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Genome-wide Studies of Verbal Declarative Memory in Nondemented Older People: The Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium

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Abstract

BACKGROUND—Memory performance in older persons can reflect genetic influences on cognitive function and dementing processes. We aimed to identify genetic contributions to verbal declarative memory in a community setting.

METHODS—We conducted genome-wide association studies for paragraph or word list delayed recall in 19 cohorts from the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium, comprising 29,076 dementia-and stroke-free individuals of European descent, aged ≥45 years. Replication of suggestive associations ($p < 5 \times 10^{-6}$) was sought in 10,617 participants of European descent, 3811 African-Americans, and 1561 young adults.

RESULTS—rs4420638, near *APOE*, was associated with poorer delayed recall performance in discovery ($p = 5.57 \times 10^{-10}$) and replication cohorts ($p = 5.65 \times 10^{-8}$). This association was stronger for paragraph than word list delayed recall and in the oldest persons. Two associations with specific tests, in subsets of the total sample, reached genome-wide significance in combined analyses of discovery and replication (rs11074779 [*HS3ST4*], $p = 3.11 \times 10^{-8}$, and rs6813517 [*SPOCK3*], $p = 2.58 \times 10^{-8}$) near genes involved in immune response. A genetic score combining 58 independent suggestive memory risk variants was associated with increasing Alzheimer disease pathology in 725 autopsy samples. Association of memory risk loci with gene expression in 138 human hippocampus samples showed cis-associations with *WDR48* and *CLDN5*, both related to ubiquitin metabolism.

CONCLUSIONS—This largest study to date exploring the genetics of memory function in ~ 40,000 older individuals revealed genome-wide associations and suggested an involvement of immune and ubiquitin pathways.

Keywords

Alzheimer disease; Dementia; Epidemiology; Genetics; Population-based; Verbal declarative memory

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DISCLOSURES

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The ability to form and retrieve memories is one of the most fundamental and complex aspects of human cognition. Decline in memory performance is a prominent marker of cognitive decline that occurs in late life and is one of the earliest signs of dementia (1,2). Verbal declarative memory, the conscious recall of information that can be retrieved verbally, can be measured using word list and paragraph recall tests. The delayed recall performance of these tests is a powerful predictor of Alzheimer disease (AD) (3).

Cognitive ability and memory performance were shown to be highly heritable (4–7). However, few consistent genetic associations have been described, mostly assessed by candidate gene association studies (8,9). Three genome-wide association studies (GWAS) of verbal declarative memory, on overlapping samples of 333 to 1073 young adults in their twenties, have identified associations of genetic variants in the *KIBRA* and *CTNNBL1* genes with delayed recall (10,11). No GWAS of verbal declarative memory delayed recall performance has been performed in older individuals to our knowledge.

Genetic determinants of verbal declarative memory are likely to differ between young and old individuals, although some may be shared across age groups (4). In young adults, developmental genes determining the neural networks required for learning, storage, and retrieval or genes involved in the molecular mechanisms of memory storage (12) could be expected to harbor most susceptibility variants. In older individuals, variants in genes involved in brain aging and neurodegenerative disease may be more likely revealed (13).

Our aim was to identify genetic variants associated with memory performance in late middle-aged and older individuals. We conducted a meta-analysis of GWAS for delayed recall performance in tests of verbal declarative memory in 29,076 older community-based individuals and sought replication and extension of findings in 13,998 independent older participants (10,617 of European descent and 3381 African-Americans) and 1561 young adults.

METHODS AND MATERIALS

GWAS Study Population

Analyses were performed in 19 population-based cohorts participating in the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium (Section 2, Table S1 in Supplement 1). All subjects were aged ≥45 years and dementia and stroke free at cognitive assessment. The study population comprised 29,076 participants of European ancestry, including 6674 participants with paragraph recall and 24,604 participants with word list recall tests. Each cohort secured approval from institutional review boards, and all participants provided written informed consent for study participation, cognitive testing, and use of DNA for genetic research. None of these studies have previously published GWAS for delayed recall performance in tests of verbal declarative memory.

Memory Tests

Participants were administered one or both types of verbal declarative memory tests: word list delayed recall (WL-dr) and paragraph delayed recall (PAR-dr). WL-dr comprised tests using visually or verbally presented word lists, with or without semantic relatedness between

the words; PAR-dr comprised tests using one or two verbally presented stories (Figure 1; Table S2 in Supplement 1). Participants were asked to remember as many words or paragraph elements as possible after a specified delay interval, preceded by an immediate recall task (Section 3 in Supplement 1). We decided a priori to run both global meta-analyses combining all tests and meta-analyses combining similar tests. Indeed, different memory tests may involve partly distinct neural networks and mechanisms (Section 3 in Supplement 1). Meta-analyses thus comprised a combination of all measures of delayed recall (ALL-dr; n = 29,076), PAR-dr (n = 6674), WL-dr (n = 24,604), and various subtypes of WL-dr tests, including Consortium to Establish a Registry for Alzheimer's Disease delayed recall (CERAD-dr, n = 4,274), Delayed Word Recall Test (n = 9,188), Rey Auditory Verbal Learning Test (RAVLT-dr, n = 4,274), California Verbal Learning Test (CVLT-dr, n = 2,950), and Hopkins Verbal Learning Test (n = 331) (Figure 1).

Genotyping and Imputation

The consortium was formed after the individual studies had finalized their GWAS platforms; hence, the studies included used different platforms. Genotyping platforms are described in Table S4 in Supplement 1. Imputation to nonmonomorphic, autosomal single nucleotide polymorphisms (SNPs) from the HapMap CEU (Utah residents with Northern and Western European ancestry from the CEPH collection) panel was performed with standard quality control filters (Section 4, Tables S5 and S6 in Supplement 1). *APOE*-ε genotypes are not available on the GWAS arrays; however, *APOE*ε had been genotyped separately in most cohorts.

Discovery GWAS

Within each cohort, a linear regression model was used to evaluate the association of raw scores for delayed recall (number of words or story elements recalled) with the number of minor alleles (0 to 2) at each SNP. Analyses were adjusted for age and sex and, if relevant, study site, familial structure, and population substructure (Section 5 in Supplement 1). We additionally adjusted for educational achievement (Table S1 in Supplement 1) in a secondary model only, as this could weaken associations with developmental genes that may impact educational attainment.

We undertook meta-analyses with METAL (14) using inverse-variance weighted meta-analysis to combine GWAS for the same memory test and effective sample size weighted meta-analysis to combine GWAS for nonidentical memory tests (Section 5 in Supplement 1). Effective sample size weighted meta-analysis is recommended when the dependent variable is measured on different scales between cohorts and does not yield any directly comparable effect estimate. For each SNP, the Z statistic was weighted by the effective sample size (product of the sample size and the ratio of the empirically observed dosage variance to the expected binomial dosage variance for imputed SNPs). A combined estimate was obtained by summing the weighted Z statistics and dividing by the summed weights. Genomic control was used to remove residual population stratification within cohorts and in the meta-analysis.

