Heritability of Different Forms of Memory in the Late Onset Alzheimer’s Disease Family Study

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Abstract

The study aim was to estimate the genetic contribution to individual differences in different forms of memory in a large family-based group of older adults. As part of the Late Onset Alzheimer’s Disease Family Study, 899 persons (277 with Alzheimer’s disease, 622 unaffected) from 325 families completed a battery of memory tests from which previously established composite measures of episodic memory, semantic memory, and working memory were derived. Heritability in these measures was estimated using the maximum likelihood variance component method, controlling for age, sex, and education. In analyses of unaffected family members, the adjusted heritability estimates were 0.62 for episodic memory, 0.49 for semantic memory, and 0.72 for working memory, where a heritability estimate of 1 indicates that genetic factors explain all of the phenotypic variance and a heritability of 0 indicates that genetic factors explain none. Adjustment for APOE genotype had little effect on these estimates. When analyses included affected and unaffected family members, adjusted heritability estimates were lower (0.47 for episodic memory, 0.32 for semantic memory, 0.42 for working memory). Adjusting for APOE slightly reduced the estimate for episodic memory (0.40) but had no effect on the remaining estimates. The results indicate that memory functions are under strong genetic influence in older persons with and without AD, only partly attributable to APOE. This suggests that genetic analyses of memory endophenotypes may help to identify genetic variants associated with AD.

Keywords

Alzheimer’s disease; memory; heritability; apolipoprotein E

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INTRODUCTION

Alzheimer’s disease (AD) is a common and devastating illness. With the aging of the U.S. population in the coming decades, the prevalence of this disease and its burden on public health are projected to markedly increase underscoring the need to develop new strategies for disease prevention [1,2]. Although the genetic contribution to AD is thought to be substantial, to date relatively few genetic variants associated with the disease have been identified and subsequently replicated in independent samples [3]. To enhance the power to detect new genes for AD, one strategy is to examine quantitative intermediate disease characteristics (i.e., endophenotypes) rather than the syndrome as a whole. There are several advantages to this approach. A quantitative endophenotype may be under greater genetic control as compared to a disease based outcome. A quantitative endophenotype such as memory function can be measured with greater precision than a dichotomous disease outcome [4, 5]. Finally, there is extensive variation in memory functioning even among individuals who do not have AD, allowing for a greater range of phenotypic variability within our sample of individuals with and without AD.

In the present study, we use data from the National Institute on Aging Late Onset Alzheimer’s Disease (LOAD) Family Study [6–8] to estimate the genetic contribution to different forms of memory. An advantage of this sample is that it includes not only individuals with AD but also their biologically related family members who are not demented. This allowed us to estimate heritability with and without inclusion of affected individuals. We also examined the effect of controlling for APOE genotype on the estimated heritability of the memory endophenotypes.

MATERIALS AND METHODS

Participants

As previously reported [6–8], many index cases were recruited through one of the federally funded Alzheimer’s disease research centers. Each center also recruited unrelated control subjects. An eligible family was required to have at least 3 biologically related members, at least two with AD diagnosed after age 60 and at least one unaffected relative. All three were required to provide clinical data and a biological sample for DNA extraction and genotyping. After the eligibility of a family group was established, additional family members were encouraged to participate. Informed consent was obtained from the participant or from a proxy if the participant lacked the capacity to consent. The study was approved by the Institutional Review Board of each participating center.

At the time of these analyses, 899 participants from 325 families had completed the initial evaluation which included cognitive testing. They had a mean age of 64.8 (SD = 11.1) and a mean of 14.2 years of education (SD = 2.9); 64.8% were women. The APOE allele frequencies were 0.027 for the ε2 allele, 0.613 for ε3, and 0.360 for ε4.

Clinical Evaluation

Data on demographic variables, diagnosis of dementia and AD, and medical history were obtained from each participant or an informant. Clinical classification of dementia and AD were based on the guidelines of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association. These require a history of cognitive decline and impairment in at least 2 cognitive domains, one of which must be memory to meet AD criteria [9]. In a subset of persons who could not be directly examined, clinical classification was based on a detailed review of medical records.
Genotyping of APOE polymorphisms (based on SNPs rs7412 and rs429358) was done at Prevention Genetics (www.preventiongenetics.com) in array tape using allele-specific PCR with universal molecular beacons as previously reported [7]. DNA sequencing of positive control DNA samples was completed to assure correct assignment of alleles.

