Published in final edited form as:

Psychol Aging. 2014 June ; 29(2): 404–417. doi:10.1037/a0035962.

Genetic Complexity of Episodic Memory: A Twin Approach to Studies of Aging

William S. Kremen,

Department of Psychiatry, Center for Behavioral Genomics, University of California, San Diego, and Center of Excellence for Stress and Mental Health, VA San Diego Health Care System, La Jolla, California;

Kelly M. Spoon,

Department of Psychiatry, Center for Behavioral Genomics, University of California, San Diego, and Computational Science Research Center, San Diego State University/Claremont Graduate University

Kristen C. Jacobson,

Department of Psychiatry and Behavioral Neuroscience, University of Chicago

Terrie Vasilopoulos,

Department of Psychiatry and Behavioral Neuroscience, University of Chicago

Jeanne M. McCaffery,

Department of Psychiatry and Human Behavior, and the Miriam Hospital and Warren Alpert School of Medicine at Brown University

Matthew S. Panizzon,

Department of Psychiatry, Center for Behavioral Genomics, University of California, San Diego

Carol E. Franz,

Department of Psychiatry, Center for Behavioral Genomics, University of California, San Diego

Eero Vuoksima,

Department of Psychiatry, Center for Behavioral Genomics, University of California, San Diego, and Department of Public Health, University of Helsinki, Helsinki, Finland

Hong Xian,

Department of Biostatistics, St. Louis University, and Research Service, and VA St. Louis Health Care System, St. Louis, Missouri

Brinda K. Rana,

Department of Psychiatry, Center for Behavioral Genomics, University of California, San Diego

Rosemary Toomey,

Department of Psychology, Boston University

Ruth McKenzie, and

Correspondence concerning this article should be addressed to William S. Kremen, Department of Psychiatry, University of California, San Diego, 9500 Gilman Drive (MC 0738), La Jolla, CA 92093. wkremen@ucsd.edu.
William S. Kremen and Matthew S. Panizzon contributed equally to this article.

Department of Psychology, Boston University

Michael J. Lyons

Department of Psychology, Boston University

Abstract

Episodic memory change is a central issue in cognitive aging, and understanding that process will require elucidation of its genetic underpinnings. A key limiting factor in genetically informed research on memory has been lack of attention to genetic and phenotypic complexity, as if “memory is memory” and all well-validated assessments are essentially equivalent. Here we applied multivariate twin models to data from late-middle-aged participants in the Vietnam Era Twin Study of Aging to examine the genetic architecture of 6 measures from 3 standard neuropsychological tests: the California Verbal Learning Test-2, and Wechsler Memory Scale-III Logical Memory (LM) and Visual Reproductions (VR). An advantage of the twin method is that it can estimate the extent to which latent genetic influences are shared or independent across different measures *before* knowing which specific genes are involved. The best-fitting model was a higher order common pathways model with a heritable higher order general episodic memory factor and three test-specific subfactors. More importantly, substantial genetic variance was accounted for by genetic influences that were specific to the latent LM and VR subfactors (28% and 30%, respectively) and independent of the general factor. Such unique genetic influences could partially account for replication failures. Moreover, if different genes influence different memory phenotypes, they could well have different age-related trajectories. This approach represents an important step toward providing critical information for all types of genetically informative studies of aging and memory.

Keywords

heritability; genetic architecture; genetic correlation; cognitive aging; free recall

Understanding episodic memory function and episodic memory changes is a central issue with respect to cognitive aging. Episodic memory refers to the ability to remember past events in conjunction with information about the spatial and temporal contexts of those events (Squire, Knowlton, & Musen, 1993; Tulving, 1972). It differs from short-term and working memory, which refer to transient and limited capacity recall that is dependent on the integrity of a different neural system than the system underlying episodic memory. It is our view that behavioral genetic studies of aging and memory have been hindered, in part, because inadequate attention has been paid to the genetic and phenotypic complexity of memory phenotypes. In this article, we demonstrate how the twin method can contribute toward elucidating that complexity. We focus on free recall for this report. Free recall is only one episodic memory phenotype, but it is a cornerstone of neurocognitive test batteries assessing normal aging, mild cognitive impairment, and dementia.

A full understanding of episodic memory in aging adults will require further elucidation of its genetic underpinnings, but very few studies have examined the extent to which different components of memory are or are not genetically related. Here we use the method of genetic

epidemiology, one of two major behavioral genetic research approaches for addressing this issue in humans (Kendler & Eaves, 2005); the other approach is gene finding. Genetic epidemiology addresses not only simple heritability estimates but also the genetic relationship between different traits and whether there are changes in genetic risk factors as a function of age or developmental stage. In this approach, which genes or how many specific genes underlie the heritability of particular traits is unknown. Put another way, the genes are anonymous.

The heritability of episodic memory may be less well established than is typically assumed. We found 16 independent studies of adults: nine family studies of neuropsychiatric patients (Antila et al., 2007; Bertisch, Li, Hoptman, & Delisi, 2010; Glahn et al., 2007; Greenwood et al., 2007; Husted, Lim, Chow, Greenwood, & Bassett, 2009; Lee, Flaquer, Stern, Tycko, & Mayeux, 2004; Tuulio-Henriksson et al., 2002; Wang et al., 2010; Wilson et al., 2011); one twin study with schizophrenia probands (Owens et al., 2011); and six normative twin studies (Finkel, Pedersen, & McGue, 1995; Giubilei et al., 2008; McGue & Christensen, 2001; Panizzon et al., 2011; Swan et al., 1999; Volk, McDermott, Roediger, & Todd, 2006). Family studies more accurately estimate familial resemblance rather than heritability because all or most of the participants are first-degree relatives who do not differ in their genetic relatedness (Kendler & Neale, 2009). Five of the six normative twin studies had samples with average ages in the midlife to older adult range. The most studied tests were versions of the California Verbal Learning Test (CVLT; word list; Delis, Kramer, Kaplan, & Ober, 1987, 2000), and the Wechsler Memory Scale (WMS) Logical Memory (LM; story recall), and WMS Visual Reproductions (VR; recall of designs; Wechsler, 1945, 1987, 1997). However, there were only two normative twin studies for each of these tests, and the same versions and measures from those tests were not used in all of those studies; heritabilities were generally in the .35 to .50 range. In addition, episodic memory scores were not always adjusted for general cognitive ability (GCA). Therefore, these heritability estimates almost certainly include some of the genetic influences on GCA in addition to genetic influences on episodic memory.

Some of the more well-known gene associations for episodic memory are *apolipoprotein E* (*APOE*), *sortilin-related receptor L1* (*SORL1*), *kidney and brain expressed protein* (*KIBRA*), *HtrA serine peptidase 2* (*HTRA2*), *brain-derived neurotrophic factor* (*BDNF*), *catechol-O-methyl transferase* (*COMT*), *glutamate receptor, metabotropic 3* (*GRM3*), and *calsystenin 2* (*CLSTN2*) although these vary in terms of consistency of replication (Papassotiropoulos & de Quervain, 2011; Sabb et al., 2009). In their review, Sabb et al. (2009) concluded that genetic associations had thus far accounted for only about 7% of the variance in a variety of memory measures.

