

## Error rate on the antisaccade task: Heritability and developmental change in performance among preadolescent and late-adolescent female twin youth

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### Abstract

We examined heritability of error rate on the antisaccade task among female twin youths. This task appears to be sensitive to prefrontal functioning, providing a measure of individual differences in inhibitory control associated with genetic risk for schizophrenia. The sample consisted of 674 11-year-olds and 616 17-year-olds, comprising the two cohorts of female twins from the Minnesota Twin Family Study, a population-based investigation of substance abuse and related psychopathology. We used biometric model-fitting methods to determine the relative magnitude of genetic and environmental influences on performance. In both age cohorts, the best fitting model contained additive genes and nonshared environment. Despite substantial age-related differences in mean performance levels (effect size = .81), additive genes accounted for greater than half the variance in performance in both age cohorts. These results are consistent with the hypothesis that antisaccade error rate might serve as an endophenotype for behavior disorders reflecting frontal lobe dysfunction or problems with inhibitory control.

**Descriptors:** Antisaccade error rate, Inhibitory control, Heritability, Biometric model-fitting, Endophenotype, Adolescents

The antisaccade task is an ocular-motor procedure designed to evaluate inhibitory capacity (Hallett, 1978). In the typical paradigm, the subject sees a fixation cue presented centrally on a CRT screen. At unpredictable intervals, the fixation cue disappears and a response cue appears simultaneously in an eccentric location in the subject's visual field. Appearance of the response cue signals the subject to make a saccade to the coordinate location *opposite* the response cue. Successful performance hence requires the subject to suppress a reflexive saccadic eye movement toward a visual cue, making a saccade in the opposite direction instead (see reviews in Broerse, Crawford, & den Boer, 2001; Everling & Fischer, 1998).

Inhibiting a "prepotent" tendency (Diamond, 1991) in order to make a response more appropriate to the task or situation at hand is the type of capacity that typically involves the prefrontal cortex (Dempster, 1992; Diamond, 1991; Fuster, 1989; Luria, 1973; Stuss & Benson, 1984). Antisaccade performance may also be depen-

dent on working memory capacity, another prefrontally modulated brain function, as increasing working memory load results in an increased number of errors, or reflexive glances at the response cue (Roberts, Hager, & Heron, 1994). Several conditions involving damage to or changes in prefrontal cortex or related structures typically impair performance on this task. These include lesions (Fukushima, Fukushima, Miyasaka, & Yamashita, 1994; Gaymard et al., 1998; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991; Walker, Husain, Hodgson, Harrison, & Kennard, 1998), Parkinson's disease (Briand, Strallow, Hening, Poizner, & Sereno, 1999; Kitagawa, Fukushima, & Tashiro, 1994), and normal aging (Butler, Zacks, & Henderson, 1999; Nieuwenhuis, Ridderinkhof, de Jong, Kok, & van der Molen, 2000; Olincy, Ross, Young, & Freedman, 1997). Although somewhat inconsistent with respect to the particular areas involved in task performance, imaging studies with human subjects suggest that a widely distributed circuit supports antisaccade performance (Doricchi et al., 1997; O'Driscoll et al., 1995; Paus, Petrides, Evans, & Meyer, 1993; Sweeney et al., 1996), which includes frontal cortices (dorsolateral prefrontal cortex, the frontal and supplementary eye fields) and closely related structures (anterior cingulate cortex and striatum). One study of single-neuron activity in animals has been conducted using a paradigm comparable to that used with human subjects (Schlag-Rey, Amador, Sanchez, & Schlag, 1997). This investigation found that activity in the superior eye fields was associated with antisaccade performance. Neuropathology, imaging, and single-unit studies thus generally support an association between antisaccade error and functioning of the prefrontal cortex.

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Elevated antisaccade error rates have also been associated with psychopathology hypothesized to reflect frontal lobe dysfunction, especially schizophrenia (Clementz, McDowell, & Zisook, 1994; Crawford et al., 1998; Curtis, Calkins, Grove, Feil, & Iacono, 2001; Curtis, Calkins, & Iacono, 2001; Fukushima, Morita, Fukushima, Chiba, et al., 1990a; Fukushima et al., 1994; Katsanis, Kortenkamp, Iacono, & Grove, 1997; McDowell, Myles-Worsley, Coon, Byerley, & Clementz, 1999; Radant, Claypoole, Wingerson, Cowley, & Roy-Byrne, 1997; Sereno & Holzman, 1995; Tien, Ross, Pearlson, & Strauss, 1996). In addition, several studies have found that schizophrenia patients with poor antisaccade performance show other signs of frontal lobe pathology. For instance, high error rates have been reported to be associated with atrophy of frontal cortex (Fukushima et al., 1994). Antisaccade error rate in schizophrenia patients has also been correlated with performance on other tasks tapping putative prefrontal function, such as the Wisconsin Card Sorting Test (Crawford et al., 1996; Karoumi, Ventre-Dominey, Vighetto, Dalery, & d'Amato, 1998; Rosse, Schwartz, Kim, & Deutsch, 1993; Tien et al., 1996) and a working memory task (Nieman et al., 2000).

