

Familial Aggregation of Eye-Tracking Endophenotypes in Families of Schizophrenic Patients

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Background: Abnormal smooth pursuit eye movements (SPEMs) are some of the most reproducible biological changes associated with the susceptibility for schizophrenia. Recent studies have suggested that deficit in predictive pursuit, a specific component of the SPEMs, marks schizophrenia susceptibility.

Objective: To test whether predictive pursuit contains less extraneous noise and may be under more direct genetic control than the traditional measure of overall pursuit performance using maintenance pursuit gain.

Design: Familial aggregation estimation of the predictive pursuit measure and the traditional maintenance pursuit measure in sibling pairs from families of schizophrenic patients.

Setting: Outpatient clinics.

Participants: Patients with schizophrenia and their full siblings were recruited, provided that at least 1 sibling pair could be formed per family. Ninety-two siblings were recruited into the study. They formed 70 sibling pairs. Ninety healthy control subjects were also recruited us-

ing targeted local community advertisements based on patients' county of residence, aiming to capture the basic demographics of the regions from which the patients were recruited.

Main Outcome Measures: Familial correlations and heritability estimates of 2 SPEM measures: maintenance pursuit gain and predictive pursuit gain.

Results: The sibling intraclass correlation coefficient of the predictive pursuit gain ($r=0.45-0.48$) was significantly higher than that of maintenance pursuit gain ($r=0.02-0.20$) ($P=.005-.007$). Variance component analysis suggested a high genetic loading for predictive pursuit (heritability= 0.90 , $SE=0.22$; $P<.001$) but relatively low heritability in the traditional maintenance pursuit measure (heritability= 0.27 , $SE=0.21$; $P=.08$).

Conclusion: These results suggest that predictive pursuit may index stronger genetic effect and may be better suited for genetic studies than the traditional SPEM measure of maintenance pursuit gain.

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DEFINING A VALID PHENOTYPE is an essential step for genetic inquiry. Researchers have been studying how abnormalities in smooth pursuit eye movements (SPEMs) can be used as endophenotype in genetic studies of schizophrenia. The rationale for following an endophenotypic approach in search of genes of multifactorial illnesses is that the path from the hypothesized vulnerability gene loci to the final clinical manifestation may be complex. Carefully chosen endophenotypes may measure neurobiological deficits that are more upstream than the clinical syndrome, thus allowing examination of the effects of individual genes, or small cluster of genes, that contribute to the clinical syndrome.¹ An important theoretical implication of the endophenotype construct is that a phenotype can be refined step by step based on its known neurobiological pathways. This research approach aims to eventually yield more specific phenotypes that capture the core neurobio-

logical process under more direct genetic control. Here we tested this approach as related to the SPEM endophenotypes.

A rich body of work from several laboratories demonstrates that abnormality in SPEMs consistently occurs in a proportion of patients with schizophrenia, that this abnormality is not an artifact of disease-related secondary factors such as medications, and that it is observed in at-risk individuals.²⁻⁷ Traditional approaches to assess the SPEM endophenotypes use measures such as maintenance pursuit gain (also called closed-loop gain), which is the ratio of eye speed divided by the target speed, averaged over a time when the subject is maintaining pursuit. This and other measures of overall pursuit performance have been the major focus of genetic studies that use SPEM endophenotype, including initial success in linkage to chromosome 6p loci in 2 independent samples.^{8,9} However, maintenance pursuit represents a final output of a highly complex and widely distributed neu-

ronal system.¹⁰ For a physiologic measure to be a useful endophenotype in genetic studies, it must represent an elementary biological phenomenon.^{1,11} Recent advances in oculomotor neurophysiology have resulted in the development of methods for examining individual components of the pursuit system.^{12,13}

