



Published in final edited form as:

Biol Psychiatry. 2015 April 15; 77(8): 749–763. doi:10.1016/j.biopsych.2014.08.027.

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

A full list of authors and affiliations appears at the end of the article.

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

Address correspondence to Stéphanie Debette, M.D., Ph.D., Boston University School of Medicine, Department of Neurology, Framingham Heart Study, 72 East Concord Street, B-622, Boston, MA 02118-2526; sdebette@bu.edu.
Authors SD, CAIV, JBr, MS, AS, JCB, GD, CW, DAB, MAI, IJD, CMvD, LL, ALF, SS, and THM contributed equally to this work.
Supplementary material cited in this article is available online at <http://dx.doi.org/10.1016/j.biopsych.2014.08.027>.

DISCLOSURES

All authors reported no biomedical financial interests or potential conflicts of interest.

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 *CTNBL1* 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 *APOE* ϵ 4 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 *APOE* ϵ 4 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 *APOE* ϵ 4; 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 *APOE* ϵ 4 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., *APOE* ϵ 4 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 *APOE* ϵ 4 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 *APOE* ϵ 4 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 *APOE* ϵ 4 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; *APOE* ϵ 4 non-carriers had slightly higher effect estimates for the association of rs11074779 with RAVLT compared with *APOE* ϵ 4 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, $p[\text{eQTL}] = 6.59 \times 10^{-7}$) with *WDR48*, encoding a ubiquitin-specific protease associated protein belonging to a family of deubiquitinating enzymes, and rs5747035 (RAVLT-dr, $p[\text{eQTL}] = 7.63 \times 10^{-3}$) 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 $[\beta] \pm SE: .0103 \pm .0045, p = .022$) and neurofibrillary tangle density ($\beta \pm SE: .0106 \pm .0035, p = .0028$). After removing the *APOE* locus from the score, the association was still significant for neurofibrillary tangle density ($\beta \pm SE: .0079 \pm .0036, p = .027$).

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 *APOE* ϵ 4 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 *APOE* ϵ 4 on memory performance (24) and even a protective effect in young adults (25). The present findings confirm a highly significant association of *APOE* ϵ 4 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, *APOE* ϵ 4 could also influence cognitive aging independently of the mechanisms underlying AD (13). The much stronger detrimental effect of *APOE* ϵ 4 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 *APOE* ϵ 4-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 *APOE* ϵ 4 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.

Authors

Stéphanie Debette, Carla A. Ibrahim Verbaas, Jan Bressler, Maaïke Schuur, Albert Smith, Joshua C. Bis, Gail Davies, Christiane Wolf, Vilmundur Gudnason, Lori B. Chibnik, Qiong Yang, Anita L. deStefano, Dominique J.F. de Quervain, Velandai Srikanth, Jari Lahti, Hans J. Grabe, Jennifer A. Smith, Lutz Priebe, Lei Yu, Nazanin Karbalai, Caroline Hayward, James F. Wilson, Harry Campbell, Katja Petrovic, Myriam Fornage, Ganesh Chauhan, Robin Yeo, Ruth Boxall, James Becker, Oliver Stegle, Karen A. Mather, Vincent Chouraki, Qi Sun, Lynda M. Rose, Susan Resnick, Christopher Oldmeadow, Mirna Kirin, Alan F. Wright, Maria K. Jonsdottir, Rhoda Au, Albert Becker, Najaf Amin, Mike A. Nalls, Stephen T. Turner, Sharon L.R. Kardina, Ben Oostra, Gwen Windham, Laura H. Coker, Wei Zhao, David S.

Knopman, Gerardo Heiss, Michael E. Griswold, Rebecca F. Gottesman, Veronique Vitart, Nicholas D. Hastie, Lina Zgaga, Igor Rudan, Ozren Polasek, Elizabeth G. Holliday, Peter Schofield, Seung Hoan Choi, Toshiko Tanaka, Yang An, Rodney T. Perry, Richard E. Kennedy, Michèle M. Sale, Jing Wang, Virginia G. Wadley, David C. Liewald, Paul M. Ridker, Alan J. Gow, Alison Pattie, John M. Starr, David Porteous, Xuan Liu, Russell Thomson, Nicola J. Armstrong, Gudny Eiriksdottir, Arezoo A. Assareh, Nicole A. Kochan, Elisabeth Widen, Aarno Palotie, Yi-Chen Hsieh, Johan G. Eriksson, Christian Vogler, John C. van Swieten, Joshua M. Shulman, Alexa Beiser, Jerome Rotter, Carsten O. Schmidt, Wolfgang Hoffmann, Markus M. Nöthen, Luigi Ferrucci, John Attia, Andre G. Uitterlinden, Philippe Amouyel, Jean-François Dartigues, Hélène Amieva, Katri Räikkönen, Melissa Garcia, Philip A. Wolf, Albert Hofman, W.T. Longstreth Jr., Bruce M. Psaty, Eric Boerwinkle, Philip L. DeJager, Perminder S. Sachdev, Reinhold Schmidt, Monique M.B. Breteler, Alexander Teumer, Oscar L. Lopez, Sven Cichon, Daniel I. Chasman, Francine Grodstein, Bertram Müller-Myhsok, Christophe Tzourio, Andreas Papassotiropoulos, David A. Bennett, Arfan M. Ikram, Ian J. Deary, Cornelia M. van Duijn, Lenore Launer, Annette L. Fitzpatrick, Sudha Seshadri, and Thomas H. Mosley Jr. **for the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium**

Affiliations

Department of Neurology (SD, ALdS, RA, ABei, PAW, SS), Boston University School of Medicine, Boston, Massachusetts; Institut National de la Santé et de la Recherche Médicale Unit 897 (SD, GC, RY, CT, J-FD, HA), Epidemiology and Public Health, Bordeaux, University of Bordeaux (SD, GC, RY, CT, J-FD, HA), Bordeaux; Department of Neurology (SD, J-FD), and Department of Medical Information (CT), University Hospital of Bordeaux, Bordeaux, France; Genetic Epidemiology Unit (CAIV, MS, NA, BO, CMvD), Department of Epidemiology, and Department of Neurology (CAIV, MS, JCvS), Erasmus Medical Center University Medical Center, Rotterdam, The Netherlands; Human Genetics Center (JBr, MF), School of Public Health, University of Texas Health Science Center at Houston, Houston, Texas; Icelandic Heart Association (AS, VG, MKJ, GE), Kopavogur; and Faculty of Medicine (AS, VG), University of Iceland, Reykjavik, Iceland; Cardiovascular Health Research Unit (JCB, BMP), Department of Medicine, University of Washington, Seattle, Washington; Centre for Cognitive Ageing and Cognitive Epidemiology (GD, RB, DCL, AJG, APat, JMSt, DP, IJD) and Department of Psychology (GD, DCL, AJG, IJD), The University of Edinburgh; and Medical Genetics Section (GD, DP), Molecular Medicine Centre, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, United Kingdom; Max Planck Institute of Psychiatry (CW, NK, BM-M), Munich, Germany; Program in Translational Neuro-Psychiatric Genomics (LBC, PLD), Department of Neurology, Brigham and Women's Hospital, Boston; Department of Biostatistics (QY, ALdS, SHC, JW, XL, ABei, SS), Boston University School of Public Health, Boston; and The National Heart Lung and Blood Institute's Framingham Heart Study (QY, ALdS, RA, ABei, PAW, SS), Framingham,