Schizotypic individuals (Gooding, 1999) and nonpsychotic relatives of schizophrenia patients make significantly more errors than psychiatric and nonpsychiatric control subjects (Clementz et al., 1994; Crawford et al., 1998; Curtis, Calkins, Grove, et al., 2001, Curtis, Calkins, & Iacono, 2001; Katsanis et al., 1997). These findings have led to suggestions that antisaccade error rate may serve as an endophenotype or indicator of genetic liability for schizophrenia (e.g., Crawford et al., 1998; McDowell et al., 1999). That is, poor antisaccade performance may represent a genetically influenced trait which, when present, reflects frontal lobe dysfunction and increased risk for developing schizophrenia.

The present study contributes to the search for candidate endophenotypes in psychiatric research by examining the extent of genetic and environmental influence on performance in a large sample of two age cohorts of female adolescent twins. Subjects in this study were drawn from the Minnesota Twin-Family Study (MTFS), a large, ongoing epidemiological study of 11- and 17-year-old twins. That the ages of the twins brackets adolescence provided an opportunity to examine how heritability may change during this period of marked behavioral and frontal lobe development.

Several recent studies have found dramatic improvement in antisaccade performance from early school-age years to early adulthood (Fischer, Biscaldi, & Gezeck, 1997; Fukushima, Hatta, & Fukushima, 2000; Klein, 2001; Klein & Foerster, 2001; Munoz, Broughton, Goldring, & Armstrong, 1998). For instance, Klein and Foerster found that mean error rates were approximately twice as great among 11- to 12-year-olds relative to 18- to 26-year-old young adult subjects. Fischer and colleagues, studying performance of a large number of subjects between 8 and 70 years of age, found that error rate declined dramatically across age groups until middle adolescence and somewhat more slowly thereafter, reaching a minimum among subjects in early adulthood. Munoz and colleagues obtained similar results. Klein explicitly modeled the developmental (regression) functions describing age-related change in performance on several antisaccade measures among subjects between 6 and 28 years of age and found that a nonlinear function best characterized developmental change, with rapid improvement in performance until approximately 16 to 18, at which time performance reached or approached an asymptote.

These studies thus agree with each other in indicating that performance on the antisaccade task improves markedly between

**Table 1.** Sample Sizes and Demographic Characteristics of the Two Cohorts

Cohort	N	Twin age	Paternal SES	Years of education	
				Paternal	Maternal
11-year-olds	674	11.7 (0.5)	3.8 (1.9)	14.3 (2.4)	14.0 (2.1)
17-year-olds	616	17.4 (0.5)	3.9 (1.9)	14.1 (2.5)	13.7 (2.0)

*Note:* N refers to the number of individual participants. All other numbers are group means, with standard deviations in parentheses. Socioeconomic status was assessed using Hollingshead's (1957) index, which uses a 7-point scale to code occupational status. A score of 1 indicates the highest status occupations, such as executives of large companies, lawyers, physicians, and other professionals, a score of 7 the lowest, corresponding to unskilled laborers. Scores were relatively uniformly distributed, with a mode of 5 in the older cohort (approximately 25% of fathers) and modes at 3 and 5 in the younger cohort (approximately 20% in each category). Occupations in category 3 consist of administrative personnel, small business owners, and "minor" professionals, such as laboratory assistants, newspaper reporters, airline pilots, and commercial artists, and those in category 5 consist of skilled manual laborers.

childhood and late adolescence, where it reaches or begins to reach adult levels. Comparison of the 11- and 17-year-old age cohorts in the present study allows us to determine whether the relative magnitude of genetic and environmental influences on antisaccade performance is similar at these two ages despite significant age-related differences in task performance and hence in the capacity to inhibit inappropriate ocular-motor responses.

## Method

### Participants

The sample consisted of reared-together female monozygotic (MZ) and dizygotic (DZ) twin youths participating in a community-based epidemiological and longitudinal investigation of the origins and development of substance use disorders and related psychopathology.<sup>1</sup> The sample was drawn from twin births in Minnesota between 1975 and 1984 and is broadly representative of the population of families with twins born in the state (see Iacono, Carlson, Taylor, Elkins, & McGue, 1999, for a comprehensive description of the MTFS, including its representativeness, and study design). The sample comprises two age cohorts. Subjects in the two cohorts were approximately 11 years old or 17 years old, respectively, at the time of assessment. All twin pairs for which both members of the pair completed the antisaccade task were included in the present study. Participants who were 18 years old at the time gave written informed consent to participate in the study. Participants under the age of 18 were asked to assent to their participation and written informed consent was obtained from one parent. Consistent with the demographics of Minnesota at the time the twins were born, the vast majority were Caucasian (94% and 98% in the younger and older cohorts, respectively). The number of individuals in each age cohort, their average ages, and parental occupational and educational status are given in Table 1.

Twin zygosity was determined by means of a combination of three independent estimates. The twins' parents completed a ques-

<sup>1</sup>Although male twins are also part of the MTFS, they were assessed at a different time, before the antisaccade task administered to the female twins was introduced.

tionnaire regarding the twins' physical similarity and the frequency with which family members and others confused one twin for the other. Research staff with the study also rated the twins with respect to similarity of physical characteristics such as eye color and ear shape, deriving an estimate of zygoty from these ratings. A third estimate was obtained from three anthropometric measures: ponderal index, defined as height divided by the cube root of weight; cephalic index, defined as head breadth divided by head length; and fingerprint ridge count. In the event that these three estimates disagreed, a serological examination of 12 blood group antigens and protein polymorphisms was conducted. The relative proportion of MZ and DZ twin pairs in each cohort is given in Table 2.

