Available online at www.sciencedirect.com
SCIENCE DIRECT®
Schizophrenia Research 71 (2004) 167–178
SCHIZOPHRENIA RESEARCH
www.elsevier.com/locate/schres

Antisaccade performance is impaired in medically and psychiatrically healthy biological relatives of schizophrenia patients

Monica E. Calkins[a,*], Clayton E. Curtis[b], William G. Iacono[c], William M. Grove[c]

[a] *Neuropsychiatry Section, Schizophrenia Research Center, University of Pennsylvania School of Medicine, 10 Gates, 3400 Spruce Street, Philadelphia, PA 19104, USA*
[b] *Department of Psychology, New York University, USA*
[c] *Department of Psychology, University of Minnesota, USA*

Received 16 July 2003; received in revised form 2 December 2003; accepted 10 December 2003
Available online 6 March 2004

Abstract

Schizophrenia patients and their relatives have been found to exhibit increased reflexive errors on the antisaccade task, suggesting the deficit reflects genetic susceptibility for schizophrenia. To evaluate the degree to which antisaccade error is elevated in schizophrenia relatives, we carried out a meta-analysis of the existing literature and a primary study examining whether the magnitude of reported differences between relative and nonpsychiatric comparison groups could be due to differences in participant inclusion criteria. Meta-analysis yielded a moderate to large effect size across studies comparing relatives and controls (Cohen's $d = 0.61$; Glass' $d_g = 0.87$). Antisaccade performance in medically and psychiatrically healthy relatives ($n = 45$), who were selected from a larger sample of relatives based on criteria applied to healthy controls, was significantly more impaired than in healthy control participants ($d = 0.81$, $d_g = 0.93$). Moreover, excluded ($n = 71$) and included relatives did not differ ($d = 0.14$, $d_g = 0.13$). The results indicate that the antisaccade deficit is a robust phenomenon in unaffected schizophrenia relatives that is not due to differences in inclusion criteria between relatives and controls, and thus are consistent with a growing literature indicating that the antisaccade deficit will be a valuable endophenotype of schizophrenia.

Keywords: Antisaccade; Schizophrenia; Endophenotype; Genetics; Eye movement dysfunction

Antisaccade impairment in schizophrenia patients has been viewed as a promising candidate endophenotype of schizophrenia, that is, a genetically influenced biobehavioral characteristic that will enhance the likelihood of identifying schizophrenia susceptibility genes (e.g., Calkins and Iacono, 2000). In the antisaccade task, the participant is required to generate a saccade in the direction opposite target movement, and thus to inhibit a reflexive saccade to the target. Failure to inhibit the prepotent reflexive saccade is considered an error response. First described in the late 1980s (Fukushima et al., 1988), the antisaccade deficit in schizophrenia patients has received considerable research attention. Between the years 2000 and 2002,

* Corresponding author. Tel.: +1-215-662-7389; fax: +1-215-662-7903.
E-mail address: mcalkins@bbl.med.upenn.edu (M.E. Calkins).

0920-9964/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2003.12.005

the number of studies of antisaccade performance in schizophrenia patients nearly doubled, with more than 40 investigations to date consistently replicating the result that schizophrenia patients evidence increased error rates in comparison with controls (Allen et al., 1996; Brenner et al., 2001; Broerse et al., 2001, 2002; Brownstein et al., 2003; Burke and Reveley, 2002; Clementz et al., 1994; Crawford et al., 1995a,b, 1996, 1998; Curtis et al., 2001a,b; Depatie et al., 2002; Fukushima et al., 1988, 1990, 1991, 1994; Gooding and Tallent, 2001; Hutton et al., 2002; Karoumi et al., 2001; Katsanis et al., 1997; Klein et al., 2000a; Levy et al., 1998; Manoach et al., 2002; Maruff et al., 1998; Matsue et al., 1994; McDowell et al., 1999, 2002; McDowell and Clementz, 1997; Muller et al., 1999; Nieman et al., 2000; Nkam et al., 2001; Radant et al., 1997; Raemaekers et al., 2002; Ross et al., 1998; Rosse et al., 1993; Sereno and Holzman, 1995; Thaker et al., 1990, 1989). The antisaccade deficit has been viewed as consistent with an impairment in inhibitory control, likely mediated by dysfunction of dorsolateral prefrontal cortex or subservient circuitry (e.g., Clementz, 1998; Curtis et al., 2001a,b; McDowell et al., 2002; Sweeney et al., 1996).

