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Research Article

Trans-Ethnic Meta-Analysis of Interactions Between Genetics and Early-Life Socioeconomic Context on Memory Performance and Decline in Older Americans

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Abstract

Background: Later-life cognitive function is influenced by genetics as well as early- and later-life socioeconomic context. However, few studies have examined the interaction between genetics and early childhood factors.

Methods: Using gene-based tests (interaction sequence kernel association test [iSKAT]/iSKAT optimal unified test), we examined whether common and/or rare exonic variants in 39 gene regions previously associated with cognitive performance, dementia, and related traits had an interaction with childhood socioeconomic context (parental education and financial strain) on memory performance or decline in European ancestry (EA, N = 10 468) and African ancestry (AA, N = 2 252) participants from the Health and Retirement Study.

Results: Of the 39 genes, 22 in EA and 19 in AA had nominally significant interactions with at least one childhood socioeconomic measure on memory performance and/or decline; however, all but one (father's education by solute carrier family 24 member 4 [*SLC24A4*] in AA) were not significant after multiple testing correction (false discovery rate [FDR] < .05). In trans-ethnic meta-analysis, 2 genes interacted with childhood socioeconomic context (FDR < .05): mother's education by membrane-spanning 4-domains A4A (*MS4A4A*) on memory performance, and father's education by *SLC24A4* on memory decline. Both interactions remained significant (p < .05) after adjusting for respondent's own educational attainment, apolipoprotein-ε4 allele (*APOE* ε4) status, lifestyle factors, body mass index, and comorbidities. For both interactions in EA and AA, the genetic effect was stronger in participants with low parental education.

Conclusions: Examination of common and rare variants in genes discovered through genome-wide association studies shows that childhood context may interact with key gene regions to jointly impact later-life memory function and decline. Genetic effects may be more salient for those with lower childhood socioeconomic status.

Keywords: Childhood SES, Cognition, Gene–environment interaction, Memory, Rare variant

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder that results in a form of dementia predominantly characterized by cognitive impairment and decline. In 2018, AD prevalence increased to approximately 50 million people worldwide, which averages to about 2 million new cases per year (1). In 2019, in the United States alone, AD and dementia costs were expected to exceed $290 billion and reach $1.1 trillion by 2050 (2). The increase of AD prevalence and associated financial costs represent a significant national public health burden (3). The high estimated rate of conversion from cognitive impairment to dementia has fueled interest in the identification of genetic factors associated with cognitive impairment and its progression. Identifying predictors of which individuals will develop cognitive impairment and who will decline the fastest is necessary for better prevention and treatment of cognitive disorders.

Recently, genome-wide association studies (GWAS) have identified multiple genetic loci that are associated with a multitude of cognitive traits, including memory (4) and general cognitive function (5), as well as AD (6). However, uncharacterized variability in cognitive impairment still remains (7). It has been hypothesized that some of the "missing heritability" may be due to rare genetic variants as well as gene–environment interactions that are not explicitly modeled (8).

Cognitive function in later life is influenced both by genetics as well as early- and later-life socioeconomic context. These factors may also interact with each other. There is evidence, for example, that educational attainment modifies the effect of genotype on episodic memory performance and decline in the Health and Retirement Study (HRS) (9). Like education, early-life conditions have been associated with later-life cognition (10), raising the possibility that childhood environment may also interact with genotype on cognitive decline and dementia in adulthood. Childhood socioeconomic status (SES) may promote aspects of development during sensitive periods of childhood that protect against later-life cognitive impairment through multiple pathways (11). Studies of gene-by-childhood SES interactions on childhood cognitive function in the United States have generally shown that genetic effects tend to be magnified at higher levels of SES, and this effect has also been observed in one of the few studies of adult cognitive function (12). However, nearly all of the gene-by-childhood SES studies conducted to date have used biometric models (twin and family studies) to estimate the genetic and environmental contributions to cognitive function, and few have examined whether socioeconomic factors from childhood interact with the known genes that influence memory performance and decline in older adulthood.

In addition, most genetic research to date has been conducted by modeling each single nucleotide polymorphism (SNP) independently, which has low power for analyzing rare variants and also results in a large multiple testing burden. Gene-based association analysis techniques have been used for the examination of relevant genomic regions with clusters of rare and common genetic variants, which may increase power by reducing the multiple testing burden and can deal with the problem of allelic heterogeneity across ancestries (13). Here, we use a gene-based strategy to evaluate gene-by-childhood SES interactions on memory performance and memory decline in non-Hispanic European ancestry (EA) and African ancestry (AA) from the HRS, using 39 genes known to be associated with cognition and dementia.