### Antisaccade Task

Study participants performed the antisaccade task as the last procedure in an ocular-motor assessment battery. The battery consisted of several tracking tasks: two variants of a smooth-pursuit task requiring the participant to track sinusoidally modulated target motion, and two tasks involving step-ramp target motion, in which an abrupt target offset is followed by a brief, constant-velocity sweep across the screen, or half the screen. In addition, and immediately preceding the antisaccade task, participants were given a "prosaccade" task, in which they were required to make a saccadic eye movement in the direction of targets appearing at one of several eccentric locations. The battery of tasks took place in a darkened room. It was administered at the same time of morning for all participants and lasted approximately 15 min.

Each participant was seated in front of a CRT screen, with a chin rest used to support the participant's head. A circle subtending  $0.4^\circ$  of visual arc appeared initially at a central fixation point 82 cm from the participant. At unpredictable times between 1.5 and 2.5 s, the central target disappeared, and a response cue, identical to the fixation stimulus, appeared approximately  $6^\circ$  to either side of the fixation point. Participants were instructed to fixate the target when in the center of the screen and to respond to the appearance of the response cue by moving their eyes to the opposite side of the CRT screen (i.e., approximately the same distance in the opposite direction). The response cue remained illuminated for 1.5 s, after which it was extinguished and the central fixation target reappeared, signaling the participant to return her gaze to the central location. Twenty trials were administered, with the response cue appearing an equal number of times to the left and right. Seventy-two subjects in the younger cohort and 95 in the older cohort received a variant of the protocol with 17 trials.

### Data Collection

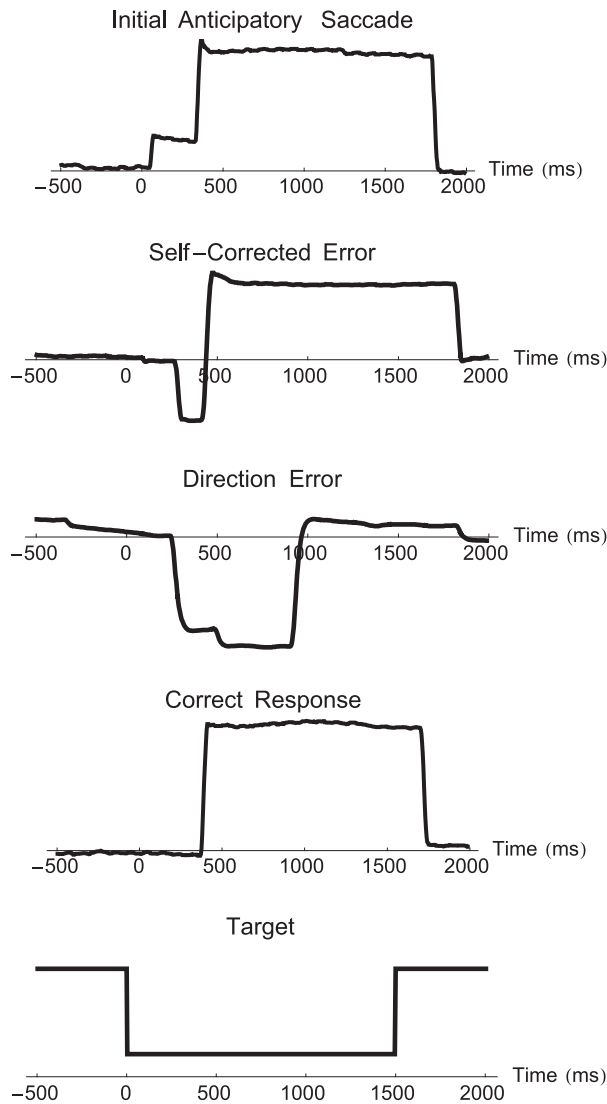
Eye movements were measured by means of the corneal reflection technique. Participants wore empty spectacle frames attached to an adjustable headband. An infrared (IR) light source mounted on the spectacle frames was reflected off the cornea and detected by a pair of sensors on either side of the IR source. An Eye Trac Model 210 (Applied Science Laboratories) monitoring system, which is linear to  $\pm 10^\circ$  with resolution of  $0.25^\circ$  of visual angle, was used. In addition, to assist with the accurate identification of saccades (Calkins, Katsanis, Hammer, & Iacono, 2001), we recorded electrooculographic (EOG) activity by means of two pairs of Ag/AgCl electrodes. One pair, placed superior and inferior to one eye, served primarily to record eye blinks and other artifacts not readily observable in the IR reflection. The second pair, placed at the outer canthi of each eye, recorded horizontal eye movements and hence served as a secondary measure of eye movement. For both EOG recordings, an electrode on the shin served as ground, and data from each pair of electrodes were input to a separate amplifier in a Grass Model 12A Neurodata acquisition system, amplified 5,000 times, and filtered with a bandpass of 0.01 to 100 Hz (6 dB attenuation, or half-amplitude frequency, with a roll-off of 6 dB per octave). All recordings were digitized at 256 Hz to 12 bits resolution.

