

UC San Diego

UC San Diego Previously Published Works

Title

Robust differences in antisaccade performance exist between COGS schizophrenia cases and controls regardless of recruitment strategies

Permalink

<https://escholarship.org/uc/item/77c229n9>

Journal

Schizophrenia Research, 163(1-3)

ISSN

0920-9964

Authors

Radant, Allen D
Millard, Steven P
Braff, David L
et al.

Publication Date

2015-04-01

DOI

10.1016/j.schres.2014.12.016

Peer reviewed



Robust differences in antisaccade performance exist between COGS schizophrenia cases and controls regardless of recruitment strategies



Allen D. Radant^{a,b}, Steven P. Millard^c, David L. Braff^{d,l}, Monica E. Calkins^e, Dorcas J. Dobie^{a,c}, Robert Freedman^f, Michael F. Green^g, Tiffany A. Greenwood^d, Raquel E. Gur^e, Ruben C. Gur^e, Laura C. Lazzeroni^h, Gregory A. Light^d, Sean P. Meichle^c, Keith H. Nuechterlein^g, Ann Olincy^f, Larry J. Seidmanⁱ, Larry J. Siever^{j,k}, Jeremy M. Silverman^{j,k}, William S. Stoneⁱ, Neal R. Swerdlow^d, Catherine A. Sugar^g, Ming T. Tsuang^d, Bruce I. Turetsky^e, Debby W. Tsuang^{a,m,*}

^a Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA

^b Department of Veteran affairs (DVA), VISN-20, Mental Health Services, Seattle, WA, USA

^c DVA, VISN-20, Mental Illness Research, Education, and Clinical Center (MIRECC), Seattle, WA, USA

^d Department of Psychiatry, University of California, San Diego, San Diego, CA, USA

^e Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

^f Department of Psychiatry, University of Colorado Health Sciences Center, Aurora, CO, USA

^g Department of Psychiatry and Biobehavioral Sciences, Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA

^h Department of Biostatistics, Stanford University, Palo Alto, CA, USA

ⁱ Massachusetts Mental Health Center, Public Psychiatry Division of the Beth Israel Deaconess Medical Center, Harvard Medical School, Department of Psychiatry,

Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, MA, USA

^j Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA

^k DVA, VISN-3, MIRECC, James J. Peters VA Medical Center, Bronx, NY, USA

^l DVA, VISN-22 MIRECC, San Diego Healthcare System, San Diego, CA, USA

^m DVA, VISN-20, Geriatric Research, Education, and Clinical Center, Seattle, WA, USA

ARTICLE INFO

Article history:

Received 23 June 2014

Received in revised form 6 December 2014

Accepted 9 December 2014

Available online 29 December 2014

Keywords:

Antisaccade task

Recruitment

ABSTRACT

The impaired ability to make correct antisaccades (i.e., antisaccade performance) is well documented among schizophrenia subjects, and researchers have successfully demonstrated that antisaccade performance is a valid schizophrenia endophenotype that is useful for genetic studies. However, it is unclear how the ascertainment biases that unavoidably result from recruitment differences in schizophrenia subjects identified in family versus case–control studies may influence patient–control differences in antisaccade performance. To assess the impact of ascertainment bias, researchers from the Consortium on the Genetics of Schizophrenia (COGS) compared antisaccade performance and antisaccade metrics (latency and gain) in schizophrenia and control subjects from COGS-1, a family-based schizophrenia study, to schizophrenia and control subjects from COGS-2, a corresponding case–control study. COGS-2 schizophrenia subjects were substantially older; had lower education status, worse psychosocial function, and more severe symptoms; and were three times more likely to be a member of a multiplex family than COGS-1 schizophrenia subjects. Despite these variations, which were likely the result of ascertainment differences (as described in the introduction to this special issue), the effect sizes of the control–schizophrenia differences in antisaccade performance were similar in both studies (Cohen's *d* effect size of 1.06 and 1.01 in COGS-1 and COGS-2, respectively). This suggests that, in addition to the robust, state-independent schizophrenia-related deficits described in endophenotype studies, group differences in antisaccade performance do not vary based on subject ascertainment and recruitment factors.

Published by Elsevier B.V.

1. Introduction

Past studies have demonstrated that schizophrenia (SZ) subjects are impaired in their ability to make correct antisaccades, especially in contrast to healthy control subjects (HCS). Evidence also suggests that

antisaccade error rate (i.e., antisaccade performance) is specifically related to a biological diathesis toward SZ (Smyrnis et al., 2003; Nieman et al., 2007), whereas in mood disorders, antisaccade performance is likely associated with illness exacerbation but not with the illnesses themselves (Garcia-Blanco et al., 2013). The multisite NIMH-funded Consortium on the Genetics of Schizophrenia (COGS) has successfully built upon these well-demonstrated findings by using the antisaccade endophenotype in genetic association and linkage analyses of SZ (Greenwood et al., 2007,

* Corresponding author at: GRECC-182; VA Puget Sound Health Care System; 1660 S. Columbian Way; Seattle, WA 98108

2013). The first COGS study (COGS-1), for example, used family-based methods to examine the heritability and genetics of antisaccade performance and other SZ-related endophenotypes (Calkins et al., 2007). In this study, which enrolled a proband, at least one unaffected sibling, and in most cases, both parents, we found that antisaccade performance was significantly heritable ($h^2 = 0.42$) (Greenwood et al., 2007). This finding parallels the work of Ettinger and colleagues (Ettinger et al., 2006), who found that oculomotor function was concordant in monozygotic twins. We also found robust differences between SZ subjects and HCS in antisaccade performance, highly significant differences between SZ subjects and HCS in the latency and gain of correct antisaccades (i.e., antisaccade metrics) (Radant et al., 2007, 2010), and suggestive evidence of antisaccade-related susceptibility regions (e.g., a linkage to 1q) (Greenwood et al., 2007, 2013) and genes (e.g., *RELN*, *GRIK4*, and *HTR2A*) (Greenwood et al., 2011). COGS-2 sought to extend these investigations via larger case-control genetic association studies.