The well-replicated result of the antisaccade deficit in schizophrenia patients suggests that it fulfills a primary and essential feature of an endophenotype reflecting genetic risk, namely, that it is associated with schizophrenia (e.g., Gottesman and Gould, 2003; Iacono, 1998). However, results of a recent report have been interpreted as suggesting that the relatives of schizophrenia patients do not exhibit the antisaccade deficit (Brownstein et al., 2003). The purpose of the current investigation was to test the hypothesis that a particular methodological feature (i.e., participant inclusion criteria) can account for the antisaccade deficit in relatives that has been reported in other family studies (Brownstein et al., 2003).

If a characteristic is to be regarded as an endophenotype manifesting genetic risk, then it must be heritable (e.g., Gottesman and Gould, 2003; Iacono, 1998). Consistent with the heritability of antisaccade performance, a large study of healthy young twins ($n = 1290$) suggested that 53–61% of the variance in antisaccade performance was attributable to additive genetic effects, with the remainder attributable to non-shared environmental influences (Malone and Iacono, 2002). Evidence of heritability in healthy individuals is supportive of the genetic influence on a characteristic. However, if the characteristic is reflective of the genetic risk for a particular disorder, then it should be observed, in excess of general population levels, in the biological relatives of individuals affected with that disorder (e.g., Gottesman and Gould, 2003; Iacono, 1998). Eleven published reports, including seventeen independent groups of relatives, have examined antisaccade performance in the biological relatives of schizophrenia patients (Brownstein et al., 2003; Clementz et al., 1994; Crawford et al., 1998; Curtis et al., 2001a; Karoumi et al., 2001; Katsanis et al., 1997; McDowell and Clementz, 1997; McDowell et al., 1999; Ross et al., 1998; Thaker et al., 1996, 2000).

The results of these investigations are summarized in Table 1. To obtain an average effect size, we conducted a meta-analysis according to the method of Hunter and Schmidt (1990). Effect sizes (d) are interpreted according to the guidelines of Cohen (1988): 0.2 = small, 0.5 = moderate, 0.8 = large. In 13 of the 17 comparisons, schizophrenia relatives evidenced increased error rates in contrast to healthy controls, as indicated by small to large individual study effect sizes, and a moderate to large mean magnitude of effect across studies (see Table 1). Thus, in the aggregate, the empirical evidence appears to suggest that biological relatives of schizophrenia patients exhibit performance difficulties on the antisaccade task consistent with those observed in schizophrenia patients. However, individual exceptions are evident in the array of study effect sizes.

In three of the four studies containing a subgroup of relatives in which a deficit was not observed, relatives were categorized based on characteristics deemed reflective of genetic risk for schizophrenia. Importantly, other subgroups of relatives within those studies *did* exhibit higher error rates than controls. Ross et al. (1998) differentiated the elderly parents of schizophrenia patients based on family history of chronic psychosis; among parental pairs, parents with a negative family history were deemed "least likely genetic carriers" (denoted as R1 in Table 1), while those with a positive family history were identified as "most likely genetic carriers" (R2). A third group of parents ("other") included those in which there was no family history or in which both parents had a family history of chronic psychosis (R3). Consistent

Table 1
Results of investigations of antisaccade error rates (percent error) in schizophrenia relatives vs. controls

Authors	Year	Grp1,2	Relative		Control		Effect sizes	
			n	Mean percent error	*n*	Mean percent error	*d*	d_g
Brownstein et al.	2003	RC	98	23.20	24	26.30	−0.16	−0.14
Clementz et al.	1994	RC	32	32.10	33	22.00	0.51	0.64
Crawford et al.	1998	RC	50	33.00	38	27.00	0.23	0.26
Curtis et al.	2001	RC	116	38.20	109	24.60	0.68	0.80
Karoumi et al.	2001	RC	21	36.60	21	20.40	0.83	1.19
Katsanis et al.	1997	RC	55	45.00[a]	38	25.00[a]	0.99	1.18
McDowell and Clementz	1997	RC	60	13.50	32	4.50	0.45	0.68
McDowell et al.	1999	R1C	60	25.00	94	15.00	0.57	0.94
McDowell et al.	1999	R2C	29	43.00	94	15.00	1.60	2.60
McDowell et al.	1999	R3C	41	41.50	94	15.00	1.59	2.44
Ross et al.	1998	R1C	8	32.00	22	47.00[b]	−0.55	−0.54
Ross et al.	1998	R2C	8	68.00	22	47.00[b]	0.82	0.75
Ross et al.	1998	R3C	16	59.00	22	47.00[b]	0.44	0.43
Thaker et al.	1996	R1C	17	24.70	46	24.30	0.02	0.02
Thaker et al.	1996	R2C	12	29.10	46	24.30	0.24	0.22
Thaker et al.	2000	R1C	34	23.17	37	25.83	−0.10	−0.10
Thaker et al.	2000	R2C	21	34.33	37	25.83	0.32	0.34
Mean (sample size weighted)				32.31		22.48[c]	0.61[d]	0.87[e]