For each trial in a given subject's record, a trained rater determined the nature of the subject's response from the IR signal. Each was categorized as one of the following (see Figure 1): a correct response, in which the subject's initial saccade went in the opposite direction from the response cue; a direction error, in which the subject either fixated the response cue or made a saccade toward the response cue followed by a return to the midline; a self-corrected error, in which the initial saccade was toward the response cue but was followed by a second saccade away from it that was required to go past the midline; an anticipatory response, defined as a saccade occurring within 80 ms of the response cue's appearance, which is unlikely to have been visually guided; and no response. Direction errors and self-corrected errors were treated as errant responses, whereas failures to respond at all and anticipatory responses were excluded. When problems existed in the IR signal, such as when it exceeded the range of the A-D converter because of signal drift, the nature of the subject's response on a given trial was determined by inspection of the horizontal EOG. The proportion of direction errors served as our measure of performance. These consist of trials on which the subject's initial saccade was in the direction of the cue, rather than in the direction opposite the cue. Even the youngest subjects in this sample typically spontaneously corrected themselves when making an errant response,

**Table 2.** Mean Error Rates and Twin Correlations by Age Cohort and Zygosity

Cohort	MZ			DZ			z	p
	N	Error rate	ICC	N	Error rate	ICC		
11-year-olds	207	45.2 (20.8)	.54*	126	45.5 (20.3)	.29*	2.68	.004
17-year-olds	203	29.6 (19.7)	.62*	102	27.2 (18.9)	.31*	3.30	<.001

*Note:* N indicates the number of twin pairs. Error rate indicates the mean percentage of direction errors, along with associated standard deviation. ICC denotes the intraclass correlation. Those marked with an asterisk are significant by one-tailed test, all p-values being .001 or less. Tests of the significance of the difference between MZ and DZ correlations are given by z, with associated one-tailed probability p.



**Figure 1.** Representative examples of each of the different types of responses. Time (in milliseconds) is given on the abscissa, eye position (in arbitrary units) on the ordinate. Target position appears at the bottom. Note the typically short latency of the secondary corrective saccade in the top trace. Because it is self-evident, we have not included an example of complete failure to respond (continued fixation of the center position). All examples come from 11-year-olds.

indicating that their having first made a saccade in the direction of the cue was not due to forgetting the task instructions or to a failure to understand the task in the first place. However, 3 subjects in the 11-year-old cohort with error rates of 100% made few or no self-corrective responses and were excluded from analyses, along with their respective cotwins. Subjects with fewer than 12 scorable trials were also excluded, resulting in the loss of an additional 4 pairs (1 in the younger cohort, 3 in the older cohort). Our measure of performance—the proportion of direction errors—was reliable, Cronbach’s alpha equaling 0.81 and 0.82 in the younger and older cohorts, respectively.

**Statistical Analyses**

The primary analytic technique used in the present study consisted of fitting univariate biometric models to the observed data. Such

models are a form of covariance structure analysis that permits the decomposition of the total observed phenotypic variance into that attributable to latent genetic and environmental factors. The basic biometric model assumes that a phenotype can be expressed as a weighted linear combination of several latent factors,

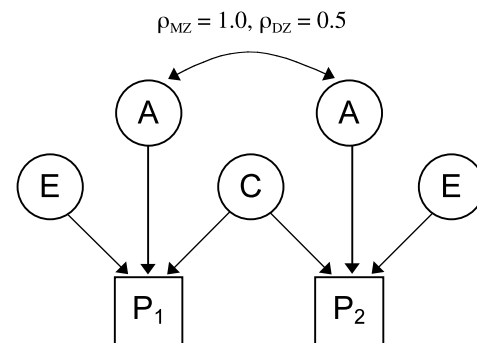
$$P = A + C + E,$$

where *P* represents the phenotype (percentage of antisaccade direction errors in the present instance) and the terms on the right-hand side of the equation represent the various latent factors thought to influence it. The biometric model is represented graphically in Figure 2. *A* represents additive genetic effects. These are the contributions of single genes that combine in an additive fashion both within a single locus and across multiple loci. Additive genetic effects are the genetic source of parent–offspring resemblance. *C* represents common, or shared, environmental effects. These are sources of environmental influence shared by members of a family that contribute to phenotypic similarity between twins. Shared environmental influences include such factors as socioeconomic status and parental education, family size, religious practices, parental warmth, and other sources of between-family variance. *E* represents nonshared, or individual-specific, environmental influences. These include all environmental influences that tend to make twins phenotypically dissimilar from each other, including experiences outside the family, such as peer and school influences, as well as experiences within the family, such as sibling relations and differences in parent–child interactions. Non-shared environment also includes error in measuring the phenotype in question.

The expected phenotypic covariances for MZ and DZ twins, respectively, are

$$\text{Cov}_{\text{MZ}} = V_A + V_C$$

$$\text{Cov}_{\text{DZ}} = \frac{1}{2}V_A + V_C.$$



**Figure 2.** Representation of the standard biometric model used in the present study. *P*<sub>1</sub> represents the phenotype for the first twin and *P*<sub>2</sub> the phenotype for the second twin. The phenotype in question for the present study is antisaccade error rate. The circles represent latent factors hypothesized to account for individual differences in performance (variance) and correlations between twins (covariance): additive genes (*A*), common environment (*C*), and nonshared, or unique, environment (*E*). These influences are described in greater detail in the text. The correlation between twins is represented by the curved, double-headed arrow. Its magnitude is given by  $\rho$ , which differs for MZ and DZ twin pairs.