Replication and Extension

We sought to replicate our strongest association signals ($p < 5 \times 10^{-6}$) in seven independent population-based cohorts including 10,617 participants of European descent. We also attempted to extend our findings to 3811 individuals of African-American ancestry and to 1561 young adults in their twenties (Section 2, Table S1 in Supplement 1; for genotyping methods, Section 4, Tables S4–S6 in Supplement 1).

Functional Annotation

Expression Quantitative Trait Loci—We analyzed the association of suggestive memory risk loci from the discovery GWAS ($p < 5 \times 10^{-6}$) with hippocampus cell line whole-genome gene expression profiles. This information was derived from 138 human premortem hippocampus samples (15). Exploratory p value thresholds of .05 were used for cis-expression quantitative trait loci (eQTL) (distance between SNP and probe < 2 Mb) and 10^{-4} for trans-eQTLs (Section 6 in Supplement 1).

Pathway Analysis—Pathway analyses were carried out using the core analysis function of the Ingenuity Pathway Analysis software (IPA; Ingenuity Systems, Redwood City, California). We performed gene-based tests for association based on results from the PAR-dr and WL-dr discovery GWAS, using the Versatile Gene-based Association Study (VEGAS) software (16). The full list of genes and gene-based p values generated by VEGAS was uploaded into IPA for use as a reference set (16,965 genes were available for the PAR-dr analysis and 16,953 for the WL-dr analysis). From this list, p value cutoffs of .01 or .05 were used to identify IPA focus molecules (Section 7 in Supplement 1). Networks generated by IPA provide insight into the molecular interactions of the focus molecules, independent of any predictions of biological function. For this analysis only, direct interactions were used, that is, where there is physical contact between the two molecules. The network building algorithm ranks focus molecules by interconnectedness (the number of triangular connections with other pairs of genes). The top molecule is taken as a seed gene and additional focus molecules are added, prioritizing those that have the most overlap with the existing network. The default IPA network size of 35 nodes was used (Section 7 in Supplement 1).

Association with AD Pathology

We examined the relation of memory risk alleles and a memory genetic score with AD pathology (intracellular neurofibrillary tangles and extracellular amyloid plaques) in the Religious Orders Study and the Rush Memory and Aging Project ($n = 725$; Section 8 in Supplement 1) (17). The memory genetic score comprised all independent SNPs ($R^2 < .25$) associated with memory performance at $p < 5 \times 10^{-6}$ (Section 9 in Supplement 1). Briefly, each participant was assigned a score value, determined by summing up the number of copies (or imputed dosage) of each memory risk allele; each SNP in the score was weighted by the corresponding Z score from the memory GWAS meta-analysis.

Candidate Genes

***APOE* Locus—**Because *APOEε4* is the major known genetic risk factor for AD, we explored its association with memory performance in discovery and replication studies where this genotype was available (n = 33,403 for WL-dr, n = 13,170 for PAR-dr), comparing *APOEε4* carriers with noncarriers. Secondary analyses stratified on the cohort's mean age (≥ 65 versus < 65) were run.

Published Memory and AD Risk Alleles—In the discovery GWAS, we tested whether memory performance was associated with published memory susceptibility SNPs and confirmed AD risk variants other than *APOEε4*; Bonferroni correction for the number of independent SNPs (R^2 < .25) (18) tested was used, corresponding to significance thresholds of p < .0029 (= .05/17) for memory risk variants and p < .0025 (= .05/20) for AD risk variants available in HapMap (Tables S11 and S12 in Supplement 2). For published memory risk variants, we extracted gene-based p values [obtained with VEGAS (16)] for genes closest to these variant SNPs (p threshold < .0036 [.05/14 genes]). We also constructed a genetic risk score comprising AD risk variants from 20 independent AD risk loci (19) to estimate the joint effect of these SNPs on memory performance (Section 10 in Supplement 1) (20).

RESULTS

GWAS of Verbal Declarative Memory

GWAS meta-analyses of verbal declarative memory comprised in total 29,076 participants (mean age 63.6 ± 7.0 years, 56.0% women; see Table S1 in Supplement 1 for detailed demographic characteristics). Quantile-quantile plots showed no evidence of spurious inflation of p values or significant population stratification (Figure S1 in Supplement 1). Genome-wide plots of p values for SNPs against their genomic position are shown in Figure S2 in Supplement 1. For replication, 10,617 participants (72.8 ± 5.4 years, 78.3% women) were available.

Two loci reached genome-wide significance (Tables 1 and 2): on chromosome 19q12 (rs4420638, $p = 1.94 \times 10^{-10}$) with PAR-dr and on chromosome 5q11 (rs13358049, $p = 9.69 \times 10^{-9}$) with CVLT-dr. The top SNPs on chromosome 19q12 are in linkage disequilibrium (LD) with *APOEε4* and are known to be associated with an increased risk of AD. They were significantly replicated ($p = 5.65 \times 10^{-8}$ for rs4420638). In the combined discovery and replication sample, rs4420638 explained approximately 1% of the variance in paragraph delayed recall performance (Table S13 in Supplement 1). Although the direction of effect was consistent, the chromosome 5q11 locus was not confirmed in the replication sample.

In total, 174 SNPs reached a suggestive p value ($p < 5 \times 10^{-6}$) in at least one GWAS meta-analysis (Table S7 in Supplement 2), representing 58 independent loci (R^2 < .25). The association between RAVLT-dr and rs11074779 (chromosome 16p12, near *HS3ST4*) was replicated ($p = 1.08 \times 10^{-3}$) and reached genome-wide significance when combining discovery and replication cohorts ($p = 3.11 \times 10^{-8}$; Figure 2, Table 3). Association of CERAD-dr with rs6813517 (chromosome 4q32.3, near *SPOCK3*) was significant in an

African-American extension sample ($p = .020$) and reached genome-wide significance when combining with the discovery GWAS ($p = 2.58 \times 10^{-8}$; Figure 2, Table 4). No European replication sample was available for CERAD-dr. Three additional SNPs were replicated at $p < .05$ with effects in the same direction, without reaching genome-wide significance (Tables 1 and 2): rs9528384 (chromosome 13q21), rs1633735 (chromosome 5p15) with PAR-dr, and rs13166268 (chromosome 5q23) with CVLT-dr.

The above findings were not significant in a sample of 1561 young adults (22.3 ± 3.4 years, 69.1% women; Table S7 in Supplement 2).

APOE and Delayed Recall Performance

The *APOE* locus (i.e., *APOEε4* and GWAS SNPs in LD) yielded genome-wide significant associations with PAR-dr, while associations with WL-dr were much less significant ($p > 5 \times 10^{-6}$), despite a larger sample size (Tables 1 and 5). When restricting analyses to older cohorts (mean age ≥65), associations of *APOEε4* with memory performance were significantly strengthened ($p = 1.22 \times 10^{-5}$ and $p = 2.64 \times 10^{-3}$ for difference with WL-dr and PAR-dr in young cohorts), still reaching weaker significance levels for WL-dr ($p = 6.25 \times 10^{-11}$) than for PAR-dr ($p = 3.84 \times 10^{-20}$). This remained true when restricting analyses to studies where the same participants underwent both tests of WL-dr ($p = 1.34 \times 10^{-17}$) and PAR-dr ($p = 6.80 \times 10^{-7}$). Associations of *APOEε4* with memory performance were substantially weakened after adjustment for the most significant GWAS proxy (rs4420638), suggesting no additional independent signal at this locus (Table 5). There was a nominally significant interaction of *APOEε4* carrier status with rs11074779 in association with RAVLT ($p = .02$) but not with other SNPs reaching genome-wide significance in the GWAS or in the combined analysis of discovery and follow-up cohorts; *APOEε4* non-carriers had slightly higher effect estimates for the association of rs11074779 with RAVLT compared with *APOEε4* carriers (Table S8 in Supplement 1).

