington, KY, USA.

9 Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA.
10 Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA, USA.
11 VA Puget Sound Health Care System, GRECC, Seattle, WA, USA.
12 Department of Neurology, Boston University School of Medicine, Boston, MA, USA.
13 The Jackson Laboratory, Bar Harbor, ME, USA.
14 UC Davis Alzheimer's Disease Research Center, Department of Neurology, University of California Davis Medical Center, Sacramento, CA, USA.
15 University of California at Riverside, Riverside, CA, USA.
16 Department of Neurology, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA.
17 Center for Alzheimer's Research and Treatment, Department of Neurology, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA.
18 Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Australia.
19 Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA.
20 Helen Wills Neuroscience Institute, University of California Berkeley, Berkeley, CA, USA.
21 Icahn School of Medicine at Mount Sinai, New York City, NY, USA.
22 Department of Radiology and Imaging Sciences, Indiana Alzheimer Disease Center, Indiana University School of Medicine, Indianapolis, IN, USA.
23 Center for Computational Biology and Bioinformatics, Indiana University School of Medicine, Indianapolis, IN, USA.
24 Department of Psychiatry and Human Behavior, Brown University School of Medicine, Providence, RI, USA.
25 Department of Neurology, Columbia University, New York, NY, USA.
26 The Taub Institute for Research on Alzheimer's Disease and The Aging Brain, Columbia University, New York, NY, USA.
27 The Institute for Genomic Medicine, Columbia University Medical Center and The New York Presbyterian Hospital, New York, NY, USA.
28 John P. Hussman Institute for Human Genomics, University of Miami School of Medicine, Miami, FL, USA.

29 Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA.
30 Department of Medicine (Biomedical Genetics), Boston University School of Medicine, Boston, MA, USA.
31 Penn Neurodegeneration Genomics Center, Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA.
32 Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA.
33 Department of Pathology, University of Washington, Seattle, WA, USA.
34 Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, USA.
35 Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA.
36 Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA.

Correspondence to: Timothy J. Hohman, PhD
Vanderbilt Memory & Alzheimer's Center
Vanderbilt University Medical Center
1207 17th Ave S
Nashville, TN 37212, USA
E-mail: Timothy.J.Hohman@vumc.org

Running title: Sex-specific genetics of resilience

Abstract

Approximately 30% of elderly adults are cognitively unimpaired at time of death despite presence of Alzheimer's disease (AD) neuropathology at autopsy. Studying individuals who are resilient to the cognitive consequences of AD neuropathology may uncover novel therapeutic targets to treat AD. It is well-established that there are sex differences in response to AD pathology, and growing evidence suggests that genetic factors may contribute to these differences. Taken together, we sought to elucidate sex-specific genetic drivers of resilience.

We extended our recent large-scale genomic analysis of resilience in which we harmonized cognitive data across four cohorts of cognitive aging, *in-vivo* amyloid PET across two cohorts, and autopsy measures of amyloid neuritic plaque burden across two cohorts. These data were leveraged to build robust, continuous resilience phenotypes. With these phenotypes, we performed sex-stratified (N*(males)*=2,093, N*(females)*=2,931) and sex-interaction (N*(both sexes)*=5,024) genome-wide association studies (GWAS), gene- and pathway-based tests, and genetic correlation analyses to clarify the variants, genes, and molecular pathways that relate to resilience in a sex-specific manner.

Estimated among cognitively normal individuals of both sexes, resilience was 20-25% heritable, and when estimated in either sex among cognitively normal individuals, resilience was 15-44% heritable. In our GWAS, we identified a female-specific locus on chromosome 10 (rs827389, *β(females)=0.08*, *P(females)=5.76E-09*, *β(males)=-0.01*, *P(males)=0.70*, *β(interaction)=0.09*, *P(interaction)=1.01E-04*) in which the minor allele was associated with higher resilience scores among females. This locus is located within chromatin loops that interact with promoters of genes involved in RNA processing, including *GATA3*. Finally, our genetic correlation analyses revealed shared genetic architecture between resilience phenotypes and other complex traits, including a female-specific association with frontotemporal dementia and male-specific associations with heart rate variability traits. We also observed opposing associations between sexes for multiple sclerosis, such that more resilient females had a lower genetic susceptibility to multiple sclerosis, and more resilient males had a higher genetic susceptibility to multiple sclerosis.

Overall, we identified sex differences in the genetic architecture of resilience, identified a female-specific resilience locus, and highlighted numerous sex-specific molecular pathways that may underly resilience to AD pathology. This study illustrates the need to

conduct sex-aware genomic analyses to identify novel targets that are unidentified in sex-agnostic models. Our findings support the theory that the most successful treatment for an individual with AD may be personalized based on their biological sex and genetic context.

Keywords: Alzheimer's disease; sex differences; resilience; genetics; GWAS

Abbreviations: ACT=Adult Changes in Thought study; AD=Alzheimer's disease; ADGC=Alzheimer's Disease Genetics Consortium; ADNI=The Alzheimer's Disease Neuroimaging Initiative; APOE=apolipoprotein E; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; eQTL=expression quantitative trait locus; FDR=false discovery rate; FTD=frontotemporal dementia; FUMA=Functional Mapping and Annotation; GMM=Gaussian Mixture Modeling; GCTA=Genome-wide Complex Trait Analysis; GNOVA=GeNetic cOVariance Analyzer; GWAS=genome-wide association study; HWE=Hardy-Weinberg Equilibrium; Hi-C=chromosome conformation capture with high throughput sequencing; HRV=heart rate variability; LD=linkage disequilibrium; MAF=minor allele frequency; MAGMA=Multi-marker Analysis of GenoMic Annotation; PACC=Preclinical Alzheimer Cognitive Composite; ROS/MAP=Religious Orders Study/Rush Memory and Aging Project; SNP=single nucleotide polymorphism; SUVR=standardized uptake value ratio

Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder leading to cognitive impairment. AD is marked by two primary neuropathologies: amyloid plaques and neurofibrillary tangles. However, approximately 30% of elderly adults are cognitively resilient to the downstream consequences of AD pathology, as they meet neuropathological criteria for AD at autopsy, yet remain cognitively unimpaired throughout life.[1] Studying resilient individuals may uncover quintessential information about AD progression and enable the discovery of novel therapeutic targets. In a recent study from our group, we conducted the largest genome-wide meta-analysis on cognitive resilience to date and demonstrated a unique genetic architecture of cognitive resilience that is distinct from that of AD.[2]

Our original analysis did not investigate whether certain variants, genes, or molecular pathways relate to cognitive resilience in a sex-specific manner. An emerging body of evidence suggests there are sex differences in response to AD neuropathology. There are notable sex differences in both AD neuropathology burden and the association between neuropathology burden and longitudinal cognitive decline. Specifically, a one unit increment in AD neuropathology at autopsy is associated with a 22-fold higher odds for clinical AD during life in females, but only a 3-fold higher odds in males.[3,4] Similar sex differences are also observed in biomarker studies of AD, such that females with more pronounced AD neuropathology biomarkers show faster cognitive decline and faster hippocampal atrophy than males with comparable levels of AD biomarkers.[5,6] Additionally, amyloid positive females show both a faster rate of CSF tau[7] and more pronounced tau accumulation in the medial temporal lobe as measured with tau PET[6] compared to amyloid positive males. Taken together, there is strong evidence that the occurrence and downstream consequences of AD neuropathology differ by biological sex.