One of the components of the system, predictive pursuit, is of special interest in schizophrenia. A SPEM can be conceptualized as a behavioral output driven by retinal and extraretinal motion signals. Retinal motion information is derived from the immediate perception of movement of a target image on the retina. However, the accuracy of pursuit eye movement cannot solely depend on immediate retinal motion because of an approximate 120-millisecond system delay, which would have rendered the eyes lagging behind a moving target. Healthy primates maintain pursuit by using mostly predictive pursuit, which is based on the internal representation of the target motion, or so-called extraretinal motion signals. Coding of extraretinal motion signals can be directly observed in monkeys by temporarily eliminating retinal motion during SPEMs using target masking^{12,14} or image stabilization methods.^{12,15} Under these conditions, some middle temporal cortex neurons “turn off,” whereas other neurons in medial superior temporal cortex continue to fire while the eyes pursue the target in the absence of retinal input.^{12,16} This suggests the anatomic specificity of predictive pursuit. Pursuit-related neurons in posterior parietal cortex,^{17,18} supplementary eye field, and frontal eye field have also been demonstrated for their role in extraretinal motion signal processing.¹⁹⁻²¹ Recent functional magnetic resonance imaging studies in humans suggest similar anatomic mechanisms in processing extraretinal motion.^{22,23}

Earlier we demonstrated that abnormality in the predictive pursuit eye movements identifies individuals at risk of schizophrenia, and this measure has a better predictive accuracy compared with traditional measures of overall performance.²⁴ In the current study, we evaluated familial aggregation of both the predictive pursuit and the maintenance pursuit measures using a sibling-pair design. We hypothesized that the predictive pursuit measure is relatively more elementary with less extraneous biological noise and that this measure would be associated with a higher genetic signal (heritability) than the traditional maintenance pursuit measure.

METHODS

SUBJECTS

All subjects gave written informed consent in accordance with University of Maryland Institutional Review Board guidelines. An additional evaluation of the capacity to sign consent forms was administered to patients to assess each subject's understanding of the planned experiments.²⁵ Patients were recruited from the outpatient clinics of the Maryland Psychiatric Research Center. The Structured Clinical Interview for DSM-IV²⁶ was administered to all subjects. Nonpatient family members and healthy controls were also screened using the Structured Interview for DSM-IV Personality Disorders.²⁷ Family members who had schizophrenia spectrum personality disorders were included; family members without schizophrenia

spectrum personality disorders but with other personality disorders were excluded. Healthy controls were excluded if there was a family history of psychotic illness based on Family History Research Diagnostic Criteria²⁸ considering first-, second-, and third-degree relatives. Two master-level research clinicians performed the initial interviews, followed by a consensus diagnosis meeting chaired by a research psychiatrist. The interrater reliabilities among the clinical interviewers were above 0.80 (κ) on these instruments. Probands were individuals with DSM-IV schizophrenia or Research Diagnostic Criteria²⁹ schizoaffective disorder (mainly schizophrenia) who were medicated and clinically stable. This group is referred to as the *schizophrenia group* henceforth. Clinical stability is defined as no change in antipsychotic medications for 4 weeks or more and no exacerbation of psychotic symptoms as judged by the treating clinician. After an eligible proband was identified, we determined whether there was at least 1 full sibling of the proband available. A proband and 1 or more of the age-eligible siblings were recruited if at least 1 sibling pair could be formed from each family. Full siblings whose ages ranged from 18 to 65 years were recruited from the families of the probands through letters and telephone contacts. Probands and their siblings with other Axis I diagnoses were excluded, with the exception of individuals who had a history of a single episode of depression in their lifetimes and were not taking antidepressants for 6 months or more before testing. All participants of our family studies were included if at least 2 siblings of a family fulfilled these criteria and had completed the target-masking pursuit eye movement task. Approximately 40% of the families have been described in a previous report.³⁰

In addition, we identified a separate sample of healthy individuals to serve as a control group. Measurements obtained from these subjects were used to estimate normative values in the overall population for the sibling recurrence risk ratio calculations. The healthy control subjects were recruited using targeted local community daily or weekly newspaper advertisements based on patients' county of residence. Thus, comparison subjects are drawn from the same communities as our patient group, aiming to capture the basic demographics of the regions from which the patients were recruited. Control subjects were without Axis I or Axis II diagnoses based on the Structured Clinical Interview for DSM-IV and the Structured Interview for DSM-IV Personality Disorders and without a family history of psychotic illness based on Family History Research Diagnostic Criteria.