Methods

Study Sample

HRS is a nationally representative longitudinal panel study of adults over age 50, launched in 1992. HRS used a multistage area probability sample design, and assesses several domains including health, cognition, family composition and interaction, employment, and wealth (14). HRS baseline interviews were all conducted face-to-face (14,15). Follow-up interviews were conducted alternating face-to-face and telephone interviews biennially. Biological and physiological measures were collected during face-to-face interviews. On average, EA and AA respondents had 7.4 (range 2–11) and 6.1 (range 2–11) waves of observation, respectively, equivalent to ~15 and ~12 years. This study includes respondents over age 50 that provided saliva samples for DNA extraction in 2006–2010. Overall, 86% of the approximately 19 000 eligible HRS participants consented to salivary DNA collection with those who self-reported as being Black (80.6%) and those with worse self-reported health (83.9%) significantly less likely to participate. All participants with at least 2 completed episodic memory assessments between 1992 and 2014 as well as genetic data (1000 Genomes Project [1000G] imputed data and/or exome chip data) were included in analysis.

Measures

Memory performance

Combined measures of immediate and delayed recall were used to assess respondents' memory performance. These assessments are considered to be sensitive measures of cognitive change (16), and have been associated with predicting diagnosis of dementia (17).

To assess memory, respondents are asked to recall a list of 10 nouns read to them by an interviewer. The measure of memory performance was comprised of the total number of words recalled immediately and after a 5-minute delay of additional test administration (range: 0–20). A principal component (PC) factor analysis from Ofstedal et al. suggested that immediate and delayed recall could be combined since they loaded onto a single factor (15). Since the recall task in early waves of the study (1992 and 1994) included 20 words instead of 10, we normalized the memory performance scores from these waves to a range of 0–20 using score distributions from respondents of similar ages in 1998. Memory performance scores were imputed by HRS for self-respondents who refused to respond to an item using a method described elsewhere (9). Memory performance was imputed if the participant was cognitively impaired or reported a diagnosis of dementia or AD. The composite recall score was randomly imputed between 0 and 4. Scores were not imputed for respondents without evidence of dementia. Imputed scores were assigned for between 1.1% and 3.9% of all respondents, depending on the interview wave.

Socioeconomic status

Childhood SES was characterized using 3 different measurements including Childhood Financial Strain Index (CFSI), father's education, and mother's education. CFSI (range: 0–4) is a composite indicator of financial strain created from indicators for whether the family ever moved due to financial problems, whether the family received help from relatives because of financial difficulties, and whether their father ever experienced a period of unemployment during the respondent's childhood, and self-reported financial status when the respondent was a child (where "poor" or "varied" were coded as 1, and "average" or "well-off" were coded as 0). CFSI = 0 represents little or no childhood financial strain while CFSI = 4 represents high childhood financial strain. Mother's or fat her's educational attainment was characterized as having at least 8 years of education or having less than 8 years. Since missingness on parental education was associated with cognitive score, we used demographic and SES variables to impute years of parental education for mothers (10% of sample) and fathers (15%) as needed using a multivariate, regression-based procedure in Imputation and Variance Estimation (IVEware) software (http://www.isr.umich.edu/src/smp/ive/). In secondary analyses, we further adjusted for the respondents' own educational attainment. Respondents were characterized as having a college degree and above, having a high school education or equivalent (high school degree), or having less than a high school degree.

Lifestyle factors and comorbidities

A lifestyle index was created as a summary measure of alcohol consumption, physical activity, and smoking status, which ranged from 0 to 3 with 0 being unfavorable and 3 being favorable, as described

in Lourida et al. (18). Body mass index (BMI) category was defined as 1 if BMI was between 18.5 and 24.9, 2 if BMI <18.5, 3 if BMI was between 25 and 29.9, and 4 if BMI was ≥30. Comorbidities including high blood pressure, diabetes, cancer, heart disease, lung disease, stroke, psychiatric disease, and arthritis were self-reported. All lifestyle factors and comorbidities were assessed at the HRS baseline interview.

Genotype data

HRS respondents were genotyped using the Illumina HumanOnmi2.5 array and the Illumina HumanExome-12v1 array. We calculated the genetic PCs for each chip separately and used the first 2 PCs and self-reported race to select analytic samples of unrelated EA and AA respondents. We further calculated ethnic-specific PCs to adjust for population stratification in each race. Genotypes from HumanOnmi2.5 array were imputed using the 1000G phase I integrated variant set (v3, released March 2012).