In addition to the notable sex differences in AD biomarkers, there is similar evidence that sex-specific genetic factors contribute to sex differences in response to AD pathology. The most robust genetic risk factor of late-onset AD, the apolipoprotein E epsilon 4 (*APOE* ε4) allele, has a stronger association with clinical AD among females compared to males, particularly between the ages of 55 and 70.[8,9] Amyloid positive females with the *APOE* ε4 allele have a faster rate of cognitive decline[10,11] and show higher tau burden compared to male counterparts.[12] Beyond *APOE*, work from our group has demonstrated sex-specific

genome-wide associations with CSF amyloid and tau levels,[13] and autopsy measures of neurofibrillary tangles,[14] including a male-specific locus (e.g., *TSPAN13*) that was recently replicated in the UK Biobank dataset.[15] Together, these findings highlight the importance of including sex-stratification in genomic models to better understand the genetic architecture of AD.

To this end, we took a precision medicine approach to elucidate sex differences in the genetic architecture of cognitive resilience to AD pathology. We harmonized cognitive data across four cohorts of cognitive aging, leveraged a published model of cognitive resilience that implements latent variable modeling,[2,16] and performed a series of sex-aware genetic analyses. We hypothesized that genetic drivers of cognitive resilience differ between males and females downstream of amyloidosis. By identifying sex-specific variants, candidate genes, and molecular pathways driving cognitive resilience to AD pathology, the results of this study will contribute to our understanding of AD progression in each biological sex and to the identification of novel therapeutic targets to treat AD.

Materials and methods

Participants

Our study included four cohorts of cognitive aging (N*(both sexes)*=5,024, N*(males)*=2,093, N*(females)*=2,931): Adult Changes in Thought (ACT), Religious Orders Study and Rush Memory and Aging Project (ROS/MAP), The Alzheimer's Disease Neuroimaging Initiative (ADNI), and Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4). The A4 study began in 2014 as part of a clinical trial and recruited cognitively unimpaired individuals.[17] ADNI launched in 2003 and is comprised of four phases of which ADNI1, ADNI2, and ADNI-GO were included in this study. There are now over 1,800 individuals ages 55-90 who have participated in ADNI and are comprised of a mix of individuals who are cognitively unimpaired and individuals that have mild cognitive impairment, or AD dementia (http://adni.loni.usc.edu/). ACT began in 1994, recruiting cognitively unimpaired individuals from the Seattle area.[18] ROS began in 1994 and recruited Catholic nuns, priests, and brothers living in orders. MAP launched in 1997 and recruited cognitively unimpaired individuals from the Chicago area.[19] Written informed consent was obtained from all participants, and research was carried out in accordance with Institutional

Review Board-approved protocols. Secondary analyses of all data were approved by the Vanderbilt University Medical Center Institutional Review Board.

Amyloid-PET Acquisition

We leveraged *in-vivo* amyloid PET data for two cohorts, ADNI and A4. ADNI's methods and protocols for their *in-vivo* amyloid PET imaging can be found on their website, http://adni.loni.usc.edu/. ADNI and A4 used a combination of GE, Philips, and Siemens technologies. Scans were conducted 50-70 minutes after tracer injection, and acquired frames were five minutes in length. Both cohorts utilized the ^{18}F-florbetapir tracer, and a portion of ADNI's study utilized the ^{11}C-Pittsburgh Compound B (PiB) tracer instead. For each brain region, standardized uptake value ratios (SUVR) were calculated and scaled using the cerebellum as the reference brain region. For each participant, a SUVR composite score was calculated, comprised of cortical brain regions. For more extensive details regarding amyloid PET acquisition, see our recent paper.[2]

Amyloid-PET Harmonization

As referenced in the above section, raw SUVR composite scores (comprised of cortical brain regions) were obtained from ADNI and A4. To normalize SUVR scores across cohorts and tracers, we performed Gaussian Mixture Modeling (GMM) within each cohort leveraging a previously published algorithm.[20] Since ADNI scores were a mix of PiB and florbetapir, we performed separate GMM for each tracer within ADNI. Models were estimated among those that were cognitively normal and then were subsequently applied to all participants. Each GMM leveraged a two-component model fit, as this best fit the bimodal property of the amyloid distribution. The mean and the standard deviation of the amyloid negative distribution from each GMM was applied to standardize SUVR composites across all participants. The resulting harmonized SUVR composite scores were on a z-score scale, representative of individual amyloid burden. Our group recently published a paper testing different methods of amyloid PET harmonization, and more details can be found in *Raghavan et al., 2020 JAMA Neurol*. Overall, we concluded that there are only minor differences between harmonization methods, and the minor differences have less import with amyloid as a linear predictor in our models.[2,21]

Post-Mortem Assessment of Neuropathology

Post-mortem assessments were conducted for participants in the ACT and ROS/MAP cohorts. A well-established measure of amyloid plaque burden, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuritic plaque staging scores, were determined for each participant using standard protocols.[17,18,21] CERAD scores were standardized between ACT and ROS/MAP, such that higher CERAD scores were representative of higher individual amyloid burden in both cohorts. For more extensive details regarding post-mortem assessment of neuropathology, see our recent paper.[2]

Cognitive Harmonization

Cognitive data were harmonized across all cohorts using published, modern psychometric techniques.[23] Briefly, qualified neuropsychologists/behavioral neurologists categorized test items into memory or executive function domains (or neither). Overlapping test items across cohorts were set as anchor items. Test items were indicators in a confirmatory factor analysis, with the scaled anchor items allowing non-overlapping test items to be freely estimated. Memory was successfully harmonized across all four cohorts, as well as executive function across ACT, ROS/MAP, and ADNI. A4 did not have sufficient anchor items for executive function harmonization, so a previously published composite, the Preclinical Alzheimer Cognitive Composite (PACC) was leveraged as an additional score across ADNI and A4. A 4-item version was calculated in each, including logical memory, mini-mental state exam along with selective reminding test and digit symbol in A4 and ADAS-cog and trail making test B in ADNI. As detailed in the supplement of our first publication with this phenotype, the PACC behaves quite comparably in both ADNI and A4 (see Supplement in Dumitrescu et al. 2020, *Brain*). The harmonized memory, executive function, and PACC composite scores were extracted and leveraged in building resilience phenotypes (see next section). For more extensive details regarding cognitive harmonization, see our recent paper.[2]

Latent Variable Modeling

Cognitive resilience models were created using previously published protocols.[2,16] Linear models were built in the combined autopsy dataset (ACT and ROS/MAP) and in the combined PET dataset (ADNI and A4). Memory and executive function harmonized scores were used as outcomes in the autopsy datasets covarying for age, sex, and CERAD staging

scores. In the PET datasets, memory and PACC harmonized scores were used as outcomes, as well as harmonized executive function in ADNI, covarying for age, sex, and harmonized amyloid PET SUVR. See **Figure 1A** for an example of harmonized memory scores by harmonized amyloid PET scores, by sex.

