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Heritability of Cognitive Traits Among Siblings with a Parental History of Alzheimer's Disease

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Abstract

Cognitive decline is one of the hallmark features of Alzheimer's disease, but many studies struggle to find strong associations between cognitive function and genetic variants. In order to identify which aspects of cognition are more likely to have a strong genetic component, we assessed the heritability of various cognitive functions related to Alzheimer's in 303 initially asymptomatic middle-aged adult siblings with a parental history of Alzheimer's from the Wisconsin Registry for Alzheimer's Prevention. Participants underwent extensive cognitive testing and six cognitive factors were identified via factor analysis. Working Memory and Visual Learning & Memory had the highest heritability (52% and 41%, respectively). Inclusion of *APOE* allele counts did not notably change heritability estimates, indicating that there are likely additional genetic variants contributing to cognition. These findings suggest that future genetic studies should focus on the cognitive domains of Working Memory and Visual Learning & Memory.

Keywords

Alzheimer's Disease; Heritability; Genetics; Cognitive Function; WRAP; *APOE*

Introduction

Alzheimer's disease (AD) is the 6th leading cause of death in the US and there is currently no known way to prevent or slow the progression of this disease [1]. As our population ages and the prevalence of AD continues to increase, it is becoming even more crucial to

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understand the biological mechanisms contributing to this disease. One of the hallmark features of AD is the antecedent decline in cognitive function, in particular memory, which makes cognitive function an important trait to study to better understand the earliest signature of the disease.

Other than age, the strongest risk factor for late-onset AD and cognitive decline is the apolipoprotein E (*APOE*) ε4 allele, with the ε2 allele protecting against cognitive decline and AD. A large-scale meta-analysis of genome-wide association studies has confirmed 19 additional genetic regions that are associated with AD [2], but genetic studies of cognitive function and decline have not resulted in replicable findings beyond the *APOE* alleles [3]. Assessing the heritability (h^2) of specific cognitive factors related to AD could identify which have a stronger genetic contribution and would thus be most beneficial to conduct a genetic association or genomic sequencing study with. In the present study, we estimated the h^2 of six cognitive factors from a factor analysis, representing the domains of memory and executive function that are likely to show decline early in the pathology of AD [4] using a sample of asymptomatic adult siblings with a parental history of AD from the Wisconsin Registry for Alzheimer's Prevention (WRAP). This unique population could provide h^2 estimates that are more specific to cognitive function related to pre-symptomatic AD pathology than h^2 estimates from the general population.

Materials and Methods

Participants

Study participants were from WRAP, a longitudinal study of initially asymptomatic middle-aged adults enriched for a parental history of late onset AD. A positive parental history was defined as having one or both parents with either autopsy-confirmed or probable AD as defined by NINCDS-ADRDA research criteria [5]. Baseline recruitment began in 2001 and the study protocol used a 4-year window between baseline and wave 2 visits, and 2-year windows for all subsequent visits. Follow-up data are still being collected and, at this time, only a few participants have developed AD. Further details of the study design and methods used have been previously described [6–8].

The present analyses focused on data collected from full sibling participants during wave 2, which is the first visit to include administration of all the neuropsychological tests related to the cognitive factors of interest in this analysis, as described in the following section. The study sample was also limited to non-Hispanic Caucasian participants due to sample size limitations of other racial groups. Participants were excluded if they reported having diseases or comorbidities that might be expected to influence cognitive test performance (e.g., multiple sclerosis, Parkinson's disease, stroke, epilepsy/seizures, or meningitis), as were those who developed AD on or before the second visit.

This study was conducted with the approval of the University of Wisconsin Institutional Review Board and all subjects provided signed informed consent before participation.

Neuropsychometric Assessments

The WRAP cognitive test battery consists of widely used standardized clinical neuropsychological tests, which were selected to provide a comprehensive estimate of cognitive abilities with an emphasis on abilities most likely to be affected in early-stage AD. The battery used at baseline assessment has been described in detail elsewhere [6]. The battery was expanded at Wave 2 assessment to include additional measures of memory, including the Brief Visuospatial Memory Test-Revised (BVMT-R)[9] and the Wechsler Memory Scale-Revised (WMS-R) – Logical Memory I and II tests [10]. The Wechsler Abbreviated Scale of Intelligence™ (WASI™) full-scale IQ was administered at baseline and Wave 2 to obtain an estimate of general cognitive ability [11].