One of the limiting factors in understanding the genetics of episodic memory is the lack of attention that is generally paid to both phenotypic and genetic complexity. Papassotiropoulos and de Quervain (2011) made this point in regard to gene finding in particular. Like our group (Kremen & Lyons, 2011), they view genetic epidemiological and gene-finding approaches as complementary strategies that need further integration. Episodic memory, like other cognitive abilities, is a polygenic trait. If it is therefore influenced by many genes, each of small effect, it will be difficult to identify and replicate those genes in traditional genome-

wide association studies in which controlling for the massive risk of Type I error means that small effects are highly unlikely to be detectable.

Too often, the phenotypic complexity of episodic memory and its underlying genetic complexity have been largely ignored. Findings from two studies illustrate the potential problem of addressing the issue as if “memory is memory” and any well-validated memory phenotype will do. Egan et al. (2003) found that a polymorphism of the *brain-derived neurotrophic factor* gene was associated with WMS-Revised (WMS-R) LM, but not CVLT, scores. On the other hand, Papassotiropoulos et al. (2006) found that the *KIBRA* gene was associated with performance on the Rey Auditory Verbal Learning Test (Rey, 1964), the Buschke Selective Reminding Test (Buschke & Fuld, 1974), another word list test, and a visual memory test in three different samples. In one instance, the same gene was associated with performance on several episodic memory tests across different samples (Papassotiropoulos et al., 2006). In the other, the same gene was associated with one, but not the other, of two episodic memory tests in the same sample (Egan et al., 2003).

Replication of gene association findings has proven to be challenging even with identical measures (Sabb et al., 2009). With different measures, it becomes more difficult to determine whether inconsistent findings within or between genetic studies are due to false-positive results or to genetic complexity of the phenotypes. The extremely large samples needed for gene discovery in genome-wide association studies require combining studies, but progress may be handicapped to the extent that different, albeit related, phenotypes are used when multiple studies are combined. On the other hand, it is unlikely that improving phenotype definition will solve all of the problems of genetic association studies, particularly when each gene influencing episodic memory is likely to have only a very small effect. Still, new approaches such as genetic-pleiotropy-informed methods and leveraging genic enrichment are showing promise over traditional genome-wide association study approaches for improving gene discovery in complex phenotypes (Andreassen et al., 2013; Schork et al., 2013).

Multivariate applications of the classical twin method, such as those used in the present study, provide a partial solution to this problem, but that is only one of the capabilities of genetic epidemiology. This approach is uniquely able to address the genetic architecture of episodic memory because multivariate twin analysis makes it possible to determine whether different phenotypes share or have independent genetic influences *before* knowing which specific genes are involved. As such, this approach can be informative as to phenotype definition for genetic studies. Twin analysis can also provide information about the genetic relationship between different traits and whether there are changes in genetic risk factors as a function of age or developmental stage. For genetic association studies, for example, it would not make sense to expect replication across two memory phenotypes if twin analysis showed that there are different genetic influences on each phenotype. For cognitive aging studies, different genetic or environmental influences would suggest that different episodic memory components may not necessarily follow the same aging trajectories. In addition, the identical cotwin control design can be used to make inferences about cause and effect, even in cross-sectional studies. If, for example, identical twins are discordant for a particular disorder, but the unaffected twins have similar memory impairment as the affected twins, it

can be inferred that the memory impairment is a risk factor for, rather than a consequence of, the disorder.

To date, there have been very limited multivariate examinations of episodic memory that have utilized the classical twin design. Finkel et al. (1995) performed two trivariate analyses, each with one short-term memory and two episodic memory measures, based on the Swedish Adoption/Twin Study of Aging and the Minnesota Twin Study of Adult Development and Aging. The goal of these studies was not to determine whether or not there was a general memory factor; rather, measures were selected for analysis so that they would result in a general factor. Specific genetic influences beyond the general memory factor were found in the second study, which included immediate free-recall measures, but not in the first study, which included only immediate recognition. In another study of adolescent female twin pairs, free recall of categorized and uncategorized word lists had both shared and measure-specific genetic influences, whereas there were no specific genetic effects for cued recall (Volk et al., 2006).

In previous work using the CVLT-2 (Delis et al., 2000), we showed that learning (based on the total score of Trials 1 through 5) had some specific genetic influences that were distinct from delayed free-recall measures (Panizzon et al., 2011). This work demonstrated different genetic effects for phenotypes even within the same test. We speculated that the genes that were specific to the learning trials likely affected acquisition processes because the learning and recall trials both involve recall, but only the former involves acquisition. This analytic approach is also informative with regard to when it is most appropriate to split apart or to use composite phenotypes. In contrast to the learning trial results, there was complete genetic overlap between measures of short- and long-delay free recall. The results of this multivariate genetic analysis suggest that it would be appropriate to combine short- and long-delay free recall. However, the finding of some distinct genetic influences among these measures also suggests that learning and free recall may not necessarily manifest the same pattern of age-related changes.

The different analyses are important for suggesting that episodic memory measures are not interchangeable at the genetic level. The results also suggest that there may be measure-specific genetic influences on free-recall measures, but not recognition or cued recall measures. Recognition is, of course, a different process from that of free recall, but it may also be that recognition measures are not of sufficient difficulty in nonpatient samples, particularly if they are not older adults. These reports are also limited in several ways with respect to the goal of the present analyses. Each set of analyses included only two or three episodic memory variables, making the possibility of more than one factor very unlikely. Our prior study (Panizzon et al., 2011) is limited because it contained only measures from a single memory test. Two of these analyses included only verbal measures (Panizzon et al., 2011; Volk et al., 2006), and two included only immediate memory measures (Finkel et al., 1995; Volk et al., 2006).

Here we addressed some of these limitations by performing multivariate twin analysis to elucidate the genetic and environmental architecture of six measures from three widely used episodic memory tests. Only free-recall measures were included; recognition and short-term

memory measures were excluded. The choice of measures meant that episodic memory could be evaluated along two major dimensions: verbal versus visual-spatial, and immediate versus delayed. We tested several possible models, each based on specific hypotheses and assumptions regarding the structure of episodic memory. Based on the small amount of prior work in the literature, and based on the phenotypic correlation matrix for our data, we hypothesized that there would be a general episodic memory factor. We also hypothesized that there would be specific genetic influences that would differ primarily as a function of test rather than immediate versus delayed recall. Finally, we examined the correlations with age of the memory factors from the best-fitting model. These correlational analyses provide information about age-related differences in a narrow age band in late midlife, an understudied period in aging research (Kremen, Moore, Franz, Panizzon, & Lyons, 2013). This work has implications for both longitudinal studies of age-related memory change and gene finding.

Method

Participants

Participants were late-middle-aged men in the first wave of the Vietnam Era Twin Study of Aging (VETSA; Kremen, Franz, & Lyons, 2013; Kremen et al., 2006). The VETSA is a national sample consisting of 1,237 individual twins (349 monozygotic [MZ] pairs, 265 dizygotic [DZ] pairs, and nine unpaired). Zygosity was determined on the basis of 25 microsatellite markers for 92% of the sample, and by questionnaire and blood group for the remainder. There was 95% agreement between the two methods. Average age was 55.4 years ($SD = 2.5$), and the average educational attainment was 13.8 years ($SD = 2.1$). All are veterans who are part of the larger Vietnam Era Twin Registry. The registry is defined on the basis of military service sometime between 1965 and 1975, not service in Vietnam. In fact, 78% report no combat experience. Participation in VETSA Wave 1 took place an average of 35 years after military service.