Standardized residuals from all linear models were extracted and entered as indicators into latent variable models in Mplus (version 7.31).[24] Two resilience models were built: residual cognitive resilience, with the standardized residuals as indicators, and a second-order latent variable, combined resilience, which included residual cognitive resilience and educational attainment as indicators (**Figure 1B**). Inclusion criteria for the models required participants to have cognitive scores for at least two of the cognitive domains. Models were run in all individuals as well as in cognitively normal individuals only. Factor scores were extracted from all models. For average resilience scores by sex, see **Table 1**, and for more extensive details regarding latent variable modeling, see our recent paper.[2]

Genotyping, Quality Control, and Imputation

Participants included in this study were genotyped using DNA extracted from either brain or whole blood. Each cohort used the following genotype chips: A4 implemented the Illumina Global Screening Array and ACT implemented the Illumina Human660W-Quad Array. ADNI implemented three chips: Human610-Quad, HumanOmniExpress, and Omni 2.5M. Finally, ROS/MAP implemented three chips: Affymetrix Genechip 6.0, Illumina Human1M, and Illumina Global Screening Array.

All genetic data were processed with a standardized quality control and imputation pipeline. Raw genetic data were filtered to remove variants with >5% sample missingness and minor allele frequency (MAF) <1%. Then genetic data were filtered to remove individuals with >1% sample missingness, related individuals, and individuals with mismatched sex. Additionally, X-chromosome genetic data were compared between sexes, and variants with differential missingness (P<1E-07) were removed. Individuals who were non-Hispanic white were retained for analysis. Those who self-reported as non-Hispanic white but were deemed to be genetic ancestry outliers in a principal component analysis (including the 1000 genomes reference dataset) were subsequently removed (based on a standard deviation +/- five cut-point or by visual inspection).

Prior to imputation, variants were lifted over to genome build 38 (hg38). Then a Hardy-Weinberg equilibrium (HWE) exact test (P<1E-06) was performed in the whole sample for autosomal variants and a HWE exact test (P<1E-06) was performed in the female sample only for X-chromosome variants and the male sample was filtered accordingly. All variants were filtered to remove palindromic variants, same position variants, and variants with alleles mismatching with the reference panel. Genetic data were then imputed on the Trans-Omics for Precision Medicine (TOPMed) program server.[25–27] Post-imputation, genetic data were filtered to remove variants with an imputed R^2<0.8 and duplicated/multi-allelic variants were dropped. All genotyped variants were then dropped from the imputed data and the original genotypes were merged back in with the rest of the imputed data, and then variants with a MAF <1% were dropped. Finally, a HWE exact test (P<1E-06) was performed on the imputed data in the whole sample for autosomal variants and in the female sample only for X-chromosome variants and the male sample was filtered accordingly.

Genetic data requiring multiple datasets to be merged (ADNI, ACT, and ROS/MAP) were then checked for overlapping samples across genotype chips. If sample overlap was present, the sample was dropped from the chip with the lower coverage. Cleaned, imputed, genetic data from each chip were compared and subsequently filtered to remove variants with mis-matching reference alleles and MAF differences of >10% and then the genetic datasets across chips were merged. The merged datasets were filtered for cryptic relatedness. Genetic ancestry was assessed in the merged dataset using a principal component analysis. Individuals who self-reported as non-Hispanic white but were deemed to be genetic ancestry outliers (based on a standard deviation +/- five cut-point or by visual inspection) were subsequently removed.

Statistical Analysis

Prior to performing genome-wide association studies (GWAS), cryptic relatedness across all four genetic datasets was assessed, removing 38 related individuals in total. In addition, for the combined ACT and ROS/MAP dataset and for the combined ADNI and A4 dataset, variants were filtered for reference allele mismatches and MAF differences >10%. Then ACT and ROS/MAP were merged to result in a combined autopsy dataset. Likewise, ADNI and A4 were merged to result in a combined PET dataset. Combined genetic datasets were subsequently used for all genetic analyses to facilitate joint analysis.

GWAS and genome-wide meta-analyses

GWAS were performed with PLINK linear association models (v1.90b5.2, https://www.cog-genomics.org/plink/1.9).[28] All GWAS were run in the combined autopsy dataset and in the combined PET dataset for all resilience phenotypes. Sex-stratified GWAS covaried for age and the first three genetic principal components. The sex-interaction GWAS also covaried for sex and included a SNP*sex interaction term. GWAS results were then meta-analyzed across cohorts using a fixed-effects model with beta and standard error input (GWAMA v2.2.2).[29] The above models were also run identically in the sample restricted to cognitively normal individuals, with the fixed effects meta-analyses implementing the minor allele frequencies calculated based on these individuals only. Additionally, an identical GWAS and meta-analysis pipeline as described above was implemented with the X-chromosome genetic data. All meta-analysis results were restricted to SNPs present in both the autopsy and the PET dataset, and these filtered results were leveraged for all post-GWAS steps discussed below.

SNP-heritability analysis

To determine the heritability of each resilience phenotype estimated in each sex and if estimates significantly differed between sexes, we performed a sex-aware heritability analysis that was outlined by Martin and colleagues.[30,31] We first leveraged the Genome-Wide Complex Trait Analysis (GCTA) software tool to calculate genetic relatedness matrices in all individuals, in males only, and in females only. Then we implemented the GCTA restricted maximum likelihood statistical method with the genetic relatedness matrices to calculate SNP-based heritability estimates in all individuals, in males only, and in females only.[32] Next, we performed a test to determine if the heritability estimates for each resilience phenotype significantly differed between sexes. To perform this test, we calculated z-scores with the following formula: $z\text{-score} = (h^2_{females} - h^2_{males}) / \sqrt{(h^2_{females}(SE)^2 + h^2_{males}(SE)^2)}$. Then, we obtained p-values for each z-score from the normal distribution based on a one-tailed test.

Variant annotation

Functional annotation was performed with Functional Mapping and Annotation (FUMA, v1.3.6a)[33] on genome-wide significant loci from the meta-analyses. All variants in linkage disequilibrium (LD) with top variants were also considered in annotation. In brief, FUMA performs three types of mapping: expression quantitative trait locus (eQTL), Hi-C 3D

chromatin interaction, and positional. Specifically, FUMA compiles chromosome conformation capture with high throughput sequencing (Hi-C) data from multiple databases. Hi-C is an assay that looks for enrichment of DNA sequences associated with chromatin loops at different locations in the genome. FUMA also looks to see if these enriched regions overlap with gene promotor or enhancer sequences. All types of mapping are performed in a tissue- and a cell-type specific manner.[34]

AD risk loci analysis

We compiled AD-risk variants from three well-known, published AD genome-wide meta-analyses.[35–37] Leveraging our meta-analysis results, we looked at each risk variant's association with residual cognitive resilience and with combined resilience in males, in females, and in the sex-interaction models.