Assessment of Memory Functions

Memory functions were measured with a battery of 7 brief tests [6, 10]. Working memory was assessed with Digit Span Forward and Digit Span Backward [11], and Digit Ordering [12]. Two measures of episodic memory were included: immediate and delayed recall of story A from the Wechsler Memory Scale-Revised [11]. Semantic memory was assessed by asking persons to name members of two semantic categories (Animals, Vegetables) in separate 1-min trials [10, 12, 13]. In previous research, these tests have been shown to have adequate reliability [11, 14, 15]. Further, change in performance on these measures has been associated with APOE genotype, and level of performance proximate to death has been associated with level of AD pathology on postmortem examination [10]. Administration of the test battery requires 10–15 min and can be done in person or by telephone.

The test battery was administered by multiple research assistants at the 18 participating centers. To maximize uniformity of test administration and scoring, each research assistant underwent a structured 4-step program of training and certification coordinated by Rush Alzheimer’s Disease Center personnel, as previously described [7]. Test administrators were recertified at 12 month intervals.

To minimize floor and ceiling artefacts and other forms of measurement error, composite memory measures were used in analyses. Based in part on a previous factor analysis [7], individual tests were grouped into 3 domains: working memory (based on 3 test measures), episodic memory (2 test measures), and semantic memory (2 test measures). Raw scores on individual tests were converted to z scores, using the mean and SD of all study participants, and z scores of tests in a given domain were averaged to yield the composite score, as previously described [7].

Data Analysis

We used the Sequential Oligogenic Linkage Analysis Routines (SOLAR) package [16] to construct a variance components model for estimating the heritability of the composite memory scores. The aim was to determine the contribution of genetic and environmental factors to variation in memory performance. In this approach, the phenotypic variance is partitioned into additive genetic ($\sigma^2_G$) and residual environmental ($\sigma^2_E$) components. The environmental variance is the mean residual variance not accounted for by additive genetic factors or covariates. Heritability was estimated as the ratio of the additive genetic variance to the sum of the additive genetic and environmental variance: $h^2 = (\text{additive}) \sigma^2_G / (\sigma^2_G + \sigma^2_E)$. Because the residual environmental variance absorbs non-additive genetic effects, such as interactions between alleles within loci (dominance effects), interactions between alleles at different loci (epistatic effects), and effects due to gene-environment interactions, this approach will generally underestimate the role of genetics in the determination of a trait.

Heritability ranges from 0 to 1, where 1 indicates total genetic influence and 0 indicates no genetic influence. Whenever the distribution of the individual cognitive scores did not conform to the multivariate normal distribution assumed by the variance component method, we used an inverse normal transformation of the variable, as implemented in SOLAR. A family was included in analyses if it included at least one sib pair or one avuncular pair. The variance components approach uses relatedness between all pairs of relatives in the data set to estimate heritability. We used allele-sharing measures to estimate relatedness between pairs of
individuals and the proportion of identity by state shared alleles as a metric of relatedness. Thus, more closely related pairs will share more alleles identical by state as compared with more distantly related pairs. In this approach, a kinship matrix is derived from pedigree data, simultaneously using all possible biological relationships to dissect the genetic architecture of a quantitative trait.

Initial analyses were conducted using only unaffected family members, first controlling for age, sex, and education and then again after controlling for these variables and number of APOE ε4 alleles. We then conducted analyses using all family members controlling for age, sex, education, and AD diagnosis in an initial series of analyses and then repeating the analyses with an additional term number of APOE ε4 alleles.

RESULTS

Of 899 participants, 277 had AD and 622 were unaffected. As shown in Table 1, 62% of those with AD came from families with at least 2 affected members in these analyses and 16% came from families with 3 or more affected persons. Individuals with AD were older than unaffected persons (76.1 [SD=7.5] vs. 64.8 [SD= 11.1]), less educated (13.3 [SD=3.1] vs 14.3 [SD=2.8]), and more likely to possess at least one copy of the APOE ε4 allele (68.1% vs 54.1%).