VETSA participants comprise a national sample that is reasonably representative of American men of the same age, in terms of sociodemographic and health characteristics, based on Centers for Disease Control and Prevention and U.S. census data (Kremen, Franz, et al., 2013; Kremen et al., 2006; Schoenborn & Heyman, 2009). Participants were community-dwelling adults who were not selected or excluded on the basis of any diagnostic characteristics. The only criteria were that participants had to be between the ages of 51 and 59 years at the time of recruitment, and both twins in a pair had to be willing to participate.

Participants visited either the University of California, San Diego, or Boston University, where identical protocols were administered. Individual twins had their choice of selecting either site, although brothers most often chose to go to the same site. A small number of participants who could not, or did not wish to, travel to the study sites were tested in their hometowns. Neuropsychological, psychosocial, and biomedical assessments were conducted; the complete protocol is described elsewhere (Kremen et al., 2006; Kremen, Franz, et al., 2013).

Measures

Both verbal and visual-spatial episodic memory measures were included in our multivariate twin analyses: the CVLT-2 short- and long-delay free recall; the WMS-III (Wechsler, 1997) LM immediate and delayed recall; and the WMS-III VR immediate and delayed recall. Standard administration was employed except for WMS-III LM. In this case, the second story in the WMS-III was read only once, whereas in the standard administration, it is read twice. The terms “test” and “measure” are often used interchangeably. Throughout this article, we use “measure” to refer specifically to the six individual episodic memory measures, and “test” to refer to the three tests from which those measures are derived. Thus, for example, “test-specific factor” refers to a composite of individual measures from one of the three tests (CVLT-2, LM, and VR).

Because specific cognitive abilities tend to be related to GCA, some of the genetic influences on episodic memory may actually reflect genes that influence overall cognitive ability. To address this issue, we adjusted all memory measures for GCA prior to the twin analyses. Our GCA measure was the Armed Forces Qualification Test (AFQT; Bayroff & Anderson, 1963), a 100-item test with sections on vocabulary, arithmetic, spatial processing, and reasoning about tools and mechanical relations. The AFQT correlates about .85 with IQ and other general intellectual ability measures; it is highly stable, with a test-retest correlation of .74 over a 35-year period in VETSA participants (Lyons et al., 2009). During the VETSA, the mean AFQT percentile score was 64 (interquartile range = 50 to 81), which is comparable with a mean IQ score of approximately 104 to 105.

Statistical Analysis

In the classical twin design, the variance of any trait can be decomposed into additive (A) genetic influences, common (C) or shared environmental influences (i.e., environmental factors that make twins similar to one another), and nonshared environmental (E) influences (i.e., environmental factors that make twins different from one another, including measurement error). In a univariate scenario, the resulting model is widely referred to as the ACE model (Eaves, Last, Young, & Martin, 1978; Neale & Cardon, 1992). Additive genetic influences are assumed to correlate perfectly between MZ twins because they typically share 100% of their genes, whereas DZ twins share, on average, 50% of their segregating genes, and are therefore assumed to correlate .50. Shared environmental influences are assumed to correlate perfectly between members of a twin pair, regardless of the zygosity. Nonshared environmental influences are, by definition, uncorrelated between twins. Multivariate twin analyses extend the univariate ACE model so as to further decompose the covariance between traits into genetic and environmental components.

In order to determine the relative contribution of genetic and environmental influences to each memory measure and to the covariance between measures, we first fit a six-variable Cholesky decomposition to the data (see Figure 1). Note that for ease of presentation, C contributions to the variance are not shown in the corresponding figures. The Cholesky imposes no specific structure on the genetic and environmental covariance. Thus, it represents the most saturated structure of the genetic and environmental relationships among the variables. Although any visual representation of the Cholesky appears to imply direction

of relationships, it should be noted that the Cholesky does not contain any such directionality. Relative to the Cholesky, multiple variations of the common pathways (psychometric factors) model were fit to the data (see Figures 2, 3, 4, 5, and 6), each of which tests a specific hypothesis about the genetic and environmental relationships among the memory measures. The common pathways model assumes that the covariance among variables is accounted for by one or more latent phenotypes/factors, the variance of which can be decomposed into genetic and environmental influences (Kendler, Heath, Martin, & Eaves, 1986; McArdle & Goldsmith, 1990). Genetic and environmental contributions to the variance in the measured variables are accounted for by the genetic and environmental influences that operate through the latent phenotype, as well as those that are variable specific (i.e., residual genetic and environmental influences).

In the single-factor model (Figure 2) the covariance among the memory measures is entirely accounted for by one latent phenotype (i.e., the general episodic memory factor). This model provides the most direct test of the assumption that all episodic memory measures assess the same latent construct, and that individual differences in those measures are driven by the same genetic and environmental influences. In the immediate versus delayed recall model (Figure 3), two correlated latent factors were fit to the data, testing whether the six memory measures corresponded to latent immediate and delayed recall phenotypes. Similarly, in the verbal versus visual-spatial memory model (Figure 4), two correlated latent factors were fit to the data in order to test whether the memory measures corresponded to verbal and visual-spatial episodic memory phenotypes.

In the test-specific factors model (Figure 5), three correlated latent factors were fit to the data, each factor representing a specific episodic memory test. This model assumes that each episodic memory measure will load most strongly onto its corresponding test-specific factor, and establishes the degree to which these factors correlate with one another at the phenotypic, genetic, and environmental levels. Finally, in the higher order factor model (Figure 6), an overarching general episodic memory latent phenotype is fit to the data in addition to three test-specific factors. The higher order factor accounts for the covariance among the test-specific factors while also allowing for the presence of genetic and environmental influences that are specific to each factor. The fit of this model relative to the correlated factors (test-specific factors) model provides a test of whether a general episodic memory phenotype can be used to explain the observed covariance among various measures of episodic memory. We also tested two additional higher order models (not shown): one with verbal and visual-spatial memory subfactors instead of three test-specific factors, and one with immediate and delayed recall subfactors.

Analyses were performed using the maximum-likelihood-based structural equation modeling software OpenMx (Boker et al., 2011). Prior to model fitting, episodic memory variables were adjusted for GCA. The adjusted (residual) scores were then standardized to a mean of 0 and a standard deviation of 1.0 in order to simplify the specification of start values and parameter boundaries. Evaluation of model fit was performed using the likelihood ratio chi-square test (LRT), which is calculated as the difference in the $-2 \log$ -likelihood ($-2LL$) of a model relative to that of a comparison model. In addition to the LRT, the Bayesian information criterion (BIC) was utilized as a secondary indicator of model fit

(Williams & Holahan, 1994). The BIC indexes both goodness of fit and parsimony, with more negative values indicating a better balance between them. The BIC has been found to perform well with regard to model selection with complex multivariate models (Markon & Krueger, 2004). Correlations and variance component estimates are shown with their 95% confidence intervals (CIs).

Results

Correlations Among Cognitive Measures

Correlations between GCA and memory measures are shown in Table 1. Phenotypic correlations with the verbal memory measures ranged from .28 to .33; for VR, the correlations were .46 for immediate recall and .38 for delayed recall (all were significant based on the 95% CIs). Genetic correlations, which represent the extent of shared genetic influences, between GCA and the episodic memory measures ranged from .40 to .75 (all except .40 were significant based on the 95% CIs).