Gene- and pathway- based tests

Gene- and pathway-level tests were performed with Multi-marker Analysis of GenoMic Annotation (MAGMA v1.09 – the version of MAGMA with the known p-value inflation bug fixed)[38] on all meta-analysis results. First, permutation-like gene tests were performed to determine if a higher number of significant variant-level p-values existed in a pre-defined gene window than expected by chance. This process was conducted across the entire genome. All gene-level results were then entered into permutation-like pathway tests to determine if there were more significant gene test p-values associated with known biological pathways than expected by chance. We leveraged two sets of curated pathway annotations from the Molecular Signatures Database (MSigDB) v.7.0 (downloaded on February 5, 2020), the curated gene set (C2) and the ontology gene set (C5).[39] In total, we tested 18,243 genes and 12,173 biological pathways. All gene and pathway tests were adjusted for multiple comparisons using the false discovery rate (FDR) procedure, and an *a priori* significance threshold was set at P.FDR<0.05.

Genetic correlation analyses

Genetic correlation tests were performed between our resilience meta-analysis summary statistics and GWAS summary statistics of 65 complex traits using the Genetic Covariance Analyzer (GNOVA).[40] To calculate genetic covariances with GNOVA, z-scores were quantified from each variant-level association in each set of GWAS summary statistics.

Linkage disequilibrium (LD) scores were also quantified from an ancestry-matched reference panel (e.g., 1000 genomes European reference panel). Then genetic covariances between trait pairs were calculated with the z-scores mentioned above. Inflation due to LD structure was adjusted by implementing the ancestry-matched genome-wide LD scores. Genetic covariances were also adjusted for sample overlap (between GWASs). For all genetic correlation analyses, we implemented GNOVA's simplest, no annotation model. After conducting the genetic correlation analyses, genetic covariances were adjusted for multiple comparisons using the false discovery rate (FDR) procedure, and an *a priori* significance threshold was set at FDR<0.05.

APOE-by-sex sensitivity analysis

A set of linear regressions were performed in R (v.4.0.3) with our resilience phenotypes as the outcomes, age and the first three genetic principal components as covariates, and inclusion of an *APOE* genotype*sex interaction term. *APOE* genotype was first coded with an *APOE* ε4 additive model and then in subsequent analyses with an *APOE* ε2 dominant model. An ε2 dominant model was implemented due to sample size constraints of homozygous ε2 individuals. All linear regressions were performed in the combined autopsy dataset and in the combined PET dataset and then meta-analyzed across cohorts (R metafor package).[41]

Data availability

Data from the ADNI and A4 studies are shared through the LONI Image and Data Archive (https://ida.loni.usc.edu/). Data from ROS/MAP can be requested at www.radc.rush.edu. Data from ACT can be accessed through the Data Query Tool (http://act.kpwashingtonresearch.org/dqt/). GWAS summary statistics will be available through NIAGADS (https://www.niagads.org/datasets/).

Results

Cohort demographics stratified by sex are presented in **Table 1**. T-tests were performed between sexes for age, education, residual cognitive resilience score, and combined resilience score. Education and combined resilience score significantly differed between sexes based on p-values from the t-tests, whereby education and combined resilience were higher in males compared to females. Age and residual cognitive resilience score did

not significantly differ between sexes. Chi-square tests were performed between sexes for amyloid status, AD diagnosis, and *APOE* Ɛ4 carrier status. Amyloid status and AD diagnosis significantly differed between sexes based on p-values from chi-square tests, whereby amyloid status and AD diagnosis were both higher in females compared to males. *APOE* Ɛ4 carrier status did not significantly differ between sexes.

SNP-heritability results

We calculated SNP-heritability estimates among the entire sample and among cognitively normal individuals, using the GCTA restricted maximum likelihood method.[32] All results are presented in **Table 2**, but we will discuss the results among cognitively normal individuals which were statistically significant. Estimated among cognitively normal individuals of both sexes, resilience was 20-25% heritable. Estimates among male cognitively normal individuals were 26-44%, whereas among female cognitively normal individuals, estimates were 15-27%. We next tested to see if these heritability estimates significantly differed between sexes by calculating z-scores and generating p-values from the normal distribution from a one-tailed test. Heritability estimates did not significantly differ between sex for any of our phenotypes. Additionally, SNP-heritability estimates were attenuated when estimated among the whole sample but remained nominally significant when estimated among males and females combined and among males only.

Variant-level results

Variant-level results are presented in **Supplementary Tables 1-12**. QQ plots for all genome-wide meta-analyses with estimates of genomic lambda are presented in **Supplementary Figures 1-3**. For our residual cognitive resilience phenotype, we did not identify any sex-specific genome-wide significant loci in all participants or among cognitively normal individuals. For our combined resilience phenotype, we identified a genome-wide significant female-specific locus on chromosome 10 (rs827389, *β(females)=0.08, P(females)=5.76E-09, β(males)=-0.01, P(males)=0.70, β(interaction)=0.09, P(interaction)=1.01E-04*) among cognitively normal individuals (**Figure 2**) whereby the minor allele was associated with higher resilience scores. Although this locus was not genome-wide significant in residual cognitive resilience, the direction of effect was the same and the locus fell just below the genome-wide significance threshold in females (*β(females)=0.16, P(females)=3.65E-07*). No significant sex-specific associations

were observed for combined resilience in all participants. We conducted *APOE*-by-sex sensitivity analyses on all resilience phenotypes. No associations were statistically significant (**Supplementary Table 13**).

Functional annotation was performed on the genome-wide significant female chromosome 10 resilience locus (among cognitively normal individuals). All variants in LD with rs827389 (top variant) were considered in annotation. The female locus was significantly enriched in Hi-C chromatin loops in multiple tissues, including fetal and adult cortex, aorta, left/right ventricle, liver, spleen, mesendoderm, mesenchymal stem cells, and trophoblast-like cells (**Supplementary Table 14**). Furthermore, enriched chromatin loops overlapped with promoter regions for multiple genes involved in RNA processing (**Supplementary Table 15**), including *GATA3*.

AD risk loci analysis

Sex-stratified and sex-interaction resilience associations with known AD genetic loci are presented in **Supplementary Tables 16-17**. In our residual cognitive resilience analysis, we observed eight nominally significant sex interactions at three AD loci whereby associations were male-specific for two loci, *MS4A6A* and *PTK2B*. Among males, the *MS4A6A* locus was positively associated with resilience and the *PTK2B* locus was negatively associated with resilience. Additionally, *PICALM* showed a flipped effect between sexes, whereby it was negatively associated in males and positively associated in females. Similarly, in our combined resilience analysis, we observed nine nominally significant sex interactions at six AD loci whereby associations were male-specific for four loci, *MS4A6A*, *PTK2B*, *KAT8*, and *SORL1*. Among males, the *KAT8* and *PTK2B* loci were negatively associated with resilience whereas the *MS4A6A* and *SORL1* loci were positively associated with resilience.