Functional Annotation

Hippocampal eQTL—Among associations of suggestive memory risk variants with RNA expression in the human hippocampus (Table S9 in Supplement 2), the most significant *cis*-associations included rs2280630 (PAR-dr, p[eQTL] $= 6.59 \times 10^{-7}$) with *WDR48*, encoding a ubiquitin-specific protease associated protein belonging to a family of deubiquitinating enzymes, and rs5747035 (RAVLT-dr, p[eQTL] $= 7.63 \times 10^{-3}$) with *CLDN5*, encoding a membranal tight junction protein that plays a critical role in determining the permeability of endothelial barriers and whose degradation is regulated by the ubiquitin-proteasome pathway (21). Associations of rs2280630 and rs5747035 with PAR-dr and RAVLT-dr were in the same direction as in the discovery GWAS in the follow-up studies but did not reach significance ($p = .058$ and .19; Tables 1 and 3).

Pathway Analysis—The networks reaching the highest score, i.e., the lowest chance of randomly finding the selected number of focus molecules in a network of the selected size, are shown in Figure S3 in Supplement 1. In the PAR-dr pathway analysis using a gene-based p value cutoff of .01, the top three networks and networks 5 and 6 (ordered by decreasing scores, respectively, of 33, 28, 26, 25, 24, 21) all included Ubiquitin C (UBC) as

a central hub. UBC was also a central hub in networks 3, 4, 5, and 6 (respective scores 27, 26, 23, and 23) of the WL-dr pathway analysis using a gene-based *p* value cutoff of .01. When using a gene-based *p* value cutoff of .05, several PAR-dr and WL-dr networks also included UBC as a central hub. As UBC has a large number ($n = 8332$) of directly related molecules, we calculated whether there are more UBC interactions in the whole focus molecule set than would be expected by chance, given the number of UBC interactions in the reference set, using the hypergeometric distribution test. The latter suggested that this over-representation was not due to chance (Table S10 in Supplement 1).

Association with AD Pathology

The *APOE* locus and four intronic SNPs in LD within the *KIAA1797* gene on chromosome 9 were associated with increasing amyloid plaque burden and neurofibrillary tangle density (false discovery rate-corrected *p* value < .05; Table S11 in Supplement 2). The memory genetic score, combining 58 independent variants associated with memory at $p < 5 \times 10^{-6}$, was significantly associated with increasing amyloid plaque burden (effect estimate [β] ± SE: .0103 ± .0045, $p = .022$) and neurofibrillary tangle density (β ± SE: .0106 ± .0035, $p = .0028$). After removing the *APOE* locus from the score, the association was still significant for neurofibrillary tangle density (β ± SE: .0079 ± .0036, $p = .027$).

Candidate Gene Analysis

Published Memory Risk Variants—None of the SNPs previously reported to be associated with memory performance, mostly in young cohorts, reached a statistically significant level of association after correction for multiple testing in our middle-aged to older samples (Table S12 in Supplement 1).

Published Risk Variants for AD—Except for *APOE*, none of the AD risk loci were significantly associated with memory performance individually (Table S14 in Supplement 1). However, an AD genetic risk score was significantly associated with worse performance on WL-dr, CERAD-dr, ALL-dr, and PAR-dr; the latter two associations remained significant after removing the *APOE* locus from the AD genetic risk score (Table S15 in Supplement 1).

DISCUSSION

Principal Findings

In this first GWAS of verbal declarative memory in almost 30,000 older nondemented community adults, we observed a genome-wide significant association of the *APOE* locus with poorer memory performance, especially for paragraph delayed recall. Two additional associations in subsets of the total sample and for specific tests, i.e., of rs11074779 near *HS3ST4* with RAVLT-dr and of rs6813517 near *SPOCK3* with CERAD-dr, were replicated and reached genome-wide significance after combining discovery and replication samples.

Results were overall similar with and without education adjustment. Associations with the *APOE* locus tended to be slightly more significant in the education-adjusted model, whereas SNPs near genes involved in neuronal development and synaptic function were more

significantly associated without education adjustment, in line with the hypothesis that effects of developmental genes may be masked by correcting for educational achievement (22).

In the Context of the Literature and Putative Mechanisms

Although *APOEε4* is a well-established risk factor for AD, its association with memory performance is controversial (9,23); some studies on relatively small samples have suggested an age-dependent detrimental effect of *APOEε4* on memory performance (24) and even a protective effect in young adults (25). The present findings confirm a highly significant association of *APOEε4* with poorer memory performance in the oldest cohorts, while the association did not reach or barely reached significance in the young and middle-aged cohorts, both in European and African-American samples. Whereas this age-dependent effect could be partly ascribed to the higher prevalence of subclinical AD with increasing age, *APOEε4* could also influence cognitive aging independently of the mechanisms underlying AD (13). The much stronger detrimental effect of *APOEε4* on PAR-dr than on WL-dr is intriguing. Word list and story listening tasks were shown to activate different brain regions, with unequal involvement of the right hemisphere (26,27), and performance on these tests is significantly but not very strongly correlated (Table S3 in Supplement 1). Our data suggest that PAR-dr may perhaps better capture *APOEε4*-related decline in memory performance than WL-dr. More broadly, these discrepancies have important implications when planning future genetic studies of cognition as they highlight how distinct memory tasks are (even when focusing on delayed recall performance) and potentially also in the context of ongoing and proposed preventive trials for cognitive decline or dementia targeting *APOEε4* carriers; our results suggest that paragraph delayed recall tests might be a more suitable end point for these studies (28).

Even after excluding *APOE*, AD genetic risk loci were associated, in aggregate, with poorer delayed recall performance. This may suggest that, even in nondemented older adults, diminished performance in verbal declarative memory may be partly mediated by early preclinical neurodegenerative processes. This was further supported by the association of the memory genetic score with a larger burden of AD pathology, which suggests that, in combination, memory risk loci distinct from the known AD risk loci also contribute to AD pathology. However, taken individually, apart from *APOE*, none of the memory risk variants reaching genome-wide significance in the combined discovery and replication sample were known AD risk variants or were associated with AD pathology, indicating that other mechanisms may be modulating memory performance in older dementia-free individuals.

We did not confirm previously reported associations with memory performance; however, previous studies were conducted mostly in young adults and did not focus exclusively on the delayed recall component of memory.

