

Successful multi-site measurement of antisaccade performance deficits in schizophrenia

Allen D. Radant^{a,b,*}, Dorcas J. Dobie^{a,b}, Monica E. Calkins^c, Ann Olincy^d, David L. Braff^{e,1}, Kristin S. Cadenhead^e, Robert Freedman^d, Michael F. Green^f, Tiffany A. Greenwood^e, Raquel E. Gur^c, Gregory A. Light^e, Sean P. Meichle^{a,b}, Jim Mintz^f, Keith H. Nuechterlein^f, Nicholas J. Schork^e, Larry J. Seidman^g, Larry J. Siever^h, Jeremy M. Silverman^h, William S. Stone^g, Neal R. Swerdlow^e, Ming T. Tsuang^{e,i,j}, Bruce I. Turetsky^c, Debby W. Tsuang^{a,b}

^a Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington, United States

^b The Department of Veteran Affairs VISN-20 Mental Illness Research, Education, and Clinical Center; Seattle, Washington, United States

^c Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, United States

^d Department of Psychiatry, University of Colorado Health Sciences Center, Denver, Colorado, United States

^e Department of Psychiatry, University of California San Diego, La Jolla, California, United States

^f Department of Psychiatry and Biobehavioral Sciences, Geffen School of Medicine at University of California Los Angeles, Los Angeles, California, United States

^g Massachusetts Mental Health Center, Public Psychiatry Division of the Beth Israel Deaconess Medical Center; Harvard Medical School Department of Psychiatry, Boston, Massachusetts, United States

^h Department of Psychiatry, The Mount Sinai School of Medicine, New York, New York, United States

ⁱ Harvard Medical School Department of Psychiatry at Massachusetts Mental Health Center, Boston, Massachusetts, United States

^j Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, Massachusetts, United States

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Abstract

The antisaccade task is a promising schizophrenia endophenotype; it is stable over time and reflects neurophysiological deficits present in both schizophrenia subjects and their first-degree relatives. Meaningful genetic research requires large sample sizes that are best ascertained using multi-site study designs. To establish the criterion validity of the antisaccade task in a multi-site design, the Consortium on the Genetics of Schizophrenia (COGS) examined whether seven sites could detect previously reported antisaccade deficits in schizophrenia subjects. Investigators presented 3 blocks of 20 antisaccade stimuli to 143 schizophrenia subjects and 195 comparison subjects. Frequent collaborator communication, standardized training, and ongoing quality assurance optimized testing uniformity. Data were discarded from only 1.2% of subjects due to poor quality, reflecting the high fidelity of data collection and scoring methods. All sites detected a significant difference in the proportion of correct antisaccades between schizophrenia and comparison subjects ($p < .02$ at all sites); group differences in gain and latency were less robust. Regression analyses to adjust for the effects of group, site, age, gender, smoking, and parental education on the proportion of correct antisaccades revealed a significant effect of group, site, and age but no effect of gender, smoking, or parental education, and no

* Corresponding author. Current postal address: VAPSHCS S-116 MHC, 1660 S. Columbian Way, Seattle, WA 98108, United States. Tel.: +1 206 277 1761; fax: +1 206 277 4472.

E-mail addresses: aradant@u.washington.edu (A.D. Radant), dbraff@ucsd.edu (D.L. Braff).

¹ For general inquiries regarding the Consortium on the Genetics of Schizophrenia (COGS).

group-by-site interactions. Intraclass correlations between proportion of correct antisaccades across the blocks of stimuli ranged from 0.87 to 0.93, demonstrating good within-session reliability at sites. These results confirm previous findings of antisaccade deficits in schizophrenia subjects and support the use of the antisaccade task as a potential schizophrenia endophenotype in multi-site genetic studies.