Grp1,2 = specification of the two groups in the comparison: R = relatives of schizophrenia patients, C = controls; numbers accompanying R reflect subsamples of relatives reported within the study as follows. McDowell et al. (1999): R1 = San Diego sample, R2 = Salt Lake City sample, R3 = Palau sample; Ross et al. (1998) R1 = least likely genetic carriers, R2 = most likely genetic carriers, R3 = "other", (all three comparisons are elderly parents vs. elderly controls); Thaker et al. (1996, 2000): R1 = no schizophrenia spectrum diagnoses, R2 = schizophrenia spectrum diagnoses. *d* = Cohen's *d*, difference between the sample size weighted means of the two groups in the comparison, divided by the sample size weighted pooled standard deviation. d_g = Glass' *d*, difference between the two means divided by the control group standard deviation. A positive effect size indicates that the relatives had higher antisaccade error rates than controls. Where percent correct was reported instead of percent error, mean percent errors were obtained by subtraction. Where multiple antisaccade tasks/conditions were reported for a given sample, means were obtained by averaging *d* values across tasks/conditions.

[a] Value is median. Standard deviations for effect size calculation were obtained from Curtis et al. (2001a), which reported data collected from the same laboratory using identical infrared oculography techniques.

[b] Means are of older healthy control participants (age = 67 ± 7), age matched to the older parents. The mean error rate for younger healthy control participants (age = 33 ± 9) was 21.00.

[c] Because the same control group was used for studies in which multiple relative subgroups were reported, the sample-size weighted mean was obtained using the mean of the 11 independent control groups.

[d] Meta-analytically derived effect size, *D*. 95% confidence interval = $0.34 < D < 0.88$.

[e] Meta-analytically derived effect size, *D*. 95% confidence interval = $0.46 < D < 1.28$.

with the effect of presumed genetic (or familial) predisposition on antisaccade error rate, the most likely genetic carriers evidenced a higher error rate than controls, while the least likely genetic carriers did not. Parents in the "other" group also evidenced increased error rates (see Table 1).

In the investigations of Thaker et al. (1996, 2000), relatives of schizophrenia patients were classified based on schizophrenia spectrum diagnoses: relatives without spectrum diagnoses (R1) and relatives with spectrum diagnoses (R2) were compared with spectrum and non-spectrum controls. In both investigations, relatives with spectrum diagnoses exhibited increased error rates compared to non-spectrum controls at a small magnitude of effect, but the relatives without spectrum diagnoses did not (see Table 1). Thus, relatives with clinical characteristics that appear to be related to schizophrenia (see, e.g., Kendler, 1985) evidenced increased antisaccade impairment. This result is consistent with reports of increased error rates in schizotypal community participants (Brenner et al., 2001; Cadenhead et al., 2002; Gooding, 1999; Gooding and Tallent, 2001; Larrison et al., 2000; O'Driscoll et al., 1998), though this finding is not

ubiquitous (Klein et al., 2000b). Moreover, schizophrenia relatives with a history of psychotic disorders have been reported to exhibit antisaccade performance that is more similar to the performance of schizophrenia patients than to relatives without a psychotic disorder history (Curtis et al., 2001a). Together, the results support the endophenotypic candidacy of the antisaccade deficit by suggesting that the deficit cosegregates with schizophrenia and related disorders (e.g., Gottesman and Gould, 2003; Iacono, 1998).

With the exception of the studies employing theoretically relevant subgroups of relatives, only one study yielded an effect size indicating that relatives of schizophrenia patients (also including relatives of schizoaffective patients) did not exhibit increased error rates compared to controls (Brownstein et al., 2003) (see Table 1). Consistent with two prior reports (Crawford et al., 1998; Curtis et al., 2001a), Brownstein et al. reported that the relatives of patients with poor performance on the antisaccade task themselves had significantly greater error rates than the relatives of patients with good performance. While this result seemingly accords with a genetic influence on antisaccade impairment, Brownstein et al. suggested that in the absence of an overall group difference between relatives and controls in their sample, the result may simply be reflective of a heritable characteristic that is not associated with genetic risk for schizophrenia (Brownstein et al., 2003). Thus, Brownstein et al. concluded that their results "do not support the interpretation that poor performance on the standard antisaccade task is a co-familial trait for schizophrenia or that it would substantially increase the power to detect linkage for a gene associated with schizophrenia" (p. 21–22).