The association of rs11074779 with RAVLT-dr was replicated and reached genome-wide significance in the combined analysis of European discovery and replication samples. Rs11074779 is located at 302 kilobase from *HS3ST4*, which is strongly expressed in the hippocampus and is thought to play a role in herpes simplex virus (HSV)-1 pathogenesis (29); it is intriguing that HSV-1 infection of the brain (herpes simplex encephalitis) preferentially affects the hippocampus and can result in profound memory loss. Further,

AD-related plaques and tangles were shown to be enriched in HSV-1 binding proteins (30), and although controversial, a possible role of HSV-1 has been suggested in AD occurrence (31–33). The association of rs6813517 with CERAD-dr was significant in an African-American extension cohort and reached genome-wide significance in the combined analysis of discovery and extension samples. Rs6813517 is located at 367 kilobase from *SPOCK3*, encoding a member of a novel family of calcium-binding proteoglycan proteins, which is strongly expressed in cerebral cortex and hippocampus. Another variant near *SPOCK3* (rs13111850, R^2 = .003 with rs6813517) was recently found to be associated with variations in cytokine secretion in response to smallpox vaccine (34). Interestingly, an immune system dysfunction has been suggested in AD based on findings from recent AD GWAS and genome-wide pathway analyses (19,35–37). Functional prediction analyses using the Kyoto Encyclopedia of Genes and Genomes and Gene Ontology suggest that *HS3ST4* is implicated in synaptic transmission and neurotransmitter receptor activity, while *SPOCK3* appears to be involved in regulation of action potential in neurons, neurotransmitter uptake, and memory (http://genenetwork.nl). Two suggestive intergenic variants associated with PAR-dr (near protocadherin 20 [*PCDH20*] and semaphorin 5A [*SEMA5A*]) reached nominal significance in the replication analysis. PCDH20 belongs to the subfamily of nonclustered protocadherins, which likely contribute to the establishment and remodeling of selective synaptic connections and to the maintenance and plasticity of adult hippocampal circuitry (38). SEMA5A belongs to the semaphorin family, which is involved in axonal guidance during neural development (39) and has been associated with autism (40).

In the pathway analyses, a larger proportion of genes appeared to bind polyubiquitin C than predicted by chance, and several eQTL associations with genes involved in ubiquitin metabolism were observed. Converging evidence suggests a major role of impaired protein degradation by the ubiquitin proteasome system in neurodegenerative disorders including AD (41,42). Ubiquitination was also demonstrated to facilitate hippocampal plasticity and hippocampal-dependent memory storage by modulating CPEB3 activity and CPEB3-dependent protein synthesis and synapse formation (43).

Strengths and Limitations

Strengths of this study include the large sample size and the diversity of populations studied. We provide a wide array of functional analyses including assessments of shared genetic variation with AD pathology and hippocampal gene expression analyses. The main limitation is the absence of replicated genome-wide significant findings in the discovery cohort apart from the *APOE* locus, despite the very large sample size and despite substantial heritability of verbal semantic memory delayed recall, with heritability estimates ranging between h^2 = .30 and h^2 = .52 ($p < 1.20 \times 10^{-4}$) in participating studies and in the literature (Section 11 in Supplement 1). Different tests have been performed across cohorts to quantify verbal memory performance: we attempted to harmonize tests by close examination of each test selected for inclusion and performed test-specific meta-analyses, although this implied smaller sample sizes, thereby reducing statistical power. This has likely reduced our ability to detect genetic associations and suggests that efforts should be made in the future to collectively define cognitive testing protocols across various large population-based samples. Age differences between discovery and follow-up studies may have reduced our

ability to replicate findings; sensitivity analyses performed in the discovery cohorts on the top loci showed that associations were slightly strengthened when focusing on a more narrow age range (Table S16 in Supplement 1). The absence of association of our top loci with memory performance in the extension cohort of young adults, although we had relatively limited power for this analysis (Table S16 in Supplement 1), also supports that genetic risk loci for memory performance may differ according to age.

The intrinsic complexity and heterogeneity of mechanisms influencing memory performance is a major challenge in deciphering the genetics of human verbal memory (28). Cognitive tests are influenced by medication, anxiety, and mood, inducing variance in the verbal memory phenotype that is not attributable to genetic variation, possibly hampering power to detect genetic susceptibility variants for memory performance (44). Moreover, effect sizes for quantitative traits are often small and may require larger sample sizes to be detected. As our aim was to identify genetic variants associated with memory performance in older community persons and not to study genetic determinants of memory performance in a selected sample of cognitively high-functioning individuals, we did not exclude participants in the low range of cognitive performance who may have been categorized as having mild cognitive impairment based on neuropsychological test results.

Conclusion and Implications

In conclusion, in a large sample of older community-dwelling adults, the *APOE* locus was associated with weaker verbal memory performance, especially in those above age 65 years. Two additional genome-wide associations, near *HS3ST4* and *SPOCK3,* were identified and other putative modulators of memory performance were revealed by a pathway approach and hippocampal gene expression analyses, warranting further exploration in independent cohorts. The differential associations according to memory test characteristics and age should be accounted for in future studies. Finally, exploring other types of genetic variation, including rare variants and epigenetic modifications, will be crucial to decipher the full spectrum of memory heritability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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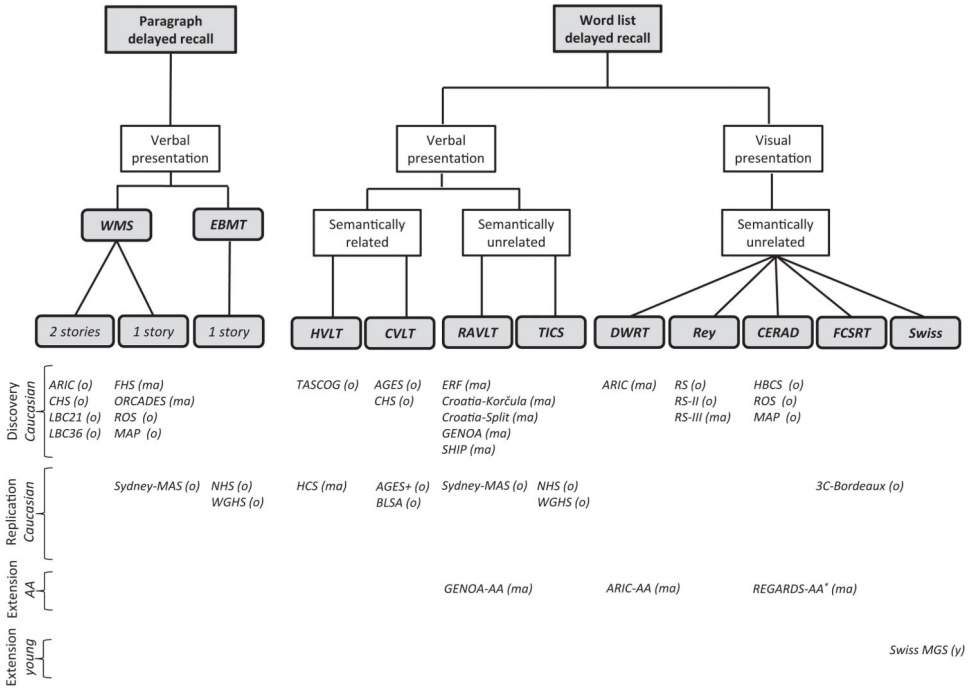

Figure 1.