Factor analysis was originally conducted to reduce a larger set of neuropsychological test scores from the baseline battery to a smaller number of reliable cognitive factors: two for the domain of memory and two for the domain of executive function. Details of the methods used and resulting factor structure are reported elsewhere [12, 13]. The factor analysis methods were recently reapplied to Wave 2 for the set of neuropsychological test scores that were included in the original factor analysis plus summary scores from the BVMT-R and the WMS-R – Logical Memory I and II tests. While the four factors reported previously [13] were retained, the BVMT-R test scores loaded together on a fifth factor (Visual Learning and Memory) and the Logical Memory I and II scores loaded together on a sixth factor (Story Recall); both of these belong to the cognitive domain of memory. The four memory factors and the two executive function factors were used in the analyses for this study. Tests comprising each of these factors are summarized in Table 1. Weights from the factor analyses were used to obtain weighted factor scores which were then standardized (~N [0,1]) into z-scores, using means and standard deviations obtained from the first time a test was used in the whole sample (i.e., baseline for 4 factors and Wave 2 for the latter two factors based on tests added at Wave 2). This approach ensured that all waves were standardized using the same values and that these values were unaffected by practice effects.

Additional Variables

In addition to the neuropsychometric outcomes outlined above, this analysis also utilized gender, age, years of education, and *APOE* ε4 and ε2 counts, all of which were collected either at baseline or wave 2 for time varying measurements. *APOE* genotyping was performed by both Athena Diagnostics, Worcester, MA, and the Atwood Lab, Madison, WI. Any genotypes that were discordant between the two labs were re-genotyped to achieve concordance.

Statistical Analysis

Variance component models have been commonly used in human genetics to estimate narrow-sense h^2 [14, 15]. In this study, h^2 estimates were calculated using variance component models, implemented using the software, Sequential Oligogenic Linkage Analysis Routines (SOLAR)[16]. SOLAR calculates h^2 from the proportion of total phenotypic variance due to the additive genetic contribution, as described in the following

equation: $h^2=\frac{\sigma_A^2}{\sigma_A^2+\sigma_E^2}$, with σ_A^2 being the additive genetic variance and σ_E^2 being the environmental variance, which combined are the total phenotypic variance. The additive genetic component is the expected proportion of shared genetics, on average, based on reported family relationships. The environmental component accounts for shared and unshared known environmental factors, such as age and gender. When added as covariates, these can reduce unexplained trait variance, which in turn can magnify the genetic signal. It is possible, however, for a covariate to decrease the genetic signal if the covariate is genetically influenced, such as cholesterol levels in the analysis of type 2 diabetes, as it would then correct for genetic factors in addition to environmental ones [15]. Further, it is important to note that because SOLAR uses narrow sense h^2, results presented here do not account for non-additive genetic effects, such as dominance or interaction effects with and between genetic variants, and the estimates are likely to underestimate the role genetics plays in cognitive function.

In this study, the h^2 of each outcome was estimated using several different models. The first model did not adjust for any covariates; the second adjusted for sex, age, and education; and the third adjusted for sex, age, education, and *APOE* ε4 and *APOE* ε2 counts, to estimate the h^2 after the effects of *APOE* alleles are removed.

Results

This study consisted of 303 full sibling participants in a total of 120 families. Families had a median of 2 siblings, with the number of siblings per family ranging from 2–9, all of which were used for this analysis. Participants were 55.6 years of age on average, fairly well educated (median education was 4 years of college), and predominantly female (72.9%). When comparing the *APOE* allele count frequencies of this population to those reported in a meta-analysis of Caucasian populations in AlzGene [17], this population has lower *APOE* ε2 allele counts than AlzGene controls (1 allele: 10.9% vs. 14.1%; 2 alleles: 0.7% vs. 0.9%), while *APOE* ε4 counts were higher (1 allele: 39.6% vs. 24.5%; 2 alleles: 7.6% vs. 2.0%). Further, *APOE* ε2 allele counts were higher in this population than in AlzGene AD cases (1 allele: 10.9% vs. 7.4%; 2 alleles: 0.7% vs. 0.3%), while *APOE* ε4 counts were lower (1 allele: 39.6% vs. 45.9%; 2 alleles: 7.6% vs. 14.5%). This was also to be expected, since even though these participants have an increased risk of AD, it is unlikely that they all will go on to develop it. Participant characteristics are described further in Table 2.

The correlations between the different cognitive factors are described in Table 3. With the exception of the correlation between Verbal Learning & Memory and Immediate Memory (r=0.62), all correlations were fairly weak. Correlations between these outcomes and the covariates (age, education, gender, *APOE* ε2 counts, and *APOE* ε4 counts), as well as within the covariates, were also explored but none were strongly correlated (all r<0.5).