Gene- and pathway-level results

Gene test results are presented in **Supplementary Tables 18-21** and pathway test results are presented in **Supplementary Tables 22-25**. We did not observe any genes or pathways that survived adjustment for multiple comparisons (FDR<0.05) for any of the resilience phenotypes. However, we did observe one gene test for combined resilience that was close to surviving adjustment for multiple comparisons among females, and that gene was *LEAP2* on chromosome 5 (P.FDR*(females)*=0.0998, P.FDR*(males)*=0.9971).

Genetic correlation results

We performed sex-stratified and sex-interaction genetic correlation analyses between our resilience phenotypes and 65 complex traits (**Supplementary Tables 26-30**). In this section, we will be presenting the male and female results, leveraging the sex-interaction results to aid in interpretation. For the entirety of the male, female, and sex-interaction genetic correlation analysis results, see **Supplementary Tables 26-30**.

In our residual cognitive resilience phenotype, associations with 11 traits in males and six traits in females survived adjustment for multiple comparisons (FDR<0.05) among all participants. For residual cognitive resilience among cognitively normal participants, 13 traits in males and nine traits in females survived adjustment for multiple comparisons (FDR<0.05). In our combined resilience phenotype, associations with 22 traits in males and seven traits in females survived adjustment for multiple comparisons (FDR<0.05) among all participants. For combined resilience among cognitively normal participants, 20 traits in males and 12 traits in females survived adjustment for multiple comparisons (FDR<0.05).

Of the traits that survived adjustment for multiple comparisons in at least one sex for residual cognitive resilience, one trait displayed a significant sex-interaction effect. This trait was frontotemporal dementia (**Figure 3A**), and it was negatively associated in females, but was not associated in males. Of the traits that survived adjustment for multiple comparisons in at least one sex for residual cognitive resilience among cognitively normal individuals, three traits displayed a significant sex-interaction effect. These traits included asthma, cannabis dependence, and multiple sclerosis, whereby asthma and multiple sclerosis were negatively associated in females and cannabis dependence was positively associated in females, and none of the three traits were associated in males.

Of the traits that survived adjustment for multiple comparisons in at least one sex for combined resilience, six traits displayed a significant sex-interaction effect. These included Celiac disease (**Figure 3B**), resting heart rate pvRSA/HF, and resting heart rate RMSSD (**Figure 3B**), which were positively associated in males and not associated in females, as well as inflammatory bowel disease and sleep duration, which were negatively associated in males and were not associated in females. In addition, multiple sclerosis had opposing effects between sexes (**Figure 3B**) such that it was negatively associated in females and positively associated in males. Of the traits that survived adjustment for multiple comparisons in at least one sex for combined resilience among cognitively normal individuals, seven traits displayed

a significant sex-interaction effect. Internalizing problems was positively associated in females and not associated in males. BMI was negatively associated in males and not associated in females. Resting heart rate pvRSA/HF and resting heart rate RMSSD were positively associated in males and not associated in females. Multiple sclerosis and asthma had opposing effects between sexes such that both traits were positively associated in males and negatively associated in females.

Discussion

We performed a series of sex-aware genetic analyses on cognitive resilience phenotypes to characterize sex-specific variant, gene, and pathway-level effects contributing to cognitive resilience to AD neuropathology. We identified a novel female-specific locus on chromosome 10, and we highlighted a number of high-quality female-specific candidate genes implicated in RNA processing linked to the top variant in the region. Finally, we characterized a number of novel sex-specific genetic covariances between cognitive resilience and relevant traits, including a female-specific association with frontotemporal dementia, male-specific associations with inflammatory bowel disease, sleep duration, BMI, and heart rate variability traits, and opposing associations between sexes for asthma and multiple sclerosis. Overall, our results highlight the value of incorporating sex-stratified analyses into genetic studies of AD and suggest that female-specific genetic drivers of resilience may lie along immune-related pathways, while male-specific genetic drivers may fall along cardiovascular-related pathways.

Cognitive resilience is a highly heritable trait in both sexes

As we reported previously, the heritability estimates of resilience traits are slightly higher when restricting the sample to cognitively normal individuals,[2] perhaps due to an increase in phenotypic heterogeneity when including individuals with dementia, and indeed we observed a similar pattern in the present heritability analyses when stratifying by sex. Specifically, in both male-stratified and female-stratified analyses we observed higher heritability estimates that reached statistical significance among normal cognition participants, and lower heritability estimates when including individuals with dementia. While we did note slightly higher heritability estimates for males compared to females, particularly for the combined resilience trait, the difference between sexes did not reach

statistical significance. As sample sizes expand in future analyses, it will be interesting to see whether sex differences in heritability do emerge, but at present we can only conclude that these resilience traits appear to be heritable in a similar manner across sexes.

Sex-specific shared genetic architecture between cognitive resilience and autoimmune disorders

We observed sex-specific genetic covariances between resilience and autoimmune traits (**Figure 3B, Supplementary Tables 26-29**), whereby genetic predisposition towards resilience was associated with reduced genetic risk for autoimmune traits among females (e.g., lupus, multiple sclerosis) and increased genetic risk for autoimmune traits among males (e.g., lupus, multiple sclerosis, Celiac disease). It is notable that there are well-documented sex differences in trait prevalence for autoimmune disorders, with much higher trait prevalence in females compared to males.[42,43] AD has known immune dysregulations and shares biology with autoimmune disorders, such as the imbalance of Th1 pro-inflammatory and Th2 anti-inflammatory cytokines in both AD and multiple sclerosis.[42,43] Thus, it is perhaps intuitive that genetic factors that predispose lower susceptibility to autoimmune diseases are related to resilience among females. In contrast, it is unclear why males would show an inverse association with higher genetic susceptibility to autoimmune conditions relating to more genetic resilience to AD.

A sex difference in the genetic architecture of cognitive resilience could be due to differences in sex hormones, sex chromosomes, or both. Sex hormones may modulate sex differences in the genetic etiology of autoimmune disorders and resilience. Reproductive years account for the largest sex differences in autoimmune trait prevalence,[42,43] and loss of estrogen has a well-established relationship with cognitive decline.[44–46] In addition, males lose their sex hormones later in life than females, coinciding with when males tend to be diagnosed with autoimmune disorders.[42,43] X-chromosome effects are another possible explanation, given the role of X-inactivation and X-chromosome instability in both autoimmunity and cognition.[47–49] Recently, a second X chromosome was shown to promote survival in aging[50] and harbor resilience[51] against AD in an aging mouse model (irrespective of clinical AD risk), further supporting the possibility of X-chromosome effects as a mechanism underlying both autoimmunity and resilience. However, in contrast, mouse models of MS and lupus have shown that a second sex chromosome confers increased susceptibility.[52,53] Additionally, having two X genes is aligned with more susceptibility to

lupus in humans.[54,55] Thus, it is unclear at this point whether X-chromosome effects could possibly be driving the resilience and autoimmunity sex difference we observed. A third possibility is that differences in metabolic processes between males and females explain genetic sex differences in autoimmunity and resilience. Age-related metabolic shifts tend to be coupled with increased neuroinflammation in females, whereas metabolic shifts do not show this same coupling in males.[56,57] Regardless of the mechanism, our results suggest dramatic sex differences in the cognitive consequences of polygenic protection against autoimmune traits that deserve future attention.