In explanation of the failure to replicate the antisaccade deficit in relatives, Brownstein et al. (2003) raised the intriguing possibility that "asymmetrical" inclusion criteria for relatives and controls could lead to the spurious appearance of a deficit in schizophrenia relatives. In particular, it was hypothesized that the pattern of results obtained by Curtis et al. (2001a) could be due to the use of more restrictive criteria for inclusion in the control group than in the relative group. The authors did not elaborate further, but presumably, they meant to imply that if inclusion criteria were more restrictive for controls than relatives, relatives might be impaired not because the antisaccade deficit is associated with genetic liability for schizophrenia, but instead because relatives have other conditions contributing to comparatively poor performance. Thus, while the bulk of the evidence presented in Table 1 suggests that relatives are impaired in comparison with healthy individuals, Brownstein et al. offered an alternative to the interpretation that the impairment is reflective of the endophenotypic candidacy of the antisaccade deficit.

There are too few studies in this domain using parallel levels of inclusion/exclusion criteria to allow us to conduct meaningful moderator analysis of existing studies that would empirically address this hypothesis (e.g., see Hunter and Schmidt, 1990, p. 292). Yet, if we understand their point correctly, then Brownstein et al. (2003) would predict that psychiatrically and medically healthy relatives of schizophrenia patients will show normal antisaccade task performance. In view of the importance of this issue for the status of the antisaccade error deficit as an inheritable endophenotype of schizophrenia, we therefore tested whether medically and psychiatrically healthy relatives of schizophrenia patients show deficits in antisaccade performance. In our 2001 report, we had a large sample that included some relatives with conditions for which potential control participants would have been excluded. Hence, we could narrow our inclusion criterion, comparing performance in "well" relatives to the performance of all relatives and of healthy controls. This tests whether the deficit in schizophrenia relatives is due to inappropriately designed participant inclusion criteria. We previously reported that when relatives and controls were excluded who had psychotic, mood, and substance dependence disorders, relatives still exhibited increased error rates compared with nonpsychiatric controls (Curtis et al., 2001a). For the current investigation, we extended our analyses with the same sample using a selected subgroup of relatives who were screened according to inclusion criteria identical to those applied to controls, except that the controls did not have a first-degree relative who had received psychiatric treatment (relatives, by definition, had a first-degree relative who had received treatment for schizophrenia).

First, we examined group differences between the highly screened relatives and essentially equally screened controls. Second, because it would be pre-

dicted that excluded relatives would exhibit higher error rates than included relatives if inclusion criteria substantially moderated the appearance of deficits, we compared the performance of excluded and included relatives. Third, we conducted analyses to ensure that the observed deficit in relatives was not due to the use of numerous related individuals from a few families. Fourth, we compared the performance of highly screened relatives of poorly performing probands to the performance of highly screened relatives of well performing probands. Finally, in order to parallel as closely as possible the analyses of Brownstein et al., we excluded both relatives and controls with schizotypal characteristics, and compared the antisaccade performance of the resulting groups.

1. Method

1.1. Participants

Methods of participant recruitment and data collection are provided in detail in Curtis et al. (2001a). Briefly, first-degree biological relatives ($n=116$) of DSM-IV diagnosed schizophrenia patients ($n=44$) were recruited through written correspondence followed by phone contact. From this total sample of relatives, relatives ($n=45$; age mean = 41, median = 41, S.D. = 12.9, range = 20–64; 25 women, 20 men; n of probands = 30) were screened and considered medically and psychiatrically healthy (i.e., "included" for the current analyses) if they met the same stringent inclusion criteria as nonpsychiatric controls. In particular, they did not have a DSM-IV mood disorder, any psychotic symptom, a lifetime substance dependence diagnosis, or a current substance abuse diagnosis. Moreover, they reported that they had never received psychiatric treatment. In addition, they were between the ages of 18 and 65, spoke English fluently, had no known history of neurological disease, nor had a systemic disease known to involve CNS functioning, ophthalmologic pathology (e.g., glaucoma, lazy eye), clinically significant head injury, or mental retardation. The nonpsychiatric control group consisted of medically and psychiatrically healthy participants ($n=109$; age mean = 35, median = 31, S.D. = 13.1, range = 18–63; 47 men and 62 women) who were recruited from the community via advertisement posters placed at family practice and other nonpsychiatric medical clinics, trade schools, and churches. Inclusion criteria for controls were identical as for relatives, except that potential controls were excluded if they had a first-degree biological relative who had ever received psychiatric treatment. Medical and psychiatric history relevant to these criteria for both relatives and controls was determined by the Structured Clinical Interview for DSM-IV (SCID), a semi-structured health history screening interview, and review of medical records (where available).