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1. Introduction

Genetic factors play an important role in the development of schizophrenia (Braff and Freedman, 2002; Gottesman, 1994; Harrison and Weinberger, 2005; Tsuang et al., 2001; Waterworth et al., 2002). However, phenocopies, genetic heterogeneity, diagnostic ambiguities, and polygenic inheritance complicate the genetic analysis of this illness (Mowry and Nancarrow, 2001). Past studies suggest that heritable biobehavioral traits known as endophenotypes may offer a useful strategy for avoiding the pitfalls of imprecise clinical phenotypes and may better facilitate the genetic dissection of schizophrenia (Braff and Freedman, 2002; Braff and Light, 2005; Gottesman and Gould, 2003). In this study, the Consortium on the Genetics of Schizophrenia (COGS) uses a quantitative genetic analytic approach that examines precise schizophrenia-related endophenotypes rather than the relatively imprecise clinical diagnosis of schizophrenia.

To be effective in genetic research, endophenotypes must be related to the disease of interest, stable, heritable, and dependably obtained at multiple sites (Berrettini, 2005; Gottesman and Gould, 2003). The antisaccade task, which assesses the ability of the oculomotor system to inhibit prepotent responses, is a promising schizophrenia-related endophenotype (Kumari et al., 2005; Louchart-de la Chapelle et al., 2005; Malone and Iacono, 2002; McDowell et al., 2001; Myles-Worsley et al., 1999). Since the initial report of Fukushima and colleagues (1988), over 40 studies have demonstrated that schizophrenia subjects perform more poorly than community comparison subjects on the antisaccade task. The stability of the antisaccade error rate is supported by several studies reporting good test–retest reliability (Calkins et al., 2003; Ettinger et al., 2003; Gooding et al., 2004). Furthermore, antisaccade abnormalities appear to be related to dysfunction in the dorsolateral prefrontal cortex and related neural circuitry, brain areas that are also disrupted in schizophrenia (Bunney and Bunney, 2000; Hutton and Ettinger, 2006; Matsuda et al., 2004). This provides indirect but compelling evidence

for an association between antisaccade abnormalities and schizophrenia.

Robust heritability is the most basic characteristic required for a useful endophenotype in clinical neuropsychiatric disorders such as schizophrenia. In recent monozygotic and dizygotic twin studies, Malone and Iacono (2002) reported antisaccade heritability of 0.57, suggesting significant genetic contributions to this trait. The heritability of this endophenotype is further supported by findings that non-psychotic first-degree relatives of schizophrenia patients also are impaired in antisaccade error rate (Calkins et al., 2004). Increased antisaccade error rates have also been observed in patients with non-dementing neuropsychiatric illnesses such as mood disorders (Curtis et al., 2001; Gooding and Tallent, 2001; Katsanis et al., 1997), ADHD (O'Driscoll et al., 2005), and OCD (Rosenberg et al., 1997), but negative findings have also been reported (Crawford et al., 1995; Maruff et al., 1999; McDowell and Clementz, 1997). Hutton and Ettinger (2006) conclude that the literature is “consistent with the hypothesis that antisaccade errors are increased in neuropsychiatric disorders that implicate frontal lobe dysfunction.”

Although rarely accomplished, replication of psychophysiological findings at multiple sites using uniform methodology is crucially important in psychiatric neuroscience. Detection of schizophrenia-comparison subject differences at multiple sites implies that a measure is valid and provides important justification for combining data from multiple sites. The feasibility of multi-site studies of antisaccade performance remains uncertain. Most studies of antisaccade performance in schizophrenia have evaluated subjects from a single site and employed a variety of diagnostic strategies and task parameters (Broerse et al., 2001; Calkins et al., 2004; Levy et al., 2004).