Given a few assumptions (see Discussion), this set of simultaneous equations can be solved using maximum likelihood estimation procedures and software such as Mx (Neale, 1997), yielding estimates of the relative magnitude of the different latent factors in determining the observed phenotypic variances and twin covariances. (The interested reader can consult a text such as Neale and Cardon, 1992.)

In addition to decomposing the observed variance–covariance matrices into components associated with unobserved factors, the biometric approach allows one to fit different models to the observed data in combination with goodness-of-fit statistics, thereby evaluating their adequacy. Our model-fitting analyses consisted of two parts. We began by determining the model that most parsimoniously fit the observed data within each age cohort. These analyses consisted of fitting a series of nested models. The full model in each case contained additive genetic effects and both shared and nonshared environmental effects (the ACE model). We subsequently fit reduced models, in which one or more factors were deleted from the model and the adequacy of the fit of the reduced model assessed. If the reduced model accounts for the observed data well, one typically infers that the factor deleted is not necessary. If the fit of the reduced model is significantly worsened relative to the fit of the more complete model, one typically infers that the deleted factor is an important one. We assessed the fit of the AE, CE, and E models in this way.

The overall fit of a given model can be assessed by means of a maximum likelihood chi-squared statistics. In addition, when one model is nested within another, as the AE, CE, and E models are all nested within the full ACE model, the difference in chi-squared statistics between the two models itself has a chi-square distribution with degrees of freedom equal to the number of deleted parameters. If this chi-square statistic is significant, one concludes that the fit of the reduced model is significantly degraded and the deleted parameter is necessary. If the chi-square is not significant, one may choose to infer on the basis of parsimony that the deleted parameter does not account for sufficient variance.

The second step in our model-fitting analyses consisted of combining data from age cohorts to test the significance of age-related differences in the magnitude of genetic and environmental influences on antisaccade error rate. This type of analysis also proceeds by means of fitting nested models. The first estimates parameters separately for each age cohort. The second constrains parameters equal across cohorts. If this significantly degrades the fit of the model, one concludes that the parameters truly differ across cohorts. If the fit of the simpler model is not significantly poorer than that of the unconstrained model, one infers equal parameters on the basis of parsimony.

## Results

Mean error rates indicate clear age-related differences in task performance (Table 2). Eleven-year-olds made errors on 16.5% more trials, on average, than 17-year-olds (45.3% versus 28.8%), which represents a 57% elevation in error rate. The between-group difference in mean performance yields an effect size of 0.81, expressed as a function of the pooled standard deviation. We will present a test of the significance of this age effect later in this section.

Table 2 also presents intraclass correlations for MZ and DZ twins. All such correlations were significant, indicating significant phenotypic resemblance for both MZ and DZ twins within each age cohort. Moreover, MZ correlations were significantly greater

in magnitude than DZ correlations, suggesting that genetic factors are an important influence on antisaccade performance among these subjects, regardless of age.

## Model-Fitting Analyses

Results of model-fitting analyses within each age cohort are presented in Table 3. The ACE model fit the observed data for both age cohorts (both  $p$  values  $> .05$ ). Point estimates of the proportion of variance accounted for by shared environmental factors were small in both cohorts,  $c^2 = .05$  and  $c^2 = .02$  for the younger and older cohorts, respectively. A model containing purely environmental influences (CE) failed to fit the data in the older cohort, reflected by a significant chi-squared value, and could be rejected at the .10 level in the younger cohort. In both cohorts, the E model, which contains purely individual-specific environmental influences (including measurement error), did not fit the observed data ( $\chi^2 > 80$  with 5  $df$  and highly significant in both cases), and has not been included in Table 3. A model containing additive genetic and nonshared environmental influences (AE) fit the observed data well in both cohorts. Moreover, likelihood-ratio tests of the CE model relative to the full model indicated that a model without additive genetic influence could be rejected in both cohorts. On the other hand, the fit of the AE model (i.e., a model without C) relative to the full model was quite adequate, reflected in likelihood-ratio chi-square values of nearly zero in both cases. On the basis of parsimony as well as goodness of fit, then, we concluded that the AE model was the best-fitting model.

Table 4 presents parameter estimates, along with 95% confidence intervals around them, derived from the AE model in both age cohorts separately and combined. These estimate the relative magnitude of the influence on antisaccade performance of additive genes and nonshared environment. Table 4 indicates that additive genes in this model accounted for over half the phenotypic variance (53% to 61%).

## Age-Related Differences and Similarities

We explicitly included mean performance levels in our models. This permitted a test of equality of mean performance across age groups. We assessed similarities and differences between age cohorts in the relative magnitude of genetic influence and in mean performance by means of a sequence of nested models. Our start-

**Table 3.** Results of Model-Fitting Analyses Within Each Age Cohort

Model	$\chi^2$ ( $df$ )	$p$	$\Delta\chi^2$	$\Delta p$
11-year-olds				
ACE	0.48 (3)	.924		
AE	0.56 (4)	.967	0.08	.777
CE	8.33 (4)	.080	7.85	.005
17-year-olds				
ACE	2.38 (3)	.498		
AE	2.39 (4)	.664	0.01	.920
CE	14.27 (4)	.006	11.89	.001

*Note:* A significant  $\chi^2$  indicates poor fit of the overall model.  $\Delta\chi^2$  is the likelihood-ratio test of the difference between the associated model and the ACE model, and  $\Delta p$  is its probability. Because one fewer parameter is estimated in each reduced model than in the full model, the likelihood-ratio test has one degree of freedom. A significant likelihood-ratio chi-square indicates a significantly poorer fit relative to the full model.