Male-specific shared genetic architecture between cognitive resilience and cardiovascular traits

We observed male-specific positive genetic covariances with three heart rate variability traits, such that more resilient males had a higher genetic susceptibility to more favorable heart rate variability (**Figure 3B**). It is well-established that higher heart rate variability (HRV) is a marker of good heart health, and that HRV decreases with aging.[58–60] The association between the genetic architecture of heart rate variability and the genetic architecture of resilience could be due to (1) heart rate variability driving more resilience in males, (2) reverse causality with genetic factors that predispose towards cognitive resilience driving better heart rate variability in males, or (3) common genetic factors drive both heart rate variability and resilience through independent pathways (i.e., pleiotropy). In support of a causal connection, evidence suggests that lower degrees of HRV are associated with cognitive impairment[61,62] and that age-related HRV differences are sex dependent. Young, healthy females have a lower HRV compared to males, but with advanced age this sex difference is no longer apparent. In fact, elderly males tend to have lower HRV than elderly females,[59] perhaps due to a survival bias[4] from male susceptibility to midlife cardiovascular events.[63] In support of reverse causality, resilience to both cognitive and HRV decline may work through similar circuitry, with prefrontal cortical brain circuitry as an example of this possible shared circuitry that could potentially drive better HRV.[58,61] Multiple groups have shown a link between prefrontal cortical brain activity and HRV, with more than one group pointing towards HRV as a possible early marker of cognitive decline.[58,61] While the possibility of better HRV driving resilience is exciting with some supporting evidence in the literature, future work must investigate each of these scenarios in great detail to determine causality.

Female-specific shared genetic architecture between cognitive resilience and frontotemporal dementia

We observed a significant negative genetic covariance in females between frontotemporal dementia (FTD) and residual cognitive resilience (**Figure 3A**), suggesting more resilient females are less genetically susceptible to FTD. Notably, the genetic covariance between resilience and AD was not significant in either sex (**Figure 3A**). Illán-Gala and colleagues[64] conducted a sex-aware analysis on bvFTD, the most common form of FTD, and observed that females had more cognitive reserve in FTD compared to males. Leveraging a residual approach similar to our study's models, this group observed that females had better-than-expected executive function scores and less behavioral changes given pathology burden compared to males.[64] Importantly, females had a higher amount of atrophy than males at FTD diagnosis, yet had similar disease progression.[64] As mentioned previously, a recent study in aging mouse models demonstrated that a second X chromosome promotes survival in aging[50] and resilience to AD[51] irrespective of clinical AD risk. Taken together, this evidence from the literature and our FTD and AD genetic covariance findings all suggest that it may be the case that there is sex-specific shared genetic architecture of reserve/resilience across dementias subtypes, which contributes to disease protection agnostic to the underlying neuropathology.

However, Illán-Gala et al.[64] also points out that AD is a posterior brain disease, with the anterior cingulum serving as a region of resilience in AD, whereas bvFTD is more of an anterior brain disease. Thus, possibly bvFTD sex-specific cognitive reserve/resilience brain regions are not the same as AD sex-specific cognitive reserve/resilience brain regions.[64] Therefore, it may alternatively be the case that sex-specific reserve/resilience brain regions across dementia subtypes differ, but sex-specific genetic factors driving reserve/resilience are shared across subtypes and harbor some protection from the downstream consequences of neuropathology agnostic to dementia subtype. Perhaps, it could also be the case that we are observing an indirect effect between FTD and resilience, such that similar genetic architecture is independently contributing to both disorders. More sex-aware studies on the genetic architecture of reserve/resilience to different dementia subtypes will need to be conducted to determine causality.

Female-specific candidate genes implicated in RNA processing

Functional annotation of the chromosome 10 genome-wide significant locus (with rs827389) in cognitively normal females (**Figure 2**) suggests its possible regulatory effects. This locus was significantly enriched in Hi-C chromatin loops at multiple gene promoters of genes implicated in RNA processing. These genes included: *KIN*, a DNA/RNA binding protein, *TAF3*, a TATA-box binding protein, and *GATA3*, a zinc-finger transcription factor (**Supplementary Table 15**). It is notable that a promising female-specific candidate gene we identified through functional annotation is *GATA3*, which encodes a "pioneer transcription factor" that can bind heterochromatin and recruit factors to change chromatin state.[65] *GATA3* is involved in sonic hedgehog signaling, a quintessential signaling pathway for pattern formation in neuronal development.[66] It is also involved in embryonic development, influencing genes involved in extracellular matrix formation.[67]

In addition to involvement with neuronal development, *GATA3* also controls immune T-cell fate.[65] Specifically, *GATA3* controls CD4+ effector cells: Th2 cells. CD4+ effector cells can produce autoantibodies against amyloid and therefore harbor protection against amyloid burden.[68] It is thought that genetic drivers of immune-cell profiles may in part explain sex differences observed in response to AD pathology.[69,70] Thus, it is noteworthy to see an immune-target arise at both the variant-level with *GATA3*, and at the whole genome level with our genetic correlation analyses. Taken together, this evidence points towards *GATA3* as a female-specific candidate gene, and overall alludes to the idea that female resilience to AD pathology may involve regulation of RNA processing, although future studies need to replicate and to further elucidate this finding.

AD genetic loci associations with cognitive resilience trend towards male-specific effects

Shown in **Supplementary Tables 16-17**, we observed nominally significant sex-specific associations with resilience at well-known AD loci.[35–37] These associations were male-specific at *MS4A6A*, *PTK2B*, *KAT8*, and *SORL1*, and a flipped effect between sexes was observed at the *PICALM* locus. Multiple groups have shown that *SORL1* may exhibit sex-specificity, including evidence showing *SORL1* variants to be detrimental in females.[71–73] This aligns with what we observed in our study, as we saw a negative association with resilience at a *SORL1* variant in females but a positive association in males. In addition, prior

evidence suggests sex-specificity at the *PICALM* locus. A recent study of cognitively unimpaired individuals demonstrated a negative association in males as well as a sex-interaction association at a protective *PICALM* variant.[74] This finding is consistent with what we observed, as we saw a negative association with resilience at a *PICALM* risk variant in males but a positive association in females. It is also noteworthy that *PICALM* contributes to multiple mechanisms involved in the AD neuropathological cascade, including neuroimmune processes.[74] Taken together, this evidence may suggest that subtle sex differences at AD genetic loci may contribute to sex differences in the downstream response to AD pathology.