Determining the effect of ascertainment strategy differences on endophenotypes is crucial for understanding genetic studies employing endophenotypes, as these studies tend to require specific recruitment procedures that, a priori, would be expected to result in ascertainment biases. For instance, familial studies such as COGS-1 require the participation of both a proband and at least one family member, and it is possible that affected subjects from these intact families may differ demographically, symptomatically, or in other ways from affected subjects in case-control genetic association studies who may not necessarily be in contact with other family members.

Given the increasing recognition of the utility of endophenotypes in genetics research (see Braff, this issue), it is particularly important to address these ascertainment-related issues. Yet to our knowledge, no study has examined the effects of ascertainment bias on the antisaccade endophenotype in SZ. Therefore, the COGS-1 and COGS-2 studies, which used identical oculomotor methods, provide an excellent opportunity to explore the effects that ascertainment bias may play in antisaccade performance and antisaccade metrics among SZ subjects and, ultimately, to extend our knowledge of the genomic substrates of these antisaccade deficits and their relationship to SZ.

2. Methods

Previous reports have described in detail the general study design of COGS-1 (Calkins et al., 2007) and COGS-2 (Swerdlow et al., 2014), as well as the specific oculomotor methods that were employed in both studies (Radant et al., 2007, 2010). In the COGS-1 and COGS-2 studies, we administered the antisaccade task to SZ subjects and HCS who spoke English, provided signed informed consent, and were between the ages of 18 and 65. COGS-1 subjects were recruited and tested at seven IRB-approved sites (University of California San Diego [UCSD], University of California Los Angeles [UCLA], University of Washington [UW], University of Pennsylvania [PENN], Mount Sinai School of Medicine [MSSM], Harvard University, and University of Colorado), and COGS-2 subjects were recruited and tested from five of the same sites (UCSD, UCLA, UW, PENN, and MSSM). COGS-1 and COGS-2 defined SZ subjects as individuals with a diagnosis of SZ or schizoaffective disorder, depressed type, and both studies defined HCS as individuals with no history of a psychotic disorder or cluster A Axis II disorder, no psychosis in first-degree relatives, no current Axis I mood disorder, and no regular treatment with psychoactive medications (Swerdlow et al., 2014). Note that subjects from COGS-1 were not eligible to participate in COGS-2.

As shown in Supplemental Table 1, the inclusion and exclusion criteria for COGS-1 and COGS-2 subjects varied only in that eligible COGS-1 SZ subjects had to meet certain family structure criteria that were not required for COGS-2 SZ subjects, namely having an unaffected sibling and, in most cases, both parents available to participate in the study (Calkins et al., 2007). Participants in both COGS-1 and COGS-2 were assessed by diagnosticians, who were trained uniformly at all sites, and the participants were administered a neurocognitive and

neurophysiological battery (Calkins et al., 2007) that included the antisaccade task (Swerdlow et al., 2014) (see the Introduction section to this issue). The COGS antisaccade task, including the calibration procedures for the oculomotor equipment; the specific parameters of the task; the programmed movements of the stimulus cues; the use of custom software to identify and characterize the accuracy, latency, and gain of response saccades; uniform training methods for all staff obtaining oculomotor endophenotypes; and the use of quality control measures to identify prominent artifacts, has been thoroughly described elsewhere (Radant et al., 2007, 2010) and did not vary between COGS-1 and COGS-2.

2.1. Statistical analysis

Between-group differences in demographic variables were assessed using one-way analysis of variance (ANOVA) for continuous variables and chi-squared analyses for categorical variables. Post hoc comparisons were based on Tukey's studentized range test (Miller, 1981). We used both simple t-tests and linear regression models to explore the difference in "proportion of correct antisaccades" and the latency and gain of correct antisaccades between SZ subjects and HCS. The initial regression models included effects for group, study (COGS-1 vs. COGS-2), site, age, gender, smoking status, and parental education (maximum grade level of mother and father), as well as all of the second-order interactions involving group (i.e., group by study, group by site, group by age, group by gender, group by smoking, and group by parental education). The final models contained only those covariates with a statistically significant ($p < 0.05$) contribution to the models. Because latency and gain are only meaningful for trials with correct antisaccade, we used weighted regression models for these metrics based on the available number of correct antisaccades, and subjects with no correct antisaccades were not included.