As described in Smith et al. (9), we conducted a literature search of the National Human Genome Research Institute - European Bioinformatics Institute (NHGRI-EBI) GWAS catalog (19) to identify GWAS that had at least one autosomal SNP that was genome-wide significantly associated (p value < 5×10^{-8}) with cognitive function/decline/impairment, episodic memory, memory function, hippocampal volume, AD, vascular dementia, or closely related phenotypes. We selected a total of 17 studies, and used SNPs meeting significance criteria from these studies for our analysis. To determine genes for our analysis, we identified all SNPs that fell within the boundaries of a gene region (± 5 kb of the gene) for each SNP of interest. A total of 39 genes were selected (see Supplementary Table S1 and Smith et al. (9) for additional details). For each gene, the region was then defined by selecting all SNPs between the gene start and stop sites, plus a 5 kb buffer on either side, with high imputation quality (INFO score > 0.5). The number of SNPs included within a single gene region ranged from 30 to 8 817 for EA 1000G data, 31 to 8 627 for AA 1000G data, 1 to 43 for EA exome chip data, and 1 to 38 for AA exome chip data (Supplementary Table S2).

In some analyses, we adjusted for the presence of at least one apolipoprotein-ε4 (*APOE* ε4) allele. The 3 major isoforms of ApoE (ε2, ε3, and ε4) are determined by 2 SNPs (T > C rs429358 and C > T rs7412). In particular, *APOE* ε4 represents a chromosome with the minor rs429358 variant and the major rs7412 variant (CC haplotype, correspondingly). The haplotype with the minor variant at both SNPs (ε1) is very rare and assumed to be zero in most populations. Thus, we used 1000G data for rs429358 to reliably classify respondents as APOE ε4 allele carriers (having at least one copy of the ε4 allele) or noncarriers.

Statistical Analysis

Memory trajectory models

In the full data set including both ancestries, a series of unconditional mixed models with random effects (20) were used to estimate the overall rate of memory change allowing random effects for individual differences from the overall pattern (21,22). By using this approach, we could account for the unbalanced data structure of longitudinal data (23,24). Age was coded as [Age at interview – 65]/10 to be approximately centered. Thus, the intercept represents the average memory performance at age 65 and the age coefficient (slope) represents the average change in memory score (memory decline) with each decade. To best model the pattern of memory change with age, we compared increasingly complex models including linear, quadratic, and cubic polynomials on age, as well as linear spline models, and examined fit using the Bayesian information criterion. The best-fitting model included an intercept, a linear age-dependent slope, and a quadratic age slope. The models were estimated using the full-information maximum likelihood estimation method with an unstructured covariance matrix for the random effects and included data from memory tests at all available timepoints (25). Additional details are described elsewhere (9).

Gene-by-childhood SES interactions with memory performance and decline

For each of the 39 genes, we evaluated whether genetic variation interacted with each childhood SES measurement to influence episodic memory performance (trajectory intercept) and decline (trajectory slope) using the interaction sequence kernel association test (iSKAT) or the iSKAT optimal unified test (iSKAT-O) (26). iSKAT is a score-based variance component test that evaluates the joint effect of multiple SNP–environment interactions in a genomic region on an outcome of interest. The test assumes that the effect size of each individual SNP–environment interaction in the region follows an arbitrary distribution with mean zero and certain variance. Under the null hypothesis that none of the SNP–environment interactions are associated with the outcome, the variance of the distribution would be zero. The test statistic assesses the alternative hypothesis by testing whether the variance of this distribution deviates from zero. The contribution of each SNP–environment interaction can be weighted by characteristics like minor allele frequency (MAF). iSKAT-O is a hybrid test that combines both the iSKAT test as well as a genetic burden test. The burden test is a method that evaluates whether a composite score of the number of minor alleles for the variants in the region has a significant interaction with the environment on the outcome. Burden tests are optimal when all of the rare variants in the gene have identical effect sizes and directions. Using the iSKAT/iSKAT-O methods, we were able to evaluate both the gene–environment interaction effects of all of the SNPs/variants within the entire gene region (including introns and regulatory regions) as well as the effects of the rare, potentially functional variants within the exome.

We performed the analyses separately for memory performance and decline, separately for each childhood SES measurement, and separately for both ancestry groups. In each model, we included sex and the top 4 ancestry-specific genetic PCs to control for population stratification (Model 1). We also adjusted for memory performance (intercept) when modeling memory decline (slope). For analysis of the 1000G data, we used iSKAT with an unweighted kernel [β (1,1)] to give equal weight to all SNPs/variants regardless of allele frequency (hereby referred to as "all SNPs/variants"). For analysis of the exome chip data, which is comprised primarily of rare, potentially functional variants, we used iSKAT-O with a weighted kernel [β (1,25)] that dramatically up-weights variants with low minor allele frequencies ("rare variants").

To determine whether educational attainment and/or presence of the *APOE* ε4 allele attenuated the associations between gene and childhood SES interaction with at least nominal significance and memory performance or decline (p < .05), we further adjusted for education (Model 2), *APOE* ε4 status (Model 3), or both (Model 4).