**Table 4.** Parameter Estimates and 95% Confidence Intervals Derived From the AE Model

Cohort	a <sup>2</sup>	c <sup>2</sup>	e <sup>2</sup>
11-year-olds	.53 (.44, .62)	—	.47 (.38, .56)
17-year-olds	.61 (.52, .68)	—	.39 (.32, .48)
Common	.57 (.51, .63)	—	.43 (.37, .50)

Note: a<sup>2</sup> represents the proportion of variance accounted for by additive genes and e<sup>2</sup> the proportion of variance accounted for by nonshared environment. The shared environment parameter, c<sup>2</sup>, was set to zero.

ing model allowed mean error rates and parameter estimates to differ between age groups, that is, mean error rates and path coefficients were estimated separately for each age. We tested two different models against this base model. The first alternative model constrained parameter estimates equal across both age groups while allowing means to vary, providing a test of the hypothesis that the magnitude of genetic and environmental influence on task performance was the same for 11- and 17-year-old subjects. A second model required mean performance levels to be equal across age groups while allowing genetic and environmental parameters to vary, providing a test of the hypothesis that mean performance was the same.

The base model and the model constraining genetic and environmental parameters equal across age groups provided acceptable fits to the data ( $\chi^2 = 4.77$  and 10.56, with 14 and 16 *df* for the two models, respectively; both  $p > .80$ ). Constraining parameter estimates equal across younger and older subjects resulted in an acceptable fit: the likelihood-ratio test of the difference between the base model, in which parameters were estimated separately for each cohort, and the reduced model, in which parameters were constrained equal, was not significant despite the size of the sample,  $\Delta\chi^2 = 5.79$ ,  $p = .055$ . The second alternative model, which constrained mean error rates equal across younger and older subjects, was significant by chi-square test,  $\chi^2_{15} = 132.09$ ,  $p < .001$ , and yielded a significantly degraded fit by likelihood-ratio test,  $\Delta\chi^2 = 127.32$ ,  $p < .001$ , thus confirming what is evident from visual inspection of the data: Error rates were significantly less among older subjects.

## Discussion

### Heritability of Task Performance

The present study represents the first attempt to investigate the magnitude of genetic and environmental influence on antisaccade performance. The biometric model-fitting approach used in this study indicated that the genetic influence on antisaccade error rate was significant in both age cohorts. A likelihood-ratio test rejected a model without an additive genetic factor (the CE model) relative to the full ACE model, confirming the importance of genetic factors, whereas a similar test of a model without shared environmental effects (the AE model) indicated that dropping C from the model did not degrade the model's fit. As is often the case in behavior-genetic research (e.g., Plomin & Daniels, 1987), then, the influence of shared environmental effects, those common to members of the same family and differentiating one family from another, was negligible. Rather, the significant environmental influence

on performance consisted of nonshared environmental effects—those experiences that are unique to each individual (in addition to measurement error) and that tend to make one twin different from her cotwin. Thus, the relevant influences on antisaccade error rate in these age groups are additive genes and nonshared environment.

Estimates of heritability were substantial, with greater than half the variance in antisaccade error rate being due to additive genetic influences. Heritability of antisaccade error rate was very similar to the heritability of measures of smooth pursuit tracking performance in male twins from the two MTFS age cohorts (Katsanis, Taylor, Iacono, & Hammer, 2000). The point estimate of heritability was somewhat greater in the older cohort than in the younger cohort, but the difference between cohorts was not significant, and the confidence intervals largely overlapped. The magnitude of the respective influences of genes and nonshared environment on antisaccade performance thus was relatively constant in the two age groups. It cannot be inferred from the present study's design that the relevant genes are the same—a molecular genetic study would ideally address this—only that the magnitude of genetic influence was quite similar.

### Implications for Psychopathology

The findings of the present investigation that direction errors on the antisaccade task, which represent failures of executive control, is heritable, coupled with other findings indicating that schizophrenia patients and their relatives have elevated error rates, are consistent with the notion that poor antisaccade performance may be an endophenotype for schizophrenia, perhaps reflecting frontal lobe impairment. Recent research suggests a possible mechanism underlying this association (Egan et al., 2001; Weinberger et al., 2001). Egan et al. examined the association between a common functional polymorphism of the gene for catechol-O-methyltransferase (COMT, an enzyme that degrades dopamine) and performance on the Wisconsin Card Sorting Test (WCST), a putative measure of prefrontally mediated cognition. These investigators found that perseverative errors on the WCST in schizophrenia patients, their unaffected siblings, and nonpsychiatric controls were related to the COMT genotype such that individuals who were homozygous for the low-activity COMT allele had fewer errors than those who were homozygous for the high-activity allele. The error rate for heterozygotes fell between these two homozygote groups. This pattern was evident in all three subject groups, but the schizophrenia families were more likely to transmit the high-activity allele that is associated with lower levels of available dopamine. In a second study, Egan et al. examined how performance on the two-back version of the *N*-back working memory task was related to COMT genotype while obtaining functional magnetic resonance brain images. The results showed that activity in the dorsolateral prefrontal and cingulate cortices was related to genotype such that homozygotes for the low-activity COMT allele showed the most prefrontal brain activation, with heterozygotes intermediate between this group and those homozygous for high COMT activity. Although the antisaccade task was not used in this particular study, it is likely to involve the dorsolateral prefrontal cortex (Broerse & Crawford, 2001) and antisaccade error has been reported to be correlated with WCST and working memory performance (Crawford et al., 1996; Karoumi et al., 1998; Nieman et al., 2000; Rosse et al., 1993; Tien et al., 1996). Hence, it is intriguing to speculate that the activity of COMT genes may be reflected in the moderately strong genetic influence on antisaccade performance observed in this study.