After complete description of the study to the participants, written informed consent was obtained.

1.2. Eye movement assessment

Oculomotor recordings were obtained in a quiet, darkened room. Eye movements were assessed monocularly (right eye) using an Applied Science Laboratories (Eyetrac Model 210) infrared oculography (IROG) monitor mounted on eyeglass frames. Sensors were positioned according to manufacturer specifications (Applied Sciences Laboratory, 1984). Participants' heads were stabilized by a dental bite bar to minimize head movement artifact. In order to reduce artifact and eye dryness, participants wearing contact lenses removed them prior to the session. Eyeblinks were recorded using vertical electro-oculography (VEOG) recordings obtained from the superior and inferior orbital rims of the left eye, with a shin ground. Electrode impedances were required to be below 10 kΩ for each participant. Blink signals were conditioned at a low frequency cutoff of 0.1 Hz and a high frequency cutoff of 1 Hz. Data were digitized off-line at a sampling rate of 256 Hz. The eye tracking measures were derived from the IROG recordings, but VEOG recordings were used to aid in the identification and removal of blinks from the IROG record, as we have previously demonstrated that blinks can masquerade as saccades when only IROG is relied upon (Calkins et al., 2001). A darkened, high-resolution flat-surface color monitor positioned 48 cm from the eyes of the participant was used to present stimuli (0.5° yellow circle, within which there was a small dot subtending a few minutes of visual arc).

The step-antisaccade task was administered in the context of a battery of eye movement tasks. In the

antisaccade task, the target began at a central fixation point. Following a 2- to 3-s pseudorandom interval, a peripheral cue appeared at 10° either left or right in an unpredictable fashion. The central fixation point extinguished contemporaneously with the onset of the peripheral cue, which lasted 2 s. Subjects were instructed not to look at the cue but instead to direct their gaze to the side opposite the cue. The stimulus then returned to central fixation, signaling the beginning of a new trial. One block of 20 trials (10 leftward and 10 rightward) was presented. Preceding the task, a practice trial was administered to ensure that participants were attentive and understood task instructions. The proportion of incorrect reflexive saccades out of all valid trials was computed (see Curtis et al., 2001a, for figure of task). We have previously reported that a subgroup of schizophrenia patients and their relatives from this sample exhibited disproportionately worse performance on the step-antisaccade task in comparison with an overlap task, presumably due to the increased inhibitory load placed on the saccade system (Curtis et al., 2001b).

1.3. Schizotypy assessment

The Schizotypal Personality Questionnaire (SPQ) was used to assess schizotypal personality traits. It is a 74-item self-report instrument that assesses the three dimensions of schizotypy as defined by DSM-III-R (Raine, 1991). We modified the SPQ to include validity scales (MMPI-2 Lie Scale, 15 items; MMPI-2 K Scale, defensiveness, 30 items; Butcher and Williams, 1992) and items modeled after the Jackson Infrequency Scale of the Personality Research Form (Jackson, 1984). Total SPQ scores were based on an unweighted sum of SPQ items endorsed in the pathological direction. Additional details of SPQ scoring and psychometric properties are provided in (Calkins et al., 2003a(in press)). We have reported that the total sample of relatives evidences increased social-interpersonal schizotypal characteristics in comparison with controls (Calkins et al., 2003a(in press)). The SPQ was added to the battery after commencement of antisaccade data collection, so it is available for only a subset of relatives ($n = 109$) and controls ($n = 84$) who also completed the antisaccade task. All diagnostic and oculomotor ratings were made blind to SPQ responses.

2. Results

Preliminary analyses revealed that relatives were significantly older than controls ($t = 2.58$, $df = 152$, $p < 0.01$). However, age was uncorrelated with antisaccade error rate within the relative ($r = 0.04$, $p = 0.82$) and control ($r = 0.02$, $p = 0.87$) groups, and thus was not considered further. Because the groups were balanced by sex (chi-square = 0.13, $p = 0.72$), and there were no differences in antisaccade error rates between males and females within each group (p's>0.05), sex was ignored in subsequent analyses.