For the COGS-1 data, parental education and smoking status contained missing values that were imputed based on regressing these covariates on age, site, and group (Little and Rubin, 2002; Radant et al., 2007, 2010). For the COGS-2 data, parental education contained missing values that were imputed in the same way. The COGS-1 and COGS-2 data were then merged, and only subjects with non-missing values for proportion correct antisaccade were included. Cohen's *d* effect size was computed as the difference in group performance means adjusted for other variables in the models and then divided by the estimated population standard deviation based on model residuals. Because the proportion of correct antisaccades had a slightly skewed distribution, we performed a sensitivity analysis by refitting the linear regression models using the arcsine-square-root transformed proportions (Zar, 2010).

As a secondary exploratory analysis, we used linear regression models to investigate the association between self-reported medication use within SZ subjects (none, typical, atypical, both) and antisaccade performance (proportion correct) and metrics (latency and gain of correct antisaccades). The initial regression models included effects for medication use along with the covariates study, site, age, gender, smoking status, and parental education. The final models contained only those covariates with a statistically significant ($p < 0.05$) contribution to the models. For these secondary analyses, effect sizes were computed for difference in performance between subjects on no medication versus the other three medication groups.

To yield easily interpretable intercept terms, baseline age was set to the rough population mean of 40 (i.e., 40 was subtracted from age) in both the primary and secondary analyses; likewise, baseline parental education was set to the rough population mean of 12. All analyses were carried out using R version 3.0.2 (R Core Team, 2013) and the *EnvStats* (Millard, 2013), *car* (Fox and Weisberg, 2011), and *multcomp* packages (Hothorn et al., 2008; Bretz et al., 2011).

3. Results

In the COGS-1 study, we obtained valid antisaccade data from 284 out of 345 (82%) SZ subjects who had at least one non-missing endophenotype, and 495 out of 517 (96%) HCS who had at least one non-missing endophenotype. In the COGS-2 study, we obtained valid antisaccade data from 997 out of 1039 (96%) SZ subjects who had at least one non-missing endophenotype, and 906 out of 917 (99%) HCS who had at least one non-missing endophenotype. Invalid data resulted from those rare instances in which the antisaccade task was not completed because the eye tracking equipment malfunctioned or because subjects were unable to complete the task due to mild discomfort or fatigue.

Several demographic characteristics differed between the two studies: namely, COGS-2 SZ subjects were an average of more than ten years older than COGS-1 SZ subjects; the time since diagnosis was on average about 7 years longer for COGS-2 SZ subjects than COGS-1 SZ subjects; and COGS-2 SZ subjects experienced more severe symptoms than the COGS-1 SZ subjects, as measured by the Schedule for the Assessment of Negative Symptoms (SANS) and the Schedule for the Assessment of Positive Symptoms (SAPS; Table 1) (Andreasen, 1984a,b). There were also significant educational differences between COGS-1 and COGS-2, as the mean education of HCS was slightly lower in COGS-2 compared to COGS-1 (0.4 years), whereas the mean education of SZ subjects was lower by 1 year for COGS-2. In addition, the educational level of the parents of the SZ subjects in COGS-2 was more than 2 years lower than that in COGS-1. The Global Assessment of Functioning (GAF) scores (Hall, 1995) of HCS were slightly higher in COGS-2 versus COGS-1, whereas they were slightly lower for the SZ subjects in COGS-2. For both COGS-1 and COGS-2, SZ subjects had a higher percentage of

males and smokers compared to HCS, and these percentages did not vary significantly between COGS-1 and COGS-2. Finally, Table 1 shows that the percentage of COGS-2 SZ subjects that were part of multiplex families (i.e., families with at least two affected individuals) was much higher than the percentage of COGS-1 SZ subjects that were part of multiplex families. This finding was expected given that eligible probands in COGS-1 had at least one unaffected sibling and one unaffected parent.

Fig. 1 shows antisaccade performance by diagnosis and study, unadjusted for any covariates, and Table 2 shows the results of simple t-tests that compare the SZ subjects and HCS within each study. For COGS-1, the difference between HCS and SZ subjects is 21 percentage points (95% CI [0.18, 0.24]), and for COGS-2 it is 24 percentage points (95% CI [0.22, 0.26]). Table 3 shows the results of the linear regression model and includes effects for group, study, site, age, gender, smoking status, and parental education, as well as all of the second-order interactions involving group; the only significant terms are group, site, age, and gender. Because the group-by-study term is not significant, there is no evidence that the difference in antisaccade performance between HCS and SZ subjects differs between the COGS-1 and COGS-2 studies. Also, because the main effect for study is not significant, there is no evidence of differences in antisaccade performance between studies after adjusting for the other variables. For example, using the full model shown in Table 3, the adjusted mean antisaccade performance for the COGS-1 and COGS-2 SZ subjects was 0.58 (95% CI [0.55, 0.61]) and 0.57 (95% CI [0.55, 0.60]), respectively, and the adjusted mean antisaccade performance for the COGS-1 and COGS-2 HCS was 0.81 (95% CI [0.79, 0.84]) and 0.79 (95% CI [0.77, 0.82]), respectively.