We were interested both in gene-based interactions that were nominally significant (p < .05) as well as those that retained significance after multiple testing correction. For each set of results from the 39 genes (all SNPs/variants and rare variants, within each ethnic group, for each memory outcome and each childhood SES measurement), we calculated the false discovery rate (FDR) (27). For

the all SNP/variants (1000G) iSKAT analyses, we also performed a meta-analysis across ethnicities using Fisher's method and calculated the FDR on the meta-*p* values. We did not perform meta-analyses on iSKAT-O tests because there could be differences in the relative weighing (ρ) of the SKAT test and the burden test because it is an optimization test. Results with FDR-adjusted *p* value <.05 were considered significant after correction for multiple testing.

For interactions with FDR *p* <.05, we performed 2 follow-up analyses. First, we modeled the interaction between the corresponding childhood SES variable and each SNP/variant in the region to identify the specific SNPs that most strongly contributed to the interaction using linear regression. Adjustment variables included sex and the top 4 ancestry-specific genetic PCs. We also adjusted for memory performance (intercept) when modeling memory decline (slope) (Model 1). Results were visualized using LocusZoom (28). For single SNP interactions of interest, contrast analyses were used to estimate the effect sizes of SNP genotypes on memory performance/decline in each childhood SES category. Second, to begin to examine potential mechanistic pathways that may be operating in the context of the FDR-significant interactions, we further adjusted the interactions for all Model 4 variables plus lifestyle index (a summary measure of alcohol consumption, physical activity, and smoking) (Model 5), then adding BMI category (Model 6), and finally adding various comorbidities (high blood pressure, diabetes, cancer, heart disease, lung disease, stroke, psychiatric disease, and arthritis) (Model 7).

Results

Descriptive Statistics

Descriptive characteristics are presented in Table 1. Most of the respondents had both 1000G and exome chip data. The average age was 57 (EA) and 56 (AA) years at the time of first cognitive assessment. Over half of the respondents attained a high school degree or equivalent, and 13% of AA and 25% of EA attained a 4-year college degree or more. A greater proportion of the EA respondents (55%) had little or no childhood financial strain (CFSI = 0) compared to AA respondents (45%), whereas fewer EA respondents (35%) had intermediate childhood financial strain (CFSI = 2 or 3) than AA (44%). Approximately 79% of EA and 58% of AA respondents had a father with more than 8 years education, and 86% of EA and 69% of AA had a mother with greater than 8 years education. Estimated memory performance at age 65 was 10.8 words recalled for EA and 9.2 words recalled for AA, and estimated memory decline was similar between ancestries (approximately 1.4 words per decade).

Gene-by-Childhood SES Interactions With Memory Performance and Decline

We examined the interactions between each of the 39 gene regions and 3 childhood SES factors (CFSI, father's education, and mother's education) separately on memory performance and decline using all SNPs/variants (1000G data) and primarily rare variants (exome chip data) in Model 1, and then further adjusted the model for respondent's own educational attainment and *APOE* ε4 status (Model 4). *p* Values for each nominally significant interaction with CFSI, father's education, and mother's education are shown in Supplementary Tables S3–S5, respectively. Out of the 39 genes tested, 22 genes in EA and 19 genes in AA had at least nominally significant interactions ($p < .05$) with one of the childhood SES factors tested on memory performance and/or decline. However, only the interaction between father's education and solute carrier family 24 member 4 (*SLC24A4*) using all SNPs/variants on memory decline AA remained significant after applying FDR correction ($p = .00054$; FDR $q = .02$). After additionally adjusting for respondent's own education and *APOE* ε4 status, the *p* value for the interaction was similar ($p = .00057$).

Table 1. Descriptive Statistics for HRS Respondents With 1000G Imputed Data and Exome Chip Data

	European Ancestry		African Ancestry	
Demographic and SES Measures[a]	1000G n = 9 920	Exome n = 10 468	1000G n = 2 226	Exome n = 2 252
Age at first cognitive assessment (years)	57.2 (8.9)	57.4 (9.0)	55.5 (7.6)	55.6 (7.6)
Gender (0 = male, 1 = female)	58%	58%	63%	64%
Educational attainment				
Less than high school degree	12%	13%	30%	30%
High school degree or equivalent	63%	62%	57%	57%
4-y college degree or equivalent	25%	26%	13%	13%
CFSI				
0	55%	55%	45%	45%
1	22%	22%	28%	28%
2	13%	13%	16%	16%
3	7%	7%	8%	8%
4	3%	2%	3%	3%
Parental education				
Father's education (8+ y)	80%	79%	58%	58%
Mother's education (8+ y)	86%	86%	69%	69%
Memory trajectories				
Memory performance (trajectory intercept at age 65)	10.8 (2.0)	10.8 (2.0)	9.2 (2.0)	9.2 (2.1)
Memory decline (trajectory slope per decade)	−1.4 (0.6)	−1.4 (0.6)	−1.4 (0.5)	−1.4 (0.5)

Notes: CFSI = Childhood Financial Strain Index; HRS = Health and Retirement Study; SES = socioeconomic status. 1000G = sample with 1000 Genomes Project imputed data. Exome = sample with exome chip data. CFSI: 0 indicates low strain and 4 indicates high strain.