Independent samples t-tests were computed to compare group differences in antisaccade error means. Means, significance test results, and effect sizes are presented in Table 2. As can be seen in Table 2, highly screened relatives had a significantly higher antisaccade error rate than controls, indicating that relatives of schizophrenia patients are more impaired even when only relatives meeting stringent control inclusion criteria are included in analyses. Among medically and psychiatrically healthy relatives, the percent of relatives with increased error rate (defined as an error rate of 59%, corresponding to >2 S.D. above the control group mean, see Curtis et al., 2001a) is very similar to the percent obtained using the total sample of relatives (included relatives = 20.0%; total sample = 19.4%).

Excluded relatives were not significantly different in their error rates than relatives who met control inclusion criteria (see Table 2). Thus, relatives who had any of the conditions for which controls would be excluded evidenced comparable error rates to medically and psychiatrically healthy relatives, indicating that the deficit is not moderated by the selection criteria applied in this investigation.

Because multiple relatives per family are represented in the sample of relatives, we conducted analyses to ensure independence of observations, following the method of Brownstein et al. (2003). First, we excluded families with more than one eligible relative per family. There were 21 families in which only one eligible relative participated. As shown in Table 2, the t-test between this subgroup of relatives and controls was highly significant; these selected relatives were significantly worse than controls. Next, among families in which one or more member per family participated, we randomly selected

Table 2
Means and significance tests of relative and control antisaccade error rate

Comparison (Group 1 vs. Group 2)	Group 1			Group 2			Significance test			Effect sizes	
	n	Mean	S.D.	*n*	Mean	S.D.	*t*	*df*	*p*	*d*	d_g
All relatives vs. controls[a]	116	38.20	22.30	109	24.63	17.00	–	–	–	0.68	0.80
Included relatives vs. controls	45	40.42	24.58	109	24.63	17.00	4.57	152	0.001	0.81	0.93
Included vs. excluded relatives	45	40.42	24.58	71	37.12	21.93	0.75	114	0.453	0.14	0.13
Included relatives from families with only one relative vs. controls	21	45.39	26.49	109	24.63	17.00	4.63	128	0.001	1.10	1.22
Randomly selected included relatives (lowest random number) from each family vs. controls	30	42.10	23.73	109	24.63	17.00	4.55	137	0.001	0.94	1.03
Randomly selected included relatives (highest random number) from each family vs. controls	30	44.15	27.85	109	24.63	17.00	4.78	137	0.001	0.99	1.15
Included relatives of poor performing probands vs. included relatives of good performing probands	15	50.92	29.38	23	31.10	13.81	2.81	36	0.008	0.92	1.44
Included relatives (also screened for schizotypal features) vs. controls (also screened for schizotypal features)[b]	34	37.65	22.89	73	24.13	17.94	3.32	105	0.001	0.69	0.75

Included relatives are the subset of relatives from the total sample meeting control inclusion criteria (except for psychiatric treatment of a first degree relative). Randomly selected relatives were selected from each family using the same method as Brownstein et al. (2003). Specifically, participants were assigned a random unique four-digit identification number; one included relative from each family was selected using this identification number. In the lowest random number analysis, we used the score of the included relative with the lowest identification number. In the highest random number analysis, we used the score of the relative with the highest identification number. d = Cohen's d, d_g = Glass' d.

[a] As described in Curtis et al. (2001).

[b] Subsample of relatives and controls who were administered both the antisaccade task and Schizotypal Personality Questionnaire.

one highly screened relative per family (i.e., first using the eligible relative in the family who had the lowest randomly assigned subject identification number and then again using the eligible relative in the family who had the highest randomly assigned subject identification number; each subject identification number is a randomly generated four-digit number). As can be seen in Table 2, both samples of relatives produced significantly higher antisaccade error rates than controls.

We next differentiated probands with antisaccade error rates >59% (2 S.D. above control group mean) from probands with antisaccade error rate falling below this cutoff. Using only relatives meeting control inclusion criteria, we found that the relatives of poor performing probands had significantly greater error rates than relatives of good performing probands (see Table 2), as in our previous report.

Finally, we used the SPQ to exclude participants for schizotypal characteristics. Raine (1991) reported that in a community sample, 55% of individuals scoring within the top 10% of total SPQ scores met criteria for DSM-III-R schizotypal personality disorder. Thus, after screening profiles for validity (see Calkins et al., 2003a(in press)), we conservatively excluded the highest scoring relatives and controls in our sample, i.e., those whose scores fell within the top 10% of control group scores. Among participants included in the aforementioned analyses, 11 controls and an additional 9 relatives were excluded based on SPQ performance. As can be seen in Table 2, this most select group of relatives exhibited significantly increased error rates in comparison with nonpsychiatric controls.