Using the final model that includes only group, site, age, and gender, the estimated difference in proportion correct between HCS and SZ

Table 1
Demographic data for schizophrenia subjects (SZ) and healthy comparison subjects (HCS) by study.^{a,b}

	COGS-1		COGS-2		p-Value ^c	Post hoc comparisons ^d
	HCS-1 (N = 495)	SZ-1 (N = 284)	HCS-2 (N = 906)	SZ-2 (N = 996)		
Age (years)	36.1 (12.6) [18, 65]	34.9 (11.0) [18, 62]	38.3 (13.1) [18, 65]	45.6 (11.3) [18, 65]	<0.0001	SZ-2 > HCS-2 > SZ-1, HCS-1
% male	43	75	50	71	<0.0001	SZ-1, SZ-2 > HCS-1, HCS-2
Education ^e	15.4 (2.4) [8, 22]	13.6 (2.1) [8, 20]	15.0 (2.2) [6, 20]	12.6 (2.0) [5, 20]	<0.0001	HCS-1 > HCS-2 > SZ-1 > SZ-2
Parent education (years) ^f	15.1 (3.1) [2, 25]	15.6 (3.6) [0, 25]	14.9 (3.2) [3, 20]	13.3 (3.4) [0, 20]	<0.0001	SZ-1 > HCS-2, SZ-2 HCS-1 > SZ-2 HCS-2 > SZ-2
% right handed ^g	89	86	86	86	0.39	
% smokers ^h	13	46	11	52	<0.0001	SZ-1, SZ-2 > HCS-1, HCS-2
GAF score ⁱ	84.1 (8.3) [45, 100]	46.3 (12.9) [15, 83]	86.2 (8.2) [45, 100]	43.5 (8.1) [21, 75]	<0.0001	HCS-2 > HCS-1 > SZ-1 > SZ-2
						95% CI for difference (SZ-2 – SZ-1)
SANS ^j		9.6 (5.9) [0, 25]		11.3 (5.3) [0, 24]	<0.0001	[1, 2.5]
SAPS ^k		6.1 (4.2) [0, 20]		6.9 (4.0) [0, 19]	0.009	[0.2, 1.3]
% on antipsychotics ^l		96 (typical = 6, atypical = 82, both = 8)		90 (typical = 7, atypical = 73, both = 10)	0.002	[-10, -3]
% multiplex ^m		7		21	<0.0001	[10, 18]
Age at onset (years) ⁿ		21.1 (5.6) [6, 51]		22.2 (6.8) [5, 59]	0.024	[0.1, 1.9]
Years since diagnosis ^o		13.7 (10.2) [0, 45]		23.4 (11.6) [0, 55]	<0.0001	[8.2, 11.2]

^a All subjects had non-missing values for proportion correct antisaccade.

^b Statistics for continuous variables are mean (standard deviation) [minimum, maximum]. Statistics for categorical variables are percentages.

^c p-Values for continuous variables are based on one-way analysis of variance. p-Values for categorical variables are based on chi-squared analysis.

^d Post hoc multiple comparisons are based on Tukey's studentized range test.

^e Missing values for education: 1 for HCS-1.

^f Missing values for parental education: 27 for HCS-1, 5 for SZ-1, 14 for HCS-2, and 105 for SZ-2.

^g Missing values for handedness: 9 for HCS-1 and 14 for SZ-1.

^h Missing values for smokers: 1 for HCS-1 and 2 for SZ-1.

ⁱ Missing values for GAF (Global Assessment of Functioning): 30 for HCS-1, 15 for SZ-1, 1 for HCS-2, and 10 for SZ-2.

^j Missing values for SANS (Schedule for the Assessment of Negative Symptoms): 5 for SZ-1 and 4 for SZ-2.

^k Missing values for SAPS (Schedule for the Assessment of Positive Symptoms): 5 for SZ-1 and 7 for SZ-2.

^l Missing values for antipsychotics: 7 for SZ-1.

^m Missing values for multiplex: 38 for SZ-2.

ⁿ Missing values for age at onset: 5 for SZ-1 and 10 for SZ-2.

^o Missing values for years since diagnosis: 5 for SZ-1 and 10 for SZ-2.

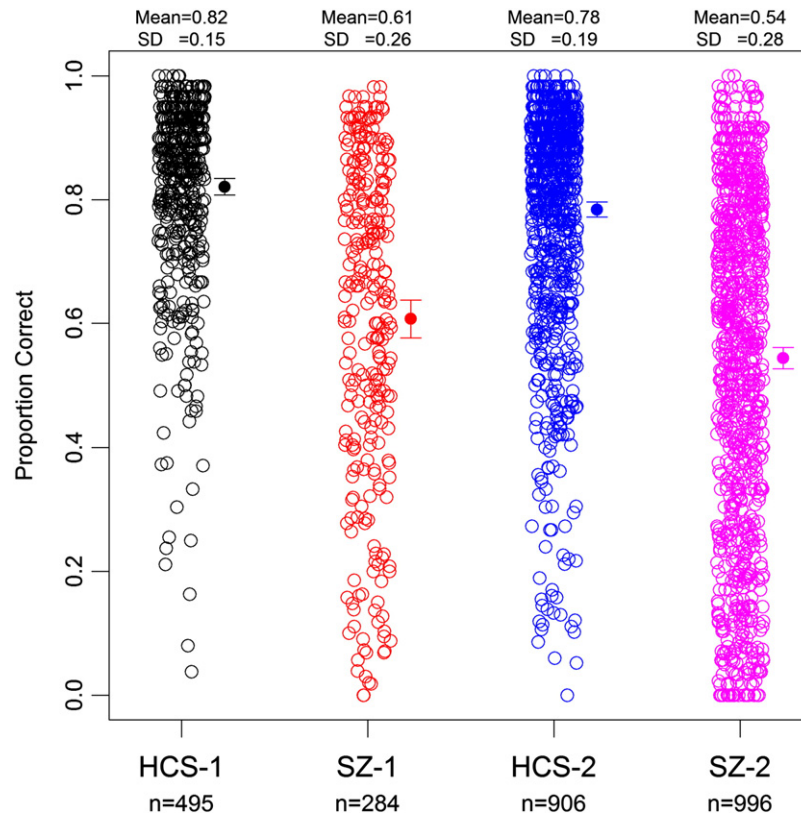


Fig. 1. Antisaccade performance for schizophrenia subjects (SZ) and healthy comparison subjects (HCS) by study. Solid circles represent the mean; line segments represent the 95% confidence interval for the mean.