As a prelude to genetic studies of endophenotypes in schizophrenia, which generally require large sample sizes, the feasibility of measuring the antisaccade endophenotype in multi-site schizophrenia research must first be established. The present study reports the initial antisaccade performance data gathered from a subset of

subjects in a National Institute of Mental Health (NIMH) multi-site collaborative family study, the Consortium on the Genetics of Schizophrenia (COGS; Calkins et al., *in press*; see <http://schizophreniaresearch.net/index.asp>). Schizophrenia and community comparison subjects completed a standardized antisaccade task, which was administered by different personnel at 7 sites; each site used the same equipment, techniques, training, and subject selection criteria. Quality assurance and data analyses were performed by oculomotor experts at the University of Washington (UW). The major aim of this study was to establish the criterion validity of the antisaccade task across all 7 sites by detecting previously reported differences between schizophrenia and comparison subjects.

2. Methods

The COGS is a 7 site NIMH funded linked RO-1 project designed to collect neuropsychological and neurophysiological endophenotypes and genetic analyses on schizophrenia subjects, their first-degree relatives, and community comparison subjects. Participating sites include Harvard University, the Mount Sinai School of Medicine (MSSM), the University of California San Diego (UCSD), the University of California Los Angeles (UCLA), the University of Colorado (UCHSC), the University of Pennsylvania (UPENN), and the University of Washington (UW). The local institutional review board of each site approved the study, and all subjects provided signed informed consent before commencing the study procedures.

2.1. Recruitment

For the purpose of this study, analyses were limited to schizophrenia subjects and community comparison subjects. At each site, medically healthy adults with and without schizophrenia were recruited through flyers, print, and electronic media. Schizophrenia subjects were also ascertained for the study by mental health providers and local chapters of the National Alliance on Mental Illness.

All subjects were between the ages of 18–65 and fluent in English. Schizophrenia subjects and comparison subjects were excluded for a history of electroconvulsive therapy in the past 6 months; a positive drug or alcohol screen; a diagnosis of substance abuse disorder in the past 30 days or substance dependence in the past 6 months; an estimated premorbid IQ of less than 70; or a history of severe head injury, seizure disorder, or other ocular, neurological, or major systemic medical pro-

blems that could influence antisaccade performance. Additionally, comparison subjects were excluded if they had a personal history of Cluster A Personality Disorder, a personal history of psychosis, or a family history of psychosis in first or second degree relatives. Schizophrenia subjects all met DSM-IV diagnostic criteria for schizophrenia per a structured interview (see below). Due to the overall COGS goal of conducting linkage analysis, schizophrenia subjects were only included if at least 1 non-psychotic sibling and 2 living parents also participated in the study. Occasionally, schizophrenia subjects with large sibships and only one parent also participated in the study (Calkins et al., *in press*). None of the schizophrenia subjects reported in this analysis were related to each other.

2.2. Assessment

All subjects underwent a standardized diagnostic and clinical assessment protocol that included a modified version of the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994), the Family Interview for Genetic Studies (NIMH, 1992), the Schedule for Assessment of Negative Symptoms (Andreasen, 1983), the Schedule for Assessment of Positive Symptoms (Andreasen, 1984), and a medical record review. Premorbid IQ was estimated using the Wide Range Achievement Test 3 (Jastak and Wilkinson, 1993). Interviewers were trained to administer the diagnostic rating scales by experienced COGS faculty members using a standardized training protocol. Following the interview, each subject was assigned a DSM-IV best-estimate final diagnosis through a consensus diagnostic process that included at least 2 faculty-level clinicians.

2.3. Study design

The antisaccade task was administered as part of the COGS research protocol, which consisted of approximately 4 h of clinical assessment and 6 h of noninvasive neuropsychological and neurophysiological testing. The COGS neuropsychological and neurophysiological tasks were presented in 1 of 2 standardized test orders. Neuropsychological and neurophysiological technicians did not participate in diagnostic assessments.

2.4. Equipment

Antisaccade stimuli were presented on a standard video monitor in a dark room. A bite bar and headrest were used to stabilize subjects' heads so that their eyes

were 47.5 cm from the screen. Horizontal eye movements were recorded using an infrared photoelectric limbus detection eye tracking device, which is accurate to 0.25° of visual angle and has a time constant of 4 ms (Applied Science Laboratories, Model 310 eye tracker, Bedford, MA). The analog output was sampled at 500 Hz and digitized at 12 bits per sample.