Results of the h^2 analysis are described in detail in Table 4. Intelligence was included as a trait in order to demonstrate the validity of the h^2 estimates, as it has consistently been found to be highly heritable, commonly reported to be about 50% and ranging up to 70%[18]. As

expected, after controlling for age, sex, and education, intelligence was found to have a relatively high h^2 of 64%.

Speed & Flexibility, Visual Learning & Memory, and Working Memory had the highest unadjusted h^2 estimates, ranging from 40–49%. After adjusting for gender, age, and education, Working Memory had the highest h^2 (52%), Visual Learning & Memory decreased to 41%, and Speed & Flexibility decreased to 29%. The h^2 of the remaining three cognitive factors (Immediate Memory, Verbal Learning & Memory, and Story Recall) remained fairly low after adjustments, ranging from 10%–19%. With the addition of *APOE* ε2 and ε4 counts to the model, the h^2 of Immediate Memory notably decreased (from 16% to 6%), while the remaining outcomes remained fairly unchanged.

To evaluate the influence of the opposing effects of the *APOE* ε2 and *APOE* ε4 alleles, h^2 estimates were also calculated excluding 14 individuals who had the *APOE* ε2/ε4 genotype (N=289). The results from this analysis were largely consistent with those reported here. The largest differences were up to 4 units higher or lower, but the statistical significance and rank of the adjusted heritability of the cognitive factors remained the same in both analyses.

Discussion

Our findings show that the cognitive factors, Working Memory and Visual Learning & Memory, have fairly strong adjusted h^2, suggesting that they are likely to have strong genetic contributions. Genetic association or sequencing studies investigating AD-related cognition or cognitive decline could benefit from focusing on aspects of cognition that capture these factors since this study sample has a parental history of AD. Interestingly, we also report that inclusion of the *APOE* allele counts did not appear to alter h^2 estimates, despite its strong association with AD and moderate association with cognitive function in the full WRAP sample [8].

Although intelligence is generally highly heritable [18], other components of cognitive function have been reported to range roughly from 20–75% [19–22]. We found that the estimates presented here were fairly consistent with other studies. In a similar study of unaffected family members of patients with AD, Working Memory was reported to have an h^2 of 72% after adjustment for age, sex, and education [20]. Estimates may have been higher due to their larger sample size (n=622), resulting in a more precise h^2 estimate, and some differences in the battery used to assess Working Memory, which similarly included Digit Span Forward and Digit Span Backward, but did not include Letter-Number Sequencing.

In a cohort study of type 2 diabetics, an age, gender, and education adjusted h^2 of 62% was reported for the Digit Symbol Substitution Task, which is considered to be a test of Working Memory [21]. They also reported an h^2 of 28% for the Stroop test, one of the tests used in the present study to assess Speed & Flexibility. Although these estimates are slightly higher that those reported here, which could be explained by the different batteries used and their larger sample size (n=526), they are still generally agreeable.

Further, a study on non-demented elderly twins reported an h^2 of 47% for Thurstone's Picture Memory Test [23], a visual, long-term memory test, which strengthens the observed

high h^2 of Visual Learning & Memory in the present study. Beyond the different test used for this estimate, the higher h^2 found in their study could also be explained by their use of structural equation modeling to estimate h^2 and because they controlled for age and gender, but not education.

There have been previous studies that found that adjustment for *APOE* ε4 count did not substantially impact h^2 estimates [20, 24]. In addition to *APOE* ε4 count, we also included the *APOE* ε2 count and similarly found that although the h^2 of Immediate Memory did marginally decrease, all other factor scores remained essentially unchanged with these adjustments. This suggests that while the *APOE* alleles may account for some of the h^2 of cognition, it is likely that other genetic variants substantially contribute to cognitive function, possibly through additive, epigenetic, epistatic, and / or gene-environment interactive effects.

It is difficult to precisely compare our findings to other studies due to the varying methods and tests used to compute factor scores, and also due to our slightly smaller sample size, which may have resulted in less precise estimates of h^2. Due to a limited number of genetic variants available for the sample used, we were unable to genetically verify that siblings were full siblings. Although WRAP staff made every effort to ensure that siblings indeed had the same parents, it is possible that a limited number of siblings were not full siblings, which could also affect h^2 estimates. Because this study included siblings who were not twins, it is possible that h^2 estimates presented are overestimates because some of the correlation seen could be due to shared environment instead of shared genes. However, neuropsychological testing was measured later in life when the influence from shared environment has likely diminished and the influence from genetics has likely increased [25]. Even given the mentioned limitations, our findings are fairly similar to those that have been previously reported.