subjects is 23 percentage points (95% CI [0.21, 0.25], effect size of 1.0). Results based on the arcsine square root transformed proportion correct data were qualitatively similar.

After applying the analyses described above for antisaccade performance to antisaccade metrics, we found that SZ subjects had significantly longer latencies and smaller gains than HCS (Supplemental Tables 2–5). Both antisaccade metrics demonstrated significant effects for site, gender, smoking, and parental education, with latency showing a significant interaction between group and gender, and gain showing a significant interaction between group and smoking. Similar to our findings concerning antisaccade performance, after adjusting for the covariates, there was no difference between COGS-1 and COGS-2 in the antisaccade metrics.

As these tables and figures demonstrate, although the demographic characteristics of COGS-1 and COGS-2 SZ subjects varied considerably, neither these variations nor the differing recruitment strategies of COGS-1 and COGS-2 resulted in between-study differences in antisaccade performance or metric deficits among SZ subjects. For a detailed review of the antisaccade results from COGS-1, which were largely replicated here, please see Radant and colleagues (Radant et al., 2007, 2010).

Table 4 shows the results of the secondary exploratory study of the relationship between antisaccade performance and self-reported medication use in SZ subjects. After adjusting for age, gender, and site,

subjects reporting no medication use showed the best performance (e.g., 0.64 proportion correct [95% CI (0.58, 0.69)]), whereas those on typical antipsychotics, atypical antipsychotics, or both performed worse by 9 percentage points (effect size 0.34), 8 percentage points (effect size 0.28), and 18 percentage points (effect size 0.69), respectively. Results based on the arcsine square root transformed proportion correct data were qualitatively similar. Only SZ subjects who were taking both typical and atypical antipsychotics during the study demonstrated significantly prolonged latency compared to SZ subjects not taking any antipsychotics (Supplemental Table 6); SZ subjects who were taking typical antipsychotics, atypical antipsychotics, or both typical and atypical antipsychotics demonstrated significant decreases in gain (Supplementary Table 7).

4. Discussion

The COGS-1 and COGS-2 studies employed two different ascertainment strategies to successfully collect benchmark, large, cohort-based antisaccade data on SZ subjects and HCS for behavioral and subsequent genomic analyses. After adjusting for important covariates, there was no statistically significant difference between the antisaccade performance or metrics of subjects in COGS-1 and COGS-2.

Our discovery that SZ subjects from COGS-2 were three times more likely to belong to multiplex families than SZ subjects from COGS-1 is

Table 2
Proportion correct antisaccade for schizophrenia subjects (SZ) and healthy comparison subjects (HCS) by study.

Study	HCS		SZ		p-Value	95% CI for difference (HCS – SZ)
	N	Mean (SD) [95% CI]	N	Mean (SD) [95% CI]		
COGS-1	495	0.82 (0.15) [0.81, 0.83]	284	0.61 (0.26) [0.58, 0.64]	<0.0001	[0.18, 0.24]
COGS-2	906	0.78 (0.19) [0.77, 0.80]	996	0.54 (0.28) [0.53, 0.56]	<0.0001	[0.22, 0.26]
Combined	1401	0.80 (0.18) [0.79, 0.81]	1280	0.56 (0.27) [0.54, 0.57]	<0.0001	[0.22, 0.26]

Table 3

Regression results for proportion correct antisaccade for schizophrenia subjects (SZ) and healthy comparison subjects (HCS).

ANOVA table based on type II sums of squares					
Term	Sums of squares	Degrees of freedom	F-value	p-Value	
Group	24.548	1	494.4207	<0.0001	
Study	0.092	1	1.8543	0.17	
Site	2.883	6	9.6764	<0.0001	
Age	1.393	1	28.0656	<0.0001	
Gender	0.296	1	5.9680	0.01	
Smoker	0.070	1	1.4054	0.24	
Parental education	0.157	1	3.1527	0.08	
Group by study	0.012	1	0.2463	0.62	
Group by site	0.470	6	1.5772	0.15	
Group by age	0.040	1	0.8128	0.37	
Group by gender	0.112	1	2.2580	0.13	
Group by smoker	0.015	1	0.2937	0.59	
Group by parental education	0.000	1	0.0000	1.00	
Residuals	131.919	2657			