### *Age-Related Differences in Performance*

Genetic influence on individual differences in performance was significant despite substantial age-related differences in mean error rate (effect size,  $d = .81$ ). That 17-year-olds significantly outperformed 11-year-olds in this study is consistent with the results of previous studies, which have found dramatic age-related improvements in task performance between childhood and late adolescence to young adulthood (Fischer et al., 1997; Fukushima et al., 2000; Klein, 2001; Klein & Foerster, 2001; Munoz et al., 1998).

Because the maturational course of prefrontal cortex appears to be gradual, it is tempting to attribute age-related improvement in performance on "prefrontal" tasks, such as the antisaccade task, to effects of maturation. However, this ignores findings that different abilities involving prefrontal cortex show considerable variation in their time course (Luciana & Nelson, 1998; Welsh, Pennington, & Groisser, 1991). Moreover, maturation of prefrontal cortex has been invoked to explain one-year-old infants' mastery of object permanence (Diamond, 1991) as well as young adults' mastery of the antisaccade task (Fischer et al., 1997). Some aspects of the saccadic system develop quite early, whereas the behavioral control required by the antisaccade task develops considerably later (Klein & Foerster, 2001). It seems imperative to go beyond appeals to maturation to account for such findings.

Several researchers have attempted to account for response inhibition in terms of attentional or working-memory resources (Engle, Conway, Tuholski, & Shisler, 1995; Roberts et al., 1994). For instance, Roberts and colleagues suggested that tasks such as the antisaccade and Stroop tasks require subjects to keep the task instructions activated in working memory and to use that information along with contextual cues to generate an appropriate response (see also Cohen & Servan-Schreiber, 1992). Working memory in the service of the executive control of behavior hence is critical to task performance. On this model, inhibition of actions incompatible with the goal of the antisaccade task occurs by default when working-memory processes are "appropriately activated and maintained" (Roberts et al., 1994, p. 376). MacDonald, Cohen, Stenger, and Carter (2000) have reported data consistent with this interpretation. Subjects in this study performed a modified version of the Stroop task in which a cue instructed them about the exact nature of the upcoming color word, that is, whether it was congruent or incongruent with the ink color. Higher levels of preparatory activity in the dorsolateral prefrontal cortex during a 5-s delay between instruction cue and stimulus onset were associated with smaller interference effects. Preparatory neural activity in the prefrontal cortex may serve as a mechanism of cognitive control of behavior by biasing competition among sensory and motor pathways, sometimes favoring pathways that would ordinarily be weakly activated but that serve important task-related functions (Miller & Cohen, 2001).

It is intriguing in this context that, whereas anticipatory neural activity, in the form of a contingent negative variation (CNV) wave, is greater prior to antisaccade than to prosaccades among normal adult subjects (Brickett, Weinberg, & Davis, 1984; Evdoki-midis, Liakopoulos, Constantinidis, & Papageorgiou, 1996; Everling, Krappmann, & Flohr, 1997), Klein and colleagues found that schizophrenics (Klein, Heinks, Andersen, Berg, & Moritz, 2000) and subjects between 10 and 11 and 15 and 16 years of age (Klein, Berg, & Hafstad, 2000) failed to show a similar differentiation. In fact, the average wave form for subjects 14 years old and younger in the latter study failed even to show a CNV in anticipation of the response cue. A significant difference in anticipatory CNV amplitude between subsequent antisaccades and prosaccades was ob-

served only among 17- to 18-year-olds. Optimal performance thus appears to require appropriate anticipatory activity. Neurons in the supplementary eye field of the prefrontal cortex of rhesus monkeys fire more often before subsequent antisaccades than prosaccades (Schlag-Rey et al., 1997), which may be the source of this anticipatory CNV. In contrast to their failure to show an anticipatory CNV in the context of the antisaccade task, 10- to 11-year-old children do show a readiness potential in anticipation of the appearance of a visual target (Chiarenza, Papakostopoulos, Giordana, & Guareschi-Cazzullo, 1983). Hence, the absence of anticipatory activity appears specific to the antisaccade task.

The models described above, taken together, suggest several possible mechanisms of developmental improvement in performance on the antisaccade task. For instance, it seems likely that, owing to the relative difficulty of the task, one must remind oneself several times of the goal of the task over the course of its many trials. Even young children possess sufficient working-memory capacity to represent the task instructions, which is the principal working-memory demand of the antisaccade task in the model of Roberts et al. (1994). But they may not recognize the necessity of maintaining this information or of reminding themselves of it over the course of the task. Young children's rehearsal strategies for remembering verbal information are relatively crude and ineffective even in free-recall tasks (Ornstein, Naus, & Liberty, 1976). In the case of a task requiring executive control over visual-motor responses, they may not recognize the need for rehearsing the task goal. In general, children and even subjects in early adolescence may have difficulty adopting and maintaining the kind of sustained, focused attention and response set that appears necessary for optimal performance on the antisaccade task. That children benefit somewhat more than adults from a warning tone prior to the response cue's appearance (Fukushima et al., 2000) is consistent with this interpretation, although this must be tempered by the absence of a significant Age Group  $\times$  Condition interaction in this study. Anticipatory set may depend critically upon dopamine activity and dopaminergic tone (Cohen & Servan-Schreiber, 1992; Miller & Cohen, 2001), which in the rhesus monkey appears not to reach adult levels until approximately the age of sexual maturity (Goldman-Rakic & Brown, 1982).