[a]Mean (*SD*) or percentage is presented.

Trans-Ancestry Meta-Analysis of Gene-by-Childhood SES Interactions With Memory Performance and Decline

We conducted a trans-ancestry meta-analysis on iSKAT tests (all SNP/variants) and performed FDR correction on the meta-*p* values. There were 2 significant gene-by-childhood SES interactions with a 5% FDR: *SLC24A4*-by-father's education on memory decline (q = .018), and membrane-spanning 4-domains subfamily A member 4A (*MS4A4A*)-by-mother's education on memory performance (q = .035; Table 2). *p* Values for the interactions remained significant at p <.05 after additional adjustment for the respondent's own educational attainment (Model 2), the *APOE* ε4 allele (Model 3), and both (Model 4), as well as with the addition of lifestyle index (Model 5), BMI category (Model 6), and comorbidities (Model 7).

Single SNP-by-Childhood SES Interactions on Memory Performance and Decline

To gain a better understanding of what SNPs were driving the significant interactions observed for *SLC24A4*-by-father's education on memory decline and *MS4A4A*-by-mother's education on memory performance, we modeled the interactions for all the SNPs within the corresponding gene region separately for EA and AA. LocusZoom plots of SNP-by-father's education interactions and SNP-by-mother's education interactions for these 2 gene regions in EA and AA are shown in Supplementary Figures S1 and S2, respectively.

The strongest SNP-by-father's education interaction in *SLC24A4* was with rs117438089 in EA and rs10135665 in AA (Supplementary Figure S1). The top SNP in EA (rs117438089) has a minor allele (C) frequency of 15.1% (Table 3), while the top SNP in AA (rs10135665) has a much lower minor allele (T) frequency of 1.7%. In both EA and AA, memory decline was greatest for those whose father had less than 8 years of education and who also carried the minor allele (Supplementary Figure S3). Contrast tests showed that the minor alleles of the top SNPs (rs117438089 in EA, rs10135665 in AA) were associated with memory decline only for those whose father had less than 8 years of education in both EA and AA. However, for those whose father had at least 8 years of education, each additional copy of the minor allele was not associated with memory decline in either EA or AA. The top SNP from EA (rs117438089) had a much lower MAF in AA (5.4%) than in EA, and the interaction between this SNP and father's education was not significant in AA. The top SNP from AA (rs10135665) was nearly monomorphic in EA (MAF = 0.005%), so we could not test for interaction.

For the SNP-by-mother's education interactions in the *MS4A4A* gene region, we also observed different top SNPs in EA and AA (Supplementary Figure S2). The top SNP for EA was rs55715159 with a MAF (C) of 11.8% (Table 3). The top SNP for AA was rs7949816 with a MAF (A) of 29.4% (Supplementary Figure S4). In EA, the genetic effect of rs55715159 was only observed for respondents whose mother had less than 8 years of education, which is similar to the *SLC24A4* interaction with father's education. Specifically, each additional copy of the minor allele was associated with a decrease of 0.36 words recalled at age 65. Given that estimated memory decline in both EA and AA participants was 1.4 words per decade, this 0.36 word decrease for each minor allele of rs55715159 is equivalent to approximately 2.6 years of additional cognitive decline, on average. No significant association, however, was observed for those whose mother had at least 8 years of education. For AA, the genetic effect of rs7949816 was significant for both respondents whose mother had

Table 2. *p* Values for Significant Gene-by-Childhood SES Interactions on Memory Trajectories in European Ancestry, African Ancestry, and Trans-Ethnic Meta-Analyses

Gene	Childhood SES Measure	Outcome	Ancestry	Genetic Measure	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
SLC24A4	Father's education	Memory decline	Meta	All SNPs/variants	0.0005[a] (0.018)	0.0005	0.0008	0.0007	0.0004	0.0004	0.0005
			EA	All SNPs/variants	0.085	0.085	0.115	0.115	0.074	0.059	0.044
			AA	All SNPs/variants	0.0005[a] (0.02)	0.0005	0.0006	0.0006	0.0005	0.0005	0.0011
MS4A4A	Mother's education	Memory performance	Meta	All SNPs/variants	0.0009[a] (0.035)	0.002	0.002	0.003	0.004	0.002	0.003
			EA	All SNPs/variants	0.007	0.009	0.007	0.01	0.01	0.007	0.013
			AA	All SNPs/variants	0.014	0.026	0.044	0.029	0.043	0.040	0.021