EYE MOVEMENT LABORATORY PROCEDURES

Scoring of the eye movement data was performed without knowledge of diagnosis and family relationship. Eye-tracking methods are described in detail elsewhere^{30,31} and only briefly described here. An infrared method (model 210; Applied Sciences Research, Bedford, Mass) was used to monitor eye position. Subjects were asked to follow a moving target (constant speed of 18.7°/s; amplitude $\pm 12^\circ$ across the computer screen) with their eyes while their head was stabilized on a chin rest. Twenty-four trials were administered, each consisting of 1.5 to 2.5 cycles of back-and-forth target motion. Each trial included a brief mask of 500 milliseconds in which the target was concealed. The subjects were told that the target would become briefly invisible but would keep moving and were instructed to continue to follow the target. The mask occurred at the change in ramp direction (**Figure**), as well as during the ramp. Under the former condition, subjects begin pursuit from zero velocity after changing direction in the absence of target motion information (ie, completely based on predictive or extraretinal information). Predictive pursuit gain is the peak predictive pursuit velocity in the direction of the expected ramp within the 500-millisecond mask that occurred at the beginning of the ramp, divided by

the expected target speed. Maintenance pursuit gain was obtained from mask-free sections of smooth pursuit (for more details see Thaker et al³¹). Data from the mask that occurred during the ramp were not included because these data require scorers' judgment, and with the change in scorers we were not able to establish interrater reliabilities across scorers over time. Scoring of the peak predictive pursuit measures and the maintenance gain measures was fully automated.

ANALYSIS

We evaluated the degree of familial aggregation of the 2 pursuit eye movement traits using 2 quantitative approaches, one based on the sibling intraclass correlation and the other based on variance components analysis. The within-sibling intraclass correlation coefficients (ICCs) were computed using the familial correlation (FCOR) program in SAGE (Statistical Analysis for Genetic Epidemiology)³² with equal weights assigned to pedigrees. The ICC values greater than 0 indicate that variation within siblings is lower than variation between unrelated individuals. If one assumes that the contribution of shared environmental factors to within-sibship variability is negligible, then 2 times the value of the sibling correlation provides an estimate of the heritability.³³ Before analysis, we used a standard linear regression model to adjust the effects of age and sex on the pursuit traits. To test for the magnitude of difference between the FCOR ICCs of the 2 traits, we used techniques described by Donner and Zou³⁴ for comparing ICCs on measures that are correlated within the same patients. The ICCs were transformed using a modification of the Fisher z -transformation that takes account of the multiple (and varying) number of observations per sibship. It allows ready calculation of the variance of each z -transformed ICC, as well as estimating the covariance of the 2 z -transformed ICCs from the within-sibship correlation of the 2 traits. The 95% confidence intervals (CIs) on the z -transformed ICCs were calculated as $[z(\text{ICC}) \pm 1.96] \times \text{SE}[z(\text{ICC})]$. Back-transformation on the upper and lower bounds of these intervals was then used to obtain a CI for the ICC.