2.5. Antisaccade task parameters

The antisaccade task used parameters that appear to maximize group differences between schizophrenia and community comparison subjects (McDowell and Clementz, 1997; McDowell et al., 1999). All stimuli were square, subtended a visual angle of 0.35°, and differed only by color. Each antisaccade trial began with a blue central fixation target of duration between 2400 and 3600 ms. During the last 200 ms of this period, a yellow antisaccade cue stimulus appeared 10° or 15° to the left or right of the central fixation dot. This overlap stimulus persisted for 800 ms after the central cue was extinguished, for a total cue display time of 1000 ms. The subjects were instructed to look to the mirror image position of this antisaccade cue (“if the yellow dot jumps to the left, you should look the same distance to the right”). After extinction of the cue, a 500 ms blue target appeared to indicate the location of a correctly performed antisaccade. Following this 500 ms interval, the next antisaccade trial was initiated.

To verify that subjects understood the task, a slower (quarter-speed) practice version of the task was presented first, and subjects were required to point to the location of a correct response for 3 successive trials. Once the practice was successfully completed, each subject was administered 3 separate blocks of 20 antisaccade presentations with a brief rest between the blocks. Stimuli in each block were presented in a standard pseudorandom order and were balanced for target location and central fixation time. Immediately preceding each stimulus block, calibration parameters were generated from the signal that was obtained during stable fixation on technician-guided target placements at the center of the screen and 15° to the left and right of center.

2.6. Cross-site training and quality assurance

Prior to data collection, neuropsychological and neurophysiological technicians and key faculty members from each site participated in a 2 day in-person training session at UCSD (the central administrative site). Technicians from all sites also received annual, in-

person refresher training on the antisaccade procedures. A script for interacting with subjects and a comprehensive manual describing the equipment, software, and subject positioning were distributed to all sites. Ongoing quality assurance consisted of data quality review, bi-weekly conference calls, ad lib consultation with the antisaccade quality assurance site, and annual onsite inspection at each of the 7 sites by a UCSD staff research associate who acted in the role of a subject.

2.7. Data analysis

At each site, oculomotor data were blinded as to subject group, transmitted electronically to the central data core at the UCLA, and then downloaded to the oculomotor quality assurance site for inspection by 2 experienced oculomotor researchers at the UW (ADR and SPM). A custom computerized pattern recognition algorithm (Radant and Hommer, 1992; Ross et al., 1998) identified and characterized all saccadic responses. A block of data was discarded if artifacts were so frequent that the computer algorithm was unable to reliably identify a response saccade, or if the block showed evidence of poor calibration. The first saccade of at least 3° in amplitude and occurring at least 80 ms after cue onset was considered the response saccade. Occasionally, a response saccade was not identified due to an artifact or the failure of the subject to make a saccade. The proportion of correct antisaccades was defined as the ratio of the number of correct antisaccades during all 3 blocks of 20 trials to the total number of interpretable response saccades (1 minus the error rate). Saccades that veered toward the cue instead of away from the cue were designated as prosaccades. Latency was defined as the duration from the onset of the antisaccade cue stimulus to the beginning of the response saccade. Antisaccade gain was defined as the amplitude of the response saccade divided by the distance between the central fixation point and the antisaccade cue.