Massachusetts; Psychiatric University Clinics and Department of Psychology (DJFdQ), Division of Cognitive Neuroscience, University of Basel, Basel, Switzerland; Stroke and Ageing Research Centre (VS), Southern Clinical School, Department of Medicine, Monash University, Melbourne; and Menzies Research Institute Tasmania (VS, RT), University of Tasmania, Hobart, Australia; Institute of Behavioural Sciences (JL, KR), University of Helsinki; and Folkhälsan Research Centre (JL, JGE), Helsinki, Finland; Department of Psychiatry and Psychotherapy (HJG), University Medicine Greifswald, HELIOS-Hospital Stralsund, Stralsund; and German Center for Neurodegenerative Diseases (HJG, WH, MMBB), Site Rostock/Greifswald, Rostock, Germany; Department of Epidemiology (JAS, SLRK, WZ), University of Michigan, Ann Arbor, Michigan; Institute of Human Genetics (LP, SC), Universitätsklinikum Bonn, Bonn, Germany; Rush Alzheimer's Disease Center (LY, DAB), Rush University Medical Center, Chicago, Illinois; Medical Research Council Human Genetics Unit (CH, AFW, VV, NDH, LZ, Institute of Genetics and Molecular Medicine, and Centre for Population Health Sciences (JFW, HC, MK, IR), University of Edinburgh, United Kingdom; Division of General Neurology (KP), Department of Neurology, Medical University and General Hospital of Graz, Austria; Institute of Molecular Medicine (MF), University of Texas-Houston Health Science Center, Houston, Texas; Departments of Neurology and Psychiatry (JBe, OLL) and Psychology (JBe), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; Max Planck Institute for Intelligent Systems(OS) and Max Planck Institute for Developmental Biology (OS), Tübingen, Germany; Centre for Healthy Brain Ageing (KAM, NJA, AAA, NAK, PSS), School of Psychiatry, University of New South Wales Medicine, University of New South Wales, Sydney, Australia; Institut National de la Santé et de la Recherche Médicale Unit 744 (VC, PA), Institut Pasteur de Lille, and Université Lille Nord de France (VC, PA), Lille, France; Department of Nutrition (QS), Harvard School of Public Health; Channing Division of Network Medicine (QS, FG), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; Harvard Medical School (QS, PMR, DIC); and Division of Preventive Medicine (LMR, PMR, DIC), Brigham and Women's Hospital, Boston, Massachusetts; Brain Aging and Behavior Section (SR, YA), Laboratory of Behavioral Neuroscience, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Centre for Clinical Epidemiology and Biostatistics (CO, EGH, PS, JA), School of Medicine and Public Health, Faculty of Health, University of Newcastle and Hunter Medical Research Institute (CO, JA), Newcastle, Australia; Institute of Neuropathology (ABec), Universitäts-klinikum Bonn, Bonn, Germany; Molecular Genetics Section, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health (MAN), Bethesda, Maryland; Department of Internal Medicine (STT), Mayo Clinic, Rochester, Minnesota; Department of Clinical Genetics (BO), Erasmus Medical Center University Medical Center, Rotterdam, The Netherlands; Department of Medicine (GW), Division of Geriatrics, University of Mississippi Medical Center, Jackson, Mississippi; Division of Public Health Sciences and Neurology (LHC), Wake Forest School of Medicine, Winston-Salem, North Carolina; Department of Neurology (DSK), Mayo Clinic, Rochester, Minnesota; Department of Epidemiology (GH),

Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Center of Biostatistics and Bioinformatics (MEG), University of Mississippi Medical Center, Jackson, Mississippi; Department of Neurology (RFG), Johns Hopkins University School of Medicine, Baltimore, Maryland; Department of Public Health (OP), Faculty of Medicine, University of Split, Split, Croatia; Department of Medicine (PS, JA), John Hunter Hospital, Newcastle, Australia; Longitudinal Studies Section (TT, LF), Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Department of Epidemiology (RTP) and Division of Gerontology, Geriatrics, and Palliative Care (REK), University of Alabama at Birmingham, Birmingham, Alabama; Center for Public Health Genomics (MMS), Department of Medicine, Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, Virginia; Department of Medicine (VGW), University of Alabama at Birmingham, Birmingham, Alabama; Alzheimer Scotland Dementia Research Centre (JMSt), The University of Edinburgh, Edinburgh, United Kingdom; Cancer Research Program (NJA), Garvan Institute of Medical Research, Darlinghurst; School of Mathematics Statistics and Prince of Wales Clinical School (NJA) and Neuroscience Research Australia and Primary Dementia Collaborative Research Centre-Assessment and Better Care (AAA), University of New South Wales, Sydney; and Neuropsychiatric Institute (NAK, PSS), Prince of Wales Hospital, Randwick New South Wales, Australia; Institute for Molecular Medicine Finland (EW, APal), University of Helsinki, Finland; Wellcome Trust Sanger Institute (APal), Wellcome Trust Genome Campus, Cambridge, United Kingdom; Department of Medical Genetics (APal), University of Helsinki and University Central Hospital, Helsinki, Finland; Neural Regenerative Medicine (Y-CH), College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan; National Institute for Health and Welfare (JGE), Helsinki; Department of General Practice and Primary Health Care, University of Helsinki, Helsinki; Helsinki University Central Hospital, Unit of General Practice, Helsinki; and Vasa Central Hospital, Vasa, Finland; Psychiatric University Clinics and Department of Psychology (CV, APap), Division of Molecular Neuroscience, University of Basel, Basel, Switzerland; Departments of Neurology and Molecular and Human Genetics (JMSh), Baylor College of Medicine and The Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Houston, Texas; Institute for Translational Genomics and Population Sciences (JR), Los Angeles Biomedical Research Institute and Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, California; Institute for Community Medicine (COS), University Medicine Greifswald, and Section Epidemiology of Health Care and Community Health (WH), Greifswald; Institute of Human Genetics (MMN), Department of Genomics, Life & Brain Research Center, University of Bonn, Bonn; and German Center for Neurodegenerative Diseases (MMN), Bonn, Germany; Netherlands Consortium for Healthy Ageing (AGU, AH, MMBB, MAI, CMvD), Leiden, the Netherlands; Department of Internal Medicine (AGU), Erasmus Medical Center University Medical Center, Rotterdam, the Netherlands; Centre Hospitalier Régional Universitaire de Lille (PA), Lille; and Laboratory of Epidemiology and Population

Sciences (MG, LL), National Institute on Aging, Bethesda, Maryland; Department of Epidemiology (AH, MMBB, MAI), Erasmus Medical Center University Medical Center, Rotterdam, The Netherlands; Departments of Neurology (WTL), Epidemiology (WTL, BMP, ALF), and Health Services (BMP), University of Washington; and Group Health Research Institute (BMP), Group Health Cooperative, Seattle, Washington; Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases (EB), University of Texas Health Science Center at Houston, Houston, Texas; Division of Neurogeriatrics (RS), Department of Neurology, Medical University of Graz, Graz, Austria; Population Health Sciences (MMBB), University of Bonn, Bonn, Germany; Department of Epidemiology (MMBB, FG), Harvard School of Public Health, Harvard University, Boston, Massachusetts; Interfaculty Institute for Genetics and Functional Genomics (AT), University Medicine Greifswald, Greifswald, Germany; The Alzheimer's Disease Research Center (OLL), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; Institute of Neuroscience and Medicine (SC), Research Center Julich, Julich, Germany; Division of Medical Genetics (SC), Department of Biomedicine, University of Basel, Switzerland; Munich Cluster for Systems Neurology (SyNergy) (BM-M), Munich, Germany; Institute of Translational Medicine (BM-M), University of Liverpool, Liverpool, United Kingdom; University Bordeaux Segalen (CT), Bordeaux, France; Department Biozentrum (APap), Life Sciences Training Facility, Basel, Switzerland; Department of Radiology (MAI), Erasmus Medical Center University Medical Center, Rotterdam, The Netherlands; Center for Medical Systems Biology (CMvD), Netherlands Genomics Initiative, Leiden University Medical Center, Leiden, The Netherlands; Department of Medicine and Neurology (THM), University of Mississippi Medical Center, Jackson, Mississippi

Acknowledgments

Aging Gene-Environment Susceptibility-Reykjavik Study: The research has been funded by National Institute on Aging contract N01-AG-12100 with contributions from National Eye Institute, National Institute on Deafness and Other Communication Disorders, and National Heart, Lung and Blood Institute; the National Institute on Aging Intramural Research Program; Hjartavernd (the Icelandic Heart Association); and the Althingi (the Icelandic Parliament).