3. Discussion

In the current investigation, the biological first-degree relatives of schizophrenia patients exhibited increased reflexive errors on the antisaccade task, even when only strictly screened medically and psychiatrically healthy relatives were included in analyses. The percent of highly screened relatives with

increased error rate was very similar to the percent obtained in the total sample. Moreover, because identical inclusion criteria were applied to relatives and controls, and because no difference was observed between relatives included or excluded according to control screening criteria, the results are not supportive of the hypothesis that asymmetrical inclusion criteria accounts for the finding of a deficit in schizophrenia relatives (Brownstein et al., 2003). Thus, the results are supportive of the suggestion that the antisaccade deficit evidences heritability in schizophrenia families as reflected by deviance in relatives.

We employed strict inclusion criteria in comparison with some other investigations. Nonetheless, the mean error rate of controls (24.6%) is very similar to the error rate of controls in the investigation of Brownstein et al. (26.3%) and to the error rate of controls averaged across investigations (22.5%) (see Table 1). Thus, it is unlikely that relatives are comparatively worse only because "super-normal" control groups leads to atypical control group performance. As can be seen in Table 1, the difference between comparisons yielding increased error rates in relatives and the comparisons yielding no group differences appears to lie, on average, in the performance of the *relatives*, not in the performance of the controls. The current investigation suggests that the impairment in relative's performance is not attributable to known medical or psychiatric conditions. Moreover, while only some previous studies corrected for age, we agree with Brownstein et al. (2003) who suggested that it is unlikely that participant age differences account for their discrepant result. The difference between age corrected and uncorrected error rates was not substantial in their sample and age was uncorrelated with antisaccade error rate in our sample. Particular antisaccade task manipulations (e.g., overlap, step) have been found to impact effect size magnitude (e.g., McDowell et al., 1999; Curtis et al., 2001b), but the current investigation, like Brownstein et al. and the majority of studies in this domain, employed a step antisaccade task.

One notable difference, however, between the relatives in the Brownstein et al. study and all other studies in this domain is that the relatives in the former were derived from a proband group that included an unspecified number of patients with schizoaffective disorder. Importantly, the authors narratively state that relatives of schizophrenia and schizoaffective patients did not differ from each other in antisaccade error rate and thus were combined for analyses. Group means and significance tests were not reported, however, so effect sizes could not be calculated comparing controls separately to (1) relatives of patients with schizophrenia and (2) relatives of patients with schizoaffective disorder. The genetic relationship between schizoaffective disorder and schizophrenia is currently unknown, but indeed, there is evidence to suggest that there may be some overlap in susceptibility for schizophrenia, schizoaffective and bipolar disorders (e.g., Bailer et al., 2002; Berrettini, 2000; Gershon, 2000). If the antisaccade deficit taps genetic susceptibility that is unique to schizophrenia, unshared with schizoaffective disorder, then we might not expect the relatives of schizoaffective patients to exhibit increased error rates. Thus, the inclusion of schizoaffective families in studies of antisaccade performance could dilute the appearance of the deficit. Conversely, if the antisaccade deficit is a reflection of genetic susceptibility that is shared among schizophrenia and schizoaffective disorder, then the relatives of both groups of patients could be expected to exhibit the antisaccade deficit. Consequently, the boundaries between shared and unique genetic susceptibility among psychotic disorders could potentially be elucidated through future studies that differentiated schizoaffective from schizophrenia family members and examined the candidate endophenotypes most strongly implicated in schizophrenia, such as antisaccade performance.

Another notable difference between the Brownstein et al. investigation and most other relative studies is that Brownstein et al. excluded relatives with schizophrenia related disorders, including schizotypal, paranoid and schizoid personality disorders (relatives were included who had a history of other Axis I disorders, except particular substance related disorders). As can be seen in Table 1, the effect sizes and error rates obtained by Brownstein et al. are consistent with those obtained in both of the other samples in which spectrum relatives were excluded (Thaker et al., 1996, 2000). Moreover, as mentioned, several studies have reported increased antisaccade error rates in community subjects who have schizotypal characteristics (Brenner et al., 2001; Cadenhead et al., 2002; Gooding, 1999; Gooding and Tallent,

2001; Larrison et al., 2000; O'Driscoll et al., 1998), suggesting that there may be an association between schizophrenia spectrum conditions and antisaccade performance. Nonetheless, the exclusion of relatives with spectrum conditions may not wholly account for the discrepant result of Brownstein et al. In the current investigation, relatives with psychotic disorders and SPQ assessed schizotypal characteristics were excluded from analyses, with little effect on relative-control group differences. The genetic significance of the relationship between schizophrenia spectrum disorders and antisaccade performance in schizophrenia families is itself an important empirical question (e.g., Cadenhead, 2002) given independent lines of evidence that both antisaccade error (see Table 1) and schizotypal characteristics (e.g., Kendler et al., 1993, 1995; Webb and Levinson, 1993) are increased in the relatives of schizophrenia patients.