2.8. Statistics

Demographic and clinical differences between groups were analyzed by *t* test for continuous variables (age and years of parental education) and by chi-square test for categorical variables (gender, handedness, and smoking). The proportion of interpretable saccades was analyzed using a 2-way, group-by-site ANOVA. The ability of each site to detect between-group differences was assessed by *t* tests (significance corrected using the Hochberg procedure) performed on the data from each

Table 1

The number of schizophrenia and community comparison subjects that completed the antisaccade task by site

Site	Schizophrenia subjects	Community comparison subjects
Harvard	10	22
MSSM	18	27
UCLA	25	20
UCSD	29	40
UCHSC	14	27
UPENN	17	36
UW	30	23
Total	143	195

site independently (Hochberg, 1988). A linear regression model was used to adjust for the impact of group, site, age, gender, smoking, parental education (maximum of mother's and father's), and second order interactions on the proportion of correct antisaccades. Only those covariates with a significant contribution to the variance in the proportion of correct antisaccades were retained in the final model. Because the proportion of correct antisaccades has a skewed distribution, analyses of this variable were replicated using arcsine-transformed data (Hoover and Blackwelder, 2001).

Antisaccade latency, prosaccade latency, and saccadic gain were analyzed with a 2-way, group-by-site ANOVA. The ability of each site to detect between-group differences on these measures was assessed by *t* tests (significance corrected using the Hochberg procedure) performed on the data from each site independently (Hochberg, 1988). Since there were 3 blocks of useable antisaccade data for most subjects, within-session reliability was assessed via intraclass correlation coefficients. Analysis of a learning effect between the 3 blocks was performed using 2-way (group-by-block) repeated measures ANOVA; post-hoc analyses were conducted by paired *t* test with Bonferroni correction. All analyses were conducted using Intercooled Stata, version 9.1 (StataCorp, 2005).

3. Results

3.1. Data acquisition

Oculomotor data was obtained from 143 schizophrenia subjects and 195 community comparison subjects. All subjects tolerated testing without difficulty. Data from 2 schizophrenia subjects and 2 community comparison subjects were excluded from the analyses due to unacceptable data quality. In the remaining subjects, an interpretable response saccade was identified for most stimulus presentations in both groups. Schizophrenia subjects had a significantly lower proportion of interpretable saccades than comparison subjects (proportion of interpretable saccades [mean \pm SD], schizophrenia subjects: 0.90 \pm 0.14; comparison subjects: 0.96 \pm 0.09; ANOVA: $F[1, 324]=26.1$, $p<.0001$). There was a significant effect of site ($F[6, 324]=2.98$, $p=.008$) but no significant site-by-group interaction ($F[6, 324]=1.71$, $p=.12$) on the proportion of interpretable saccades.

3.2. Sample characteristics

The number of subjects tested at each site is presented in Table 1. Basic demographic information is presented in Table 2. Subjects with schizophrenia were slightly younger, more likely to be male, more likely to smoke, and reported slightly higher paternal education than community comparison subjects.

3.3. Proportion of correct antisaccades

The proportion of correct antisaccades was significantly lower in schizophrenia subjects than in community comparison subjects (proportion of correct saccades [mean \pm SD], schizophrenia subjects: 0.60 \pm 0.25; comparison subjects: 0.82 \pm 0.15; $t(336)=9.90$; $p<.0001$). A significant difference in the proportion of correct antisaccades between schizophrenia subjects and

Table 2

Demographic data for schizophrenia and community comparison subjects

	<i>N</i>	Schizophrenia subjects	<i>N</i>	Community comparison subjects	Significance
Age: mean years (\pm SD) ^a	143	34.25 (10.69)	195	36.95 (11.85)	$p=.03$
Sex: % male ^b	143	69.9	195	43.6	$p<.001$
Handedness: % right-handed ^b	131	84.73	188	87.77	$p=.524$
Smoking: % who smoke ^b	142	43.7	194	17.0	$p<.001$
Mother's education: mean years (\pm SD) ^a	127	14.51 (3.06)	177	14.00 (2.74)	$p=.13$
Father's education: mean years (\pm SD) ^a	127	15.24 (3.72)	174	14.38 (3.28)	$p=.03$

^a *t* test.