The Atherosclerosis Risk in Communities Study: The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL70825, R01HL087641, R01HL59367, and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. We thank the staff and participants of the Atherosclerosis Risk in Communities Study for their important contributions. Infrastructure was partly supported by Grant number UL1RR025005, a component of the National Institutes of Health and National Institutes of Health Roadmap for Medical Research.

The Austrian Stroke Prevention Study: We thank the staff and the participants of the Austrian Stroke Prevention Study for their valuable contributions. We thank Birgit Reinhart for her long-term administrative commitment and Ing Johann Semmler for the technical assistance at creating the DNA-bank.

The Cardiovascular Health Study: This Cardiovascular Health Study research was supported by National Heart, Lung and Blood Institute contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, and N01HC85086 and National Heart, Lung and Blood Institute Grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, and R01HL120393 with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was

provided through R01AG023629, R01AG20098 and R01AG05133 NIA. A full list of principal Cardiovascular Health Study investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported, in part, by the National Center for Advancing Translational Sciences, Clinical and Translational Sciences Institute Grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center Grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Croatian Cohorts–Split and Kor uľa: The CROATIA-Kor uľa and CROATIA-Split studies were funded by Grants from the Medical Research Council (United Kingdom), European Commission Framework 6 project EUROSPAN (Contract No. LSHG-CT-2006-018947), and Republic of Croatia Ministry of Science, Education and Sports research Grants to IR (108-1080315-0302). We acknowledge the invaluable contributions of the recruitment teams in Kor uľa and Split, the administrative teams in Croatia and Edinburgh, and the people of Kor uľa and Split. The single nucleotide polymorphism genotyping for the CROATIA-Kor uľa cohort was performed in Helmholtz Zentrum München, Neuherberg, Germany. The single nucleotide polymorphism genotyping for the CROATIA-Split cohort was performed by AROS Applied Biotechnology, Aarhus, Denmark.

Erasmus Rucphen Family Study: This study is financially supported by the Netherlands Organization for Scientific Research, the Internationale Stichting Alzheimer Onderzoek, the Hersenstichting Nederland, and the Centre for Medical Systems Biology (*1 and 2*) in the framework of the Netherlands Genomics Initiative. We thank the participants from the Genetic Research in Isolated Populations, Erasmus Rucphen Family, who made this work possible.

Framingham Heart Study: From the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. This work was supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195) and its contract with Affymetrix, Inc. for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. Analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the Single Nucleotide Polymorphism Health Association Resource project. This study was also supported by Grants from the National Institute of Neurological Disorders and Stroke (NS17950) and the National Institute on Aging (AG08122, AG16495, AG033193, AG031287).

Genetic Epidemiology Network of Arteriopathy: Support for the Genetic Epidemiology Network of Arteriopathy was provided by the National Heart, Lung and Blood Institute (HL054464, HL054457, HL054481, HL071917, and HL87660) and the National Institute of Neurological Disorders and Stroke (NS041558) of the National Institutes of Health. Genotyping was performed at the Mayo Clinic (STT, Mariza de Andrade, Julie Cunningham) and was made possible by the University of Texas Health Sciences Center (EB, Megan L. Grove-Gaona). We also thank the families that participated in the Genetic Epidemiology Network of Arteriopathy study.

Helsinki Birth Cohort Study: We thank all study participants as well as everybody involved in the Helsinki Birth Cohort Study. The Helsinki Birth Cohort Study has been supported by Grants from the Academy of Finland, the Finnish Diabetes Research Society, Folkhälsan Research Foundation, Novo Nordisk Foundation, Finska Läkaresällskapet, Signe and Ane Gyllenberg Foundation, University of Helsinki, Ministry of Education, Ahokas Foundation, Emil Aaltonen Foundation, Juho Vainio Foundation, and Wellcome Trust (Grant number WT089062).

Lothian Birth Cohort 1921 and Lothian Birth Cohort 1936: We thank the cohort participants and team members who contributed to these studies. Phenotype collection in the Lothian Birth Cohort 1921 was supported by the Biotechnology and Biological Sciences Research Council, The Royal Society, and The Chief Scientist Office of the Scottish Government. Phenotype collection in the Lothian Birth Cohort 1936 was supported by Research Into Ageing (continues as part of Age United Kingdom The Disconnected Mind project). Genotyping of the cohorts was funded by the United Kingdom Biotechnology and Biological Sciences Research Council. The work was undertaken by The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (G0700704/84698). Funding from the Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, and Medical Research Council is gratefully acknowledged.

Orkney Complex Disease Study: Orkney Complex Disease Study was supported by the Chief Scientist Office of the Scottish Government, the Royal Society, the Medical Research Council Human Genetics Unit, Arthritis Research United Kingdom, and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). DNA extractions were performed at the Wellcome Trust Clinical Research Facility in Edinburgh. We acknowledge the invaluable contributions of Lorraine Anderson and the research nurses in Orkney, the administrative team in Edinburgh, and the people of Orkney.

The Rotterdam Study: The generation and management of genome-wide association study genotype data for the Rotterdam Study is supported by the Netherlands Organisation of Scientific Research Investments (nr. 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative/Netherlands Organisation for Scientific Research project nr. 050-060-810. We thank Pascal Arp, Mila Jhamai, Marijn Verkerk, Lizbeth Herrera, and Marjolein Peters for their help in creating the genome-wide association study database and Karol Estrada and Maksim V. Struchalin for their support in creation and analysis of imputed data.

The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam; Netherlands Organization for the Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly; the Ministry of Education, Culture and Science; the Ministry for Health, Welfare and Sports; the European Commission (DG XII), and the Municipality of Rotterdam. The Rotterdam Scan Study is supported by the Netherlands Organization of Scientific Research project nrs. 918-46-615, 904-61-096, 904-61-133, 948-00-010, and 916-13-054 (ZonMW) and International Parkinson Fonds. Dr. Ikram was supported by a ZonMW Veni Grant: 916.13.054. We are grateful to the study participants, the staff from the Rotterdam Study, and the participating general practitioners and pharmacists.

The Religious Order Study and Rush Memory and Aging Project: The Religious Order Study and Rush Memory and Aging Project Study are supported in part by National Institute on Aging Grants P30AG10161, R01AG15819, R01AG17917, R01AG30146, K08AG34290, and K25AG41906.