To supplement these analyses, we estimated the heritability of the 2 smooth pursuit trait measures using a variance components analysis as implemented in the SOLAR (Sequential Oligogenic Linkage Analysis Routines) software program.³⁵ The total trait variance was partitioned into 2 components: a genetic component due to additive polygenic effects and a random environmental component due to factors that are uncorrelated among siblings. This method applies maximum likelihood estimation to a mixed-effects model that incorporates fixed effects for known covariates and variance components for genetic and random environmental effects.³⁵ When estimating the additive genetic effects, we simultaneously estimated the (fixed) effects of age and sex on phenotypic variability. The heritability estimate from this model thus reflects the contribution of additive genetic factors to the residual trait variation. After obtaining the heritability estimates of the pursuit eye movement traits, we tested for equality of the heritability estimates of the 2 traits by first evaluating the likelihood of a full model in which we estimated the heritability estimate on trait 1 and then evaluating the likelihood of a nested model in which the heritability of trait 1 was constrained to be equal to the upper (or lower) boundary of the 95% CI obtained for trait 2. The difference between the likelihoods was evaluated by the likelihood ratio test.

In addition to evaluating familial aggregation of the quantitatively distributed eye-tracking measures, we also defined individuals to be affected or unaffected based on predefined thresholds of the eye-tracking measurements and then computed the sibling recurrence risk ratio associated with each threshold value as the prevalence of abnormal pursuit gain in siblings of affected probands di-

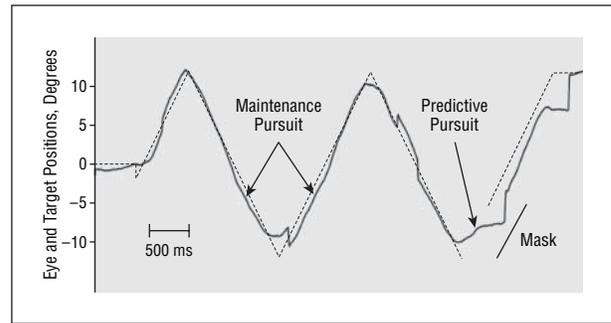


Figure. An example of maintenance and predictive smooth pursuit. Predictive pursuit was measured using a target mask manipulation. Dashed line indicates target eye traces; solid line, actual eye traces. In this trial, a mask of 500-millisecond duration occurs in the beginning of the cycle. The subject's eyes turn and pursue for approximately 250 milliseconds without immediate target motion information.

vided by the prevalence of abnormal pursuit gain in the entire population. For these analyses, the pursuit gain measures were standardized using the means and standard deviations of the healthy control subjects and then the standardized measures were expressed as z scores. A sibling was designated as affected in the particular pursuit measure if his or her z score of that pursuit measure was below a specified cutoff score.³⁶ A series of cutoff scores were empirically chosen: 1.00, 1.25, 1.50, 1.75, and 2.00 SDs below the population mean. To compare the magnitude of differences of the risk ratios of the 2 traits, we used the generalized estimating equation (GEE) method to account for correlations of the 2 traits, because they were observations from the same subject. The GEE logistic model for incomplete repeated measures (PROC GENMOD in SAS, version 6.14; SAS Institute Inc, Cary, NC) was used to test whether the recurrence risk for siblings of probands affected by one trait was significantly different from the recurrence risk for siblings of probands affected by another trait. Finally, we parametrically compared the pursuit gain measures between siblings of affected probands and siblings of unaffected probands as defined by each cutoff score. Group effects of the dependent measures were compared using a mixed-model analysis of variance (PROC MIXED in SAS, version 6.14) to account for the unbalanced design as siblings are correlated within the same family.

RESULTS

A total of 92 siblings from families of schizophrenic patients and 90 unrelated healthy control subjects participated in the study. The siblings were from 39 sibships and formed a total of 70 sibling pairs. Among the sibships, 31 (79%) had 2 members (forming 1 pair per sibship), 3 (8%) had 3 members (3 pairs per sibship), and 5 (13%) had 4 members (6 pairs per sibship). Summary characteristics of the study subjects are given in **Table 1**. Post hoc tests showed that patients had reduced maintenance pursuit gain compared with nonschizophrenic siblings ($P=.001$; effect size in Cohen $d=0.73$) and healthy controls ($P<.001$; $d=0.95$). Nonschizophrenic siblings did not significantly differ from healthy controls ($P=.60$; $d=0.18$). For predictive pursuit gain, patients had reduced predictive gain compared with nonschizophrenic siblings ($P=.05$; $d=0.48$) and healthy controls ($P<.001$; $d=0.78$). Nonschizophrenic siblings did not differ from healthy controls in this sample ($P=.19$; $d=0.33$).