Memory test categories and analysis strategy. Middle-aged (ma) cohorts aged >45 years, with an average age <65 years; old (o) cohorts aged >65 years; young (y) cohorts aged <45 years. *in REasons for Geographic and Racial Differences in Stroke (REGARDS) the Consortium to Establish a Registry for Alzheimer's Disease delayed recall (CERAD-dr) test was administered by phone.

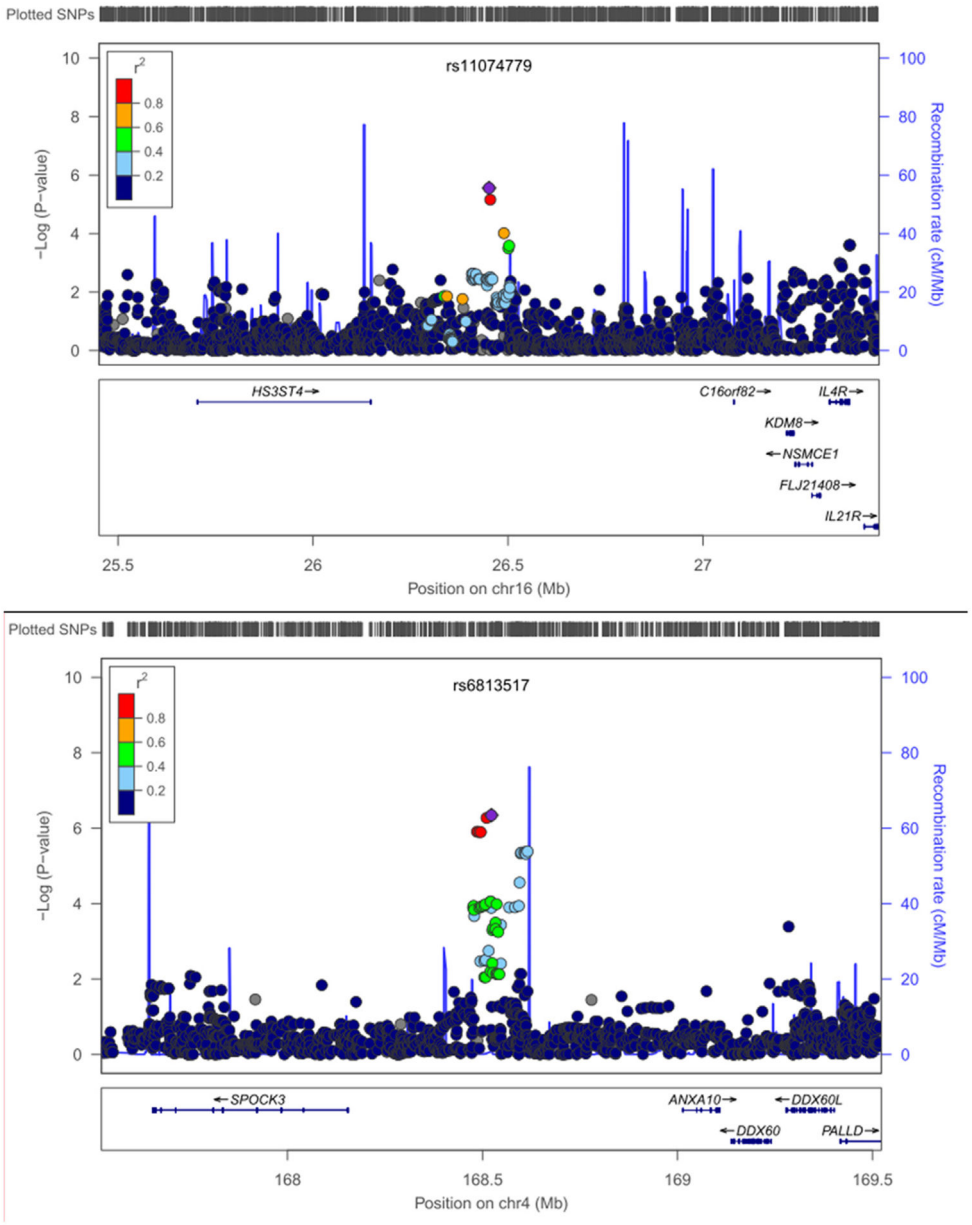

Figure 2.

Regional association plots in the discovery genome-wide association study (GWAS) centered on rs11074779 (Rey Auditory Verbal Learning Test delayed recall [RAVLT-dr]) and rs6813517 (Consortium to Establish a Registry for Alzheimer's Disease delayed recall [CERAD-dr]). Regional plot for associations in region centered on rs11074779 (RAVLT-dr) and rs6813517 (CERAD-dr), drawn using the LocusZoom software (45). All single nucleotide polymorphisms (SNPs) based on imputed results (dots) are plotted with their GWAS meta-analysis *p* values against their genomic position. The color of the dots represents the linkage disequilibrium between SNPs. Purple line represents estimated

recombination rates. Genes and exons are shown as dark blue arrows and vertical lines, respectively.

Table 1

Most Significant Genetic Associations with Paragraph Delayed Recall

									Meta Discovery $n = 6674$			Meta Replication $n = 6496$		Meta All $n = 13,170$		Extension AA $n = 416$	
SNP	**chr**	**Position**	**Function**	**Gene**	**dist**[a]	**EA**	**EAF**	**SNPs**[b]	**dir**[c]	***p***	***p*(het)**	**dir**[d]	***p***	**dir**[e]	***p***	**dir**	***p***
Adjusted for Age and Gender																	
rs4420638	19	50114786	Downstream	*APOC1*	340.0	A	.82	1	+++++++	5.57×10^{-10}	.15	+++	5.65×10^{-8}	++	1.36×10^{-16}	+	.71
rs6857	19	50084094	3′UTR	*PVRL2*	wg	T	.16	1	------+	3.06×10^{-7}	7.67×10^{-4}	---	3.97×10^{-7}	--	5.32×10^{-13}	−	.067
rs2075650	19	50087459	Intronic	*TOMM40*	wg	A	.86	1	++++++	3.15×10^{-7}	9.66×10^{-4}	+++	8.53×10^{-6}	++	1.45×10^{-11}	NA	NA
rs13172717	5	21807809	Intronic	*CDH12*	wg	T	.46	3	-------	6.17×10^{-7}	.42	+-+	.39	+-	1.54×10^{-3}	+	.39
rs9528384	13	61200566	Intergenic	*PCDH20*	313.3	A	.71	1	++++++	1.50×10^{-6}	.54	-++	.040	++	1.06×10^{-6}	−	.13
rs1633735	5	8596190	Intergenic	*SEMA5A*	491.9	T	.25	1	-+-----	4.90×10^{-6}	.59	---	.046	--	3.05×10^{-6}	+	.75
Adjusted for Age, Gender, and Education																	
rs4420638	19	50114786	Downstream	*APOC1*	.3	A	.82	1	+++++++	1.94×10^{-10}	.37	+++	1.73×10^{-7}	++	1.56×10^{-16}	+	.62
rs6857	19	50084094	3′UTR	*PVRL2*	wg	T	.16	1	------+	5.36×10^{-8}	3.85×10^{-3}	---	1.43×10^{-6}	--	4.19×10^{-13}	−	.043
rs2075650	19	50087459	Intronic	*TOMM40*	wg	A	.86	1	++++++	6.77×10^{-8}	2.88×10^{-3}	+++	2.65×10^{-5}	++	1.36×10^{-11}	NA	NA
rs11720125	3	39177345	Intergenic	*AXUD1*	7.2	A	.78	8	+++++++	4.51×10^{-7}	.36	++-	.64	++	7.49×10^{-5}	NA	NA
rs11711871	3	39203047	NS-coding	*XIRP1*	wg	T	.78	4[f]	+++++++	9.6×10^{-7}	.34	++-	.50	++	6.38×10^{-5}	NA	NA
rs1913243	3	39239499	Intergenic	*XIRP1*	30.4	T	.29	2	-------	2.33×10^{-6}	.47	+-+	.39	-+	6.23×10^{-3}	+	.17
rs2280630	3	39170968	Upstream	*AXUD1*	.9	T	.32	1	----+--	2.57×10^{-6}	.29	---	.058	--	2.47×10^{-6}	−	.70
rs9870795	3	39218299	Intergenic	*XIRP1*	9.2	T	.23	1	-------	4.99×10^{-6}	.60	---	.32	--	7.51×10^{-5}	+	.011
rs13172717	5	21807809	Intronic	*CDH12*	wg	T	.46	3	-------	1.38×10^{-6}	.34	+-+	.45	-+	1.77×10^{-3}	+	.38