Study of Health in Pomerania: Study of Health in Pomerania is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (Grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs, and the Social Ministry of the Federal State of Mecklenburg-West Pomerania. Genome-wide data have been supported by the Federal Ministry of Education and Research (Grant no. 03ZIK012) and a joint Grant from Siemens Healthcare, Erlangen, Germany and the Federal State of Mecklenburg-West Pomerania. The University of Greifswald is a member of the Center of Knowledge Interchange program of the Siemens AG. This work was also funded by the German Research Foundation (DFG: GR 1912/ 5-1).

The Tasmanian Study of Gait and Cognition is supported by Project Grants from the National Health and Medical Research Council (NHMRC IDs 403000, 491109, 606543) and a Grant from the Wicking Dementia Education and Research Centre, Hobart. Velandai Srikanth is supported by a National Health and Medical Research Council/ National Heart Foundation Career Development Fellowship (ID 606544). Matthew Brown is supported by a National Health and Medical Research Council Principal Research Fellowship.

Baltimore Longitudinal Study of Aging: The Baltimore Longitudinal Study of Aging is supported by the Intramural Research Program of the National Institutes of Health, National Institute on Aging.

Hunter Community Study: We thank the men and women participating in the Hunter Community Study as well as all the staff, investigators, and collaborators who have supported or been involved in the project to date. The cohort was made possible with support from the University of New-castle's Strategic Initiative Fund, the Vincent Fairfax Family Foundation, and the Hunter Medical Research Institute.

Nurses' Health Study: This study was supported by research Grants CA87969, CA49449, HL34594, U01HG004399, DK058845, CA65725, CA67262, CA50385, 5U01CA098233, EY09611, EY015473, HG004728, HL35464, CA55075, CA134958, and DK070756 from the National Institutes of Health. The genotyping was partly supported by an unrestricted Grant from Merck Research Laboratories. Dr. Sun is supported by a career development award K99HL098459 from the National Heart, Lung, and Blood Institute.

REasons for Geographic and Racial Differences in Stroke: This research project is supported by a cooperative agreement U01 NS041588 (G. Howard, Principal Investigator) from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Services. Genotyping was performed under Grant R01 DK084350 (Michele Sale, Principal Investigator). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke, the National Institute of Diabetes and Digestive and Kidney Diseases, or the National Institutes of Health. Representatives of the funding agency have been involved in the review of the manuscript but not directly involved in the collection, management, analysis, or interpretation of the data. We thank the other investigators, the staff, and the participants of the REasons for Geographic and Racial Differences in Stroke study for their valuable contributions. A full list of participating REasons for Geographic and Racial Differences in Stroke investigators and institutions can be found at <http://www.regardsstudy.org>.

Sydney Memory and Ageing Study: We acknowledge and thank the Sydney Memory and Ageing Study participants and the Sydney Memory and Ageing Study Research Team. DNA was extracted by Genetic Repositories Australia, an Enabling Facility, supported by National Health & Medical Research Council Grant 401184. Preparation of the DNA samples was undertaken in the laboratory of Peter Schofield and John Kwok,

Neuroscience Research Australia. Genome-wide genotyping was performed by the Ramaciotti Centre, University of New South Wales. The Sydney Memory and Ageing Study is supported by Australian National Health & Medical Research Council Program Grant 350833 and Capacity Building Grant 568940. Henry Brodaty is supported by the Australian Government-funded Dementia Collaborative Research Centre at the University of New South Wales. Nicola Armstrong is supported by the National Health & Medical Research Council Project Grant 525453.

Three City Study: We thank the staff and the participants of the Three City Study for their important contributions. The Three City Study is conducted under a partnership agreement between the Institut National de la Santé et de la Recherche Médicale, the Victor Segalen–Bordeaux II University, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The Three City Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, Mutuelle Générale de l'Éducation Nationale, Institut de la Longévité, Conseils Régionaux de Aquitaine and Bourgogne, Fondation de France, and Ministry of Research–Institut National de la Santé et de la Recherche Médicale Programme “Cohortes et collections de données biologiques.” Lille Génomole received an unconditional Grant from Eisai. We thank A. Boland (Centre National de Génotypage) for her technical help in preparing the DNA samples for analyses. This work was supported by the National Foundation for Alzheimer’s Disease and Related Disorders, the Institut Pasteur de Lille, and the Centre National de Génotypage. Stéphanie Debette is a recipient of a Chaire d’Excellence Grant from the French national research agency (Agence Nationale de la Recherche).

Women’s Genome Health Study: The Women’s Genome Health Study is supported by HL043851 and HL080467 from the National Heart, Lung, and Blood Institute and CA047988 from the National Cancer Institute, the Donald W. Reynolds Foundation, and the Fondation Leducq, with collaborative scientific support and funding for genotyping provided by Amgen.

Swiss Memory Genetics Study: This work was funded by the Swiss National Science Foundation (Sinergia grant CRSI33_130080 to DQ and AP).

The hippocampal gene expression study was supported by the German Federal Ministry of Education and Research through the Integrated Genome Research Network MoodS (Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia, under the auspices of the National Genome Research Network plus).

Co-investigator list. TASCOG: Jim Stankovich (Ph.D., Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia); Matthew Brown (M.D., University of Queensland Diamantina Institute, Princess Alexandra Hospital, Woolloongabba, Brisbane, Australia). Sydney Memory and Ageing Study: John B. Kwok (Ph.D., Neuroscience Research Australia and School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia); Peter Schofield (Ph.D., Neuroscience Research Australia and School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia); Henry Brodaty (M.D., Primary Dementia Collaborative Research Centre, School of Psychiatry and Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales Medicine, University of New South Wales; Aged Care Psychiatry, Prince of Wales Hospital, Sydney, New South Wales, Australia). Hunter Community Study: Mark McEvoy (MMedSc, School of Medicine and Public Health, Faculty of Health, University of Newcastle, Australia); Rodney Scott (Ph.D., School of Biomedical Sciences and Pharmacy, University of Newcastle, Australia); Roseanne Peel (MPH, School of Medicine and Public Health, Faculty of Health, University of Newcastle, Australia). Hippocampal Gene Expression Study: Katharina Pernhorst (MS, Institute of Neuropathology, Universitätsklinikum Bonn, Bonn, Germany); Benno Pütz (Ph.D., Max Planck Institute of Psychiatry, Munich, Germany); Karsten Borgwardt (Ph.D., Max Planck Institutes for Developmental Biology and for Intelligent Systems, Tübingen, Germany); Bernhard Schölkopf (Ph.D., Max Planck Institute for Intelligent Systems, Tübingen, Germany); Johannes Schramm (M.D., Department of Neurosurgery, Universitätsklinikum Bonn, Bonn, Germany); Per Hoffmann (Ph.D., Institute of Human Genetics, Universitäts-klinikum Bonn, Bonn, Germany). Rotterdam Study: Sven van der Lee (Genetic Epidemiology Unit, Department of Epidemiology, Erasmus Medical Center University Medical Center, Rotterdam, The Netherlands); Hieab Adams (Department of Epidemiology, Erasmus Medical Center University Medical Center, Rotterdam, The Netherlands). 3C-Dijon: Sabrina Schilling (MS, Inserm U897, Epidemiology, and University of Bordeaux, France).