APOE effects not observed in resilient females

It was notable that we did not observe any statistically significant *APOE*-by-sex effects with resilience in our sensitivity analyses. Multiple groups have shown differential *APOE* effects by sex in females.[75–78,12] As highlighted in our original manuscript, accounting for cognitive variance related to amyloid appears to massively reduce the *APOE* signal, and thus the reduced effect of *APOE* may partially explain the lack of *APOE*-by-sex effects here. Additionally, our cohort is on average older (mean age=77) when the effects of APOE on cognition are attenuated[8,9] and the effects of circulating estrogens (that have been hypothesized to modify *APOE* effects) are dramatically reduced.

Comparison of study findings across resilience phenotypes

Although significant variant associations and genetic covariances between residual cognitive resilience and combined resilience differed, the pattern of results was largely shared across resilience phenotypes. For example, the female chromosome 10 resilience locus that was genome-wide significant for combined resilience (with rs827389) fell just below genome-wide significant for residual cognitive resilience. In addition. the HRV genetic covariance findings in males and the multiple sclerosis genetic covariance finding in females in the combined resilience phenotype also held true in the residual cognitive resilience phenotype. However, it is notable that genetic covariances for more traits were significant in at least one sex for combined resilience compared to residual cognitive resilience. Overall, we are gaining additional power by leveraging a second-order latent variable, combined resilience, in genetic analyses due to the contributions of educational attainment in conferring resilience. We believe this framework should be integrated into future analyses.

Strengths and Limitations

Our study had multiple strengths. We harmonized data across four deeply characterized cohorts of cognitive aging, leveraged well-validated measures of amyloid, and implemented sex-aware statistical genetic analysis pipelines to identify sex-specific effects. Moreover, our variant, gene, pathway, and cross-trait analyses provide novel insight into the shared genetic architecture between cognitive resilience and other complex traits. However, our study also had limitations. We were underpowered to detect genome-wide sex-interaction effects. While we did not detect X-chromosome variant-level sex effects, we did not investigate imprinting, epigenetic, or transcriptomic X-chromosome effects and are excited for future projects to dive into X-chromosome biology in greater depth. Our study did not include measures of tau or other known age-related neuropathologies. In addition, we did not include measures of neurodegeneration. We were additionally limited in the cognitive domains included in our cognitive resilience models, including investigation of sub-domain effects. Finally, our study was limited to non-Hispanic white individuals, and there was limited heterogeneity in educational attainment, both attenuating the generalizability to other populations.

Conclusions

The findings of our sex-aware genetic study identified a locus, candidate genes, and molecular pathways that relate to resilience to the cognitive consequences of the AD neuropathological cascade in a sex-specific manner. Our findings suggest that the best target to enhance cognitive resilience to AD pathology may depend on both the biological sex and the genetic context of an individual.

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Competing interests

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Supplementary material

Supplementary material is available at *Brain* online.

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Figure Legends

Figure 1. Cognitive and biomarker data harmonization and cognitive resilience model. Memory, executive function, and Preclinical Alzheimer Cognitive Composite (PACC) scores were harmonized across cohorts. Additionally, *in-vivo* amyloid PET standardized uptake value ratios (SUVR) were harmonized with Gaussian Mixture Modeling. **(A)** Harmonized *in-vivo* amyloid PET SUVR by harmonized memory scores are plotted by sex. (**B)** Linear models leveraging harmonized cognitive and amyloid data (harmonized *in-vivo* PET or autopsy measures of amyloid plaque burden, CERAD scores) were residualized and fed as indicators into a residual cognitive resilience latent variable model. The combined resilience latent variable model included educational attainment as an additional indicator.

Figure 2. Minor allele of female-specific genome-wide significant locus on chromosome 10 (with rs827389) associated with higher combined resilience scores among cognitively normal individuals. (A) Miami plot with female variant associations on the top in pink and male variant associations on the bottom in blue. (**B)** Forest plot of rs827389 by cohort and by sex, including fixed-effects meta-analysis estimates. (**C)** Locus Zoom plots displaying the genomic region surrounding the chromosome 10 locus, by sex.

Figure 3. Sex-specific shared genetic architecture between resilience and complex traits. Genetic covariance estimates with 95% confidence intervals are shown in the figure, with female estimates in pink and male estimates in blue. Grey confidence intervals denote a non-significant covariance estimate irrespective of sex. **(A)** Genetic covariance estimates with residual cognitive resilience, by sex, for Alzheimer's disease and for frontotemporal dementia. **(B)** Genetic covariance estimates with combined resilience, by sex, for three heart rate variability traits and for two autoimmune traits.

Table 1 Cohort demographics by sex

	Males (N = 2093)	Females (N = 2931)	Both Sexes (N=5024)
Age, years	76.70 ± 8.80	76.84 ± 10.26	76.78 ± 9.68
Education*, years	17.01 ± 3.07	16.05 ± 2.84	16.45 ± 2.98
Residual Cognitive Resilience Score	0.06 ± 0.89	0.06 ± 0.87	0.06 ± 0.88
Combined Resilience Score*	0.08 ± 0.42	−0.02 ± 0.39	0.02 ± 0.40
Amyloid Status*	857 (40.95%)	1287 (43.91%)	2144 (42.68%)
Alzheimer's Disease Diagnosis*	236 (11.28%)	381 (13.00%)	617 (12.28%)
APOE ε4 Carrier Status	659 (31.49%)	898 (30.64%)	1557 (30.99%)

Categorial values given in N (%); continuous values given in mean ± SD.
*Significant difference between sexes via a t-test (continuous variables) or via a chi-square test (categorical variables).

Table 2 SNP-heritability estimates by sex

	Both Sexes			Males			Females			Sex Differences Test	
	h^2	h^2(SE)	P-value	h^2	h^2(SE)	P-value	h^2	h^2(SE)	P-value	Z-score	P-value
Residual Cognitive Resilience	4.16%	4.75%	0.11	7.65%	9.09%	0.10	5.61%	10.60%	0.31	−0.15	0.88
Residual Cognitive Resilience (CN)	20.90%	5.48%	6.80×10^{-11}	25.82%	11.60%	5.07×10^{-5}	27.17%	9.86%	1.24×10^{-4}	0.09	0.93
Combined Resilience	19.71%	8.89%	0.01	29.42%	19.48%	0.03	0.0001%	14.50%	0.50	−1.21	0.23
Combined Resilience (CN)	25.25%	7.95%	2.33×10^{-7}	44.11%	18.64%	9.57×10^{-5}	14.93%	12.37%	0.06	−1.30	0.19

CN = cognitively normal. h^2 values are the V(G)/Vp estimates calculated from the GCTA restricted maximum likelihood statistical method (with genetic relatedness matrices). Sex differences test p-values were generated from the normal distribution based on a one-tailed test.