Sibling-sibling correlations for maintenance pursuit gain and predictive pursuit gain were 0.03 (95% CI,

Table 1. Demographics and Pursuit Gain Measures

Variable	Affected Siblings (n = 40)	Unaffected Siblings (n = 52)	Healthy Controls (n = 90)	χ^2 or $F_{2,33}$ Value	P Value
Sex, F:M	15:25	30:22	40:50	4.07*	.13
Ethnicity, B:W, %	11:27	12:35	25:61	0.21*	.90
Age, mean \pm SD, y	39.3 \pm 10.8	39.7 \pm 11.0	39.3 \pm 13.5	0.02*	.98
Maintenance pursuit gain, mean \pm SD	0.62 \pm 0.21	0.76 \pm 0.17	0.79 \pm 0.16	11.53†	<.001
Predictive pursuit gain, mean \pm SD	0.44 \pm 0.22	0.53 \pm 0.18	0.59 \pm 0.18	7.36†	.002

Abbreviations: B, black; W, white.

*Pearson χ^2 test.

†F value based on mixed-model analysis of variance.

Table 2. Qualitative and Parametric Comparisons of Pursuit Gain Measures

Cutoff z Score	Qualitative Comparisons				Parametric Comparisons					
	Schizophrenic Probands*	Siblings*	Healthy Controls*	Sibling Recurrence Risk Ratio	Siblings of Affected Probands		Siblings of Unaffected Probands		F Value	P Value
					No.	Mean (SD)†	No.	Mean (SD)†		
Maintenance Pursuit Gain										
-1.00	22/40 (55)	15/33 (45)	15/90 (17)	2.7	33	0.72 (0.18)	20	0.82 (0.18)	5.34	.02
-1.25	18/40 (45)	8/29 (28)	11/90 (12)	2.3	29	0.72 (0.18)	24	0.80 (0.15)	2.98	.09
-1.50	13/40 (32)	2/23 (9)	8/90 (9)	1.0	23	0.71 (0.17)	30	0.79 (0.16)	3.41	.07
-1.75	11/40 (28)	2/18 (11)	4/90 (4)	2.5	18	0.68 (0.17)	35	0.80 (0.16)	6.20	.02
-2.00	9/40 (22)	2/14 (14)	4/90 (4)	3.2	14	0.67 (0.19)	39	0.79 (0.16)	5.01	.03
Predictive Pursuit Gain										
-1.00	17/39 (42)	9/20 (45)	12/90 (13)	3.4	20	0.42 (0.14)	33	0.59 (0.18)	11.67	.001
-1.25	15/39 (38)	8/17 (47)	7/90 (8)	6.1	17	0.41 (0.14)	36	0.58 (0.18)	12.05	.001
-1.50	13/39 (32)	6/15 (40)	2/90 (2)	18.0	15	0.39 (0.14)	38	0.58 (0.18)	12.53	.001
-1.75	11/39 (28)	3/14 (21)	2/90 (2)	9.8	14	0.39 (0.15)	39	0.57 (0.18)	12.55	.001
-2.00	7/39 (19)	2/9 (22)	2/90 (2)	10.0	9	0.33 (0.14)	44	0.56 (0.17)	15.58	<.001

*Number of subjects designated as affected under this cutoff value of the z scores. Percentages are in parentheses. Note that the denominators for schizophrenic patient probands and healthy controls are always the same under each cut score, but the denominators for the siblings change based on different cut scores. For example, in the first row, at a cutoff score of -1, 22 probands (55%) were classified as having abnormal maintenance pursuit gain. There were 33 siblings who were from these 22 families, and 45% of the 33 siblings were abnormal. The sibling recurrence risk at this cutoff was the ratio of 45% abnormal in siblings divided by 17% abnormal in healthy controls.