References

1. Elias MF, Beiser A, Wolf PA, Au R, White RF, D’Agostino RB. The preclinical phase of alzheimer disease: A 22-year prospective study of the Framingham Cohort. *Arch Neurol.* 2000; 57:808–813. [PubMed: 10867777]
2. Amieva H, Jacqmin-Gadda H, Orgogozo JM, Le Carret N, Helmer C, Letenneur L, et al. The 9 year cognitive decline before dementia of the Alzheimer type: A prospective population-based study. *Brain.* 2005; 128:1093–1101. [PubMed: 15774508]

3. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: Revising the NINCDS-ADRDA criteria. *Lancet Neurol.* 2007; 6:734–746. [PubMed: 17616482]
4. Glahn DC, Kent JW Jr, Sprooten E, Diego VP, Winkler AM, Curran JE, et al. Genetic basis of neurocognitive decline and reduced white-matter integrity in normal human brain aging. *Proc Natl Acad Sci U S A.* 2013; 110:19006–19011. [PubMed: 24191011]
5. Deary IJ, Johnson W, Houlihan LM. Genetic foundations of human intelligence. *Hum Genet.* 2009; 126:215–232. [PubMed: 19294424]
6. Finkel D, Pedersen NL, McLearn GE, Plomin R, Berg S. Cross-sequential analysis of genetic influences on cognitive ability in the Swedish adoption/twin study of ageing. *Aging Neuropsychol Cogn.* 1996; 3:84–99.
7. Reynolds CA, Finkel D, McArdle JJ, Gatz M, Berg S, Pedersen NL. Quantitative genetic analysis of latent growth curve models of cognitive abilities in adulthood. *Dev Psychol.* 2005; 41:3–16. [PubMed: 15656733]
8. Payton A. The impact of genetic research on our understanding of normal cognitive ageing: 1995 to 2009. *Neuropsychol Rev.* 2009; 19:451–477. [PubMed: 19768548]
9. Wisdom NM, Callahan JL, Hawkins KA. The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. *Neurobiol Aging.* 2011; 32:63–74. [PubMed: 19285755]
10. Papassotiropoulos A, Stefanova E, Vogler C, Gschwind L, Ackermann S, Spalek K, et al. A genome-wide survey and functional brain imaging study identify CTNBL1 as a memory-related gene. *Mol Psychiatry.* 2013; 18:255–263. [PubMed: 22105620]
11. Papassotiropoulos A, Stephan DA, Huentelman MJ, Hoernli FJ, Craig DW, Pearson JV, et al. Common Kibra alleles are associated with human memory performance. *Science.* 2006; 314:475–478. [PubMed: 17053149]
12. Kandel ER. The molecular biology of memory storage: A dialogue between genes and synapses. *Science.* 2001; 294:1030–1038. [PubMed: 11691980]
13. Deary IJ, Whiteman MC, Pattie A, Starr JM, Hayward C, Wright AF, et al. Cognitive change and the APOE epsilon 4 allele. *Nature.* 2002; 418:932. [PubMed: 12198535]
14. Willer CJ, Li Y, Abecasis GR. METAL: Fast and efficient meta-analysis of genome-wide association scans. *Bioinformatics.* 2010; 26:2190–2191. [PubMed: 20616382]
15. Kohli MA, Lucae S, Saemann PG, Schmidt MV, Demirkan A, Hek K, et al. The neuronal transporter gene SLC6A15 confers risk to major depression. *Neuron.* 2011; 70:252–265. [PubMed: 21521612]
16. Liu JZ, McRae AF, Nyholt DR, Medland SE, Wray NR, Brown KM, et al. A versatile gene-based test for genome-wide association studies. *Am J Hum Genet.* 2010; 87:139–145. [PubMed: 20598278]
17. Chibnik LB, Shulman JM, Leurgans SE, Schneider JA, Wilson RS, Tran D, et al. CR1 is associated with amyloid plaque burden and age-related cognitive decline. *Ann Neurol.* 2011; 69:560–569. [PubMed: 21391232]
18. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, et al. International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature.* 2009; 460:748–752. [PubMed: 19571811]
19. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet.* 2013; 45:1452–1458. [PubMed: 24162737]
20. Dastani Z, Johnson T, Kronenberg F, Nelson CP, Assimes TL, Marz W, et al. The shared allelic architecture of adiponectin levels and coronary artery disease. *Atherosclerosis.* 2013; 229:145–148. [PubMed: 23664276]
21. Mandel I, Paperna T, Volkowich A, Merhav M, Glass-Marmor L, Miller A. The ubiquitin-proteasome pathway regulates claudin 5 degradation. *J Cell Biochem.* 2012; 113:2415–2423. [PubMed: 22389112]
22. Deary IJ, Johnson W. Intelligence and education: Causal perceptions drive analytic processes and therefore conclusions. *Int J Epidemiol.* 2010; 39:1362–1369. [PubMed: 20504860]

23. Small BJ, Rosnick CB, Fratiglioni L, Backman L. Apolipoprotein E and cognitive performance: A meta-analysis. *Psychol Aging*. 2004; 19:592–600. [PubMed: 15584785]
24. Liu F, Pardo LM, Schuur M, Sanchez-Juan P, Isaacs A, Slegers K, et al. The apolipoprotein E gene and its age-specific effects on cognitive function. *Neurobiol Aging*. 2010; 31:1831–1833. [PubMed: 19004527]
25. Mondadori CR, de Quervain DJ, Buchmann A, Mustovic H, Wollmer MA, Schmidt CF, et al. Better memory and neural efficiency in young apolipoprotein E epsilon4 carriers. *Cereb Cortex*. 2007; 17:1934–1947. [PubMed: 17077159]
26. Vigneau M, Beaucousin V, Herve PY, Jobard G, Petit L, Crivello F, et al. What is right-hemisphere contribution to phonological, lexico-semantic, and sentence processing? Insights from a meta-analysis. *Neuroimage*. 2011; 54:577–593. [PubMed: 20656040]
27. Giraud AL, Truy E, Frackowiak RS, Gregoire MC, Pujol JF, Collet L. Differential recruitment of the speech processing system in healthy subjects and rehabilitated cochlear implant patients. *Brain*. 2000; 123:1391–1402. [PubMed: 10869051]
28. Papassotiropoulos A, de Quervain DJ. Genetics of human episodic memory: Dealing with complexity. *Trends Cogn Sci*. 2011; 15:381–387. [PubMed: 21835680]
29. Tiwari V, O'Donnell CD, Oh MJ, Valyi-Nagy T, Shukla D. A role for 3-O-sulfotransferase isoform-4 in assisting HSV-1 entry and spread. *Biochem Biophys Res Commun*. 2005; 338:930–937. [PubMed: 16259945]
30. Carter CJ. Alzheimer's disease plaques and tangles: Cemeteries of a pyrrhic victory of the immune defence network against herpes simplex infection at the expense of complement and inflammation-mediated neuronal destruction. *Neurochem Int*. 2011; 58:301–320. [PubMed: 21167244]
31. Letenneur L, Peres K, Fleury H, Garrigue I, Barberger-Gateau P, Helmer C, et al. Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: A population-based cohort study. *PLoS One*. 2008; 3:e3637. [PubMed: 18982063]
32. Zimmer C. Microbiology. Do chronic diseases have an infectious root? *Science*. 2001; 293:1974–1977. [PubMed: 11557857]
33. Itzhaki RF, Wozniak MA. Herpes simplex virus type 1 in Alzheimer's disease: The enemy within. *J Alzheimers Dis*. 2008; 13:393–405. [PubMed: 18487848]
34. Kennedy RB, Ovsyannikova IG, Pankratz VS, Haralambieva IH, Vierkant RA, Poland GA. Genome-wide analysis of polymorphisms associated with cytokine responses in smallpox vaccine recipients. *Hum Genet*. 2012; 131:1403–1421. [PubMed: 22610502]
35. Lambert JC, Heath S, Even G, Campion D, Slegers K, Hiltunen M, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet*. 2009; 41:1094–1099. [PubMed: 19734903]
36. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet*. 2009; 41:1088–1093. [PubMed: 19734902]
37. Lambert JC, Grenier-Boley B, Chouraki V, Heath S, Zelenika D, Fievet N, et al. Implication of the immune system in Alzheimer's disease: Evidence from genome-wide pathway analysis. *J Alzheimers Dis*. 2010; 20:1107–1118. [PubMed: 20413860]
38. Kim SY, Mo JW, Han S, Choi SY, Han SB, Moon BH, et al. The expression of non-clustered protocadherins in adult rat hippocampal formation and the connecting brain regions. *Neuroscience*. 2010; 170:189–199. [PubMed: 20541594]
39. Fiore R, Rahim B, Christoffels VM, Moorman AF, Puschel AW. Inactivation of the Sema5a gene results in embryonic lethality and defective remodeling of the cranial vascular system. *Mol Cell Biol*. 2005; 25:2310–2319. [PubMed: 15743826]
40. Weiss LA, Arking DE, Daly MJ, Chakravarti A. A genome-wide linkage and association scan reveals novel loci for autism. *Nature*. 2009; 461:802–808. [PubMed: 19812673]
41. Ciechanover A, Brundin P. The ubiquitin proteasome system in neurodegenerative diseases: Sometimes the chicken, sometimes the egg. *Neuron*. 2003; 40:427–446. [PubMed: 14556719]
42. Bertram L, Hiltunen M, Parkinson M, Ingelsson M, Lange C, Ramasamy K, et al. Family-based association between Alzheimer's disease and variants in UBQLN1. *N Engl J Med*. 2005; 352:884–894. [PubMed: 15745979]