Regression coefficients for terms in final model					
Term	Estimate	SE	t-Value	p-Value	95% CI
Intercept	0.79	0.012	67.48	<0.0001	[0.76, 0.81]
Group = SZ	−0.23	0.0092	−25.0	<0.0001	[−0.25, −0.21]
Age	−0.0023	0.00035	−6.50	<0.0001	[−0.0030, −0.0016]
Gender = female	−0.022	0.009	−2.42	0.02	[−0.04, −0.004]
Site = UCO	0.13	0.023	5.56	<0.0001	[0.08, 0.17]
Site = HU	0.064	0.026	2.45	0.01	[0.01, 0.11]
Site = UCLA	0.0082	0.014	0.60	0.55	[−0.02, 0.03]
Site = MSSM	−0.037	0.015	−2.45	0.01	[−0.07, −0.01]
Site = UPENN	0.0035	0.014	0.25	0.80	[−0.02, 0.03]
Site = UW	0.054	0.013	4.03	<0.0001	[0.03, 0.08]

Final model includes only terms for group, site, age, and gender. Intercept term (Baseline) represents fitted value for Group = HCS, Gender = Male, Age = 40, and Site = UCSD. Coefficients for Group and Site represent difference from baseline; coefficient for Age represents change per each additional year.

Site abbreviations: UCSD = University of California San Diego, UCO = University of Colorado, HU = Harvard University, UCLA = University of California Los Angeles, MSSM = Mount Sinai School of Medicine, UPENN = University of Pennsylvania, UW = University of Washington. SE = standard error.

very likely explained by differences in inclusion and exclusion criteria between the two studies. As part of the COGS-1 inclusion criteria, only SZ subjects with at least one unaffected sibling and one unaffected parent were enrolled in the study. This means, for example, that individual SZ patients from four-person families which included two children with SZ or two parents with SZ could be included in COGS-2 but not COGS-1. Given these differences, it is therefore not surprising that COGS-2 SZ

subjects were more likely to belong to multiplex families than COGS-1 SZ subjects.

The family requirements of COGS-1 may also have contributed to the age differences we found in COGS-1 and COGS-2 SZ subjects. With the exception of families with very large sibships, COGS-1 only enrolled SZ subjects with living parents who were willing to participate in genotyping, whereas COGS-2 had no enrollment requirements related to the parents of SZ subjects. Thus, because from an actuarial standpoint, older individuals are more likely to have deceased parents (an exclusion in COGS-1) than younger individuals, it is not surprising that older subjects were more likely to be enrolled in COGS-2.

After controlling for the significant covariates, the adjusted means of antisaccade performance and antisaccade metrics from COGS-1 and COGS-2 were not influenced by any of the moderator variables. Indeed, our findings soundly demonstrate that antisaccade performance, latency, and gain differences between SZ subjects and HCS are robust enough to overcome substantial variance in recruitment methodology. This suggests that antisaccade performance, latency, and gain are stable measurements of pathophysiological disturbances in SZ.

That said, because ascertainment strategy was not randomized, we cannot be certain whether unmeasured factors, such as socioeconomic factors, may have led to differences in the characteristics of SZ subjects of COGS-1 and COGS-2. For instance, our study did not collect in-depth data on employment history or psychosocial stressors, and therefore, we were unable to determine whether these factors may have influenced subject characteristics in COGS-1 or COG-2. Our finding that the mean education of HCS, SZ subjects, and the parents of SZ subjects was lower for COGS-2 than COGS-1, especially for SZ subjects and their parents, may be related to differences in socioeconomic factors during the early 2000s (COGS-1) and the early 2010s (COGS-2) or to cryptic unidentified factors. These interpretive limitations may be in part related to the fact that our study did not include an a priori focus

Table 4

Regression results for proportion correct antisaccade for schizophrenia subjects and relationship to medication use.

Term	Estimate	SE	t-Value	p-Value	95% CI
Intercept	0.64	0.029	21.84	<0.0001	[0.58, 0.69]
Med use = typical	−0.089	0.038	−2.33	0.02	[−0.16, −0.01]
Med use = atypical	−0.075	0.026	−2.86	0.004	[−0.13, −0.02]
Med use = both	−0.18	0.035	−5.20	<0.0001	[−0.25, −0.11]
Age	−0.0025	0.00063	−3.95	<0.0001	[−0.0037, −0.0013]
Gender = female	−0.041	0.017	−2.43	0.02	[−0.07, −0.008]
Site = UCO	0.16	0.046	3.38	0.0007	[0.07, 0.25]
Site = HU	0.057	0.055	1.04	0.30	[−0.05, 0.16]
Site = UCLA	0.022	0.023	0.96	0.34	[−0.02, 0.07]
Site = MSSM	−0.064	0.027	−2.39	0.02	[−0.12, −0.01]
Site = UPENN	0.011	0.023	0.49	0.62	[−0.03, 0.06]
Site = UW	0.069	0.023	3.08	0.002	[0.03, 0.11]

Final model includes only terms for antipsychotic medication use, site, age, and gender. Intercept term (Baseline) represents fitted value for Med use = none, Gender = male, Age = 40, and Site = UCSD. Coefficients for Med use and Site represent difference from baseline; coefficient for Age represents change per each additional year.

Site abbreviations: UCSD = University of California San Diego, UCO = University of Colorado, HU = Harvard University, UCLA = University of California Los Angeles, MSSM = Mount Sinai School of Medicine, UPENN = University of Pennsylvania, UW = University of Washington. SE = standard error.

on ascertainment bias. Nonetheless, our wealth of demographic data, large number of subjects, and careful attention to reliable between-site measurements make it likely that our results are generalizable beyond the COGS-1 and COGS-2 studies.