^b Chi-square ($df=1$).

community comparison subjects was detected at every site (Fig. 1). An analysis of covariance (ANCOVA) was used to determine the main effect of group and the residual effects of site, age, smoking status, gender, and parental education on the proportion of correct antisaccades. In an initial model that included all covariates and second-order interactions, smoking status, gender, and parental education had no effect on the proportion of correct antisaccades and no second-order interactions were significant. The final model that included the retained covariates of group, site, and age revealed that schizophrenia subjects had a significantly lower proportion of correct antisaccades than community comparison subjects (95% CI of difference between groups [0.18, 0.27]; $F[1, 329]=105.1, p<.0001$). There were small but significant effects of age ($F[1, 329]=11.8; p=.0007$) and site ($F[6, 329]=2.4; p=.03$) on the proportion of correct antisaccades. Analysis of arcsine-transformed data on the proportion of correct antisaccades, conducted because this distribution of proportions was skewed, yielded the same pattern of significance as the untransformed data.

Investigators have previously reported that age is correlated with the proportion of correct antisaccades (McDowell and Clementz, 1997; Olincy et al., 1997). However, in this study, the actual effect of age on antisaccade performance was small, with a decrease of 0.003 in the proportion of correct antisaccades per year. Multiple comparisons analysis, based on Sidák's method (Sidák, 1967), showed that the site differences noted in the final model were attributable primarily to the difference between subjects at the site with the

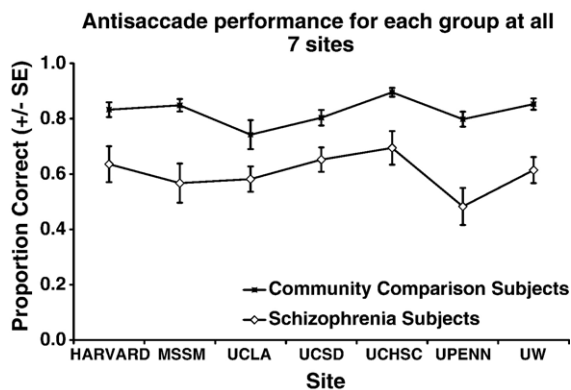


Fig. 1. Proportion of correct antisaccades for both groups at the 7 sites. After correcting for multiple comparisons by the method of Hochberg, t tests indicated that the proportion of correct antisaccades differed significantly between groups at all sites (Hochberg, 1988): Harvard: $t(30)=3.4, p<.002$; MSSM: $t(43)=5.2, p<.0001$; UCLA: $t(43)=2.3, p<.02$; UCSD: $t(67)=3.0, p<.002$; UCHSC: $t(39)=4.1, p<.0001$; UPENN: $t(51)=5.2, p<.0001$; UW: $t(51)=4.2, p<.0001$.

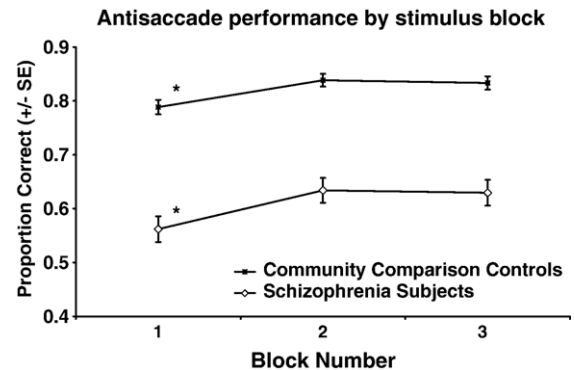


Fig. 2. There was a significant learning effect of equal magnitude in both groups (ANOVA: Block number: $F[2, 634]=32.6, p<.0001$; interaction between group and Block number: $F[2, 634]=1.1, p=.33$). Analysis is based on the 130 schizophrenia subjects and 189 community comparison subjects who completed all three blocks. * $p<.02$ (Bonferroni corrected) between Block 1 and the other 2 Blocks in each group.

highest overall proportion of correct antisaccades (UCHSC) and the site with the lowest overall proportion of correct antisaccades (UPENN); otherwise no significant site-to-site differences were found.