43. Pavlopoulos E, Trifilieff P, Chevalyere V, Fioriti L, Zairis S, Pagano A, et al. Neuralized1 activates CPEB3: A function for nonproteolytic ubiquitin in synaptic plasticity and memory storage. *Cell*. 2011; 147:1369–1383. [PubMed: 22153079]
44. Kendler KS, Neale MC. Endophenotype: A conceptual analysis. *Mol Psychiatry*. 2010; 15:789–797. [PubMed: 20142819]
45. Pruim RJ, Welch RP, Sanna S, Teslovich TM, Chines PS, Gliedt TP, et al. LocusZoom: Regional visualization of genome-wide association scan results. *Bioinformatics*. 2010; 26:2336–2337. [PubMed: 20634204]

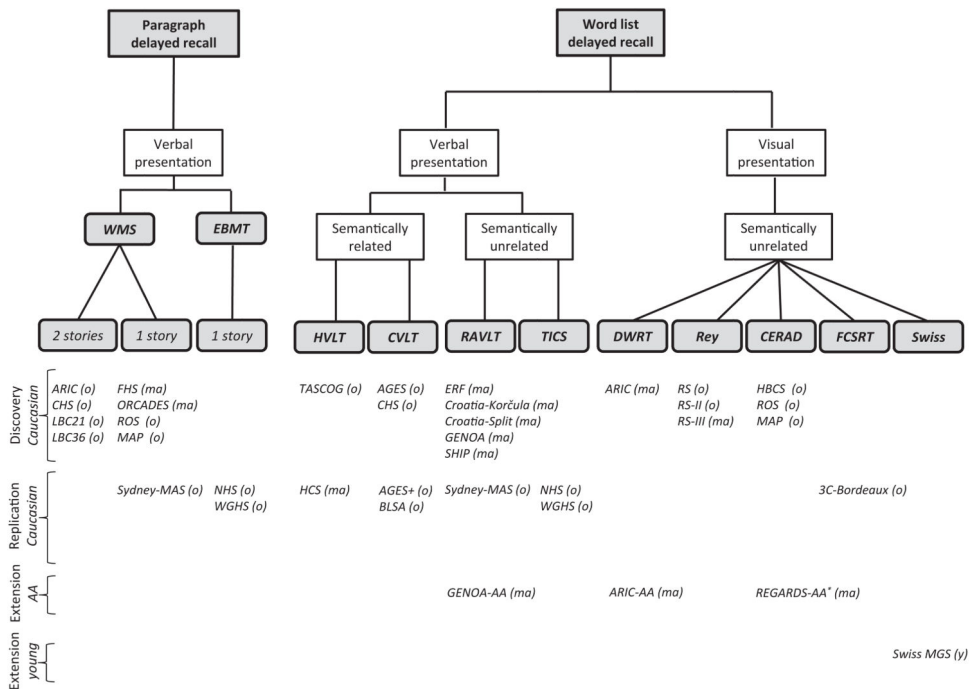


Figure 1. Memory test categories and analysis strategy. Middle-aged (ma) cohorts aged >45 years, with an average age <65 years; old (o) cohorts aged >65 years; young (y) cohorts aged <45 years. * in REasons for Geographic and Racial Differences in Stroke (REGARDS) the Consortium to Establish a Registry for Alzheimer’s Disease delayed recall (CERAD-dr) test was administered by phone.