The antisaccade endophenotype has been successfully deployed to study neurophysiology (Cutsuridis et al., 2014), genetics (Greenwood et al., 2013), regional brain function (Fukumoto-Motoshita et al., 2009), neuropharmacology (Petrovsky et al., 2013), and cognitive processing (Cutsuridis et al., 2014) in SZ. Because the antisaccade endophenotype is so widely used in these studies, it is important to understand how ascertainment bias may affect antisaccade performance and metrics in SZ subjects. The current study shows that these antisaccade deficits in SZ are not influenced by ascertainment or symptom status (a key endophenotype characteristic per Gottesman and Gould) (Gottesman and Gould, 2003) and that antisaccade performance and antisaccade metrics are viable, robust neurophysiological endophenotypes in a multisite context. As in prior behavioral family genetic studies (Radant et al., 2007; Greenwood et al., 2011, 2013), the larger cohort of SZ patients in COGS-2 will allow us to perform extensive and functional genomic analyses on the antisaccade endophenotype in future research.

Funding

This material is based upon work supported (or supported in part) by the Office of Research and Development Medical Research Service (or) Health Services R&D Service, Department of Veterans Affairs. This study was supported by NIMH grants R01 MH65571, R01 MH65588, R01 MH65562, R01 MH65707, R01 MH65554, R01 MH65578, and R01 MH65558.

Contributors

Dr. Radant composed the manuscript and provided training and ongoing quality assurance for the antisaccade task at the COGS-1 and COGS-2 sites. Dr. Millard led the statistical analyses for the manuscript. All other authors participated in aspects of study design, including subject recruitment, antisaccade testing, and validation of the clinical and endophenotype data. All authors were responsible for reviewing, editing, and approving the final version of the manuscript.

Conflicts of interest

Dr. Green has been a consultant to AbbVie, Biogen, DSP, EnVivo/Forum and Roche, and he is on the scientific advisory board of Mnemosyne. He has received research funds from Amgen. Dr. Lazzaroni is an inventor on a patent application filed by Stanford University on genetic polymorphisms associated with depression. Dr. Light has been a consultant to EnVivo/Forum and Astellas and serves on an advisory board for Neuroverse. Dr. Nuechterlein has received unrelated research support from Janssen Scientific Affairs, Genentech, and Brain Plasticity, Inc., and he has consulted for Genentech, Otsuka, Janssen, and Brain Plasticity, Inc. Dr. Swerdlow has been a consultant for Genco Sciences, Ltd. All other authors declare that they have no conflict of interest.

Acknowledgment

The authors wish to thank all of the subjects and their family members for participating in this study. We also thank Andrew David for his editorial assistance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.schres.2014.12.016>.

References

- Andreasen, N., 1984a. *The Scale for the Assessment of Negative Symptoms (SANS)*. University of Iowa, Iowa City, IA.
- Andreasen, N., 1984b. *The Scale for the Assessment of Positive Symptoms (SAPS)*. University of Iowa, Iowa City, IA.
- Bretz, F., Hothorn, T., Westfall, P., 2011. *Multiple Comparisons Using R*. CRC Press, Boca Raton, FL.
- Calkins, M.E., Dobie, D.J., Cadenhead, K.S., Olincy, A., Freedman, R., Green, M.F., Greenwood, T.A., Gur, R.E., Gur, R.C., Light, G.A., Mintz, J., Nuechterlein, K.H., Radant, A.D., Schork, N.J., Seidman, L.J., Siever, L.J., Silverman, J.M., Stone, W.S., Swerdlow, N.R., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Braff, D.L., 2007. The Consortium on