Notes: AA = African ancestry; EA = European ancestry; *MS4A4A* = membrane-spanning 4-domains A4A; SES = socioeconomic status; *SLC24A4* = solute carrier family 24 member 4; SNP = single nucleotide polymorphism. The interaction sequence kernel association test/iSKAT optimal unified test (iSKAT/iSKAT-O) was used to model the interaction between childhood SES and each gene region separately on memory decline (memory trajectory slope per decade). iSKAT using the β (1, 1) weighting was used for 1000 Genomes Project data analyses (all SNPs/variants). ρ represents the relative weighting between the SKAT test (ρ = 0) and the burden test (ρ = 1), and is presented for analyses conducted using iSKAT-O. Model 1 adjusted for sex, the top 4 ancestry-specific genetic principal components, and memory performance (intercept). Model 2 = Model 1 + respondent's own educational attainment (high school and college). Model 3 = Model 1 + presence of the apolipoprotein-ε4 (*APOE* ε4) allele. Model 4 = Model 1 + respondent's own educational attainment (high school and college) + presence of the *APOE* ε4 allele. Model 5 = Model 4 + lifestyle index. Model 6 = Model 5 + body mass index category. Model 7 = Model 6 + comorbidities including high blood pressure, diabetes, cancer, heart disease, lung disease, stroke, psychiatric disease, and arthritis. *p* Values are reported only for gene-by-childhood SES interactions that had false discovery rate (FDR) q <.1 in Model 1 meta-analyses.

[a]Interactions with FDR q <.1 in Model 1, and the corresponding q values are presented in the parentheses.

Table 3. Genetic Effects of the Most Significant SNP/Rare Variant on Memory Trajectories by Childhood SES Group for Regions With Gene-by-Childhood Interaction FDR q <.1 for European Ancestry and African Ancestry HRS Respondents

Environment	Outcome	Ancestry	Data Source	Gene	SNP	Coded Allele Frequency	Coded Allele	Noncoded Allele	N	β (95% CI) of Genetic Effect for Low Parental Educational Attainment	β (95% CI) of Genetic Effect for High Parental Educational Attainment
Father's education	Memory decline	EA	1000G	*SLC24A4*	rs117438089	0.151	C	T	9886	**−0.061 (−0.114, −0.008)**	0.022 (−0.005, 0.048)
Father's education	Memory decline	AA	1000G	*SLC24A4*	rs10135665	0.017	T	G	2212	**−0.436 (−0.629, −0.244)**	0.104 (−0.066, 0.273)
Mother's education	Memory performance	EA	1000G	*MS4A4A*	rs55715159	0.118	C	A	9901	**−0.359 (−0.581, −0.136)**	0.0738 (−0.018, 0.165)
Mother's education	Memory performance	AA	1000G	*MS4A4A*	rs7949816	0.294	A	T	2219	**−0.416 (−0.649, −0.183)**	**0.196 (0.032, 0.361)**

Notes: AA = African ancestry; EA = European ancestry; FDR = false discovery rate; HRS = Health and Retirement Study; *MS4A4A* = membrane-spanning 4-domains A4A; SES = socioeconomic status; *SLC24A4* = solute carrier family 24 member 4; SNP = single nucleotide polymorphism. Follow-up analysis was performed in order to better understand the magnitudes and directions of gene-by-childhood SES interactions with FDR q <.1 in interaction sequence kernel association test/iSKAT optimal unified test (iSKAT/iSKAT-O) analyses (Model 1). Since the interactions were detected using all SNPs/variants (1000 Genomes Project [1000G] data, iSKAT), equivalent variant-by-childhood SES interaction models were conducted on the same outcome for each individual SNP/variant in that region to identify the most significant variant-by-childhood SES interaction in each ancestry group. Contrast tests were performed for the most significant SNPs with minor allele frequency >0.01 to obtain β coefficients and 95% confidence intervals (CIs) associated with the variant for the high (father's or mother's educational attainment ≥8 y of education) and low (father's or mother's educational attainment <8 y of education) childhood SES group. Significant β coefficients and 95% CIs are bolded.

less than 8 years or at least 8 years of education; however, the direction of the effect was opposite. Each additional copy of the minor allele of rs7949816 was associated with an increase of 0.20 words recalled at age 65 for those whose mother had at least 8 years of education (equivalent to approximately 1.4 years less decline), and was associated with a decrease of 0.42 words recalled at age 65 for those whose mother had less than 8 years of education (equivalent to approximately 3.0 years greater decline). Neither of the EA or AA top SNPs had significant interaction effects with mother's education in the other ethnic group.