†Mean (SD) of pursuit gains.

-0.21 to 0.29) and 0.45 (95% CI, 0.21 to 0.65), respectively ($z=2.70$; $P=.007$; for difference in ICC). Adjusted for age and sex, the values were 0.02 (95% CI, -0.21 to 0.28) and 0.45 (95% CI, 0.22 to 0.65), respectively ($z=2.79$; $P=.005$), suggesting a significant difference in familial correlations of the 2 traits. To make the results directly comparable to previous reports (eg, Ettinger et al⁷), we analyzed the correlations by restricting the sibships to discordant pairs. Here the correlation coefficient for maintenance pursuit gain was 0.20 (95% CI, -0.12 to 0.49; $P=.10$); for predictive pursuit gain the coefficient was 0.48 (95% CI, 0.20 to 0.69; $P<.001$). Assuming no shared environmental influences, heritability can be estimated at 0.06 (unadjusted), 0.04 (age and sex adjusted), or 0.40 (discordant pair) for maintenance pursuit gain and 0.90 (unadjusted), 0.90 (age and sex adjusted), or 0.96 (discordant pair) for predictive pursuit gain.

In variance components analysis, age was significantly associated with maintenance pursuit gain ($P=.05$) but not

predictive pursuit gain. The estimated mean \pm SE heritability for maintenance pursuit gain, after accounting for age, was 0.27 ± 0.21 ($P=.08$). The heritability of predictive pursuit gain was 0.90 ± 0.22 ($P<.001$). A likelihood ratio test showed that the magnitude of the heritability estimate for predictive gain was statistically higher than that of the maintenance pursuit gain ($\chi^2_1=5.03$, 2-tailed $P=.02$).

The estimated sibling recurrence risks for both measures are given in **Table 2**. The risk ratios for predictive pursuit gain were higher than that of the maintenance pursuit gain across all cut scores chosen (Table 2). The GEE logistic regression showed that the sibling recurrent risk ratios of the 2 traits were significantly different at a cutoff score of $z=-1.5$ ($\chi^2_1=8.12$; 2-tailed $P=.004$), which remained significant after a Bonferroni correction for 5 comparisons. The risk ratios were not statistically significant at other cutoff scores ($P=.08-.73$), possibly because of the smaller number of subjects as the cutoff score became more stringent. When siblings were divided based on probands' affected or unaffected status in a particular measure (Table 2), maintenance pur-

suit gain in siblings of affected probands was marginally smaller than that in siblings of unaffected probands ($P = .02-.09$); none was significant after a Bonferroni correction (of 5 comparisons). In comparison, predictive pursuit gain in siblings of affected probands was consistently smaller than that in siblings of unaffected probands across all cut scores (all $P < .001$); all remained statistically significant after a Bonferroni correction.

COMMENT

The results suggest a strong familial aggregation in the predictive pursuit measure based on all 3 methods we used to compute familiarity of traits. In addition, there was a general agreement between quantitative and qualitative analyses, all of which show a significantly higher familiarity of the predictive pursuit measure compared with the maintenance pursuit measure. The sibling-pair correlation coefficients (0.02-0.20) and heritability estimate (0.27) for the traditional maintenance pursuit gain were significantly smaller than the correlation coefficients (0.45-0.48) and heritability estimates (0.90) for predictive pursuit gain. This difference between the 2 measures is remarkable considering that maintenance and predictive gains were generated from the same eye-tracking record. Results from the current study demonstrate that the use of physiologically more specific eye-tracking measure substantially increased the heritability estimate of the eye-tracking phenotype by 2- to 3-fold.