									Meta Discovery *n* = 6674			Meta Replication *n* = 6496		Meta All *n* = 13,170		Extension AA *n* = 416	
SNP	**chr**	**Position**	**Function**	**Gene**	**dist**[a]	**EA**	**EAF**	**SNPs**[b]	**dir**[c]	***p***	***p*(het)**	**dir**[d]	***p***	**dir**[e]	***p***	**dir**	***p***
rs9907597	17	56790279	Intronic	*BCAS3*	wg	A	.28	1	−−−−−−−	1.75×10^{-6}	.90	−−−	.64	−−	1.78×10^{-4}	+	.37
rs1990292	17	56799540	Intronic	*BCAS3*	wg	A	.79	1	+++−++−	4.61×10^{-6}	.19	++−	.94	+−	1.55×10^{-3}	−	.78
rs4555854	5	38752487	Intergenic	*LIFR*	121.2	T	.73	3	++−−−−−	1.95×10^{-6}	.06	−++	.55	−+	2.74×10^{-3}	−	.68
rs6672300	1	51696814	syn-coding	*EPS15*	wg	T	.29	1	+++++++	3.87×10^{-6}	.78	−−−	.024	+−	.085	+	.059
rs10493155	1	51711785	Intronic	*EPS15*	wg	T	.24	1	+++++++	4.40×10^{-6}	.83	−−−	.064	+−	.044	+	.10

Only SNPs with $p < 5 \times 10^{-6}$ are shown (also see Table S7 in Supplement 2); − means EA is associated with lower score on PAR-dr; + means EA is associated with higher score on PAR-dr.

AA, African-Americans (ARIC-AA); ARIC, Atherosclerosis Risk in Communities Study; chr, chromosome; CHS, Cardiovascular Health Study; dir, direction; dist, distance; EA, effect allele; EAF, effect allele frequency; FHS, Framingham Heart Study; het, heterogeneity; LBC21, Lothian Birth Cohort 1921; LBC36, Lothian Birth Cohort 1936; LD, linkage disequilibrium; MAP, Rush Memory and Aging Project; NHS, Nurses' Health Study; NS, nonsynonymous; ORCADES, Orkney Complex Disease Study; PAR-dr, paragraph delayed recall; ROS, Religious Order Study; Sydney MAS, Sydney Memory and Ageing Study; SNP, single nucleotide polymorphism; UTR, untranslated region; wg, within gene; WHGS, Women's Genome Health Study.

[a] Distance in kilobase.

[b] Number of SNPs in locus (top SNP + SNPs in LD $R^2 > .80$).

[c] Directions are in the following order: ARIC, CHS, FHS, LBC21, LBC36, MAP, ORCADES, ROS.

[d] Directions are in the following order: NHS, Sydney MAS, WGHS.

[e] Directions are in the following order: Discovery, Replication in European cohorts (meta-analysis results combining all European and AA samples are given in Table S7 in Supplement 2).

[f] Of which one other nonsynonymous coding (rs3732383).

Table 2

Most Significant Genetic Associations with Performance on California Verbal Learning Test Delayed Recall

									Meta Discovery $n = 2950$					Meta Replication $n = 2237$		Meta All $n = 5187$	
SNP	**chr**	**Position**	**Function**	**Gene**	**dis**[a]	**EA**	**EAF**	**SNPs**[b]	**dir**[c]	**beta**	**SE**	***p***	***p*(het)**	**dir**[d]	***p***	**dir**[e]	***p***
Adjusted for Age and Gender																	
rs13358049	5	50578216	Intergenic	*ISL1*	136.5	T	.07	15	−−	−.85	.15	2.29×10^{-8}	.58	+−	.97	−−	2.71×10^{-5}
rs13360092	5	50564932	Intergenic	*ISL1*	149.8	A	.07	15	−−	−.85	.15	2.36×10^{-8}	.55	?−	.73	−−	1.25×10^{-7}
rs157092	20	55685666	Intronic	*TMEPAI*	wg	T	.26	4	−−	−.46	.09	8.50×10^{-7}	.29	+−	.82	−+	5.88×10^{-4}
rs13177865	5	120494952	Intergenic	*PRR16*	444.1	A	.09	2	+?	.74	.15	1.29×10^{-6}	1	?+	.79	++	1.03×10^{-5}
rs13166268[f]	5	120387817	Intergenic	*PRR16*	337.0	C	.90	2	−+	−.60	.13	7.20×10^{-6}	.006	−−	.016	−−	8.28×10^{-7}
rs1445765	5	103572875	Intergenic	*NUDT12*	646.5	T	.69	1	−−	−.40	.09	4.29×10^{-6}	.58	−+	.45	−−	9.42×10^{-5}
Adjusted for Age, Gender, and Education																	
rs13358049	5	50578216	Intergenic	*ISL1*	136.5	T	.07	16	−−	−.85	.15	9.69×10^{-9}	.66	+−	.89	−−	1.09×10^{-5}
rs13360092	5	50564932	Intergenic	*ISL1*	149.8	A	.07	16	−−	−.85	.15	1.00×10^{-8}	.63	?−	.51	−−	2.71×10^{-8}
rs157092	20	55685666	Intronic	*TMEPAI*	wg	T	.26	5	−−	−.46	.09	3.69×10^{-7}	.26	+−	.81	−+	3.50×10^{-4}
rs1445765	5	103572875	Intergenic	*NUDT12*	646.5	T	.69	2	−−	−.39	.08	3.29×10^{-6}	.52	−+	.55	−−	1.13×10^{-4}

Only SNPs with $p < 5 \times 10^{-6}$ are shown (also see Table S7 in Supplement 2). − means EA is associated with lower score on CVLT-dr; + means EA is associated with higher score on CLVT-dr; ? means this SNP was not available in the corresponding dataset.