3.4. Within-session reliability

Presentation of 3 blocks of antisaccade stimuli per subject permitted assessment of within-session reliability of the antisaccade task at each site (Fig. 2). The intraclass correlation coefficient between the 3 blocks was 0.92 for all subjects and ranged from 0.87 to 0.93 at the individual sites. Proportion of correct antisaccades increased significantly from Block 1 to Block 2 but plateaued at Block 3. However, there was no significant interaction between group and Block number, indicating that this learning effect was the same in both groups.

3.5. Additional antisaccade measures

Antisaccade latency: mean latency of correct antisaccades was significantly longer among the schizophrenia subjects (426 ± 101 ms) than among comparison subjects (389 ± 69 ms). An ANOVA showed main effects of group ($F[1, 324]=15.2, p<.0001$), but no effect of site ($F[6, 324]=0.8, p=.6$) nor site-by-group interaction ($F[6, 324]=0.6, p=.7$). While the latency of schizophrenia subjects' antisaccades was longer than that of community comparison subjects at all 7 sites, the difference was statistically significant only at 1 site.

Prosaccade latency: mean latency of prosaccades was significantly shorter among the schizophrenia subjects

(241 \pm 73 ms) than among community comparison subjects (260 \pm 74 ms). An ANOVA showed significant main effects of group ($F[1, 324]=3.9, p=.05$) but no effect of site ($F[6, 324]=0.9, p=.5$) nor site-by-group interaction ($F[6, 324]=0.9, p=.5$). While the latency of schizophrenia subjects' prosaccades was shorter than that of community comparison subjects at 6 of 7 sites, the difference was not statistically significant at any site.

Antisaccade gain: mean gain of antisaccades was significantly smaller among the schizophrenia subjects (0.88 \pm 0.20) than among the community comparison subjects (0.95 \pm 0.16). An ANOVA showed main effects of group ($F[1, 324]=16.2, p<.0001$) and site ($F[6, 324]=2.5, p=.02$) but no site by group interaction ($F[6, 324]=1.1, p=.36$). While the gain of schizophrenia subjects' antisaccades was less than that of community comparison subjects at all 7 sites, the difference was statistically significant at only 1 site.

4. Discussion

In the overall 7 site COGS sample, the antisaccade performance of schizophrenia subjects was significantly poorer than that of community comparison subjects. The magnitude of the difference between schizophrenia and comparison subjects at each site was consistent with that reported in the literature (Broerse et al., 2001). These observations support the criterion validity of this multi-site strategy for collecting a large quantity of antisaccade data. Moreover, the overall technical quality of the study data, as measured by the percent of interpretable saccades, was good in both groups. Only 4 subjects had unusable data due to poor quality. This indicates that highly accurate data were obtained across multiple sites using standardized equipment, training, tasks, and test procedures.

The consistency of these findings across sites may be attributed to careful training, monitoring, automated data analysis, and well-selected task parameters. The overlap version of the antisaccade task was selected because this strategy may maximize differences between schizophrenia and comparison subjects (McDowell and Clementz, 1997; McDowell et al., 1999); although, not all studies report this finding (Curtis et al., 2001). The influence of other task parameters such as content of instructions, the presence of a cue defining correct target location, target timing, and target color on antisaccade performance is less well understood.

To our knowledge, only one other study has employed uniform antisaccade task methodology at more than one site (McDowell et al., 1999). In that 3-site study, the proportion of correct antisaccades of schizo-

phrenia subjects was similar across sites. This study confirms and extends those findings by employing identical diagnostic procedures across sites, reporting site-specific data on community comparison subjects, and testing statistically for the effect of site on between-group differences.

Studies have shown good test–retest reliability of antisaccade error rate over periods ranging from several months to many years (Calkins et al., 2003; Ettinger et al., 2003; Gooding et al., 2004, 2005). This study examined the stability of the proportion of correct antisaccades within a single session across 7 sites. The excellent within-session reliability achieved by all 7 sites is consistent with the results reported by McDowell and Clementz (1997) using a similar antisaccade task, thus confirming the integrity of the methodological approach used in this study. Similarly, Curtis et al. (2001) found that group means from the first half of a session were not significantly different from those in the second half.