Discussion

Using a gene-based strategy, we were able to evaluate the interactions between genes known to be associated with cognitive function and multiple childhood SES factors on longitudinal measures of cognition. We found multiple genes that had nominally significant interactions with one or more of the childhood socioeconomic measures tested on memory performance and/or decline; however, only one interaction with memory decline in AA remained significant after correction for multiple testing. One additional gene region interacted with childhood SES on memory performance was found in the trans-ethnic meta-analysis. For both interactions, the genetic effect was stronger in participants with low levels of parental education.

Childhood SES has been shown to be associated with later-life cognition (29) and changes to the surface area of the cerebral cortex, especially hippocampus and amygdala volumes (30). In addition, studies have suggested the presence of gene-by-childhood SES interactions on adult cognitive function using variance component models in twin analysis (12). However, the investigation of the interaction between childhood SES and specific genes associated with cognitive function has been limited. To our knowledge, this is the first study to evaluate the interaction of both common and rare variants in genes for cognition and related traits with multiple childhood SES factors in EA and AA, using longitudinal measures of cognition.

We found interactions between *SLC24A4* and father's education on memory decline, and *MS4A4A* and mother's education on memory performance in trans-ancestry meta-analysis after accounting for multiple testing. *SLC24A4*, a member of the potassium-dependent sodium/calcium exchanger protein family, is expressed primarily in brain tissue (31). This gene has been linked to age-related cognitive decline (32) but demonstrated association with late-onset AD has been inconsistent (33,34). In addition, Yu et al. have suggested that there is an association between brain DNA methylation in *SLC24A4* and AD (35). Recent studies have linked mutations in the *SLC24A4* to amylogenesis imperfecta, a genetic disease presented with abnormal tooth formation and development (36,37) and olfactory deficits (38). Interestingly, tooth loss and olfactory deficits may be associated with cognitive impairment (39,40). More research is needed to characterize the precise biological mechanisms by which parental education modifies the effect of *SLC24A4* on later-life cognitive performance.

The *MS4A4A* gene encodes a member of the membrane-spanning 4A gene family and displays unique expression patterns in hematopoietic stem cells and nonlymphoid tissues (41). *MS4A4A* has been associated with late-onset AD (42) and a central AD biomarker, β-amyloid, in cerebrospinal fluid (43). *MS4A4A* is located on chromosome 11 and is close to *MS4A6A*, a gene that has also been associated with cognitive function in previous studies (42,44). Genes in the MS4A cluster are known to activate T cells and trigger inflammatory cytokine production (45), while childhood SES has

been inversely associated with inflammation (46). This implicates a potential underlying biological mechanism linking the interaction with childhood SES and cognitive function, which is consistent with Miller's biological embedding model. The biological embedding model suggests that early adversity (eg, low childhood SES) might become "programmed" into immune cells through epigenetic marks, creating proinflammatory tendencies that make the individual more susceptible to chronic diseases across the life span (47).

While *SLC24A4* and *MS4A4A* had significant interactions with childhood SES in our study, a previous study that evaluated the main effects of these genes in HRS showed that they were not significant in either ethnic group (9). This suggests that the genetic effects may be operating only in certain environmental contexts reflecting early-life exposures. Potential biological mechanisms underlying increased genetic effects in certain lower childhood socioeconomic contexts may include differences in inflammation levels, health behaviors, hypertension, and/or other comorbidities that may not be operating in early life. However, our follow-up analyses that adjusted for lifestyle index, BMI, and primary comorbidities suggests that the interactions may act through mechanisms independent of the potential confounders/mediators that we evaluated. Further studies are warranted to elucidate the mechanisms of these interactions.

The identified interactions with our set of genes varied in significance across ancestries and childhood SES factors. This inconsistency may be a consequence of childhood SES factors having differential effects on cognition for EA compared to AA (48), or heterogeneity in allele frequencies or genetic effects across ancestral groups. Neither of the 2 genes that interacted with childhood SES was shown to interact with respondent's own educational attainment in previous HRS studies (9). In fact, only a few genes (*TREM2* and *CLU* in EA and *PICALM* and *SLC24A4* in AA) had interactions at $p < .05$ with both respondents' own education (high school degree) and parental education. Further, the significant interactions with parental education in the current study were not strongly attenuated after adjusting for the respondents' education level. This suggests that these genetic effects do not influence cognition primarily through educational attainment in this cohort, which is consistent with previous studies (49). However, we should not entirely rule out potential underlying biological mechanisms that involve educational attainment because the measure of education used here (ie, having a college degree/high school degree or not) may not fully reflect the quality of an individual's educational experience or their cognitive ability at the time of graduation.