Table 2 shows the phenotypic correlation matrix for the six episodic memory measures adjusted for AFQT. These were estimated from the full ACE Cholesky. Correlations between measures in the same test were moderate to high (.56 to .84). Correlations between verbal measures from different tests ranged from .28 to .37, and correlations between verbal and visual-spatial measures ranged from .15 to .28.

Genetic Analyses

Table 3 presents the standardized variance components of the six individual episodic memory measures estimated from the full ACE Cholesky, both unadjusted and adjusted for GCA. The estimates based on memory scores adjusted for GCA indicate modest heritability estimates that were highest for LM. It should be noted, however, that the 95% CIs for all of the heritability estimates overlap substantially, making it unlikely (although not certain) that they are significantly different from one another. Shared environmental influences accounted for relatively small and nonsignificant proportions of the variance, and the majority of variance was accounted for by nonshared environmental factors in all cases. Compared with measures that were not adjusted for GCA, heritability estimates for the adjusted measures were reduced by 18% and 24% for CVLT measures, 11% and 9% for LM measures, and 42% and 28% for VR measures.

Prior to testing the different factor models, we compared the fit of the ACE Cholesky with an AE Cholesky. All shared environmental influences could be fixed at zero without causing a significant deterioration in model fit ($LRT = 7.33$, $df = 21$, $p = .9974$). Because three of the individual episodic memory measures had C estimates that accounted for more than 10% of the phenotypic variance, we decided to keep C freely estimated in all subsequent models. Doing so avoided introducing bias into our estimates of genetic variance and covariance.

Model-fitting results for the common pathways models are shown in Table 4. As can be seen by the p values for the LRTs, only two of the models had a good fit to the data relative to the Cholesky: the three-correlated-factors common pathways models (Model 5) and the hierarchical common pathways model (Model 6). The hierarchical common pathways model

with three test-specific subfactors had the lower BIC, suggesting that it provided the more optimal representation of the data. Because this hierarchical common pathways model is a nested submodel of the three-correlated-factors model, the two can be compared directly. The change in model fit was nonsignificant ($LRT = 5.21$, $df = 14$, $p = .2664$), thus supporting the conclusion that the hierarchical model was the best-fitting model. Parameter estimates from this hierarchical common pathways model (Model 6) are shown in Figure 7; for ease of presentation, parameters that were estimated at zero are not shown.

In Model 6, a single higher order factor accounted for all of the covariance among three test-specific factors, each of which comprised the two measures from each of the three tests (see Figure 7). The higher order latent factor had a heritability of .60 (the square of the parameter estimate of .78 in Figure 7 [with rounding error]), indicating that 60% of the covariance among the three latent test-specific factors was due to common genetic influences. Nonshared environmental influences accounted for 29% of the covariance among the test-specific factors, and shared environmental influences accounted for a nonsignificant 11% of the covariance.

For purposes of the present study, it is more important to point out that there were also significant genetic influences that were unique to two of the three test-specific factors. The LM and VR factors each showed specific genetic influences that accounted for a significant proportion of the phenotypic variance independent of the general episodic memory factor (28% and 30%, respectively). Specific genetic influences accounted for 6% of the observed variance in the CVLT-2 factor, but this was not statistically significant.

The standardized variance components for the test-specific latent factors estimated from the hierarchical common pathways model are shown in Table 5. Heritabilities were .34 for the CVLT-2 factor, .48 for the LM factor, and .43 for the VR factor. These values can be calculated by following the paths in Figure 7. For example, the heritability of the CVLT-2 latent factor is $(.78 \times .68)^2 + .24^2 = .34$.

The proportion of the genetic variance—as opposed to the overall phenotypic variance—that is unique to each test-specific factor is easily calculated. For example, squaring the A parameter of .53 for the LM latent factor in Figure 7 results in .28. As noted, the heritability of the LM factor was .48. Therefore, 58% (.28/48) of the heritability of the LM factor is accounted for by genetic influences that are unique to LM and independent of the general episodic memory factor. Similarly, 70% of the heritability of the VR factor and 18% of the heritability of the CVLT-2 factor were due to test-specific genetic influences. There were no significant measure-specific genetic influences in this analysis. Because E includes error and all of the measures have some error, all of the measure-specific E effects were significant.

Correlations With Age

Phenotypic correlations with age were significant for each of the GCA-adjusted memory factors except LM: general episodic memory factor ($r = -.11$, $p < .0002$), CVLT factor ($r = -.10$, $p < .0007$), LM factor ($r = -.04$, $p = .13$), and VR factor ($r = -.11$, $p < .0001$). We also examined the correlations after additionally adjusting for general episodic memory scores. After adjusting for the general factor, the CVLT factor was uncorrelated with age ($r = -.01$,

$p = .62$), the LM factor was positively correlated with age ($r = .07, p < .02$), and the VR factor remained negatively correlated with age ($r = -.07, p < .02$).

Discussion

As described in the introduction, three reports on four samples have shed some light on the genetic architecture of episodic memory (Finkel et al., 1995; Panizzon et al., 2011; Volk et al., 2006). However, those analyses were also limited in several ways. In the present study, we conducted confirmatory model testing to determine which of several possible models best characterized the genetic architecture of free recall in episodic memory. As predicted, we found a heritable general episodic memory factor. Approximately 60% of the covariance among the tests (factors) was accounted for by common genetic influences, and approximately 30% was accounted for by nonshared environmental influences. The correlations of the memory measures with the AFQT suggest that without adjusting for AFQT scores, some of the common variance accounted for by GCA would likely have been misattributed to episodic memory. It is also worth noting that the higher order factor may simply be an emergent property of the correlations among the different tests and measures (cf. van der Maas et al., 2006). Its position at the top of Figure 7 should not be construed to imply that ability on the various tests and measures stem from, or are caused by, the higher order factor.

In our view, of greater importance than the general factor is the fact that—as hypothesized—the results also clearly demonstrate that different episodic memory tests do not entirely assess the same latent construct at the genetic level. First, the single-factor common factor model provided a poor fit to the data. In addition, based on estimates from the best-fitting higher order factor model, there were significant unique genetic influences underlying two of the three test-specific latent factors. In fact, these unique genetic influences accounted for the large majority of the genetic variance for each test. Almost 60% of the genetic influences on LM, and 70% of the genetic influences on VR, were specific to those latent factors. The genetic influences specific to LM are also independent of the CVLT-2. Thus, although researchers may be tempted to think that either of the classic, well-validated verbal episodic memory measures used in the present study would be fine for genetic studies, it is important to note that our results demonstrate considerable nonoverlapping genetic influences underlying these tests. These conclusions are consistent with prior results of a test of a single gene in relation to these two tests (Egan et al., 2003).

There were significant correlations with age for all of the memory factors except LM. Although these correlations were small, we think they are meaningful, given the narrow age range of basically only 9 years in this sample (only four individuals were 60 years). After accounting for general episodic memory, CVLT was no longer correlated with age. That result was expected, given the absence of test-specific influences on CVLT. In contrast, the VR factor remained negatively correlated with age, but the LM factor was now positively correlated. One possibility is that this positive correlation reflects some sort of compensatory ability that can partially offset age-associated declines in general episodic memory. Although some studies have adjusted for GCA, we are unaware of any cross-sectional or longitudinal studies of memory that have examined specific memory measures after

accounting for general memory ability. These results support our conclusion that the specific genetic influences on the different memory components means that they may change differently with age.