The heritability estimates for the maintenance gain measure in the current study are within the range of previously reported values. Ettinger et al⁷ reported sibling-sibling correlations in 24 pairs discordant for schizophrenia: 5 of the 6 measures during pursuit maintenance (pursuit gain and saccades in 2 target velocities) showed insignificant correlations (all $r < 0.29$) and 1 (gain at 10°/s target speed) showed a significant correlation ($r = 0.44$). Katsanis et al³⁷ performed a twin study in 64 monozygotic and 48 dizygotic healthy twins using a maintenance pursuit task. The correlation coefficients associated with various pursuit gain and saccadic measures in dizygotic twins were in the range of 0.1 to 0.3. Note that dizygotic twins share genetic factors similar to full siblings but may have a higher level of shared environmental factors. In this context, we note that a number of other specific component measures are shown to be abnormal in some schizophrenia patients and in some of their family members. These component measures include velocity discrimination,⁵ pursuit initiation,^{5,38,39} catch-up saccades,^{40,41} anticipatory saccades,^{41,42} and leading saccades.⁶ It would be important to take a similar approach to test whether these proposed specific components also showed enhanced heritability compared with those more global performance measures.

Neurophysiologic studies in monkeys, as well as results from psychophysical studies of the smooth pursuit system in humans, show that smooth pursuit eye movements are maintained by both retinal (perceptual) and extraretinal (predictive) motion-processing mechanisms.^{12,13} We previously modeled the relative contributions of retinal motion component and predictive com-

ponent to smooth pursuit maintenance.³¹ The results indicated that the smooth pursuit maintenance in healthy subjects depends primarily on the predictive mechanism, whereas relatives of schizophrenic patients showed deficits in this component of the pursuit response, suggesting that pursuit deficit associated with schizophrenia susceptibility may be specific to the predictive component. Based on these data, we argued that such a specific or elementary deficit is more likely to be proximate to putative genetic effects than a measure of overall performance such as maintenance pursuit gain. The results from the current study showing improved sibling-pair correlation and heritability associated with the predictive pursuit gain support the hypothesis. The ancillary qualitative analyses also showed that abnormal predictive pursuit has higher sibling recurrence risk than abnormal maintenance pursuit across all cut scores examined in these sibships. Note however that the number of affected siblings became very small as cutoff scores became stringent. A larger sample is required to obtain a more stable estimate of sibling recurrence risk ratios on the pursuit measures.

Previous studies have reported that both maintenance pursuit gain and predictive pursuit gain were abnormal in schizophrenic patients and in their nonschizophrenic relatives, suggesting that both measures may be marking genetic risk for schizophrenia.^{4,30,43,44} In the present sample, although maintenance pursuit gain showed a larger patient-control effect size (0.95) compared with the predictive pursuit gain (0.78), the heritability estimates of the latter was much higher. This suggests that the bigger effect sizes of a phenotype derived from patient-control comparisons do not necessarily translate into higher estimates of heritability. The robust patient-control differences in a broader phenotype may often represent additive effects of disease-related secondary factors (eg, medications) or other genetic and/or environmental factors. By dissecting the smooth pursuit system and isolating the core neurobiological deficit associated with the disease, one is able to obtain better heritability estimates. We should also emphasize that the sibling correlation represents an upper limit of the heritability estimates because siblings share their early environment.⁴⁵ Shared environmental factors, if they affect the measure of interest, can artificially inflate the heritability estimates. On the other hand, nonshared environmental factors, such as medications or other disease-related factors present only in the proband, can artificially deflate the heritability estimates. Ultimately, the usefulness of an endophenotype in identifying disease genes will have to be proven in genetic linkage or association studies. In this context, we note that our preliminary examination of associations between eye-tracking deficits and Val^{108/158} Met polymorphism in the catechol O-methyltransferase gene⁴⁶ validates the use of predictive pursuit measure.

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