We note that different measures of SES had strikingly different genetic interactions on memory outcomes. This may be because the SES variables influence cognitive function through different causal pathways. For example, higher financial strain may be associated with poor quality housing, inability to afford healthy foods, difficulty accessing healthcare and greater psychosocial stress. While lower parental education certainly can lead to increased financial strain, it may also reduce social capital (eg, reduced ability to help children learn skills for navigating society and getting high-paying jobs). Maternal and paternal education may also show different patterning with respect to cognitive trajectories. For example, in this generation, paternal educational attainment may be predictive of financial well-being related to family and material resources. Maternal educational attainment, on the other hand, may be more strongly associated with the child's own cognitive development in younger ages due to the more frequent maternal interactions with the child. This implies that the effect of paternal and maternal education may also interact differently with genes to shape memory trajectories.

In both EA and AA, minor alleles of the most strongly associated SNPs in *SLC24A4* and *MS4A4A* were negatively associated with cognitive function in those with low parental education. This suggests that these genetic effects present most strongly in those whose parents had less than 8 years of education, corresponding to a stress diathesis model (50). However, the effect sizes were relatively small (range: −0.416 to −0.061) even with the most strongly associated SNPs. For those whose mother had at least 8 years of education, the minor allele of the most strongly associated SNP in *MS4A4A* in AA was positively associated with memory performance. Notably, our finding that genetic effects were strongest in those with lower childhood socioeconomic context is contrary to previous findings from twin studies in the United States which tend to show stronger genetic effects in higher childhood SES groups for cognition in both childhood and adulthood (12). One reason for this difference may be that our study examined specific genes rather than estimating a genome-wide genetic effect biometrically, or that some gene-by-childhood SES effects may be different for child and adult cognition, as demonstrated by a study of German participants (51). We also note our current findings are consistent with our previous study of gene-by-adult SES effects on cognitive function in HRS, where we found that lower SES groups had larger genetic effects (9).

Our study has notable strengths. By assessing memory performance, as well as decline estimated over a long period of time using up to 11 timepoints, we were able to identify differential genetic interactions for each trait. The use of both CFSI and parental education allowed us to evaluate interactions between genes and different aspects of childhood SES. In addition, utilization of a gene-based approach allowed us to test all genetic polymorphisms within a gene region at the same time, ultimately reducing multiple testing burden and enhancing the overall power of the analysis (13). This methodology may also be preferred over single SNP analysis when comparing associations across ethnic groups, because differences in allele frequencies and linkage disequilibrium make it challenging to assess effects of gene regions (52). Lastly, instead of using a candidate gene approach that relies on a priori information regarding the biological mechanisms of a disease, we investigated a set of genes that had previously shown to be significantly associated with memory as well as other traits related to cognitive diseases and brain physiology. We used this approach because the etiology of dementia may be multifaceted, and difficult to identify due to the significant overlap of symptoms across other cognitive diseases (53).

Unfortunately, the present study faces some limitations. First, although we assessed gene-by-environment interactions in an EA and AA sample, as well as combined via trans-ancestry meta-analysis, the genes used were derived from GWAS primarily composed of EA subjects, which could have led to increased power in the EA sample and inconsistent findings across ethnic groups. Secondly, we combined immediate and delayed recall into a summary measure to obtain more robust estimates of memory function. With this approach, we are not able to discern whether genetic interactions are driven primarily by immediate or delayed recall. Third, we only examined limited aspects of childhood SES. We also dichotomized parental education (<8 vs ≥8 years). One reason for this is because the exact number of years of parental education was not available for participants in the earliest HRS waves. While this is certainly a limitation of the data, the rationale for phrasing the question this way was that the parents of people born in the 1930s were less likely to have high levels of education. In current study, 58-86% of participants had parental education ≥ 8 years, which is similar to the percentage of parents with

≥12 years (high school) education that is often used as a threshold in younger cohorts. Finally, although our sample is nationally representative, there may be mortality-related selection bias in older age groups (54).

Examination of common and rare variants in genes discovered through previous GWAS show that childhood SES may interact with a few key gene regions to jointly impact memory function and decline in later life. Genetic effects may be more salient for those with lower childhood SES. The results highlight the importance of incorporating trajectories of SES throughout childhood in genetic research to potentially account for some of the missing heritability in cognitive function across ethnic groups. This ultimately may provide opportunities to more effectively identify genetically susceptible subgroups of the population that have an increased risk of cognitive impairment in later life through lower childhood SES.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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Author Contributions

J.D.F., J.A.S., and C.M. conceptualized and designed the study. M.K., J.D.F., J.A.S., and K.E.R. wrote the manuscript. M.K., W.Z., and M.Y. conducted the analysis. J.D.F. and J.A.S. provided funding. All authors contributed substantive revisions to the manuscript and approved the final version.

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