Subjects in this study showed evidence of a learning effect between Block 1 and Block 2. The nearly identical proportion of correct antisaccades for Blocks 2 and 3 suggests that any learning effect appears to quickly plateau. While a number of studies have documented a learning effect over longer periods of time (Ettinger et al., 2003; Gooding et al., 2005), this study is unique in demonstrating the presence of short-term learning effects. The magnitude of the learning effect was similar in both diagnostic groups. This suggests that learning the antisaccade task is not associated with a diagnosis of schizophrenia.

The lack of significant interactions between group and site on the additional antisaccade measures of antisaccade latency, prosaccade latency, and antisaccade gain supports cross-site methodological homogeneity. Several other groups have reported the same differences between schizophrenia and comparison subjects in saccadic latency and saccadic gain that were found in this study (Ettinger et al., 2004; Polli et al., 2006). There is evidence that latency differences between schizophrenia and comparison subjects might also be under genetic control (Ettinger et al., 2006). However, in contrast to the consistent and robust between-group differences in the proportion of correct antisaccades, most sites individually failed to detect significant between-group differences in these measures. Antisaccade latency, prosaccade latency, and antisaccade gain may reflect different aspects of antisaccade neurophysiology than the proportion of correct antisaccades; perhaps schizophrenia-control differences are inherently smaller in gain and latency. Furthermore, compared to

determining the proportion of correct antisaccades, antisaccade gain is technically more difficult to measure precisely and saccadic latencies are inherently more variable. Imprecision stemming from these methodological issues may limit the utility of gain and latency for genetic studies. In this study, the proportion of correct antisaccades clearly conforms to the definition of an ideal endophenotype better than saccadic latencies or antisaccade gain.

There are several limitations to the data presented in this report. Most notably, the scope of the COGS project makes it logistically impractical to conduct a more formal evaluation of cross-site reliability. Such an endeavor would require testing the same group of subjects, ideally with a range of antisaccade deficits, at all 7 sites. Instead, the COGS has opted to use criterion validity as the means of establishing the methodological consistency of the antisaccade task across sites.

Data gathered from first-degree relatives of schizophrenia subjects are not presented in the current report. Although past cumulative study results suggest that relatives of schizophrenia subjects make more antisaccade errors than comparison subjects, individual study results have not consistently yielded significant group differences (Calkins et al., 2004; Levy et al., 2004). Therefore, results from relatives would not advance the goal of establishing the cross-site criterion validity of the COGS methods. Indeed, interpretation of the findings on relatives will rely on the validity of antisaccade methods across sites as established in the current study.

Finally, this report does not address the impact of other clinical covariates (e.g., duration and severity of illness, medication effects, and symptom profiles) on antisaccade performance. This will be more suitably addressed with larger sample sizes in future COGS analyses. Those analyses will also enable assessment of any ascertainment bias resulting from the COGS inclusion criteria: most particularly, the requirement that schizophrenia subjects have at least 3 relatives willing to participate in the study. Indeed, the finding here that schizophrenia subjects have slightly higher paternal education than community comparison subjects suggests that these schizophrenia subjects may have unusually high premorbid socioeconomic status. However, the data is too preliminary to draw firm conclusions.

The proportion of correct antisaccades has been shown to be stable, associated with schizophrenia, and present in family members: characteristics that are essential for use as an endophenotype in genetic studies. This study confirms the presence of schizophrenia-related deficits in antisaccade performance and demonstrates that as many

as 7 sites can measure the proportion of correct antisaccades reliably and precisely. Hence, the precisely measured antisaccade endophenotype appears to be useful in multi-site genetic studies. Such schizophrenia-related endophenotypes are promising tools for overcoming the imprecision of clinical diagnosis in dissecting the genetics of schizophrenia.

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