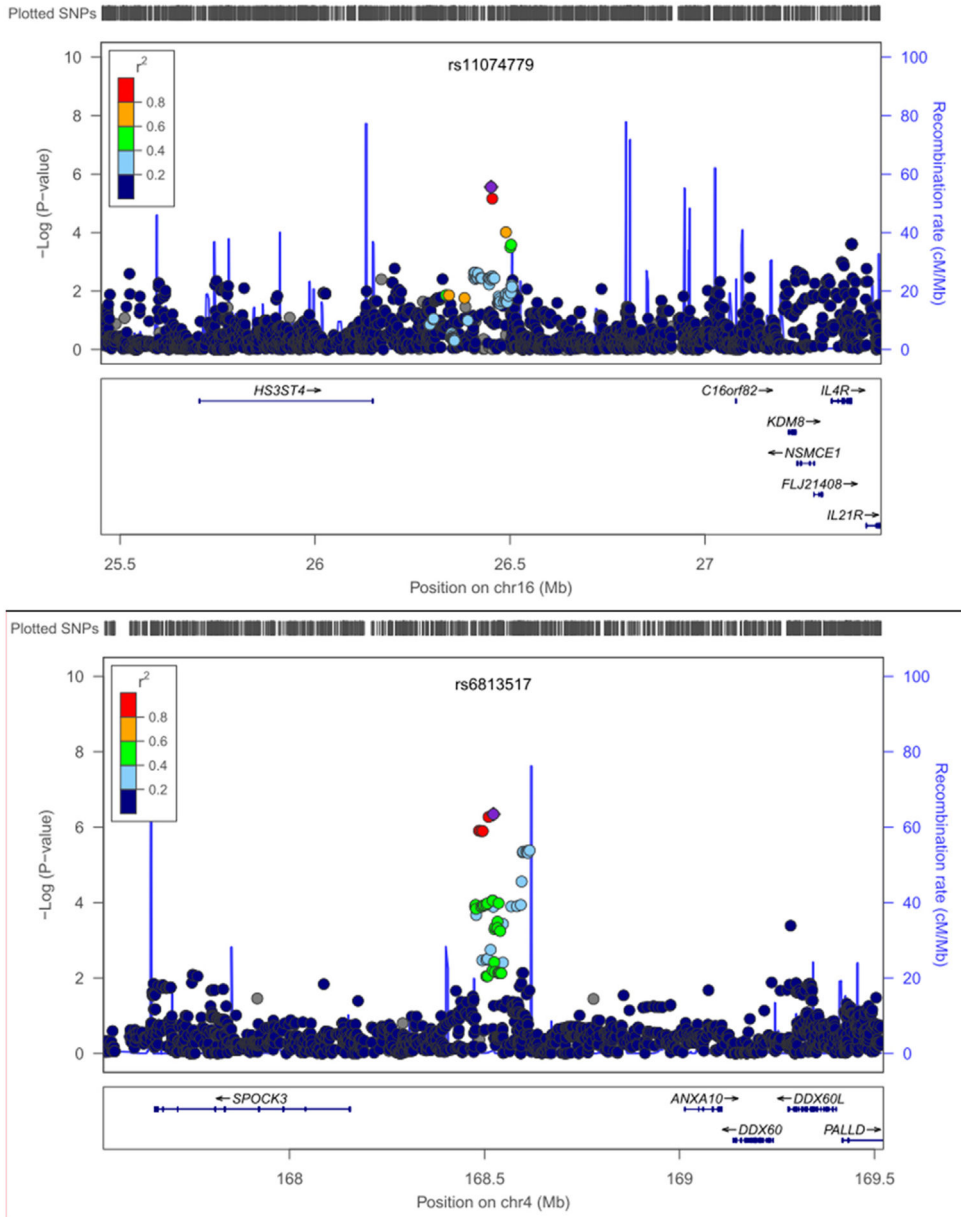


Figure 2. Regional association plots in the discovery genome-wide association study (GWAS) centered on rs11074779 (Rey Auditory Verbal Learning Test delayed recall [RAVLT-dr]) and rs6813517 (Consortium to Establish a Registry for Alzheimer’s Disease delayed recall [CERAD-dr]). Regional plot for associations 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.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Most Significant Genetic Associations with Paragraph Delayed Recall

SNP	chr	Position	Function	Gene	dist ^d	EA	EAF	SNP ^b	Meta Discovery n = 6674			Meta Replication n = 6496			Meta All n = 13,170			Extension AA n = 416	
									p	dir ^c	p(het)	dir ^d	p	dir ^e	p	dir ^e	p	dir	p
Adjusted for Age and Gender																			
rs4420638	19	50114786	Downstream	<i>APOC1</i>	340.0	A	.82	1	+++++++	5.57×10^{-10}	.15	+++	5.65×10^{-8}	++	1.36×10^{-16}	+	.71		
rs6857	19	50084094	3'UTR	<i>PVRL2</i>	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	<i>TOMM40</i>	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	<i>CDH12</i>	wg	T	.46	3	-----	6.17×10^{-7}	.42	+++	.39	+-	1.54×10^{-3}	+	.39		
rs9528384	13	61200566	Intergenic	<i>PCDH20</i>	313.3	A	.71	1	+++++++	1.50×10^{-6}	.54	---	.040	++	1.06×10^{-6}	-	.13		
rs1633735	5	8596190	Intergenic	<i>SEMA5A</i>	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	<i>APOC1</i>	.3	A	.82	1	+++++++	1.94×10^{-10}	.37	+++	1.73×10^{-7}	++	1.56×10^{-16}	+	.62		
rs6857	19	50084094	3'UTR	<i>PVRL2</i>	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	<i>TOMM40</i>	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	<i>AXUD1</i>	7.2	A	.78	8	+++++++	4.51×10^{-7}	.36	+++	.64	++	7.49×10^{-5}	NA	NA		
rs11711871	3	39203047	NS-coding	<i>XIRP1</i>	wg	T	.78	4f	+++++++	9.6×10^{-7}	.34	+++	.50	++	6.38×10^{-5}	NA	NA		
rs1913243	3	39239499	Intergenic	<i>XIRP1</i>	30.4	T	.29	2	-----	2.33×10^{-6}	.47	+++	.39	+-	6.23×10^{-3}	+	.17		
rs2280630	3	39170968	Upstream	<i>AXUD1</i>	.9	T	.32	1	-----+	2.57×10^{-6}	.29	---	.058	--	2.47×10^{-6}	-	.70		
rs9870795	3	39218299	Intergenic	<i>XIRP1</i>	9.2	T	.23	1	-----	4.99×10^{-6}	.60	---	.32	--	7.51×10^{-5}	+	.011		
rs13172717	5	21807809	Intronic	<i>CDH12</i>	wg	T	.46	3	-----	1.38×10^{-6}	.34	+++	.45	+-	1.77×10^{-3}	+	.38		

SNP	chr	Position	Function	Gene	dist ^d	EA	EAF	SNPs ^b	Meta Discovery n = 6674			Meta Replication n = 6496			Meta All n = 13,170			Extension AA n = 416	
									dir ^c	p	p(het)	dir ^d	p	dir ^e	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	
rs455854	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	EPSI5	wg	T	.29	1	+++++++	3.87×10^{-6}	.78	---	.024	+-	.085	+		.059	
rs10493155	1	51711785	Intronic	EPSI5	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.

^aDistance in kilobase.

^bNumber of SNPs in locus (top SNP + SNPs in LD $R^2 > .80$).

^cDirections are in the following order: ARIC, CHS, FHS, LBC21, LBC36, MAP, ORCADES, ROS.

^dDirections are in the following order: NHS, Sydney MAS, WHGS.

^eDirections 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).

^fOf which one other nonsynonymous coding (rs3732383).

Table 2
Most Significant Genetic Associations with Performance on California Verbal Learning Test Delayed Recall

SNP	chr	Position	Function	Gene	dis ^a	EA	EAF	SNP ^b	dir ^c	Meta Discovery n = 2950			Meta Replication n = 2237			Meta All n = 5187		
										beta	SE	p	p(het)	dir ^d	p	dir ^e	p	dir ^e
Adjusted for Age and Gender																		
rs13358049	5	50578216	Intergenic	<i>ISL1</i>	136.5	T	.07	15	--	-.85	.15	2.29 × 10 ⁻⁸	.58	+-	.97	--	2.71 × 10 ⁻⁵	
rs13360092	5	50564932	Intergenic	<i>ISL1</i>	149.8	A	.07	15	--	-.85	.15	2.36 × 10 ⁻⁸	.55	?-	.73	--	1.25 × 10 ⁻⁷	
rs157092	20	55685666	Intronic	<i>TMEPA1</i>	wg	T	.26	4	--	-.46	.09	8.50 × 10 ⁻⁷	.29	+-	.82	+-	5.88 × 10 ⁻⁴	
rs13177865	5	120494952	Intergenic	<i>PRR16</i>	444.1	A	.09	2	+?	.74	.15	1.29 × 10 ⁻⁶	1	?+	.79	++	1.03 × 10 ⁻⁵	
rs13166268 ^f	5	120387817	Intergenic	<i>PRR16</i>	337.0	C	.90	2	+-	-.60	.13	7.20 × 10 ⁻⁶	.006	--	.016	--	8.28 × 10 ⁻⁷	
rs1445765	5	103572875	Intergenic	<i>NUDT12</i>	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	<i>ISL1</i>	136.5	T	.07	16	--	-.85	.15	9.69 × 10 ⁻⁹	.66	+-	.89	--	1.09 × 10 ⁻⁵	
rs13360092	5	50564932	Intergenic	<i>ISL1</i>	149.8	A	.07	16	--	-.85	.15	1.00 × 10 ⁻⁸	.63	?-	.51	--	2.71 × 10 ⁻⁸	
rs157092	20	55685666	Intronic	<i>TMEPA1</i>	wg	T	.26	5	--	-.46	.09	3.69 × 10 ⁻⁷	.26	+-	.81	+-	3.50 × 10 ⁻⁴	
rs1445765	5	103572875	Intergenic	<i>NUDT12</i>	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.