AGES, Aging Gene-Environment Susceptibility-Reykjavik Study; BLSA, Baltimore Longitudinal Study of Aging; chr, chromosome; CHS, Cardiovascular Health Study; CVLT-dr, California Verbal Learning Test Delayed Recall; dir, direction; dist, distance; EA, effect allele; EAF, effect allele frequency; het, heterogeneity; LD, linkage disequilibrium; SNP, single nucleotide polymorphism; wg, within gene.

[a] Distance in kilobase.

[b] Number of SNPs in locus (top SNP + SNPs in LD $R^2 > .80$).

[c] Directions are in the following order: AGES, CHS.

[d] Directions are in the following order: AGES-plus (n = 1525), BLSA (n = 712).

[e] Directions are in the following order: Discovery, Replication.

[f] rs13166268 was added to the list of SNPs for replication despite a p value slightly above the 5×10^{-6} threshold to serve as a proxy for rs13177865 ($R^2 = 1$), with data available in both discovery and both replication cohorts (rs13177865 is available only in one discovery and one replication cohort).

Table 3

Most Significant Genetic Associations with Rey's Auditory Verbal Learning Test Delayed Recall

										Meta Discovery *n* = 4274				Replication *n* = 880		Meta All *n* = 5154		Extension AA *n* = 708	
SNP	**chr**	**Position**	**Function**	**Gene**	**dist**[a]	**EA**	**EAF**	**dir**[b]	**SNPs**[c]	**beta**	**SE**	***p***	***p*(het)**	**dir**[d]	***p***	**dir**[e]	***p***	**dir**[f]	***p***
Adjusted for Age and Gender																			
rs963798	13	38287693	Intronic	*FREM2*	wg	A	.52	+++++	3	.29	.06	1.46×10^{-6}	.65	−	.34	+−	2.00×10^{-5}	+	.92
rs11074779	16	26358944	Intergenic	*HS3ST4*	302.4	T	.81	+++++	1	.36	.08	3.05×10^{-6}	.93	+	1.08×10^{-3}	++	3.11×10^{-8}	−	.48
rs5747035	22	16098606	Intergenic	*CECR1*	27.8	T	.93	−−−−−	1	−.65	.14	3.50×10^{-6}	.89	−	.19	−−	1.38×10^{-6}	+	.93
rs11237982	11	79119342	Intergenic	*ODZ4*	918.5	T	.85	+++++	1	.40	.09	4.33×10^{-6}	.29	+	.099	++	9.73×10^{-7}	+	.31
Adjusted for Age, Gender, and Education																			
rs5747035	22	16098606	Intergenic	*CECR1*	27.8	T	.93	−−−−−	1	−.65	.14	2.61×10^{-6}	.92	−	.18	−−	1.03×10^{-6}	−	.97
rs963798	13	38287693	Intronic	*FREM2*	wg	A	.52	+++++	1	.28	.06	2.71×10^{-6}	.47	−	.27	+−	4.15×10^{-5}	−	.87
rs11237982	11	79119342	Intergenic	*ODZ4*	918.5	T	.85	+++++	1	.39	.08	3.68×10^{-6}	.22	+	.087	++	7.63×10^{-7}	+	.29
rs16991213	20	44402546	Intergenic	*SLC35C2*	9.0	A	.07	+++++	1	.57	.12	4.81×10^{-6}	.93	−	8.63×10^{-4}	+−	1.10×10^{-3}	−	.84

Only SNPs with $p < 5 \times 10^{6}$ are shown (also see Table S7 in Supplement 2); − means EA is associated with lower score on RAVLT-dr; + means EA is associated with higher score on RALVT-dr. AA, African-Americans (GENOA-AA); chr, chromosome; dir, direction; dist, distance; EA, effect allele; EAF, effect allele frequency; ERF, Erasmus Rucphen Family Study; GENOA, Genetic Epidemiology Network of Arteriopathy; het, heterogeneity; LD, linkage disequilibrium; RAVLT-dr, Rey's Auditory Verbal Learning Test delayed recall; SHIP, Study of Health in Pomerania; SNP, single nucleotide polymorphism; Sydney MAS, Sydney Memory and Ageing Study; wg, within gene.

[a] Distance in kilobase.

[b] Directions are in the following order: ERF, GENOA, CROATIA-Korcula, SHIP, CROATIA-Split.

[c] Number of SNPs in locus (top SNP + SNPs in LD $R^2 > .80$).

[d] Sydney MAS.

[e] Directions are in the following order: Discovery, Replication in European cohorts (meta-analysis results combining all European and AA samples are given in Table S7 in Supplement 2).

[f] GENOA-AA.

Table 4

Most Significant Genetic Associations with Consortium to Establish a Registry for Alzheimer's Disease Delayed Recall

										Meta Discovery $n = 4274$				Extension AA $n = 627$			Meta All $n = 4901$		
SNP	**chr**	**Position**	**Function**	**Gene**	**dist**[a]	**EA**	**EAF**	**dir**[b]	**SNPs**[c]	**beta**	**SE**	***p***	***p*(het)**	**beta**	**SE**	***p***	**beta**	**SE**	***p***
Adjusted for Age and Gender																			
rs6813517	4	168759326	Intergenic	*SPOCK3*	367.0	T	.79	+++	5	.36	.07	4.96×10^{-7}	.57	.34	.15	.026	.36	.07	3.49×10^{-8}
rs298210	8	65452923	Upstream	*BHLHB5*	202.4	A	.05	−−−	1	−.67	.14	1.04×10^{-6}	.84	.52	.52	.32	−.59	.13	7.05×10^{-6}
rs6046393	20	19800250	Intergenic	*RIN2*	18.0	T	.8	+++	4	.35	.07	1.47×10^{-6}	.11	.14	.12	.24	.30	.06	1.96×10^{-6}
rs4292676	8	21564528	Intergenic	*GFRA2*	29.3	T	.61	+++	3	.28	.06	3.48×10^{-6}	.72	.20	.17	.23	.27	.06	1.69×10^{-6}
rs1890709	14	48171583	Intergenic	*RPS29*	942.2	A	.29	+++	1	.28	.06	4.28×10^{-6}	.73	−.03	.14	.83	.23	.06	3.49×10^{-5}
rs10894804	11	133753052	Downstream	*B3GAT1*	.6	A	.53	−−−	1	−.31	.07	4.31×10^{-6}	.22	−.11	.16	.50	−.28	.06	6.25×10^{-6}
rs17053482	4	168836226	Intergenic	*ANXA10*	414.1	C	.09	−−−	4	−.48	.10	4.79×10^{-6}	.38	.10	.14	.47	−.28	.08	1.06×10^{-3}
Adjusted for Age, Gender, and Education																			
rs6813517	4	168759326	Intergenic	*SPOCK3*	367.0	T	.79	+++	5	.37	.07	4.12×10^{-7}	.62	.35	.15	.020	.37	.07	2.58×10^{-8}
rs298210	8	65452923	Upstream	*BHLHB5*	202.4	A	.05	−−−	1	−.69	.14	6.83×10^{-7}	.95	.44	.52	.40	−.62	.13	4.45×10^{-6}
rs17053482	4	168836226	Intergenic	*ANXA10*	414.1	C	.09	−−−	6	−.51	.11	162×10^{-6}	.34	.10	.14	.48	−.29	.08	6.27×10^{-4}
rs10894804	11	133753052	Downstream	*B3GAT1*	.6	A	.53	−−−	1	−.32	.07	2.78×10^{-6}	.19	−.10	.16	.54	−.28	.06	5.35×10^{-6}

Only SNPs with $p < 5 \times 10^{-6}$ and available in the AA extension sample are shown (also see Table S7 in Supplement 2); − means EA is associated with lower score on CERAD-dr; + means EA is associated with higher score on CERAD-dr.