Our results also suggest that the underlying genetic and environmental architecture of episodic memory does not support separate dimensions of immediate versus delayed recall, or separate verbal and visual-spatial modalities, as both of the two-correlated-factors models had poor fits to the data. The absence of a distinction between immediate and delayed recall is consistent with our previous finding from the CVLT-2 alone (Panizzon et al., 2011). The similar absence for the verbal and visual-spatial modalities may be less certain. We included four verbal measures, but only two visual-spatial measures, in the present analysis. The VR factor had the weakest loading on the general episodic memory factor. It is possible that testing a model with a more even balance of verbal and visual-spatial measures might result in separate modality factors.

It is important to remember that the latent factors for CVLT, LM, and VR each consist of two measures from a given episodic memory test. Therefore, results from our latent factor models cannot simply be extrapolated to the specific individual measures from each test. In previous work with this sample, we found that heritabilities for the individual episodic memory measures tend to be lower than the factors (Kremen, Moore, et al., 2013). Moreover, some measures of episodic memory may not be reliable enough to be consistently heritable. For example, four of the five individual trials on the CVLT-2 were not significantly heritable in the VETSA sample (Kremen, Moore, et al., 2013). Trial 1, which had a zero heritability in the VETSA sample, in particular, is not considered a good episodic memory measure, as indicated in the test manual (Delis et al., 2000). Researchers conducting large-scale studies, particularly those using telephone-based assessments, may be inclined to utilize a single reading of a word list, but these considerations suggest that caution is warranted for single-trial administration of a supraspan word list in genetic or other studies of memory.

The present analyses represent one of the first attempts to extensively examine the genetic architecture of episodic memory in midlife or older adults. A longitudinal twin study, showed evidence for both global and domain-specific genetic influences on cognitive performance in individuals ages 50–96 years (Tucker-Drob, Reynolds, Finkel, & Pedersen, 2014). Memory was the only one of four cognitive domains with significant domain-specific genetic influences on change in those aged 65 to 96 years. Phenotypic analyses did not support a strong global factor in those aged 50 to 65 years, and longitudinal genetic analyses were not performed separately on that subgroup. In the present study, we examined the next level of analysis, namely, the genetic architecture of global and specific effects *within* a single cognitive domain. Examining processes and subprocesses within a domain is consistent with a more neuroscience-oriented approach in which the goal is to understand the specific neural correlates of cognitive processes. In our view, it is important for research on the genetics of cognitive aging to move in that direction as well.

For purposes of understanding the processes preceding cognitive changes in older adulthood, our results also support the value of more intensive focus on level and change of cognitive

abilities within narrow age bands in middle adulthood. Here we examined the genetic architecture of episodic memory at a single point in time, so we cannot know the extent to which the pattern of individual differences reflects aging-related or preexisting differences. Consequently, we see this work as an early step in what needs to be an ongoing process. Longitudinal analyses (ongoing in the VETSA) are needed to determine whether the extent of genetic and environmental influences on episodic memory change differ across these different measures, but even in longitudinal analyses of midlife or older adults, this uncertainty always exists for the first time point.

Longitudinal twin analysis can also address the question of whether genetic or environmental factors become more prominent with increasing age, and the extent to which the same or different genes are influencing various episodic memory phenotypes at different ages. Gene–environment correlation or gene–environment interaction could also play a role in different patterns of episodic memory change. Consistent with the hypothesis of Baltes and Lindenberger (1997) that brain aging involves increasing common limitations in multiple functional systems, there could be an aging-related increase in the heritability of the global episodic memory factor that might be accounted for by a gene–environment correlation. For example, individuals with gene variants that predispose to good maintenance of one of the memory abilities may be more inclined to continue to engage in activities that stimulate brain function, thereby enhancing expression of the “good memory” genes. Individuals with gene variants that predispose them toward some aspect of memory decline might begin to withdraw from challenging activities, thereby reducing brain stimulation and furthering more widespread memory difficulties.

Thus far, the results suggest that composite indices based on each pair of measures from the three tests would be useful phenotypes for genetic association studies, but it is also important to remember that such composite indices are very measure-dependent. As shown by our previous work (Panizzon et al., 2011), it cannot be assumed that different measures from these tests (e.g., CVLT-2 learning trials) can be included in those composite factors. The finding of a general episodic memory factor using the current CVLT-2, LM, and VR measures might suggest that it would be best to combine these measures into a single composite phenotype for genetic association studies. After all, 60% of the variance in the underlying latent factor was accounted for by genes, and it represents genetic influences that are common among all six measures. But a general composite episodic memory phenotype may be less useful for understanding the genetics of age-related memory change because it does not allow for the possibility of differential changes across different aspects of episodic memory. This may be particularly important when examining the stability of mild cognitive impairment or Alzheimer’s disease over time.

With the finding of a general episodic memory factor as well as genetic influences that are specific to each test, genetic association studies that separately examine test components might yield important information about the complexity of mechanisms underlying cognitive aging. Recall that we use “test” to refer to the CVLT-2, LM, and VR, and “measure” to refer to the individual variables that may be derived from each test. One approach to the general episodic memory factor might be to look for common genes that have been associated with these different episodic memory measures across different studies. The strong inference

would be that those must be some of the genes that influence the general episodic memory factor. Of course, the power to detect associations in each of those individual studies would be limited by the sample size of each study. Thus, it is not a substitute for examining the general episodic memory factor score in all of the studies.

Therefore, it is our view that researchers will need to use multivariate approaches by including several episodic memory measures within the same study. In that way, individual measures and general factors can both be examined in order to understand the genetics of memory. The feasibility of multivariate approaches may be questioned, given the very large samples that are needed for genome-wide studies. But we think that more extensive measurement will, in the long run, be more time and cost effective than multiple studies that have inadequate phenotypes. Multivariate approaches may be all the more important for studies of aging because there is no necessary reason that each of these measures must change in the same way.

A great advantage of the twin approach is its capacity to assess the genetic uniqueness or similarity of phenotypes so that we can determine which tests tap different sets of genetic influences. Moreover, it makes it possible to obtain genetic information, and thereby make informed choices about phenotypes, in advance of knowing what the specific genes are. Thus, without knowing the specific genes, the genetic correlations observed in the present study indicated substantial nonshared genetic variance among all three episodic memory tests. As such, they suggest the strong possibility of inconsistent replications of gene associations between studies using different neuropsychological measures. These features make multivariate twin analysis very useful as a first step before embarking on gene-finding studies (Kremen & Lyons, 2011; Papassotiropoulos & de Quervain, 2011). Although, as we have noted, there are still other limitations to genetic association studies, our approach, which addresses pleiotropy across different episodic memory phenotypes, may be useful in conjunction with genetic-pleiotropy-informed methods for genome-wide association studies (cf. Andreassen et al., 2013).

Given the large number of studies of the genetics of memory and the importance of memory in cognitive aging, it is surprising that there has been so little systematic study of the genetic architecture of memory. The present analysis is a step in that direction, but it by no means provides the final answers. Although there does not appear to be strong evidence for sex differences in the genes underlying episodic memory, it is possible that our results may not generalize to women. As noted, we had fewer visual-spatial than verbal episodic memory tests. There are also several other episodic memory processes that we did not examine, such as acquisition and encoding, or recognition. These processes remain an understudied gap in the behavioral genetic cognitive aging literature.

Good episodic memory function is of great importance for successful aging, and episodic memory is vulnerable to aging, brain injury, and disease. If different genes underlie different episodic memory phenotypes, it also means that those phenotypes could well have different age-related trajectories. Therefore, this work provides important information for genetically informative studies of aging and episodic memory. Longitudinal behavior genetic studies are particularly needed to address the question of whether or not the same genes influence

variation in episodic memory at different life stages. The present results were based on VETSA Wave 1 when participants were 51 to 60 years old. Wave 2 data collection—when participants were 56 to 65 years old—was just completed at the time of this writing, and will allow us to begin to address some of these key issues regarding the genetics of aging-related memory change.

Acknowledgments

This work was supported by National Institute on Aging Grants R01 AG018386, AG022381, and AG022982 (to William S. Kremen), R01 AG018384 (to Michael J. Lyons), and Academy of Finland Grant 257075 (to Eero Vuoksimaa). This material was, in part, the result of work supported with resources of the VA San Diego Center of Excellence for Stress and Mental Health Care System. The content is solely the responsibility of the authors and does not necessarily represent official views of the National Institute on Aging, National Institutes of Health, or the Department of Veterans Affairs. The Cooperative Studies Program of the U.S. Department of Veterans Affairs provided financial support for development and maintenance of the Vietnam Era Twin Registry. Numerous organizations provided invaluable assistance in the conduct of this study, including the Department of Defense; the National Personnel Records Center, National Archives and Records Administration; the Internal Revenue Service; the National Opinion Research Center; the National Research Council, National Academy of Sciences; and the Institute for Survey Research, Temple University. Most importantly, the authors gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families. Without their contribution, this research would not have been possible. We also appreciate the time and energy of many staff and students on the VETSA projects.

References

- Andreassen OA, Djurovic S, Thompson WK, Schork AJ, Kendler KS, O'Donovan MC, Dale AM. Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular disease risk factors. *American Journal of Human Genetics*. 2013; 92:197–209. [PubMed: 23375658]
- Antila M, Tuulio-Henriksson A, Kieseppa T, Soronen P, Palo OM, Paunio T, Lonnqvist J. Heritability of cognitive functions in families with bipolar disorder. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics*. 2007; 144:802–808.
- Baltes PB, Lindenberger U. Emergence of a powerful connection between sensory and cognitive functions across the adult life span. *Psychology and Aging*. 1997; 12:12–21. [PubMed: 9100264]
- Bayroff, AG.; Anderson, AA. Development of Armed Forces Qualification Tests 7 and 8 (Technical Research Report 1122). Alexandria, VA: U.S. Army Research Institute; 1963.
- Bertisch H, Li D, Hoptman MJ, Delisi LE. Heritability estimates for cognitive factors and brain white matter integrity as markers of schizophrenia. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics*. 2010; 153:885–894.
- Boker S, Neale MC, Maes H, Wilde M, Spiegel M, Brick T, Fox J. OpenMx: An open source extended structural equation modeling framework. *Psychometrika*. 2011; 76:306–317. [PubMed: 23258944]
- Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology*. 1974; 24:1019–1025. [PubMed: 4473151]
- Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. The California Verbal Learning Test. San Antonio, TX: Psychological Corporation; 1987.
- Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. California Verbal Learning Test (CVLT-2). 2nd. San Antonio, TX: Psychological Corporation; 2000.
- Eaves LJ, Last KA, Young PA, Martin NG. Model-fitting approaches to the analysis of human behavior. *Heredity*. 1978; 41:249–320. [PubMed: 370072]
- Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Weinberger DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*. 2003; 112:257–269. [PubMed: 12553913]

- Finkel D, Pedersen NL, McGue M. Genetic influences on memory performance in adulthood: Comparison of Minnesota and Swedish twin data. *Psychology and Aging*. 1995; 10:437–446. [PubMed: 8527064]
- Giubilei F, Medda E, Fagnani C, Bianchi V, De Carolis A, Salvetti M, Stazi MA. Heritability of neurocognitive functioning in the elderly: Evidence from an Italian twin study. *Age and Ageing*. 2008; 37:640–646. [PubMed: 18641001]
- Glahn DC, Almasy L, Blangero J, Burk GM, Estrada J, Peralta JM, Escamilla MA. Adjudicating neurocognitive endophenotypes for schizophrenia. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics*. 2007; 144:242–249.
- Greenwood TA, Braff DL, Light GA, Cadenhead KS, Calkins ME, Dobie DJ, Schork NJ. Initial heritability analyses of endophenotypic measures for schizophrenia: The Consortium on the Genetics of Schizophrenia. *Archives of General Psychiatry*. 2007; 64:1242–1250. [PubMed: 17984393]
- Husted JA, Lim S, Chow EW, Greenwood C, Bassett AS. Heritability of neurocognitive traits in familial schizophrenia. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics*. 2009; 150:845–853.
- Kendler, KS.; Eaves, LJ., editors. *Psychiatric genetics*. Washington, DC: American Psychiatric Publishing; 2005.
- Kendler KS, Heath AC, Martin NG, Eaves LJ. Symptoms of anxiety and depression in a volunteer twin population: The etiologic role of genetic and environmental factors. *Archives of General Psychiatry*. 1986; 43:213–221. [PubMed: 3954540]
- Kendler KS, Neale MC. “Familiality” or heritability (letter to the editor). *Archives of General Psychiatry*. 2009; 66:452–453. [PubMed: 19349315]
- Kremen WS, Franz CE, Lyons MJ. VETSA: The Vietnam Era Twin Study of Aging. *Twin Research and Human Genetics*. 2013; 16:399–402. [PubMed: 23110957]
- Kremen, WS.; Lyons, MJ. Behavior genetics of aging. In: Schaie, KW.; Willis, SL., editors. *Handbook of the psychology of aging*. 7th. San Diego, CA: Elsevier; 2011. p. 93-107.
- Kremen, WS.; Moore, CS.; Franz, CE.; Panizzon, MS.; Lyons, MJ. Cognition in middle adulthood. In: Finkel, D.; Reynolds, CA., editors. *Behavior genetics of cognition across the lifespan*. New York, NY: Springer; 2013. p. 105-134.
- Kremen WS, Thompson-Brenner H, Leung YJ, Grant MD, Franz CE, Eisen SA, Lyons MJ. Genes, environment, and time: The Vietnam Era Twin Study of Aging (VETSA). *Twin Research and Human Genetics*. 2006; 9:1009–1022. [PubMed: 17254445]
- Lee JH, Flaquer A, Stern Y, Tycko B, Mayeux R. Genetic influences on memory performance in familial Alzheimer disease. *Neurology*. 2004; 62:414–421. [PubMed: 14872023]
- Lyons MJ, York TP, Franz CE, Grant MD, Eaves LJ, Jacobson KC, Kremen WS. Genes determine stability and environment determines change in cognitive ability during 35 years of adulthood. *Psychological Science*. 2009; 20:1146–1152. [PubMed: 19686293]
- Markon KE, Krueger RF. An empirical comparison of information-theoretic selection criteria for multivariate behavior genetic models. *Behavior Genetics*. 2004; 34:593–610. [PubMed: 15520516]
- McArdle JJ, Goldsmith HH. Alternative common factor models for multivariate biometric analyses. *Behavior Genetics*. 1990; 20:569–608. [PubMed: 2288547]
- McGue M, Christensen K. The heritability of cognitive functioning in very old adults: Evidence from Danish twins aged 75 years and older. *Psychology and Aging*. 2001; 16:272–280. [PubMed: 11405315]
- Neale, MC.; Cardon, LR. *Methodology for genetic studies of twins and families*. Dordrecht, Netherlands: Kluwer; 1992.
- Owens SF, Picchioni MM, Rijdsdijk FV, Stahl D, Vassos E, Rodger AK, Touloupoulou T. Genetic overlap between episodic memory deficits and schizophrenia: Results from the Maudsley Twin Study. *Psychological Medicine*. 2011; 41:521–532. [PubMed: 20459888]
- Panizzon MS, Lyons MJ, Jacobson KC, Franz CE, Grant MD, Eisen SA, Kremen WS. Genetic architecture of learning and delayed recall: A twin study of episodic memory. *Neuropsychology*. 2011; 25:488–498. [PubMed: 21463045]

- Papassotiropoulos A, de Quervain DJ. Genetics of human episodic memory: Dealing with complexity. *Trends in Cognitive Sciences*. 2011; 15:381–387. [PubMed: 21835680]
- Papassotiropoulos A, Stephan DA, Huentelman MJ, Hoernndli FJ, Craig DW, Pearson JV, de Quervain DJ. Common Kibra alleles are associated with human memory performance. *Science*. 2006; 314:475–478. [PubMed: 17053149]
- Rey, A. L'examen clinique en psychologie [The clinical examination in psychology]. Paris, France: Presses Universitaires de France; 1964.
- Schoenborn CA, Heyman KM. Health Characteristics of Adults Aged 55 Years and Over: United States, 2004–2007. National Health and Statistics Reports. 2009; 16:1–32. Retrieved from <http://www.cdc.gov/nchs/data/nhsr/nhsr016.pdf>.
- Sabb FW, Burggren AC, Higier RG, Fox J, He J, Parker DS, Bilder RM. Challenges in phenotype definition in the whole-genome era: Multivariate models of memory and intelligence. *Neuroscience*. 2009; 164:88–107. [PubMed: 19450667]
- Schork AJ, Thompson WK, Pham P, Torkamani A, Roddey JC, Sullivan PF. The Schizophrenia Psychiatric Genomics Consortium. All SNPs are not created equal: Genome-wide association studies reveal a consistent pattern of enrichment among functionally annotated SNPs. *PLoS Genetics*. 2013; 9:e1003449. [PubMed: 23637621]
- Squire LR, Knowlton B, Musen G. The structure and organization of memory. *Annual Review of Psychology*. 1993; 44:453–495.
- Swan GE, Reed T, Jack LM, Miller BL, Markee T, Wolf PA, Carmelli D. Differential genetic influence for components of memory in aging adult twins. *Archives of Neurology*. 1999; 56:1127–1132. [PubMed: 10488814]
- Tucker-Drob EM, Reynolds CA, Finkel D, Pedersen NL. Shared and unique genetic and environmental influences on aging-related changes in multiple cognitive abilities. *Developmental Psychology*. 2014; 50:152–166. [PubMed: 23586942]
- Tulving, E. Episodic and semantic memory. In: Tulving, E.; Donaldson, W., editors. *Organization of memory*. New York, NY: Academic Press; 1972. p. 381–403.
- Tuulio-Henriksson A, Haukka J, Partonen T, Varilo T, Paunio T, Ekelund J, Lonnqvist J. Heritability and number of quantitative trait loci of neurocognitive functions in families with schizophrenia. *American Journal of Medical Genetics*. 2002; 114:483–490. [PubMed: 12116181]
- van der Maas HL, Dolan CV, Grasman RP, Wicherts JM, Huizenga HM, Raijmakers ME. A dynamical model of general intelligence: The positive manifold of intelligence by mutualism. *Psychological Review*. 2006; 113:842–861. [PubMed: 17014305]
- Volk HE, McDermott KB, Roediger HL, Todd RD 3rd. Genetic influences on free and cued recall in long-term memory tasks. *Twin Research and Human Genetics*. 2006; 9:623–631. [PubMed: 17032541]
- Wang Q, Vassos E, Deng W, Ma X, Hu X, Murray RM, Li T. Factor structures of the neurocognitive assessments and familial analysis in first-episode schizophrenia patients, their relatives and controls. *Australian and New Zealand Journal of Psychiatry*. 2010; 44:109–119. [PubMed: 20113299]
- Wechsler D. A standardized memory scale for clinical use. *Journal of Psychology: Interdisciplinary and Applied*. 1945; 19:87–95.
- Wechsler, D. *Manual for the Wechsler Memory Scale - Revised*. San Antonio, TX: Psychological Corporation; 1987.
- Wechsler, D. *Wechsler Memory Scale (WMS-III)*. San Antonio, TX: Psychological Corporation; 1997.
- Williams LJ, Holahan PJ. Parsimony-based fit indices for multiple-indicator models: Do they work? *Structural Equation Modeling*. 1994; 1:161–189.
- Wilson RS, Barral S, Lee JH, Leurgans SE, Foroud TM, Sweet RA, Bennett DA. Heritability of different forms of memory in the Late Onset Alzheimer's Disease Family Study. *Journal of Alzheimer's Disease*. 2011; 23:249–255.

Figure 1.

Cholesky decomposition. Multivariate biometrical models of free recall in episodic memory. Rectangles represent measured variables; circles represent latent variables. For simplicity, shared/common environmental influences are not shown. A = additive genetic influences; E = unique environmental influences; CVLT-2 = California Verbal Learning Test-Version 2; SD = short delay; LD = long delay; LM = Logical Memory; VR = Visual Reproductions; Immed. = immediate.

Figure 2.

Single-factor common pathways model. Multivariate biometrical models of free recall in episodic memory. Rectangles represent measured variables; circles and ellipses represent latent variables. For simplicity, shared/common environmental influences are not shown. A = additive genetic influences; E = unique environmental influences; CVLT-2 = California Verbal Learning Test-Version 2; SD = short delay; LD = long delay; LM = Logical Memory; VR = Visual Reproductions; Immed. = immediate.

Figure 3.

Two correlated factors common pathway model (immediate and delayed recall). Multivariate biometrical models of free recall in episodic memory. Rectangles represent measured variables; circles and ellipses represent latent variables. For simplicity, shared/common environmental influences are not shown. A = additive genetic influences; E = unique environmental influences; CVLT-2 = California Verbal Learning Test-Version 2; SD = short delay; LD = long delay; LM = Logical Memory; VR = Visual Reproductions; Immed. = immediate.

Figure 4.

Two correlated factors common pathway model (verbal and visual-spatial memory).

Multivariate biometrical models of free recall in episodic memory. Rectangles represent measured variables; circles and ellipses represent latent variables. For simplicity, shared/common environmental influences are not shown. A = additive genetic influences; E = unique environmental influences; CVLT-2 = California Verbal Learning Test-Version 2; SD = short delay; LD = long delay; LM = Logical Memory; VR = Visual Reproductions; Immed. = immediate.

Figure 5.

Three correlated factors common pathway model (test specific). Multivariate biometrical models of free recall in episodic memory. Rectangles represent measured variables; circles and ellipses represent latent variables. For simplicity, shared/common environmental influences are not shown. A = additive genetic influences; E = unique environmental influences; CVLT-2 = California Verbal Learning Test-Version 2; SD = short delay; LD = long delay; LM = Logical Memory; VR = Visual Reproductions; Immed. = immediate.

Figure 6.

Higher order common pathways model. Multivariate biometrical models of free recall in episodic memory. Rectangles represent measured variables; circles and ellipses represent latent variables. For simplicity, shared/common environmental influences are not shown. A = additive genetic influences; E = unique environmental influences; CVLT-2 = California Verbal Learning Test-Version 2; SD = short delay; LD = long delay; LM = Logical Memory; VR = Visual Reproductions; Immed. = immediate.

Figure 7.

Best-fitting biometrical model of free recall in episodic memory. Parameter estimates are shown with standardized proportions of variance in parentheses below each parameter estimate; for simplicity of presentation, parameters that were estimated to be zero are not shown. A parameters for the Logical Memory and Visual Reproductions factors are highlighted to emphasize the fact that there are genetic influences underlying these factors that are distinct from those underlying the general factor. A = additive genetic influences; C = common environmental influences; E = unique environmental influences; CVLT-2 = California Verbal Learning Test-Version 2; SD = short delay; LD = long delay; Immed. = immediate.

Phenotypic and Genetic Correlations Between General Cognitive Ability (AFQT) and Individual Episodic Memory Measures

Table 1

	CVLT-2 Short-Delay FR	CVLT-2 Long-Delay FR	Logical Memory IR	Logical Memory DR	Visual Reproductions IR	Visual Reproductions DR
r _p with AFQT	.28 (.23, .34)	.32 (.27, .38)	.33 (.28, .39)	.32 (.26, .37)	.46 (.41, .51)	.38 (.32, .43)
r _G with AFQT	.40 (−.07, 1)	.61 (.30, .98)	.44 (.24, .63)	.45 (.26, .68)	.75 (.51, 1)	.56 (.35, .80)

Note. 95% confidence intervals are presented in the parentheses. AFQT = Armed Forces Qualification Tests; CVLT-2 = California Verbal Learning Test - Version 2; FR = free recall; IR = immediate recall; DR = delayed recall; r_p= phenotypic correlation; r_G= genetic correlation.

Table 2

Phenotypic Correlations for Individual Episodic Memory Measures (Adjusted for General Cognitive Ability)

	CVLT-2 Short-Delay FR	CVLT-2 Long-Delay FR	Logical Memory IR	Logical Memory DR	Visual Reproductions IR
CVLT-2 Long-Delay FR	.80 (.73, .88)				
Logical Memory IR	.28 (.22, .35)	.33 (.27, .40)			
Logical Memory DR	.31 (.25, .37)	.37 (.30, .43)	.84 (.77, .93)		
Visual Reproductions IR	.15 (.10, .22)	.18 (.12, .24)	.17 (.11, .23)	.17 (.11, .23)	
Visual Reproductions DR	.24 (.18, .30)	.28 (.22, .34)	.20 (.14, .26)	.23 (.17, .30)	.56 (.50, .63)

Note. 95% confidence intervals are presented in the parentheses. General cognitive ability was assessed with the Armed Forces Qualification Test. CVLT-2 = California Verbal Learning Test – Version 2; FR = free recall; IR = immediate recall; DR = delayed recall.

Table 3

Standardized Variance Components for Individual Episodic Memory Measures

Measure	a ² (95% CI)	c ² (95% CI)	e ² (95% CI)
Adjusted for general cognitive ability			
CVLT-2 Short-Delay Free Recall	.23 (.04, .41)	.13 (.00, .30)	.64 (.56, .72)
CVLT-2 Long-Delay Free Recall	.28 (.08, .47)	.15 (.00, .33)	.57 (.49, .65)
Logical Memory Immediate Recall	.42 (.21, .51)	.01 (.00, .18)	.57 (.49, .65)
Logical Memory Delayed Recall	.48 (.29, .56)	.01 (.00, .17)	.51 (.44, .59)
Visual Reproductions Immediate Recall	.20 (.03, .36)	.13 (.01, .27)	.67 (.59, .76)
Visual Reproductions Delayed Recall	.29 (.08, .41)	.04 (.00, .21)	.67 (.58, .76)
Unadjusted			
CVLT-2 Short-Delay Free Recall	.28 (.09, .45)	.12 (.00, .30)	.60 (.53, .68)
CVLT-2 Long-Delay Free Recall	.37 (.15, .53)	.10 (.00, .29)	.53 (.46, .61)
Logical Memory Immediate Recall	.47 (.27, .58)	.04 (.00, .21)	.49 (.42, .57)
Logical Memory Delayed Recall	.53 (.35, .61)	.02 (.00, .17)	.45 (.39, .53)
Visual Reproductions Immediate Recall	.35 (.16, .50)	.12 (.00, .28)	.53 (.46, .61)
Visual Reproductions Delayed Recall	.40 (.21, .49)	.02 (.00, .18)	.58 (.51, .67)

Note. General cognitive ability was assessed with the Armed Forces Qualification Test. Estimates are based on the Full ACE Cholesky. a²= additive genetic variance; c²= common/shared environmental variance; e²= nonshared environmental variance; 95% CI = 95% confidence interval; CVLT-2 = California Verbal Learning Test – Version 2.

Table 4**Multivariate Model Fitting Results**

ACE Cholesky and comparison models	-2LL	df	BIC	LRT	df	p
1. ACE Cholesky	16985.95	7272	-29806.08	—	—	—
2. Single-Factor Common Pathways	18550.65	7309	-28479.45	1564.70	37	<.0001
3. Two Correlated Factors Common Pathways (Immediate and Delayed Recall)	18547.57	7304	-28450.35	1561.62	32	<.0001
3a. Higher Order Common Pathways (Two subfactors: Verbal and Visual-Spatial Memory)	18551.12	7304	-28446.81	1565.18	32	<.0001
4. Two Correlated Factors Common Pathways (Verbal and Visual-Spatial Memory)	18351.55	7304	-28646.38	1365.60	32	<.0001
4a. Higher Order Common Pathways (Two subfactors: Immediate and Delayed Recall)	18140.20	7304	28857.73	1154.25	32	<.0001
5. Three Correlated Factors Common Pathways	17003.14	7296	-29943.31	17.19	24	.8404
6. Higher Order Common Pathways (Three test-specific subfactors)	17008.35	7300	-29963.84	22.40	28	.7624

Note. All models are tested against the fit of the ACE Cholesky and were based on measures adjusted for general cognitive ability. $-2LL = -2 \log$ likelihood; df = degrees of freedom; EP = number of estimated parameters; CON = number of constraints; BIC = Bayesian information criterion; LRT = likelihood ratio test; df = change in degrees of freedom; p = significance of LRT.

Table 5

Standardized Variance Components for Latent Factors in the Higher Order Common Pathways Model

Latent factor	a ² (95% CI)	c ² (95% CI)	e ² (95% CI)
CVLT-2	.34 (.10, .54)	.12 (.00, .33)	.54 (.45, .63)
Logical Memory	.48 (.29, .59)	.03 (.00, .19)	.49 (.41, .57)
Visual Reproductions	.43 (.26, .56)	.02 (.00, .16)	.55 (.44, .66)

Note. Model is based on measures adjusted for general cognitive ability. a²= additive genetic variance; c²= common/shared environmental variance; e²= nonshared environmental variance; 95% CI = 95% confidence interval; CVLT-2 = California Verbal Learning Test – Version 2.