Regardless of the correct interpretation of the course of developmental improvement in performance on the antisaccade task, though, individual differences in performance were considerable; standard deviations in the two cohorts were at least as great as the magnitude of the difference in mean error rate between the groups. The present study indicates that additive genes constitute the major influence on such individual differences.

### *Limitations and Caveats*

It is important to keep in mind that the biometric approach rests on several assumptions. The model represented in Figure 2 assumes that genetic and environmental influences are independent; there are no paths in the figure depicting gene-environment interaction or correlation. This assumption is largely pragmatic, as comparisons of MZ and DZ twins are not particularly effective at detecting correlations or interactions between genes and environment (Plomin, DeFries, & Loehlin, 1977). Failure to meet this assumption has an indeterminate effect on heritability estimates. The biometric model also rests on two additional assumptions. One is that the parents of the twins in this sample did not select each other as mates based on the phenotype in question. Such assortative mating would cause the correlation for additive genetic effects between DZ twins to deviate from .5, the value assumed by the model (see

Figure 2). Failing to meet this assumption would lead us to underestimate the magnitude of genetic influence on antisaccade performance. The other major assumption is that shared environment contributes equally to the phenotypic similarity of MZ and DZ twins, termed the equal environments assumption. Failing to meet this assumption would lead one to overestimate heritability. However, at least with respect to personality and cognitive abilities, behavioral genetic research tends to support the validity of this assumption (see Plomin, DeFries, McClearn, & Rutter, 1997).

The number of trials used in the present study is consistent with procedures used in the schizophrenia literature, but is somewhat limited from the perspective of those studying ocular-motor control per se. Nevertheless, estimates of the reliability of our percent error measure were quite good, with Cronbach's alpha greater than .80. These values yield a correlation between our percent error measure and true error rate (Nunnally, 1967) of approximately .90, indicating that our measure is highly likely to have yielded a close approximation to subjects' true level of performance. To the degree that our measure is imperfect, however, this would place an upper bound on heritability estimates derived from it.

The present study examined a single measure of performance, one that has sparked interest as a candidate endophenotype for schizophrenia. Researchers interested in ocular-motor control typically assess several measures of performance, including latency on correct and error trials as well as the percentage of spontaneous error corrections (although only the former loaded on the same principal component as error rate in Klein's, 2001, analysis of various measures of performance among subjects spanning the ages of subjects in the present study). Several investigators have found that schizophrenic patients have longer latency antisaccades than controls (Crawford et al., 1998; Curtis, Calkins, Grove, et al., 2001; Fukushima et al., 1990; Karoumi et al., 1998; McDowell et al., 1999; Sereno & Holzman, 1995). However, this has not always been found (Clementz et al., 1994), and one report indicated that latency did not correlate with error rate among those with schizophrenia (Crawford et al., 1996). Moreover, error rate and latency might reflect different developmental processes (Klein & Foerster, 2001). However, it might be of interest in future research to investigate the heritability of other measures of antisaccade performance and to determine whether common genes or

environmental influences account for the patterns of correlations among them.

In the present study, a prosaccade task immediately preceded the antisaccade task. This presumably primed subjects to make reflexive saccades on the antisaccade task and thus to make more frequent errors. Indeed, Roberts et al. (1994) found that subjects made reflexive looking errors on an antisaccade task approximately 50% more often if they had just completed a prosaccade task than if the order of tasks were reversed. That subjects would have been primed to make such errors in our study is likely to account, in part, for the fact that our error rates tended to be somewhat greater than those reported in other studies (e.g., Fukushima et al., 2000; Klein & Foerster, 2001). In fact, the ratio of mean error rates in our study to those reported by Klein and Foerster are very similar in the two age groups, suggesting that subjects in both age groups were affected to a similar degree. Nevertheless, our design does not allow us specifically to address whether younger subjects were more susceptible to any carryover effects from the prosaccade task. On the other hand, priming subjects in this way clearly imposes a greater load on participants' capacity for inhibitory control of their ocular-motor behavior, a desirable feature of our design and one that undoubtedly increased variability in performance, which is advantageous for the biometric analyses at the heart of the present investigation.

A significant strength of the present study is its use of a population-based sample. Nevertheless, although the sample represents the population of the state of Minnesota at the time study participants were born, the overwhelming majority was Caucasian. Results may not generalize to other racial groups or to other age groups. Furthermore, the present findings may be specific to female youth, although there is little reason based on the existing literature to assume that gender moderates antisaccade performance. In addition, further research is required to assess the usefulness of antisaccade error rate as an endophenotype among preadolescent children and to describe the developmental course of this endophenotype. Despite these shortcomings, the present study furthers the search for endophenotypes associated with genetic risk for psychopathology by establishing in a large and representative sample of adolescent females that the magnitude of genetic influence on antisaccade performance is substantial.

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