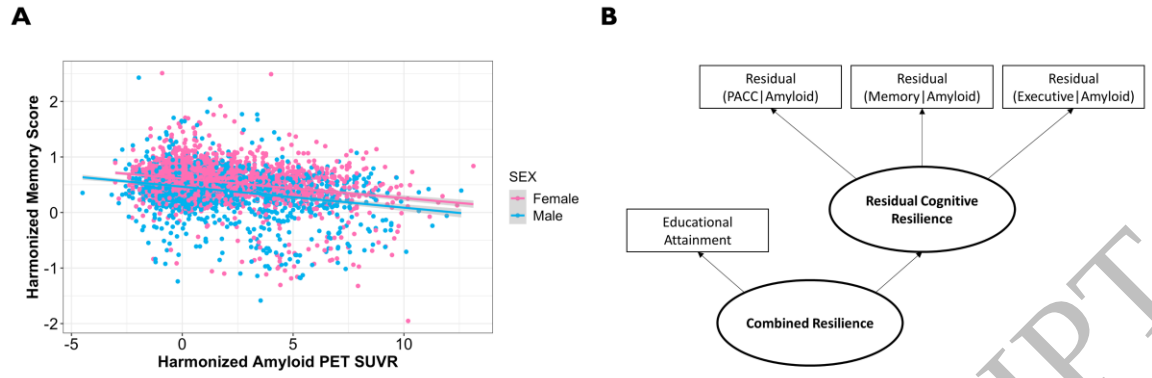

Figure 1
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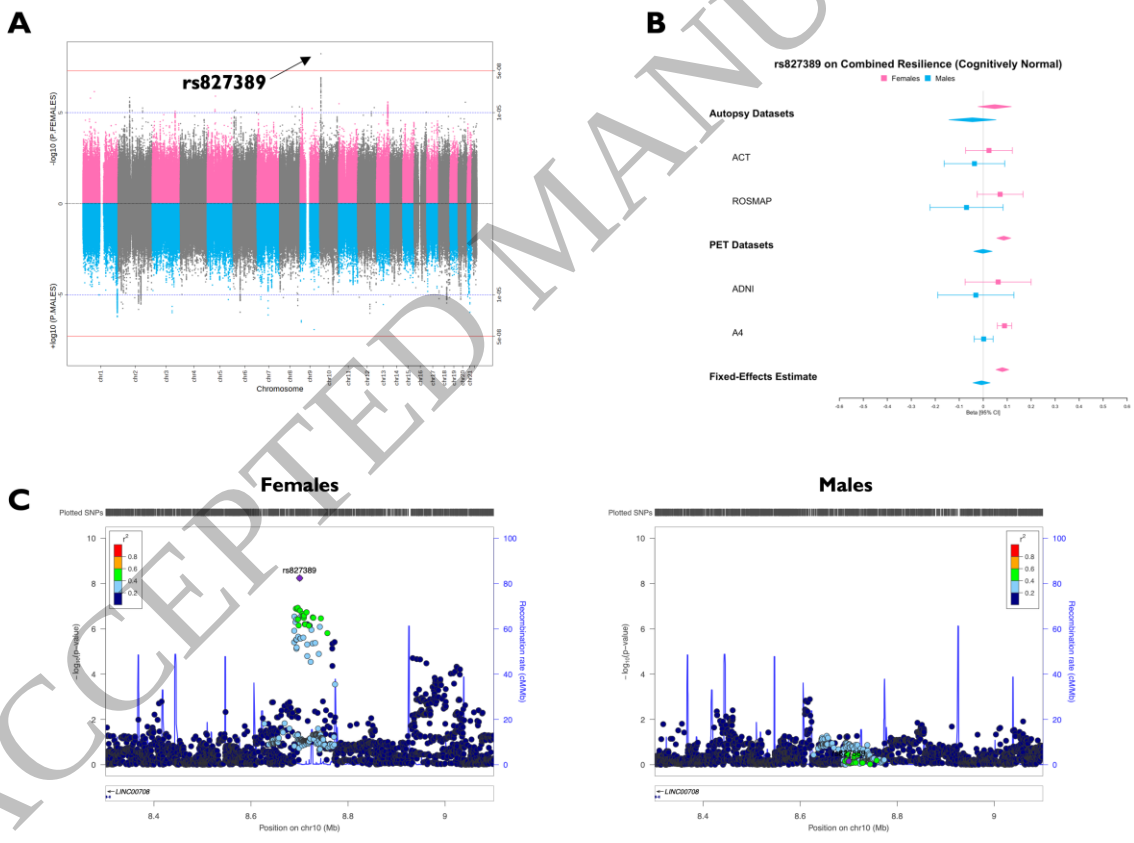

Figure 2
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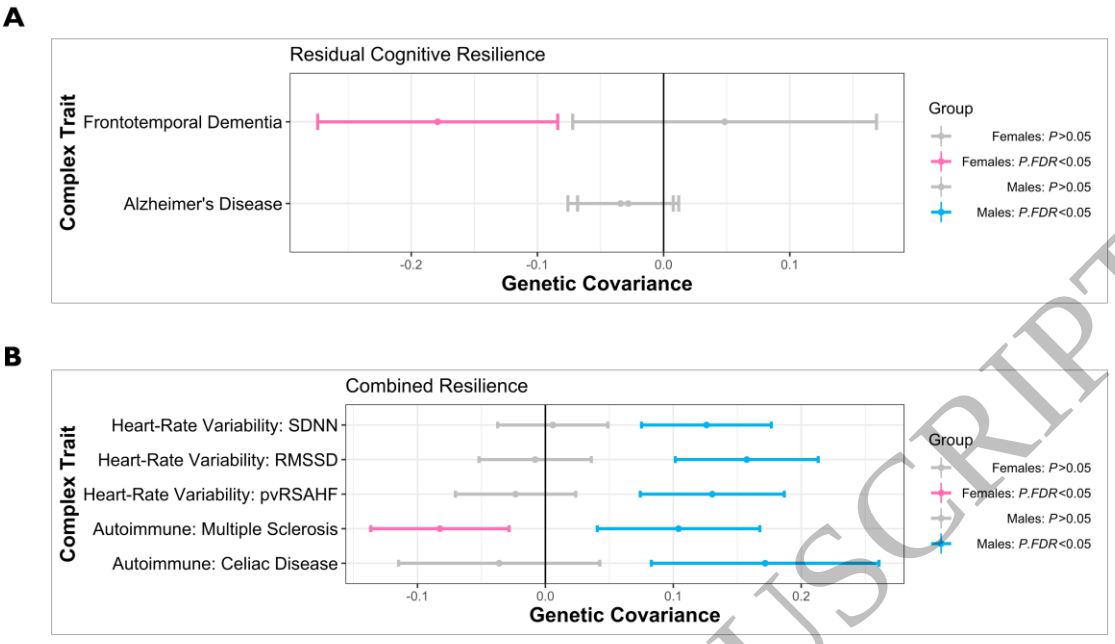

Figure 3
159x92 mm (1.2 x DPI)