^aDistance in kilobase.

^bNumber of SNPs in locus (top SNP + SNPs in LD $R^2 > .80$).

^cDirections are in the following order: AGES, CHS.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

^dDirections are in the following order: AGES-plus ($n = 1525$), BLSA ($n = 712$).

^eDirections are in the following order: Discovery, Replication.

^frs13166268 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

SNP	chr	Position	Function	Gene	dist ^a	EA	EAF	dir ^b	SNPs ^c	Meta Discovery n = 4274			Replication n = 880			Meta All n = 5154			Extension AA n = 708		
										beta	SE	p	p(het)	dir ^d	p	dir ^e	p	dir ^f	p		
Adjusted for Age and Gender																					
rs963798	13	38287693	Intronic	<i>FREM2</i>	wg	A	.52	+++++	3	.29	.06	1.46×10^{-6}	.65	-	.34	+-	2.00×10^{-5}	+	.92		
rs11074779	16	26358944	Intergenic	<i>HS3ST4</i>	302.4	T	.81	+++++	1	.36	.08	3.05×10^{-6}	.93	+	1.08×10^{-3}	++	3.11×10^{-8}	-	.48		
rs747035	22	16098606	Intergenic	<i>CECR1</i>	27.8	T	.93	-----	1	-.65	.14	3.50×10^{-6}	.89	-	.19	--	1.38×10^{-6}	+	.93		
rs11237982	11	79119342	Intergenic	<i>ODZ4</i>	918.5	T	.85	+++++	1	.40	.09	4.33×10^{-6}	.29	+	.099	++	9.73×10^{-7}	+	.31		
Adjusted for Age, Gender, and Education																					
rs747035	22	16098606	Intergenic	<i>CECR1</i>	27.8	T	.93	-----	1	-.65	.14	2.61×10^{-6}	.92	-	.18	--	1.03×10^{-6}	-	.97		
rs963798	13	38287693	Intronic	<i>FREM2</i>	wg	A	.52	+++++	1	.28	.06	2.71×10^{-6}	.47	-	.27	+-	4.15×10^{-5}	-	.87		
rs11237982	11	79119342	Intergenic	<i>ODZ4</i>	918.5	T	.85	+++++	1	.39	.08	3.68×10^{-6}	.22	+	.087	++	7.63×10^{-7}	+	.29		
rs16991213	20	44402546	Intergenic	<i>SLC35C2</i>	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 RAVLT-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.

^aDistance in kilobase.

^bDirections are in the following order: ERF, GENOA, CROATIA-Korcula, SHIP, CROATIA-Split.

^cNumber of SNPs in locus (top SNP + SNPs in LD $R^2 > .80$).

^dSydney MAS.

^eDirections 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).

^fGENOA-AA.

Table 4
 Most Significant Genetic Associations with Consortium to Establish a Registry for Alzheimer’s Disease Delayed Recall

SNP	chr	Position	Function	Gene	dist ^a	EA	EAF	dir ^b	SNPs ^c	Meta Discovery n = 4274			Extension AA n = 627			Meta All n = 4901			
										beta	SE	p	p(het)	beta	SE	p	beta	SE	p
Adjusted for Age and Gender																			
rs6813517	4	168759326	Intergenic	<i>SPOCK3</i>	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	<i>BHLHB5</i>	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	<i>RIN2</i>	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	<i>GFR2</i>	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	<i>RPS29</i>	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	<i>B3GAT1</i>	.6	A	.53	---	1	-.31	.07	4.31×10^{-6}	.22	-.11	.16	.50	-.28	.06	6.25×10^{-6}
rs17053482	4	168836226	Intergenic	<i>ANXA10</i>	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	<i>SPOCK3</i>	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	<i>BHLHB5</i>	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	<i>ANXA10</i>	414.1	C	.09	---	6	-.51	.11	1.62×10^{-6}	.34	.10	.14	.48	-.29	.08	6.27×10^{-4}
rs10894804	11	133753052	Downstream	<i>B3GAT1</i>	.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; w.g, within gene.

^aDistance in kilobase.

^bDirections are in the following order: HBCS, MAP, ROS.

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

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 5

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

AD Risk Allele	Position	Gene	Model	All European		Old ^a European: Overlapping Samples for PAR and WL ^b		Middle-Aged ^a European		African-American		Young European ^d									
				PAR-dr	WL-dr	PAR-dr	WL-dr	PAR-dr	WL-dr	PAR-dr ^c	WL-dr ^d	PAR-dr	WL-dr	PAR-dr	WL-dr						
				Age: 71.9	<i>n</i> : 33,403	Age: 74.0	<i>n</i> : 10,258	Age: 73.3	<i>n</i> : 15,118	Age: 74.3	<i>n</i> : 7934	Age: 74.4	<i>n</i> : 7641	Age: 58.8	<i>n</i> : 18,285	Age: 71.8	<i>n</i> : 416	Age: 57.6	<i>n</i> : 3184	Age: 22.3	<i>n</i> : 1561
				<i>p</i> (PAR)	<i>p</i> (WL)	<i>p</i> (PAR)	<i>p</i> (WL)	<i>p</i> (PAR)	<i>p</i> (WL)	<i>p</i> (PAR)	<i>p</i> (PAR)	<i>p</i> (WL)	<i>p</i> (WL)	<i>p</i> (PAR)	<i>p</i> (WL)	<i>p</i> (PAR)	<i>p</i> (WL)	<i>p</i> (PAR)	<i>p</i> (WL)	<i>p</i> (PAR)	<i>p</i> (WL)
rs4420638-G	19:50114786	<i>APOC1</i>	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	.79	.79	.79	.79	.79	.79	.79
rs6857-T	19:50084094	<i>PVRL2</i>	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	NA	NA	NA	NA	NA	NA	NA
rs2075650-G	19:50087459	<i>TOMM40</i>	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	NA	NA	NA	NA	NA	NA	NA
Epsilon-4 ^e	19:50103781/50103919	<i>APOE</i>	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	NA	NA	NA	NA	NA	NA	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}	.18	.18	.12	.23	NA	NA	NA	NA	NA	NA	NA	NA
			C	6.44×10^{-7}	.47	3.91×10^{-5}	3.33×10^{-3}	4.06×10^{-5}	.043	.49	.074	.17	NA	NA	NA	NA	NA	NA	NA	NA	NA
			D	1.00×10^{-7}	.090	2.09×10^{-5}	2.36×10^{-3}	2.47×10^{-5}	.034	.72	.12	.14	NA	NA	NA	NA	NA	NA	NA	NA	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, TASCOC); 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 Arteropathy; HBCS, Helsinki Birth Cohort Study; HCS, Hunter Community Study; LBC21, Lothian Birth Cohort 1921; LBC36, 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 educational achievement; 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-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; TASCOC, Tasmanian Study of Gait and Cognition; WGHs, Women's Genome Health Study; WL-dr, word list delayed recall.

^aYoung 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, TASCOC, BLSA, RS-II, HBCS, 3C-Bordeaux, ROS, MAP, NHS, WGHs, Sydney MAS).

^bStudies 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).

^cARIC-AA.

^dARIC-AA and GENOA-AA.

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

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript