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Genetic Architecture of Context Processing in Late Middle Age: More Than One Underlying Mechanism

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Abstract

Studies comparing young and older adults suggest a deficit in processing context information as a key mechanism underlying cognitive aging. However, the genetic architecture of context processing has not been examined. Consistent with previous results, we found evidence of functionally dissociable components of context processing accuracy in 1127 late middle-aged twins ages 51–60. One component emphasizes use of context cues to prepare responses (proactive cognitive control); the other emphasizes adjustment of responses after probes are presented (reactive control). Approximately one-quarter of the variance in each component was accounted for by genes. Multivariate twin analysis indicated that genetic factors underlying two important components of context processing were independent of one another, thus implicating more than one underlying mechanism. Slower reaction time (RT) on non-context processing trials was positively correlated with errors on the strongly proactive control component on which young adults outperform older adults, but RT was negatively correlated with errors on the strongly reactive control component on which older adults perform better. Although this RT measure was uncorrelated with chronological age in our age-homogeneous sample, slower RT was associated

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with performance patterns that were more like older adults. However, this did not generalize to other processing speed measures. Genetic correlations, which reflect shared genetic variance, paralleled the phenotypic correlations. There was also a positive genetic correlation between general cognitive ability and accuracy on the proactive control component, but there were still mostly distinct genetic influences underlying these measures. In contrast, the reactive control component was unrelated to general cognitive ability.

Keywords

twins; heritability; context processing; cognitive aging; processing speed

Some of the major accounts of key processes underlying cognitive change in middle and older adulthood focus on declines in overall processing speed (Salthouse, 1996), working memory capacity (Hultsch, Hertzog, Dixon, & Small, 1998; Salthouse, 1991; Wingfield, Stine, Lahar, & Aberdeen, 1988), episodic memory (Kausler, 1994), or efficiency of inhibitory control (Hasher & Zacks, 1988). A deficit in the ability to process context information (Braver & Barch, 2002; Braver et al., 2001) is another mechanism that has been proposed to account for age-related cognitive changes, and that may contribute to deficits in these other domains. Context representations consist of internally-represented, task-relevant information that are used to influence planning and behavior (Braver, Cohen, & Barch, 2002). Context representations serve both mnemonic and control functions in working memory (Braver, Satpute, Rush, Racine, & Barch, 2005). These representations become increasingly important as the required degree of cognitive control increases (e.g., when one must select between conflicting or strongly competing responses).

Phenotypic studies have shown functionally dissociable components of context processing that appear to be differentially affected by aging. There is also a strong theoretical model for this research paradigm which posits that the selective attention, working memory, and inhibitory processes of executive control functions can be accounted by a unitary underlying mechanism (Braver, Barch, & Cohen, 1999; Braver & Cohen, 2000; Cohen, Braver, & O'Reilly, 1996).

Examination of the components of context processing has been conducted almost exclusively at the phenotypic level. In the present study, we combined behavior genetic and cognitive neuroscience approaches in order to examine the genetic and environmental influences affecting the components of context processing and their relationship to general cognitive ability. It is important to keep in mind that underlying phenotypic and genetic factors are not necessarily the same (Friedman et al., 2008; Kremen et al., 2008). Elucidating the underlying genetic architecture of these processes would, thus, constitute an important step toward a fuller understanding of cognitive and brain aging. Elucidating these processes at the genetic level by means of the twin method could also serve as a guide for studies of specific genes that influence different components of context processing and cognitive aging.

Prefrontal Function, Dopamine, and Cognitive Aging

Both theoretical models and empirical findings strongly support the notion that reduced efficiency in context processing, changes in dopamine modulation, and changes in prefrontal cortex may account for many changes associated with cognitive aging (Bäckman, Lindenberger, Li, & Nyberg, 2010; Braver & Barch, 2002; Braver et al., 1999; Braver et al., 2001; Li, Lindenberger, & Backman, 2010; Li, Lindenberger, & Sikstrom, 2001; Suhara et al., 1991; Volkow et al., 2000; Volkow et al., 1998; West, 1996). Age-related structural

differences tend to be greater in prefrontal cortex than in other parenchymal regions (Fjell et al., 2009; Jernigan et al., 2001; Raz & Rodrigue, 2006), and functional neuroimaging studies provide substantial evidence for age-associated differences in prefrontal function (Braver, Paxton, Locke, & Barch, 2009; Cabeza, 2002; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006) . Normal aging includes declines in dopamine function that affect prefrontal function, and the role of prefrontal dopamine modulation in cognitive control is a key feature of computational models of context processing (Bäckman et al., 2010; Braver & Barch, 2002; Braver et al., 1999; Braver et al., 2001; Li et al., 2010; Li et al., 2001; Suhara et al., 1991; Volkow et al., 2000; Volkow et al., 1998). Both computational modeling and empirical studies support the notion that dopamine receptor density and dopamine transmission (particularly for D_1 and D_2 receptors) are associated with the distinctiveness of neural (internal) representations as well as response speed (Bäckman et al., 2010; Braver & Barch, 2002; Braver et al., 1999; Li et al., 2010; Li et al., 2001). In turn, decreases in dopamine receptor density and/or efficiency of dopamine transmission in later life result in signal-to-noise reductions such that context representations are less robust and more susceptible to decay over time and to interfering effects of task-irrelevant inputs.

Reduced dopamine availability is also associated with reduced consistency of within-individual performance, a pattern that is consistent with idea that dopamine reductions result in less robust context representations which are indicators of greater neural noise (Bäckman et al., 2010; S. W. MacDonald, Cervenka, Farde, Nyberg, & Backman, 2009; Servan-Schreiber, Printz, & Cohen, 1990). These age-related changes in dopamine systems—particularly prefrontal dopamine—can result in declines in processing speed, working memory, updating, selective attention, and interference susceptibility. It is also well known that genetic factors play a substantial role in all of these processes (Bäckman et al., 2010; Bouchard & McGue, 2003; Kremen & Lyons, in press; Kremen, Prom-Wormley et al., 2010; Schmitt et al., 2007). Thus, genes that influence dopaminergic function may influence context processing and age-related changes in context processing as well.

Assessing Context Processing with the *AX*-CPT

Many studies aimed at parsing the specific cognitive components of context processing have used a Continuous Performance Test (CPT), originally developed by Rosvold and colleagues (1956) and modified to examine components of context processing by Servan-Schreiber and colleagues (1996). In this modified version is referred to as the *AX*-CPT, letters are presented one at a time on a computer monitor in sequences of cue-probe pairs (see Figure 1). The goal is to make a target response to the *X* probe only when it immediately follows an *A* cue, and to make a non-target response to all other cues or probes. A high frequency of target (*AX*) trials introduces biases that interact differentially with context processing, thus allowing for a test of different context processing components. The tendency to make a target response to an *X* probe leads to a bias toward incorrect responses to *X* probes when they follow a non-*A* cue (referred to as *BX* trials, with *B* indicating any non-*A* cue). On trials in which the *A* cue is not followed by an *X* probe, attention to the cue's predictive context will increase the bias toward a false alarm. Such trials are denoted as *AY* trials, with *Y* indicating any non-*X* probe.

Both *BX* and *AY* trials involve combinations of response preparation, working memory, and inhibitory control that manifest differential patterns in cross-sectional studies of normal and pathological aging (Braver & Barch, 2002; Braver et al., 2001). If context processing is intact, *BX* trials will involve little response conflict, require little inhibitory control, and will not elicit high error rates. Once a non-*A* cue is presented, the examinee knows that the probe cannot be a target. If context maintenance and response preparation are solidly intact, *AY* trials will require enhanced inhibitory control and will be more likely to elicit false alarms or slow responses because the *A*-cue primes the examinee for a target response (incorrect on

AY trials). If, however, the cue is not stably maintained, response conflict and the need for inhibitory control may be heightened by the *X* probe on *BX* trials, but these tendencies will be reduced on *AY* trials.

Therefore, if aging is associated with less efficient context processing, older adults should perform poorly on *BX* trials relative to their performance on *AY* trials in comparison with younger adults. Previous results support this prediction for both accuracy and reaction time (Braver et al., 2001; Braver et al., 2009; Braver et al., 2005; Paxton, Barch, Racine, & Braver, 2008; Paxton, Barch, Storandt, & Braver, 2006; Rush, Barch, & Braver, 2006), making it one of the rare cases in which older adults perform relatively faster than younger adults on a cognitive measure. Older adults with early stage Alzheimer's disease have additional deficits in non-context processing, compared with age-matched healthy adults (Braver et al., 2005). These non-context processing errors are referred to as *BY* errors because they occur on trials with non-*A* cues followed by non-*X* probes, where there are no contextual biases.

Context Processing and General Cognitive Ability

Little is known about the relationship between general cognitive ability (sometimes referred to as Spearman's *g*) and context processing. There is abundant evidence for substantial genetic influences on general cognitive ability (Bouchard & McGue, 2003; Lyons et al., 2009; Plomin & Spinath, 2002). Executive functions and working memory—which are important in *AX*-CPT performance—are also associated with general cognitive ability at both the phenotypic and genetic levels (Friedman et al., 2006; Luciano et al., 2001). It has even suggested that working memory may be essentially the same as general intellectual ability (Kyllonen, 1996). Yet, it is also well known that patients with frontal lobe damage may exhibit substantial executive function deficits but perform within normal limits on tests of general intellectual ability (Lezak, Howieson, & Loring, 2004). Friedman et al. (2006) found that only the executive function of updating—but not set-shifting or inhibition—was strongly associated with general cognitive ability. Their updating tasks involved working memory and context maintenance, which bear some similarity with the demands of the *AX*-CPT.

In a study that included the *AX*-CPT, MacDonald et al. (2005) identified two independent phenotypic factors: a context processing factor (with high loadings for *AX* and *BX* trials) and a preparatory factor (with high loadings for *AY* and *AX* trials). General cognitive ability was positively correlated with the context processing, but not the preparatory, factor. Examining genetic, in addition to phenotypic, associations with general cognitive ability would provide useful information about the different cognitive components underlying context processing and about which components may be leading indicators of age-related cognitive change.

Genetically-Informative Studies

We are aware of only two genetically-informative studies of context processing. One found no relationship between the catechol-O-methytransferance genotype and *AX*-CPT performance in 464 adults ages 30 to 54 (A. W. MacDonald, III, Carter, Flory, Ferrell, & Manuck, 2007). In the other, eight middle-aged and older male Apolipoprotein E ε4 homozygotes made more errors than other groups on *AY* trials (Reinvang, Winjevoll, Rootwelt, & Espeseth, 2009). If aging is associated with better *AY* performance because older adults have less efficient maintenance of context (and thus, a reduced tendency toward *AY* false alarms), then one might expect fewer *AY* errors in ε4 homozygotes because this group may be expected to manifest poorer cognitive aging. Thus, replication of this genetic association is warranted.

It is well known from twin studies that cognitive functions and regional brain structure are heritable, i.e., a significant proportion of variance in individual differences is accounted for by genetic influences (Bouchard & McGue, 2003; Kremen, Prom-Wormley et al., 2010; Peper, Brouwer, Boomsma, Kahn, & Hulshoff Pol, 2007; Schmitt et al., 2007). On the other hand, evidence that a particular cognitive domain is heritable does not mean that performance on all tests tapping that domain will be heritable (Kremen & Lyons, 2010). For example, some executive function and working memory measures have strong evidence of heritability (Ando, Ono, & Wright, 2001; Kremen, Jacobsen et al., 2007) whereas others do not (Chou, Kuo, Lin, & Chen, 2009; Kremen, Eisen, Tsuang, & Lyons, 2007). The lack of heritability may be due, in part, to the multi-determined nature of some tasks (e.g., Wisconsin Card Sorting Test), making it difficult to distinguish between overall performance indices and specific deficits (Kremen & Lyons, 2010). The design of the *AX*-CPT may circumvent this problem because the pattern of different error types and response tendencies is elucidated for each individual.

Twin studies are also important for elucidating genetic and environmental influences on cognitive and brain aging (Kremen & Lyons, 2010), and we are unaware of any twin studies of context processing. Although it seems intuitive that accumulated environmental exposures lead to a relative increase in the impact of environmental influences with age, twin studies have shown that the impact of genetic factors on variability in general cognitive ability or brain ventricular volume is greatest in older adults (Haworth et al., 2009; Kremen, Panizzon et al., 2010; Lyons et al., 2009). On the other hand, twin studies have indicated that the amount of cognitive change over time is often due almost entirely to environmental factors (Lyons et al., 2009; Reynolds, Finkel, Gatz, & Pedersen, 2002).

The Present Study

We utilized the *AX*-CPT to examine the genetic and environmental influences on accuracy for different components of context processing in a large twin sample of late middle-aged men. We estimated the heritability of a signal detection index (d' context), error rates for *AX*, *BX*, and *AY* trials, and reaction times (RTs) for *BY* trials. We also conducted bivariate and multivariate twin analyses in order to examine the genetic architecture of the error measures, and the genetic and environmental relationship of accuracy (errors) to processing speed and general cognitive ability.

When genetic influences are observed in twin analyses, they provide direct evidence of underlying mechanisms because the direction of effect must go from gene to phenotype. Although there is evidence that the different *AX*-CPT trial types reflect functionally dissociable processes at the phenotypic level, the formal context processing model is based on the notion of a single underlying mechanism subserving these different processes (Braver et al., 1999; Braver & Cohen, 2000; Cohen et al., 1996). The factor analytic results of MacDonald et al. (2005) contradict the notion of a single mechanism at the phenotypic level, but it is possible to have one phenotypic factor and more than one genetic factor (Kremen et al., 2008) or the reverse (Friedman et al., 2008). Moreover, unlike that phenotypic analysis, the genetic analyses are directly informative about underlying mechanisms. In the present study, we used multivariate twin analyses to whether there was a single or common genetic factor underlying performance on *AX*, *BX*, and *AY* trials.

There is now a body of evidence suggesting that context processing is an important mechanism accounting for a number of age-related cognitive changes. Clarifying the genetics of different context processing components constitutes an important step toward elucidating the determinants of age-related cognitive changes. It can also be important for improving phenotype definition in association studies aimed at finding the specific genes that are associated with these different component processes.

Method

Participants

The participants completed wave 1 of the longitudinal Vietnam Era Twin Study of Aging (VETSA). The goal of the VETSA was to establish a reasonably representative community-dwelling sample of middle-aged men at the baseline assessment. Thus, the only inclusion/exclusion criteria were that twins had to be between ages 51 and 59 at the time of recruitment, and both members of a pair had to agree to participate. The VETSA comprises 1237 male twins (614 pairs and 9 unpaired twins; 55% monozygotic [MZ] and 45% dizygotic [DZ] pairs) between the ages of 51 and 60 because four twins turned 60 by the time of their assessment (mean age=55.4, SD 2.5). The inclusion of unpaired twins—whose co-twin did not participate—allows for more precise estimates of the phenotypic correlations between the variables, despite their not being able to contribute to the genetic analyses. The mean level of formal education completed was 13.84 years (SD=2.11; range: 8–20). Most of the participants were married (79%), employed full-time 78%), and Caucasian (86%).

VETSA participants were randomly selected from a previous, large study of psychological health that included all available twins from the Vietnam Era Twin Registry (Tsuang, Bar, Harley, & Lyons, 2001). The Registry includes male-male MZ) and DZ twin pairs in which both twins served in the United States military at some time between 1965 and 1975. The majority of participants did not serve in combat or in Vietnam (Eisen, True, Goldberg, Henderson, & Robinette, 1987; Henderson et al., 1990). Demographic and health comparisons indicate that VETSA participants were largely representative of the Registry sample and of American men in their age range (Kremen et al., 2006; National Health and Nutrition Examination Survey (NHANES III), 1999–2004).

Zygosity was determined on the basis of 25 microsatellite markers. For a small number (97 [7.8%]) of participants whose DNA was not useable, zygosity was determined by a combination of DNA testing, questionnaire, and blood group methods (Eisen, Neuman, Goldberg, Rice, & True, 1989). For those with zygosity determined by genotype, the questionnaire-based method agreed with the DNA results in 95% of cases. Written informed consent was provided by all study participants.

Procedures and Measures

Participants live throughout the United States and were given the option of coming to the University of California, San Diego or Boston University for the same daylong series of assessments; 635 came to San Diego and 569 came to Boston, and 33 were tested in their hometowns. Tests and equipment were identical at each site. *AX*-CPT parameters were the same as in the baseline condition in the study of Braver et al. (2001). Letters were presented one at a time on a computer monitor. Participants who used their right hand to control the mouse were instructed to press the left mouse button on target trials and the right mouse button on non-target trials. These instructions were reversed for those who used their left hand to control the mouse. Target trials were defined as those in which an *A* cue was immediately followed by an *X* probe. The letters *K* and *Y* were not included because of their visual similarity to the letter *X*. Letters were presented in pseudorandom order with 70% of the trials being target (*AX*) trials. The 30% non-target trials comprised 10% *BX* trials consisting of an invalid (non-*A*) cue preceding the *X* target, 10% *AY* trials consisting of a valid (*A*) cue followed by a nontarget (non-X) probe, and 10% *BY* trials consisting of an invalid (non-*A*) cue followed by an invalid (non-*X*) probe.

Letters were presented centrally in red, 24-point upper case Helvetica font on a black background. Stimulus duration was 300 ms with a delay of 4,900 ms between presentation of the cue and probe, and an intertrial interval of 1,000 ms. Responses had to be within

1,300 ms of the stimulus to be counted. The test was presented via Presentation software, version 0.81 (Neurobehavioral Systems, Albany, CA) on Dell notebook computers with 15. 4 inch monitors. Log files generated by Presentation were transferred to an Access database.

The test consisted of six blocks of 30 trials each. Block 1 was considered a practice block, so that test scores were based on the 150 trials comprising blocks 2–5. Examiners used standardized written instructions to explain the task, including examples of the different trial types shown on paper and a sample letter shown on the computer monitor. After going through the standard instructions, examiners answered questions and reiterated portions of the instructions as needed to ensure that participants clearly understood the task. Brief breaks were provided between blocks. The *AX*-CPT was part of a larger neurocognitive test battery that has been reported on elsewhere (Franz et al., in press; Kremen et al., 2006).

A signal detection index (d') has been computed in previous studies of the *AX*-CPT by using *AX* hits and *BX* false alarms rather than all false alarms. This measure is referred to as d' context because on *AX* and *BX* trials, whether or not the probe is a target is determined by differences in context (Braver et al., 2001; Cohen, Barch, Carter, & Servan-Schreiber, 1999). The d' context index was adapted from Corwin (1994): hit rate for *AX* trials – false alarm rate for *BX* trials. Correction factors were applied to avoid dividing by zero based on formulas provided by Corwin (1994): hit rate=(number of hits+.5)/number of target+.01); false alarm rate=(number of false alarms+.5)/(number of distracters+1).

We measured general cognitive ability with the Armed Forces Qualification Test (AFQT; Bayroff & Anderson, 1963), a 50-min paper-and-pencil test consisting of 100 multiple-choice items that was administered at age 20 on average and again during the VETSA at an average age of 55. As we have described elsewhere, the AFQT is highly correlated with measures of IQ or other indices of general intellectual ability and was highly stable (r=.74) over a period of 35 years (Lyons et al., 2009). AFQT scores are based on percentiles, but in statistical analyses we transformed the raw percentile scores to their normal deviates (Lyons et al., 2009). The mean AFQT percentile score for VETSA participants was 61.13 (interquartile range: 46–80.50) at age 20 and 64.07 (interquartile range: 50–81) during the VETSA assessment. These scores are comparable to a mean IQ score of approximately 104–105. The genetic correlation (defined in the Statistical Analysis section) between AFQT scores at age 20 and 55 was 1.0, indicating that the same genetic influences on AFQT performance were operating at both times.

Many age-related cognitive declines have been associated with age-related slowing of processing speed (Salthouse, 1996). As in previous *AX*-CPT studies, we included RT on *BY* trials—which are essentially unconfounded by demands for context processing—as a gauge of processing speed within this test. We also included three other external processing speed measures[1]. Simple reaction time (SRT) consisted of 10 left- and 10 right-hand trials in response to an asterisk appearing on the computer monitor. Choice reaction time (CRT) consisted of 21 trials in which the asterisk randomly appeared on either the left or right side of the screen and participants had to respond with the left or right hand, respectively. Trails 2 was the number sequencing condition of the Delis-Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001)Trail Making Test; it is similar to the traditional Trails A. Scores for the SRT and CRT were the mean RTs in milliseconds. The Trails 2 score was the time to completion in seconds.

[1]The inclusion of additional external processing speed measures was suggested by the editor and an anonymous reviewer.

Statistical Analysis

The twin method capitalizes on the fact that MZ twins shared 100% of their genes, whereas DZ twins share, on average, 50% of their genes. Both MZ and DZ twin pairs share some environmental experiences, but not others. These features can be used to construct models that are tested by means of the maximum-likelihood based structural equation modeling program Mx (Neale, Boker, Xie, & Maes, 2004). Given the proportions of shared genes, additive genetic factors are assumed to correlate 1.0 for MZ twins and 0.50 for DZ twins. In twin models, common environmental factors are assumed to correlate 1.0 for both types of twin pairs, and unique environmental factors are assumed to correlate 0.00 for both types of twins. These relationships are depicted in Figure 2 in what is referred to as the standard univariate ACE model in which variance of a phenotype is decomposed into additive genetic influences (A), common or shared environmental influences (C), and unique or nonshared environmental influences (E) (Eaves, Last, Young, & Martin, 1978; Neale & Cardon, 1992). When the values are standardized, squaring the coefficients denoted by the lowercase a, c, and e in Figure 2 provides the proportion of phenotypic variance accounted for by each component.

Note that the genetic and environmental variance components in these models are latent constructs; we do not know which or how many genes are involved, and we do not know what the specific environmental factors may be. Nevertheless, the proportions of variance accounted for can still be calculated. For example, an MZ twin correlation is derived from genes (100%) and environmental factors that are shared. Even without knowing what the environmental factors are, we can determine that if the MZ correlation for trait X is .70, 30% of the phenotypic variance (1 – .70) must be due to unique environmental experiences. In part because they are latent constructs, the definitions of these environmental variance components are sometimes misunderstood. They are statistical, rather than substantive, definitions (Carey, 2003). Common environment is defined as aspects of the environment that make twins similar. Unique environment is defined as aspects of the environment that make twins different; it also includes measurement error, which is assumed to be random, and therefore uncorrelated within twin pairs.

The univariate ACE model is easily extended to examine the genetic and environmental correlations between multiple variables. A correlation is simply the covariance between two variables divided by the square root of the product of the variance of each variable. Taking advantage of the ability of the twin design to decompose genetic and environmental variances, a genetic correlation is calculated by dividing the *genetic* covariance by the square root of the product of each variable's *genetic* variance (Neale & Cardon, 1992). Essentially, it indicates the amount of genetic overlap between phenotypes. A unique environmental correlation is analogous to a genetic correlation except that it is based solely on the unique environmental covariance and the unique environmental variances for each variable.

In the present study, we tested multivariate twin models. The primary measures were error rates (misses and false alarms) for the different trial types. Error rates were not normally distributed and could not be normalized by data transformations. Due to fact that twin analyses assume that the variables of interest are normally distributed, we converted the error scores into ordinal measures with 6 levels (0–5) and calculated polychoric correlations to determine associations between the measures. *BY* RT was found to be normally distributed, but Mx does not currently allow for the simultaneous examination of ordinal and continuous data; therefore, we converted *BY* RT to a 10-level ordinal variable so that it could be analyzed alongside the error scores. SRT, CRT, Trails 2, and AFQT were also converted to ordinal variables.

In the first set of analyses, we examined the degree of genetic and environmental overlap between the *AX*, *BX*, and *AY* error scores. *BY* errors were not included because anyone with more than a very few *BY* errors is considered to have not understood or to have not been able to do the test. We initially fit a Cholesky decomposition model in order to estimate the heritability of each variable, as well as the genetic and environmental correlations between variables. The Cholesky decomposition is the simplest multivariate twin model in that it decomposes the phenotypic relationships into genetic and environmental components while imposing no formal structure on covariance. Relative to the Cholesky, we fit a common pathways model in order to determine whether common genetic and environmental factors underlie performance on the different trial types, and whether specific genetic and environmental for each trial type were present. The common pathway is a nested submodel of the Cholesky in which it is assumed that the covariation among the measures operates through a single latent phenotype[2].

In the second set of analyses, we examined the genetic and environmental relationships between *BY* RT and *BX* and *AY* errors. In this analysis, we focused on the trial types that reflect the key processes of interest with respect to context processing while also taking processing speed into account. We only utilized a Cholesky model because our primary interest was in the correlations between *BY* RT and each of the two error types, and because we did not think it made sense to expect speed and accuracy phenotypes to be accounted for by a common factor. The third set of analyses tested bivariate models for AFQT and *AX*-CPT error scores.

For each set of analyses, model fits were compared against that of the full Cholesky using the likelihood-ratio chi-square test (LRC). The LRC is calculated by comparing the −2 log-likelihood (−2LL) of the full Cholesky to the −2LL of a nested submodel model, with degrees of freedom equal to the difference in the number of free parameters in most cases (Eaves et al., 1978; Neale & Cardon, 1992). A nonsignificant LRC indicates that there is not a significant reduction in fit for the reduced model, suggesting that the reduced model is more parsimonious because it has an adequate fit to the data with fewer parameters. We also used the Akaike Information Criterion to compare models (AIC; Akaike, 1987; Williams & Holahan, 1994). If two or more competing models have nonsignificant LRCs, the one with the lowest AIC is the most parsimonious because it achieves statistically equivalent goodness-of-fit with fewer parameters. Because a reduced model does not actually have a better fit to the data than its comparison model with more parameters, we refer to the model with the lowest AIC as the most parsimonious model instead of the more conventional label of best-fitting model.

Results

Signal Detection (d′ Context)

The heritability of *d′* context was .40 (95% confidence interval [CI]=.31; .49), and the unique environmental variance was estimated at .60 (95% CI=.51; .69).

Genetic Architecture of AX, BX, and AY Errors

Table 1 presents the phenotypic correlations and the results from the AE Cholesky model (because dropping the C parameters had very little impact on the fit of the model). There were modest, but significant positive phenotypic correlations between *AX* and both *BX* and *AY* errors. The correlations were slightly stronger between *AX* and *BX* errors. *BX* and *AY*

[2]We also considered testing an independent pathways model, but with only three phenotypes, we could not empirically test an independent pathways model against the full (Cholesky) model (McArdle & Goldsmith, 1990).

errors were not significantly correlated. In the full (ACE) trivariate model for *AX*, *BX*, and *AY* errors, the estimates for A were .20 for *AX* errors, .28 for *BX* errors, and .24 for *AY* errors. Common environmental influences (C) accounted for very small and nonsignificant proportions of variance (7% for *AX* errors, 0% for *BX* errors, and 2% for *AY* errors). Model-fitting results for the trivariate analysis of *AX*, *BX*, and *AY* errors are shown in Table 2. When compared with the full Cholesky, the most parsimonious model was a common pathways model with A-only covariance (Table 2, Model 5). This model, along with the parameter estimates derived from it, is depicted in Figure 3. As can be seen in Figure 3, it is referred to as an A-only covariance model because the covariance among the three error types can be explained entirely by common genetic influences.

In order to test for the presence of genetic influences specific to each variable, we also fit a measurement model to the data (Table 2, Model 6). The measurement model is the same as the common pathways model except that it assumes no specific genetic or common environmental effects. In other words, the specific A and C parameters are set to zero (Specific effects are denoted by the "s" subscripts in Figure 3). The E parameters can never be set to zero because the variables examined are never free of measurement error. The measurement model was more parsimonious than the full Cholesky, but it had a substantially worse fit to the data than the A-only covariance model (Model 5). In contrast to the measurement model, the A-only common pathways model does indicate specific genetic variance for *AY* errors. As can be seen in Figure 3, the heritabilities are of similar magnitude for each of the error types—ranging from .25 to .29. However, only a small amount of genetic variance in *AY* errors comes from the latent factor; most (72%) of the genetic influences on *AY* errors are accounted for by genetic factors that are specific to that trial type. Thus, there are common genetic factors that influence overall performance, but there are also other independent genetic factors that influence differences in reactive control, i.e., response selection following stimulus exposure rather than planning ahead.

Correlated Factors Model for BX and AY Errors Accounting for Processing Speed

With respect to phenotypic correlations, *BY* RT and *BX* errors were positively correlated (r=.30) whereas *BY* RT and *AY* errors were negatively correlated (r=−.32; see Table 3). The trivariate Cholesky model for *BY* RT and *BX* and *AY* errors generated the following standardized variance components for *BY* RT: A=.37 (95% CI=.21; .47); C=.00 (95% CI=.00; .0003); and E=.63 (95% CI=.53; .74). As already noted, the C estimates for *BX* and *AY* errors were near zero. Thus, an AE model was more parsimonious than the ACE model (−2LL=10301.28, df=3350, LRC=.25, Δdf=6, p>.999, AIC=−11.75). The genetic correlations followed a pattern similar to that of the phenotypic correlations: r_g=.41 for *BY* RT and *BX* errors; and r_g=−.38 for *BY* RT and *AY* errors. In this model, the unique environmental correlations also followed a pattern similar to that of the genetic correlations r_g=.26 for *BY* RT and *BX* errors; and r_g=−.30 for *BY* RT and *AY* errors.

BX errors had a significant phenotypic correlation with Trails 2 (r=.17, p<.0001), but *AY* errors did not (r=−.02, p=.55). Although the direction of the correlations was again positive for *BX* and negative for *AY* errors, both had nonsignificant phenotypic correlations with SRT (r=.03, p=.30; r=.05, p=.09) and with CRT (r=−.05, p=.08; r=−.02, p=.52). Correlations of the other processing speed measures with *BY* RT were as follows: Trails 2 (r=.20; p<.0001); SRT (r=.29, p<.0001); CRT (r=.33; p<.0001). Given the general lack of significant phenotypic correlations between error scores and these additional processing speed measures, we did not perform multivariate genetic analyses with these processing speed measures.

Bivariate Genetic Analysis of AX-CPT Errors and General Cognitive Ability

With a genetic correlation between midlife and young adult general cognitive ability (AFQT scores) that did not differ from 1.0, there was virtually no difference in the results for AFQT scores at either time point. We did not examine genetic correlations for AFQT change scores because our previous work (Lyons et al., 2009) indicated that unique environmental factors primarily accounted for AFQT change; there were not significant genetic influences. With no significant genetic influences on the change phenotype, there could not be any genetic correlations between it and any other phenotype.

Age 20 and age 55 AFQT scores were not phenotypically correlated with *AY* errors (*r*s=.004 and .03, ps>.30). Table 4 shows the correlations of AFQT scores with *AX* and *BX* errors. Models were compared with a model that included ACE models for each variable and genetic, shared environmental, and unique environmental covariances. Here we summarize the results for the age 55 AFQT, but full model-fitting results for both age 20 and age 55 AFQT are available on request. In all cases, the most parsimonious models consisted of AE models for each of the individual variables and no shared environmental covariance. For age 55AFQT and *AX* errors, the most parsimonious model included the unique environmental covariance (−2LL= 9645.65, df=2343, LRC=.50, Δdf=3, p>.92, AIC=−5.50). For age 55 AFQT and *BX* errors, the most parsimonious model did not include the unique environmental correlation. As is readily apparent in Table 4, the results were essentially the same for AFQT scores in young adulthood and in late middle age. Thus, *AX* and *BX* errors (representing poor use of context to plan responses) both share some genetic influences with overall cognitive ability. *AY* errors (representing poor response selection when the ability to plan ahead is limited), which have some genetic influences that are distinct from *AX* and *BX* errors, have genetic influences that are distinct from overall cognitive ability as well.

Discussion

To our knowledge, this is the first study of both genetic and environmental influences on *AX*-CPT performance. There was moderate heritability for *d′* context, but further examination of specific component processes served to more fully elucidate the genetic influences underlying *AX*-CPT performance. Genetic influences accounted for about one-quarter of the variance in *AX*, *BX*, and *AY* errors. The remaining variance was primarily accounted for by unique environmental influences. Common environmental influences could be dropped from the models without a significant reduction in fit. The strongest phenotypic correlation was between *AX* and *BX* errors. Similar to previous studies (e.g., Braver et al., 2001), *BX* and *AY* errors were not significantly phenotypically correlated. There was a far smaller degree of genetic overlap between *AX* and *AY* errors, and there was no overlap in the environmental influences on any of the error types. Given that the genetic correlation between *AX* and *BX* errors was not significantly different from 1.0 and the unique environmental correlation was near zero, we can conclude that the phenotypic correlation was almost entirely due to fact that the same genetic influences were operating on each trial type. Taken together, the results indicate that there are far more common genetic influences underlying the common processes shared by *AX* and *BX* trials than there are in the common processes shared across *AX* and *AY* trials. The common process in *AX* and *BX* trials is that using context cues to prepare responses maximizes performance. On *AY* trials, the context cue works against optimal performance and response choice can only be made after the probe is presented.

These conclusions were supported by the trivariate model-fitting results for these three trial types. The A only covariance model supported by that analysis indicates that the shared variance among the three trial types can be accounted for solely by common genetic influences that operate through a common latent factor. All of the genetic influences on *AX*

and *BX* errors are from the genes that underlie the latent factor. In contrast, most of the genetic influences on *AY* errors come from genes that are specific to that trial type and independent of the genes underlying the latent genetic factor. Thus, it is largely different genetic factors that influence performance on *BX* and *AY* trials. This relative independence indicates that these phenotypic functionally dissociable processes are genetically dissociable as well. MacDonald et al. (2005) found that *BX* and *AY* error scores loaded on independent phenotypic factors. The present results provide a causal mechanism in that there are also some independent genetic influences underlying *BX* and *AY* performance.

Overall, our results suggest that a single underlying mechanism—as proposed in the formal context processing models—is insufficient to account for the performance patterns. The absence of a phenotypic correlation between *BX* and *AY* performance casts doubt on the notion of a single underlying mechanism, but the presence of independent genetic factors indicated by the lack of a genetic correlation between the two essentially confirms the presence of at least two underlying mechanisms. Different genetic influences contributing to different components of context processing may make it easier to account for varied within-individual performance or differential changes with age. This finding appears to be consistent with the dual mechanisms of control model which postulates that “it should be possible to modulate reactive control without affecting proactive control” (p. 7355) (Braver et al., 2009). Reactive control refers to reliance on probe information to determine responses, whereas proactive control refers to reliance on cue information which allows for planning ahead (Braver et al., 2009; Braver et al., 2005). Strategy differences might make it necessary to postulate an additional underlying mechanism for modulating shifts between different trial types, i.e., for adaptively switching between emphasis on proactive or reactive cognitive control modes. Modulating speed of response could be one way to do that. Alternatively, it may be that *AY* performance primarily reflects a response style that is independent of both *BX* performance and overall cognitive ability. It might be analogous to response bias (β) in signal detection paradigms, i.e., how liberal or conservative people are in their threshold for calling something a target.

In virtually all previous cross-sectional, non-genetically informative studies (Braver et al., 2001; Braver et al., 2009; Braver et al., 2005; Paxton et al., 2008; Paxton et al., 2006; Rush et al., 2006), chronological age and slower *BY* RTs were both associated with increased *BX* errors and fewer *AY* errors. With the chronologically age-homogeneous sample that is part of the VETSA study design, chronological age was not associated with *BX* or *AY* errors. Yet, the same pattern of correlations between *BY* RT and either *BX* or *AY* errors was present in our sample. Thus, VETSA participants who tend to have more *BX* and fewer *AY* errors (and slower *BY* RT) appear to be functioning in a way that is similar to chronologically older individuals; that is, they appear to be relying more heavily on reactive control relative to proactive control strategies.

On the other hand, this same pattern of correlations with *BX* and *AY* errors was not present for any of our other external processing speed measures. Taken together, these results suggest that *BY* RT is an indicator of task-specific, rather than general, processing speed. Thus, a subset of our relatively young VETSA participants may be functioning like older adults on the *AX*-CPT, but not necessarily on other tests. With these participants being only in their 50s at the time of this assessment, it may be that those with *AX*-CPT performance that is more similar to that of older adults are at increased risk for earlier or greater cognitive declines in VETSA follow-up assessments. As an index of cognitive variation this is independent of chronological age in this sample, it might be tentatively suggested this pattern of performance could constitute a cognitive analog of BioAge (Baltes & Lindenberger, 1997; Wahlin, MacDonald, deFrias, Nilsson, & Dixon, 2006).

Given substantial prior evidence indicating that executive function is associated with general cognitive ability, it was also of interest to examine the relationship of context processing components to overall cognitive ability. These associations can be somewhat puzzling because the ability of patients with frontal lobe damage and impaired executive function to manifest little or no impairment on IQ tests suggests a dissociation between executive function and general cognitive ability. This paradoxical set of findings may be partially explained by findings such as those of Friedman et al. (2006) who showed that updating, but not shifting or inhibition, were strongly associated with general cognitive ability. Our results are partially consistent with that pattern. *AX* and *BX* errors had negative genetic correlations with general cognitive ability, the stronger relationship being with *BX* errors. This indicates that there are shared genetic influences between context processing and general cognitive ability; however, the correlations were far from −1.00, indicating that there are substantially different genetic influences as well. In contrast, *AY* errors were independent of general cognitive ability.

This pattern is consistent with the phenotypic factor analysis of MacDonald et al. (2005) in which the factor with strong *AY* loadings was independent of the factor containing strong *BX* loadings, and only the latter factor was significantly correlated with general cognitive ability. MacDonald et al. suggested a parallel between *AY* trials and go/no-go tasks, a class of tasks that require inhibitory reactive control and tend to be impaired when there is greater impulsivity. Given evidence that response inhibition is poorer in older than in young adults (Zacks, Hasher, & Li, 2000; Zacks, Radvansky, & Hasher, 1996), this view makes it difficult to account for older adults having better *AY* performance than young adults. The logic of the context processing model has been that *AY* performance is better because older adults have poorer context maintenance, not because they have better inhibitory control. If older adults—or those functioning more like older adults—do not maintain the context well, the prepotent response tendency (expectation of an *X* following an *A*) will be weaker and the downstream effect would be that less inhibitory control is needed. Therefore, *AY* trials may have a strong go/no-go component, but only for individuals with good context maintenance.

Consistent with this notion, Rush et al. (2006) found that *AY* errors were significantly correlated with go/no-go errors in young adults (mean age=20 years) but not in older adults (mean age=75 years). *AY* errors were also significantly positively correlated with *BX* errors in the study of Rush et al. (2006), but only in the older adults. Again, this pattern of correlations is consistent with the idea that *AY* performance may be more strongly influenced by maintenance of context in older adults, but more by response inhibition in younger adults. This idea may also account for an apparent paradox; a more conservative approach, which is often seen in older adults, would be consistent with fewer *AY* false alarms, but not faster RTs. However, if *AY* trials effectively lose their go/no-go element when individuals reach a certain age, they would not experience the response conflict and subsequent slowing of younger adults. Like the young adults, *BX* and *AY* errors were uncorrelated in middle-aged adults (mean age=55 years in the present study; mean age=44 years in the MacDonald et al. (2005) study). We might, therefore, expect to see this pattern change as VETSA participants get older.

It is important to note that previous studies of *AX*-CPT performance and aging have been cross-sectional, with the difference in patterns of performance between young and old adults suggesting an age-associated shift from more proactive to more reactive control (Braver et al., 2009; Braver et al., 2005; Rush et al., 2006). That is, younger adults perform better on *BX* trials, reflecting an emphasis on planning ahead for responses based on context cues. Older adults perform better on *AY* trials, reflecting an emphasis on making response decisions after appearance of a probe. Braver et al. (2009), however, also suggested that variability in these two cognitive strategies may be present even within a small sample of

young adults. These findings raise some key questions that we may begin answer in the ongoing longitudinal assessment of the large VETSA sample: whether some individuals experience an age-related shift toward greater reliance on reactive control, and some do not; and whether particular patterns of *AX*-CPT performance in midlife indicate increased risk for mild cognitive impairment or dementia.

In the present study, we examined *AX*-CPT performance to determine the genetic and environmental influences on components of context processing in late middle age. Approximately 40% of the variance in signal detection (d' context) and one-quarter of the variance in individual error scores were accounted for by genetic influences. Multivariate analyses demonstrated common genetic influences across the different component processes, but additional independent genetic influences on *AY* performance. We concluded that there are genetic influences on reactive cognitive control (based on *AY* scores) that are independent of the genetic influences on proactive cognitive control (based primarily on *BX* scores). Unlike proactive control, reactive control was also independent of general cognitive ability. Within a narrow age range, slower CPT RTs were associated with error patterns similar to older adults, but these associations did not generalize to external RT measures. Given our results indicating more than one genetic mechanism underlying context processing performance, further investigation is warranted to determine how these mechanisms may differentially affect age-related changes in context processing components.

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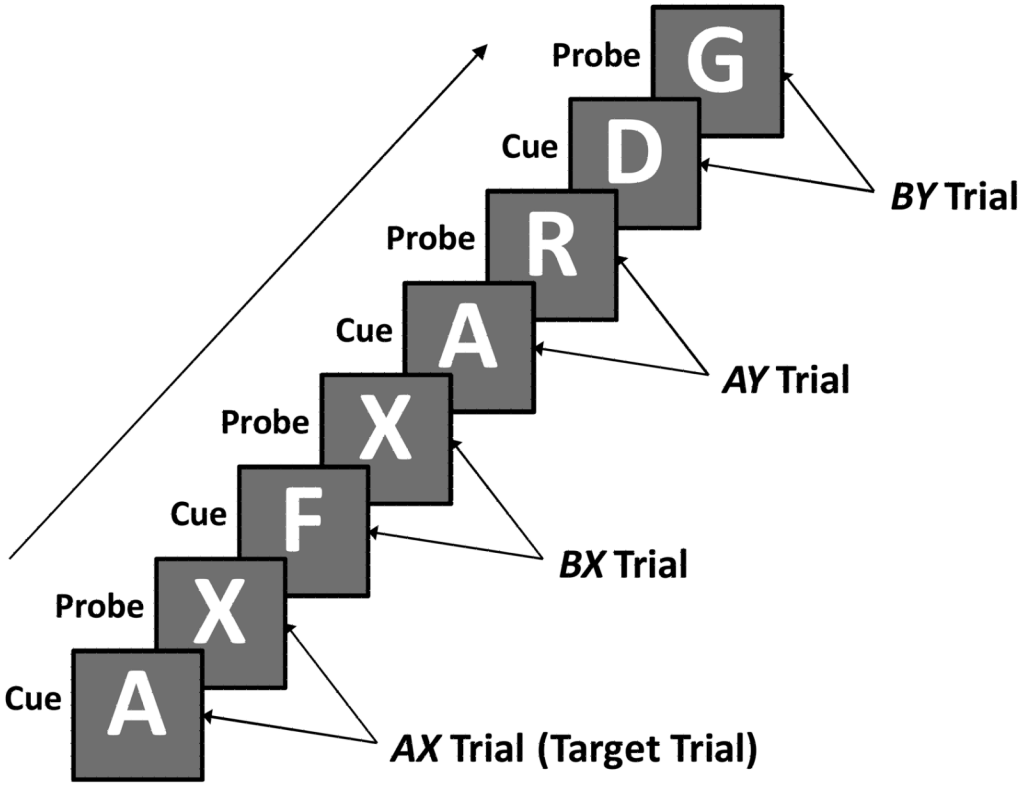

Figure 1.
Sample sequence *AX*-CPT trials. Letters appear one at a time. *B* refers to any non-*A* cue. *Y* refers to any non-*X* probe. The target button is the correct response only for probes on the target (*AX*) trials. The non-target button is the correct response for probes on all other trials and for all cues.

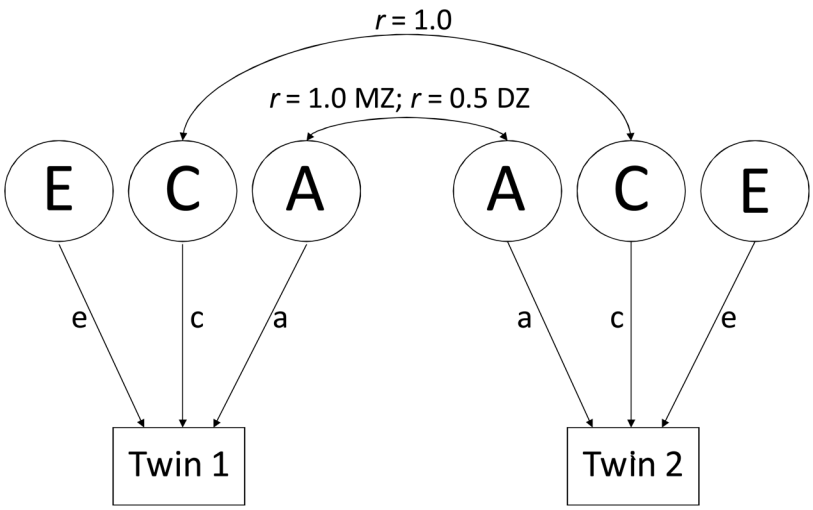

Figure 2.
Univariate twin model. A=latent additive genetic influences; C=latent common (shared) environmental influences; E=latent nonshared (unique) environmental influences. Lowercase a, c, and e refer to the parameter estimates (path coefficients); squaring these parameters yields the proportion of variance in the phenotype that is accounted for by the latent factors. Under the model, additive genetic influences correlate 1.0 for MZ twins and . 50 for DZ twins; common environmental influences correlation 1.0 for all twins; and nonshared environmental influences (which include measurement error) are uncorrelated.

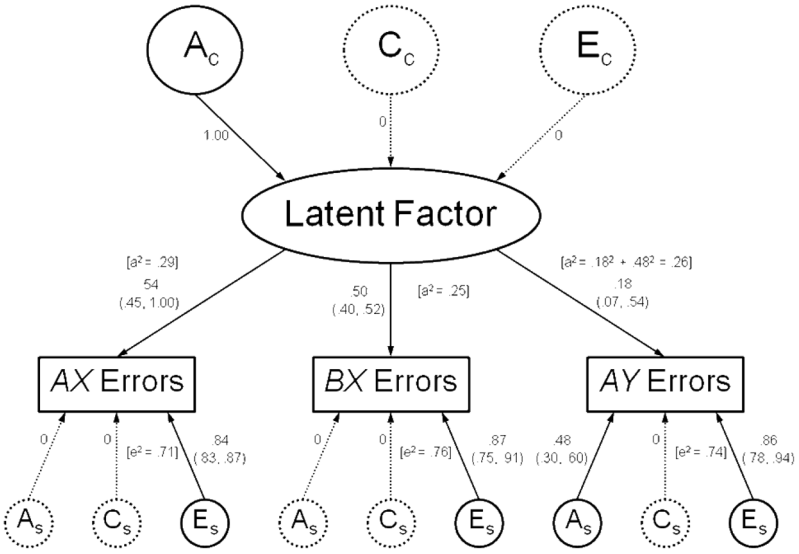

Figure 3.

Common pathways model for *AX*, *BX*, and *AY* errors. Standardized parameter estimates with 95% confidence intervals are shown. To simplify the display, only one twin is represented in the diagram. A=Additive genetic influences; C=Common environmental influences; E=Unique environmental influences; a^2=Proportion of variance accounted for by additive genetic influences (heritability); e^2=Proportion of variance accounted for by unique environmental influences. Subscript $_C$=Influences that are *common* to all three trial types. Subscript $_S$=Influences that are *specific* to a particular trial type. Dotted lines represent variance components that were very small and could be dropped from the model without any significant reduction in fit.

*p<.05

Table 1

Phenotypic, Genetic, and Unique Environmental Correlations for AX, BX, and AY Errors

	***AX* Errors**	***BX* Errors**
Phenotypic Correlations		
BX Errors	.28 (.21, .34)	
AY Errors	.11 (.05, .18)	.06 (−.02, .13)
Genetic Correlations		
BX Errors	.95 (.60, 1.00)	
AY Errors	.40 (.09, .78)	.32 (−.11, .65)
Unique Environmental Correlations		
BX Errors	.03 (−.08, .15)	
AY Errors	.01 (−.11, .13)	−.04 (−.16, .12)

Note. Genetic and unique environmental correlations are from the AE Cholesky model. Numbers in parentheses are 95% confidence intervals.

Table 2

Model-Fitting Results for Trivariate Twin Analysis of AX, BX, and AY Errors

Model	−2LL	df	LRC	Δdf	p	AIC
1. ACE Cholesky	10156.56	3348	n/a	n/a	n/a	n/a
2. AE Cholesky	10156.89	3354	0.33	6	.999	−11.67
3. ACE Covariance Common Pathways	10158.12	3351	1.56	3	.668	−4.44
4. AE Covariance Common Pathways	10158.12	3355	1.56	7	>.999	−12.44
5. A Only Covariance Common Pathways	**10158.74**	**3358**	**2.18**	**10**	**.995**	**−17.82**
6. Measurement Model	10169.54	3359	12.98	11	.295	−9.02

−2LL = −2 Log-Likelihood; df = Degrees of Freedom; LRC = Likelihood Ratio Chi-square test, which is equal to the change in −2LL between the comparison model and the ACE Cholesky; Δdf = Change in df; AIC = Akaike's Information Criterion, which is equal to [LRC – 2(Δdf)].

The fit of models 2–6 shown in the Table was determined relative to the ACE Cholesky.

An additional test of Model 6 relative to Model 5 (the most parsimonious model) indicated a significantly worse fit for Model 5 (LRC = 10.80; Δdf = 1; p = .001; AIC = 8.80).

Table 3

Phenotypic Correlations, and Genetic and Unique Environmental Correlations from Most Parsimonious Model for BY Reaction Time (RT) and BX, and AY Errors

	***BY* RT**	***BX* Errors**
Phenotypic Correlations		
BX Errors	.30 (.23, .36)	
AY Errors	−.32 (−.39, −.26)	.06 (−.02, .14)
Genetic Correlations		
BX Errors	.41 (.10, .66)	
AY Errors	−.38 (−.66, −.08)	.27 (−.15, .69)
Unique Environmental Correlations		
BX Errors	.26 (.12, .38)	
AY Errors	−.30 (−.42, −.24)	−.01 (−.16, .14)

Note. Numbers in parentheses are 95% confidence intervals.

Table 4

Phenotypic Correlations, and Genetic and Unique Environmental Correlations from Most Parsimonious Models for General Cognitive Ability (AFQT) and AX and BX Error

	Age 20 AFQT	Age 55 AFQT
Phenotypic Correlations		
AX Errors	−.13 (−.19, −.07)	−.19 (−.25, −.12)
BX Errors	−.15 (−.21, −.08)	−.22 (−.29, −.15)
Genetic Correlations		
AX Errors	−.29 (−.43; −.15)	−.30 (−.45, −.15)
BX Errors	−.33 (−.53; −.17)	−.49 (−.72; −.33)
Unique Environmental Correlations		
AX Errors	----	−.11 (−.22; −.001)
BX Errors	----	----

Note. Numbers in parentheses are 95% confidence intervals. Separate bivariate analyses were performed for the age 20 and age 55 AFQT scores. There are empty cells for unique environmental correlations because those correlations were dropped from the models.