As shown in Table 2, there was wide variability in memory performance. In unaffected family members, better performance on the composite measures was associated with younger age (r = −.33 for episodic memory, r = −.40 for semantic memory, r = −.19 for working memory, all p <.001) and more education (r = .28 for episodic memory, r = .35 for semantic memory, r = .33 for working memory, all p <.001). The correlations between the composite memory measures were moderate in unaffected subjects (r = .44 for episodic-semantic, r = .28 episodic–working, r = .34 for semantic–working, all p <.001) and much larger in all family members (r = .79 for episodic-semantic, r = .65 for episodic-working, r = .73 for semantic-working, all p<.001). As expected, memory performance in those with AD (episodic memory mean = -1.14 [SD = 0.38]; semantic memory mean = -1.05 [SD = 0.62]; working memory mean = -0.86 [SD = 0.87]) was substantially lower than performance in unaffected persons.

Heritability Estimates in Unaffected Family Members

The initial analyses were restricted to unaffected family members. The heritability estimates were high for all three memory measures adjusting for age, sex, and education. As shown for model A in Table 3, the estimates were 0.62 for episodic memory, 0.49 for semantic memory, and 0.72 for working memory. Because inheritance of one or more copies of the APOE ε4 allele is a well established risk factor for late life dementia and cognitive decline, we repeated each model adjusting for number of ε4 alleles. In these analyses (Table 3, Model B), the residual estimated heritability of each memory measure was nearly identical to the original model, suggesting that APOE genotype does not strongly contribute to the heritability of the memory scores among unaffected family members.

Heritability Estimates Using All Family Members

We next repeated the above analyses including the AD cases in the models. In these analyses, the adjusted heritability estimates of all three measures were lower than the estimates based on unaffected members only, ranging from .32 to .49 (Table 3, Model C). In analyses controlling for APOE genotype, the residual heritability estimate for the episodic memory measure was reduced from .49 to .40, but the estimates for the semantic and working memory measures were unchanged (Table 3, Model D) suggesting that the heritability estimates for the memory scores among all family members did not strongly depend on APOE genotype.
DISCUSSION

In this study of familial AD, about 900 older adults from more than 300 families completed brief tests of episodic, semantic, and working memory. In each domain of memory functioning, much of the variability in performance was genetically influenced. The results indicate that quantitative measures of memory should be useful phenotypes to identify genetic variants associated with AD.

Knowledge about the heritability of memory in old age is based primarily on twin studies. In these studies, estimates of the heritability of episodic memory measures based on recall of stories or word lists have, with some exceptions [17], been in the .4 to .6 range [18–21]. By comparison, the heritability of summary measures of a word recall test ranged from .3 to .4 in older unaffected Caribbean Hispanic individual from families with multiple members with AD [22]. The heritability of category fluency tests like those used in the present study to assess semantic memory was estimated to be nearly .4 in older Danish twins [20] and more than .5 in older Italian twins [21]. Comparable estimates of between .3 and .6 have been reported for letter fluency tasks [21, 23]. The heritability of both category fluency and letter fluency was lower in the Caribbean Hispanic familial AD cohort, however, being about .2 and .3, respectively [22]. The heritability of digit span tasks similar to those used in the present study was about .3 in older Danish twins and in older Swedish twins, and about .5 in older twins from the United States [20, 24]. Comparable estimates have been reported for younger twins for digit span and more experimental working memory tasks [25, 26]. Overall, therefore, the heritability estimates for the episodic and semantic memory measures in the present study were comparable to estimates for similar measures from twin studies and somewhat higher than estimates from a previous study of familial AD. The heritability of the working memory measure in the present study was higher than previous estimates. The rigorous performance-based training and certification of cognitive examiners and the use of composite cognitive outcomes are likely to have reduced measurement error and may thereby have contributed to the relatively high estimates of heritability in the present study. The reason for the particularly high level of heritability for the working memory measure is uncertain. It suggests that genes related to working memory may also be related to risk of developing AD.

Inheritance of at least one copy of the APOE ε4 allele has been associated with cognitive decline in old age, particularly in episodic memory [27, 28]. In this study, adjustment for the ε4 allele had little effect on the estimated heritability of semantic memory or working memory, whereas the heritability of episodic memory was slightly reduced, indicating that some of the estimated heritability of episodic memory was due to APOE ε4 alleles. Nevertheless, even after accounting for APOE ε4, the remaining heritability of episodic memory was still relatively high and the reduction only occurred when affected individuals were included in the analysis. These results are consistent with previous research and suggest that memory functioning in familial AD is under strong genetic influence that is only partly attributable to APOE genotype [22].

One potential source of variability in estimates of the heritability of memory function in old age is whether persons with clinically manifest dementia are included in analyses. Some studies have confronted this issue by excluding persons with dementia or severe cognitive impairment whereas other studies have conducted analyses with and without such individuals [17, 19]. In studies of the latter type, excluding those with dementia or cognitive impairment resulted in slightly lower estimates of the heritability of measures of memory and cognition [20, 22]. In the present study, excluding affected family members increased heritability estimates somewhat in each domain of memory function. The reasons for this effect are uncertain. It may be that the tests measure memory with more error in affected than unaffected persons. Consistent with this idea, many episodic memory scores in the AD group were at or near the
Further, in a progressive disorder such as AD, level of memory performance at a single point in time is an imperfect indicator of how rapidly memory is declining [29], the principal clinical manifestation of the disease. Overall, these data suggest that estimates of the heritability of memory and cognitive abilities in old age do not strongly depend on the presence of dementia in the cohort.

The majority of studies seeking to identify genetic variation responsible for AD have been case-control studies comparing persons with AD to those without dementia. However, this approach has limitations. In particular, the dichotomous system used to classify persons as having AD obscures the fact that the disease does not neatly fall into distinct categories as AD develops slowly over many months or years. As loss of episodic memory and other cognitive abilities are the principal clinical manifestations of AD, it is likely that more power could be gained by examining cognition as a quantitative intermediate phenotype [4,5]. For example, several studies suggest that the relation of APOE to change in episodic memory is stronger than its association with clinical AD [5,28]. The NIA-LOAD Family Study is currently collecting longitudinal cognitive data. There are other intermediate phenotypes that could be targeted by this strategy for gene discovery such as psychotic features [8,30] and neuropathologic indices [31]. These data too are currently being collected on NIA-LOAD Family Study participants.

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**REFERENCES**


### Table 1

Information on families in the Late Onset Alzheimer’s Disease Family Study

<table>
<thead>
<tr>
<th>Number of Individuals</th>
<th>Alzheimer’s Disease</th>
<th>Unaffected</th>
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<tbody>
<tr>
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<td>Number of Families</td>
<td>Number of Individuals</td>
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<tr>
<td>0</td>
<td>142</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>3</td>
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<tr>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>&gt;4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>325</td>
<td>277</td>
</tr>
</tbody>
</table>
Table 2

Psychometric information on composite and individual cognitive measures

<table>
<thead>
<tr>
<th>Cognitive Measure</th>
<th>Unaffected Family Members (n=622)</th>
<th>Mean (SD)</th>
<th>All Family Members (n=899)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic Memory</td>
<td>0.56 (0.66)</td>
<td>0.04 (0.98)</td>
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</tr>
<tr>
<td>Semantic Memory</td>
<td>0.54 (0.60)</td>
<td>0.05 (0.95)</td>
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<tr>
<td>Working Memory</td>
<td>0.37 (0.59)</td>
<td>-0.01 (0.89)</td>
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<td></td>
</tr>
<tr>
<td>Logical Memory Ia</td>
<td>12.0 (4.0)</td>
<td>8.9 (5.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logical Memory IIa</td>
<td>11.1 (4.1)</td>
<td>8.0 (5.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluency, animals</td>
<td>19.5 (5.4)</td>
<td>15.8 (7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluency, vegetables</td>
<td>17.3 (5.1)</td>
<td>13.8 (7.2)</td>
<td></td>
<td></td>
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<tr>
<td>Digit span forward</td>
<td>8.8 (2.1)</td>
<td>8.0 (2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit span backward</td>
<td>6.4 (2.3)</td>
<td>5.5 (2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit ordering</td>
<td>7.8 (1.7)</td>
<td>6.4 (2.9)</td>
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</tr>
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</table>
Table 3

Heritability of Memory Measures *

<table>
<thead>
<tr>
<th>Memory Measure</th>
<th>Unaffected Family Members</th>
<th>All Family Members</th>
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<tbody>
<tr>
<td></td>
<td>Model A</td>
<td>Model B</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>0.62</td>
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</tr>
<tr>
<td>Semantic memory</td>
<td>0.49</td>
<td>0.49</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.72</td>
<td>0.70</td>
</tr>
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</table>

* Estimated using variance components methods adjusted for age, sex, and education. Models B and D also adjusted for number of apolipoprotein E ε4 alleles and Models C and D adjusted for diagnosis of Alzheimer’s disease.