In conclusion, our study confirms that Working Memory and Visual Learning & Memory are indeed highly heritable cognitive factors. Further, we found that *APOE* ε4 and *APOE* ε2 counts do not explain much of the heritability of cognitive function, suggesting that the effects of other genetic variants play an important role in these domains. These findings suggest that Working Memory and Visual Learning & Memory could be important cognitive domains for future genetic studies to investigate and that such studies may have the potential to unveil novel genetic variants involved in cognitive function as well as AD.

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Table 1

Six cognitive factors by domain identified in the WRAP battery.

Factor name	Cognitive test
Memory domain	
Immediate Memory	Rey Auditory Verbal Learning Test – Trials 1 & 2[26]
Verbal Learning & Memory	Rey Auditory Verbal Learning Test – Trials 3 through 5 & Delayed Recall [26]
Story Recall	WMS-R – Logical Memory I and II – Sum of Story A and B Immediate Recall and Sum of Story A and B Delayed Recall [10]
Visual Learning & Memory	Brief Visuospatial Memory Test – Sum of Trials 1 through 3 and Delayed Recall [9]
Executive function domain	
Working Memory	Digit Span Forward, Digit Span Backward, and Letter-Number Sequencing (Wechsler Adult Intelligence Scale-III)[27]
Speed & Flexibility	Stroop Color-Word Test – Interference Trial [28] Trail-Making Test – Parts A & B [29]

Table 2

WRAP Participant Characteristics.

Characteristic	Mean (SD) or N (%)
Age (years)	55.6 (6.6)
Gender (female)	221 (72.9)
Family Gender Distributions	
Mixed Genders	44 (36.7)
All Females	66 (55.0)
All Males	10 (8.3)
Education	
High School or Equivalent	38 (12.5)
Some College/Technical School	113 (37.1)
College Graduate	90 (29.5)
Post-Graduate	64 (21.0)
APOE ε2 Count	
0	268 (88.5)
1	33 (10.9)
2	2 (0.7)
APOE ε4 Count	
0	160 (52.8)
1	120 (39.6)
2	23 (7.6)
Siblings per Family	
2	88 (73.3)
3	20 (16.7)
4	4 (3.3)
5	3 (2.5)
6+	5 (4.2)

Based on related participants who completed wave 2 (N=303 individuals, 120 families).

Table 3

Pearson Correlations (*r*) of Cognitive Outcomes

	IM	VBM	SR	VSM	WM	SF	IQ
Immediate Memory (IM)		.62	.31	.30	.26	.33	.13
Verbal Learning& Memory (VBM)	--		.41	.45	.20	.31	.20
Story Recall (SR)	--	--		.35	.24	.18	.34
Visual Learning & Memory (VSM)	--	--	--		.14	.29	.35
Working Memory (WM)	--	--	--	--		.34	.30
Speed & Flexibility (SF)	--	--	--	--	--		.14
WASI Full-Scale (IQ)	--	--	--	--	--	--	

*All correlations in the table are statistically significant (p<.05)

Table 4

Heritability of Outcomes, N=303 Related Individuals.

Outcome	No Adjustments			Gender, Age, and Education Adjusted			Gender, Age, Education, and *APOE* ε2 and ε4 Adjusted		
	h^2	SE†	p-value	h^2	SE	p-value	h^2	SE	p-value
Immediate Memory	.17	.12	.05	.16	.12	.08	.06	.13	.31
Verbal Learning & Memory	.09	.15	.27	.19	.15	.09	.18	.14	.10
Story Recall	**.17**	.12	**.047**	.10	.12	.19	.09	.11	.19
Visual Learning & Memory	**.44**	.14	**.0002**	**.41**	.14	**.0008**	**.42**	.15	**.001**
Working Memory	**.49**	.14	**<.0001**	**.52**	.14	**<.0001**	**.52**	.14	**<.0001**
Speed & Flexibility	**.40**	.14	**.0008**	**.29**	.15	**.02**	**.26**	.15	**.03**
WASI Full-Scale IQ	**.72**	.14	**<.0001**	**.64**	.14	**<.0001**	**.64**	.14	**<.0001**

† Standard Error, SE

Bolded values are statistically significant (p<0.05).

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