AA, African-Americans (REGARDS-AA); CERAD-dr, Consortium to Establish a Registry for Alzheimer's Disease delayed recall; chr, chromosome; dir, direction, dist, distance; EA, effect allele; EAF, effect allele frequency; HBCS, Helsinki Birth Cohort Study; het, heterogeneity; LD, linkage disequilibrium; MAP, Rush Memory and Aging Project; REGARDS, REasons for Geographic and Racial Differences in Stroke; ROS, Religious Order Study; SNP, single nucleotide polymorphism; wg, within gene.

[a] Distance in kilobase.

[b] Directions are in the following order: HBCS, MAP, ROS.

[c] Number of SNPs in locus (top SNP + SNPs in LD $R^2 > .80$).

Table 5

Association of *APOE* Variants with Memory Performance According to Test Type, Age, and Ethnicity

				All European		Old[a] European		Old[a] European: Overlapping Samples for PAR and WL[b]		Middle-Aged[a] European		African-American		Young European[a]
				PAR-dr	WL-dr	PAR-dr	WL-dr	PAR-dr	WL-dr	PAR-dr	WL-dr	PAR-dr[c]	WL-dr[d]	WL-dr
				Age: 71.9	Age: 65.4	Age: 74.0	Age: 73.3	Age: 74.3	Age: 74.4	Age: 64.6	Age: 58.8	Age: 71.8	Age: 57.6	Age: 22.3
				n: 13,170	*n*: 33,403	*n*: 10,258	*n*: 15,118	*n*: 7934	*n*: 7641	*n*: 2912	*n*: 18,285	*n*: 416	*n*: 3184	*n*: 1561
AD Risk Allele	Position	Gene	Model	*p* (PAR)	*p* (WL)	*p* (PAR)	*p* (WL)	*p* (PAR)	*p* (WL)	*p* (PAR)	*p* (WL)	*p* (PAR)	*p* (WL)	*p* (WL)
rs4420638-G	19:50114786	*APOC1*	A	4.18×10^{-10}	2.57×10^{-4}	8.05×10^{-17}	6.26×10^{-10}	1.68×10^{-13}	3.97×10^{-6}	.23	.10	.71	.60	.79
rs6857-T	19:50084094	*PVRL2*	A	2.51×10^{-7}	1.24×10^{-3}	2.41×10^{-14}	5.09×10^{-7}	8.08×10^{-12}	2.03×10^{-4}	.83	.13	.067	.62	NA
rs2075650-G	19:50087459	*TOMM40*	A	2.58×10^{-7}	3.03×10^{-3}	2.52×10^{-12}	1.88×10^{-5}	3.55×10^{-10}	1.57×10^{-3}	.56	.10	NA	.39	NA
Epsilon-4[e]	19:50103781/50103919	*APOE*	A	2.67×10^{-21}	1.28×10^{-7}	3.84×10^{-20}	6.25×10^{-11}	1.34×10^{-17}	6.80×10^{-7}	2.64×10^{-3}	.28	.078	.23	NA
			B	6.58×10^{-23}	6.53×10^{-9}	6.55×10^{-21}	2.07×10^{-12}	2.48×10^{-18}	4.07×10^{-7}	5.77×10^{-4}	.18	.12	.23	NA
			C	6.44×10^{-7}	.47	3.91×10^{-5}	3.33×10^{-3}	4.06×10^{-5}	.043	4.85×10^{-3}	.49	.074	.17	NA
			D	1.00×10^{-7}	.090	2.09×10^{-5}	2.36×10^{-3}	2.47×10^{-5}	.034	1.14×10^{-3}	.72	.12	.14	NA

These results include both discovery and replication cohorts, and in all analyses, except the young European sample, the AD risk allele was associated with worse memory performance. Some cohorts did not have epsilon genotypes available (NHS, CROATIA-Split, SHIP, HBCS, HCS, ORCADES, TASCOG); conversely, AGES-repli had genotypes for the epsilon polymorphism but not for rs4420638, rs6857, and rs2075650; thus sample sizes for these analyses were 10,685 (mean age 71.8 years) for PAR-dr and 29,669 (61.8 years) for WL-dr.

AA, African-Americans; AD, Alzheimer disease; AGES, Aging Gene-Environment Susceptibility-Reykjavik Study; ARIC, Atherosclerosis Risk in Communities Study; BLSA, Baltimore Longitudinal Study of Aging; 3C-Bordeaux, Three City Study-Bordeaux; CHS, Cardiovascular Health Study; ERF, Erasmus Rucphen Family Study; FHS, Framingham Heart Study; GENOA, Genetic Epidemiology Network of Arteriopathy; HBCS, Helsinki Birth Cohort Study; HCS, Hunter Community Study; LBC21, Lothian Birth Cohort 1921; LBC 36, Lothian Birth Cohort 1936; MAP, Rush Memory and Aging Project; Model A, adjusted for age and gender; Model B, adjusted for age, gender, and educational achievement; Model C, adjusted for age, gender, and rs4420638; Model D, adjusted for age, gender, rs4420638, and educational achievement; NHS, Nurses Health Study; ORCADES, Orkney Complex Disease Study; PAR-dr, paragraph delayed recall; ROS, Religious Order Study; RS, Rotterdam Study; RS-II, Rotterdam Study-II; RS-III, Rotterdam Study-III; SHIP, Study of Health in Pomerania; Swiss MGS, Swiss Memory Genetics Study; Sydney MAS, Sydney Memory and Ageing Study; TASCOG, Tasmanian Study of Gait and Cognition; WGHS, Women's Genome Health Study; WL-dr, word list delayed recall.

[a] Young corresponds to cohorts aged <45 years (Swiss MGS), Middle-Aged to cohorts aged >45 years, with an average age <65 years (PAR: FHS, ORCADES; WL: ERF, CROATIA-Split, CROATIA-Korcula, GENOA, SHIP, HCS, ARIC, RS, RS-III), and Old by an average age >65 years (PAR: ARIC, CHS, LBC21, LBC36, ROS, MAP, NHS, WGHS, Sydney MAS; WL: AGES, CHS, TASCOG, BLSA, RS-II, HBCS, 3C-Bordeaux, ROS, MAP, NHS, WGHS, Sydney MAS).

[b] Studies with measures for both paragraph and word list delayed recall on largely overlapping samples were included in this analysis (ROS, MAP, Sydney MAS, NHS, WGHS).

[c] ARIC-AA.

[d] ARIC-AA and GENOA-AA.

[e]The epsilon polymorphism corresponds to a haplotype of rs429358 and rs7412.