- the Genetics of Endophenotypes in Schizophrenia: model recruitment, assessment, and endophenotyping methods for a multisite collaboration. *Schizophr. Bull.* 33 (1), 33–48.
- Core Team, R., 2013. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria.
- Cutsuridis, V., Kumari, V., Ettinger, U., 2014. Antisaccade performance in schizophrenia: a neural model of decision making in the superior colliculus. *Front. Neurosci.* 8, 13.
- Ettinger, U., Picchioni, M., Hall, M.H., Schulze, K., Touloupoulou, T., Landau, S., Crawford, T.J., Murray, R.M., 2006. Antisaccade performance in monozygotic twins discordant for schizophrenia: the Maudsley twin study. *Am. J. Psychiatry* 163 (3), 543–545.
- Fox, J., Weisberg, S., 2011. *An R Companion to Applied Regression*. 2nd ed. Sage Publications, Thousand Oaks, CA.
- Fukumoto-Motoshita, M., Matsuura, M., Ohkubo, T., Ohkubo, H., Kanaka, N., Matsushima, E., Taira, M., Kojima, T., Matsuda, T., 2009. Hyperfrontality in patients with schizophrenia during saccade and antisaccade tasks: a study with fMRI. *Psychiatry Clin. Neurosci.* 63 (2), 209–217.
- Garcia-Blanco, A.C., Perea, M., Salmeron, L., 2013. Attention orienting and inhibitory control across the different mood states in bipolar disorder: an emotional antisaccade task. *Biol. Psychol.* 94 (3), 556–561.
- Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am. J. Psychiatry* 160 (4), 636–645.
- Greenwood, T.A., Braff, D.L., Light, G.A., Cadenhead, K.S., Calkins, M.E., Dobie, D.J., Freedman, R., Green, M.F., Gur, R.E., Gur, R.C., Mintz, J., Nuechterlein, K.H., Olincy, A., Radant, A.D., Seidman, L.J., Siever, L.J., Silverman, J.M., Stone, W.S., Swerdlow, N.R., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Schork, N.J., 2007. Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. *Arch. Gen. Psychiatry* 64 (11), 1242–1250.
- Greenwood, T.A., Lazzaroni, L.C., Murray, S.S., Cadenhead, K.S., Calkins, M.E., Dobie, D.J., Green, M.F., Gur, R.E., Gur, R.C., Hardiman, G., Kelsoe, J.R., Leonard, S., Light, G.A., Nuechterlein, K.H., Olincy, A., Radant, A.D., Schork, N.J., Seidman, L.J., Siever, L.J., Silverman, J.M., Stone, W.S., Swerdlow, N.R., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Freedman, R., Braff, D.L., 2011. Analysis of 94 candidate genes and 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. *Am. J. Psychiatry* 168 (9), 930–946.
- Greenwood, T.A., Swerdlow, N.R., Gur, R.E., Cadenhead, K.S., Calkins, M.E., Dobie, D.J., Freedman, R., Green, M.F., Gur, R.C., Lazzaroni, L.C., Nuechterlein, K.H., Olincy, A., Radant, A.D., Ray, A., Schork, N.J., Seidman, L.J., Siever, L.J., Silverman, J.M., Stone, W.S., Sugar, C.A., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Light, G.A., Braff, D.L., 2013. Genome-wide linkage analyses of 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. *Am. J. Psychiatry* 170 (5), 521–532.
- Hall, R.C., 1995. Global assessment of functioning. A modified scale. *Psychosomatics* 36 (3), 267–275.
- Hothorn, T., Bretz, F., Westfall, P., 2008. Simultaneous inference in general parametric models. *Biom. J.* 50 (3), 346–363.
- Little, R., Rubin, D., 2002. *Statistical Analysis with Missing Data*. John Wiley & Sons, New York.
- Millard, S., 2013. *EnvStats: An R Package for Environmental Statistics*. Springer-Verlag, New York.
- Miller, R., 1981. *Simultaneous Statistical Inference*. Springer Verlag, New York.
- Nieman, D., Becker, H., van de Fliert, R., Plat, N., Bour, L., Koelman, H., Klaassen, M., Dingemans, P., Niessen, M., Linszen, D., 2007. Antisaccade task performance in patients at ultra high risk for developing psychosis. *Schizophr. Res.* 95 (1–3), 54–60.
- Petrovsky, N., Ettinger, U., Quednow, B.B., Landsberg, M.W., Drees, J., Lennertz, L., Frommann, I., Heilmann, K., Strater, B., Kessler, H., Dahmen, N., Mossner, R., Maier, W., Wagner, M., 2013. Nicotine enhances antisaccade performance in schizophrenia patients and healthy controls. *Int. J. Neuropsychopharmacol.* 16 (7), 1473–1481.
- Radant, A.D., Dobie, D.J., Calkins, M.E., Olincy, A., Braff, D.L., Cadenhead, K.S., Freedman, R., Green, M.F., Greenwood, T.A., Gur, R.E., Light, G.A., Meichle, S.P., Mintz, J., Nuechterlein, K.H., Schork, N.J., Seidman, L.J., Siever, L.J., Silverman, J.M., Stone, W.S., Swerdlow, N.R., Tsuang, M.T., Turetsky, B.I., Tsuang, D.W., 2007. Successful multi-site measurement of antisaccade performance deficits in schizophrenia. *Schizophr. Res.* 89 (1–3), 320–329.
- Radant, A.D., Dobie, D.J., Calkins, M.E., Olincy, A., Braff, D.L., Cadenhead, K.S., Freedman, R., Green, M.F., Greenwood, T.A., Gur, R.E., Gur, R.C., Light, G.A., Meichle, S.P., Millard, S.P., Mintz, J., Nuechterlein, K.H., Schork, N.J., Seidman, L.J., Siever, L.J., Silverman, J.M., Stone, W.S., Swerdlow, N.R., Tsuang, M.T., Turetsky, B.I., Tsuang, D.W., 2010. Antisaccade performance in schizophrenia patients, their first-degree biological relatives, and community comparison subjects: data from the COGS study. *Psychophysiology* 47 (5), 846–856.
- Smyrnis, N., Evdokimidis, I., Stefanis, N.C., Avramopoulos, D., Constantinidis, T.S., Stavropoulos, A., Stefanis, C.N., 2003. Antisaccade performance of 1,273 men: effects of schizotypy, anxiety, and depression. *J. Abnorm. Psychol.* 112 (3), 403–414.
- Swerdlow, N.R., Light, G.A., Sprock, J., Calkins, M.E., Green, M.F., Greenwood, T.A., Gur, R.E., Gur, R.C., Lazzaroni, L.C., Nuechterlein, K.H., Radant, A.D., Ray, A., Seidman, L.J., Siever, L.J., Silverman, J.M., Stone, W.S., Sugar, C.A., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Braff, D.L., 2014. Deficient prepulse inhibition in schizophrenia detected by the multi-site COGS. *Schizophr. Res.* 152 (2–3), 503–512.
- Zar, J., 2010. *Biostatistical Analysis*. 5th ed. Pearson Prentice Hall, Upper Saddle River, NJ.