Relatives were excluded in the present study in order to test a particular hypothesis. However, schizophrenia research has not yet provided sufficient knowledge about the genetic transmission of schizophrenia and related disorders to summarily exclude particular relatives from assessment based on their clinical presentation. Certainly, we must be concerned that without attending to the psychiatric and medical histories of research volunteers, we might taint the assessment and interpretation of candidate endophenotypes. A recommended research approach balancing these concerns is to conduct family studies in which relevant biological relatives are assessed regardless of medical or psychiatric history. This approach reduces the risk of the a priori exclusion of potentially genetically informative relatives, and provides for post hoc analyses that empirically address whether particular medical or psychiatric conditions are associated with poor performance on salient measures.

Using this method, we found that the medically and psychiatrically healthy relatives of schizophrenia patients evidence saccadic disinhibition in the antisaccade task, consistent with the aggregate of studies in this domain and with the suggestion that the antisaccade deficit is a candidate endophenotype of schizophrenia. This work therefore adds to a growing body of empirical evidence indicating that the antisaccade deficit exhibits properties of an endophenotype. The deficit has been reported in first-episode (Broerse et al., 2002; Hutton et al., 1998, 2002) and remitted (Curtis et al., 2001b) schizophrenia patients, suggesting that it has trait-like properties and is not merely a reflection of chronic illness or clinical state. Moreover, consistent with a trait-like deficit, antisaccade performance has been reported as evidencing adequate temporal stability (Calkins et al., 2003b; Thaker et al., 1989) and has not been found to be associated with antipsychotic medication (Allen et al., 1996; Broerse et al., 2002; Clementz et al., 1992; Fukushima et al., 1988; Karoumi et al., 1998, 2001; Maruff et al., 1998; McDowell and Clementz, 1997; Nkam et al., 2001; Raemaekers et al., 2002), although some medications may actually *improve* antisaccade performance (e.g., Burke and Reveley, 2002; Chaudhry et al., 2002). Thus, by fulfilling essential criteria of an endophenotype (e.g., Gottesman and Gould, 2003; Iacono, 1998), saccadic disinhibition in the antisaccade task appears to be a promising candidate endophenotype that can assist in the identification of susceptibility loci contributing to the development of schizophrenia.

Acknowledgements

Data collection and processing were supported by grants from the National Institute of Mental Health (MH 49738 and MH 17069), an Eva O. Miller Fellowship (CEC), and a University of Minnesota Graduate School Doctoral Dissertation Fellowship (MEC). Data analyses and preparation of this manuscript were supported by Neuropsychiatry Post-Doctoral Traineeship MH 19112 and a Scottish Rite Schizophrenia Research Fellowship (MEC). We thank the participants of this study for their time and effort, and Joshua Brosz, Heather Conklin, Kate Delaney, Thomas Dinzeo, Kathleen Feil, Joanna Fiszdon, Amy Hallberg, David Lake, Boyd Lebow, Craig Moen, and Beth Snitz for their contributions to participant recruitment and data collection.

References

Allen, J., Lambert, A., Johnson, F., Schmidt, K., Nero, K., 1996. Antisaccadic eye movements and attentional asymmetry in schizophrenia in three Pacific populations. Acta Psychiatr. Scand. 94, 258–265.

Bailer, U., Leisch, F., Meszaros, K., Lenzinger, E., Willinger, U., Strobl, R., Heiden, A., Gebhardt, C., Doge, E., Fuchs, K., Sieghart, W., Kasper, S., Hornik, K., Aschauer, H.N., 2002. Genome scan for susceptibility loci for schizophrenia and bipolar disorder. Biol. Psychiatry 52, 40–52.

Berrettini, W.H., 2000. Genetics of psychiatric disease. Annu. Rev. Med. 51, 465–479.

Brenner, C.A., McDowell, J.E., Cadenhead, K.S., Clementz, B.A., 2001. Saccadic inhibition among schizotypal personality disorder subjects. Psychophysiology 38, 399–403.

Broerse, A., Holthausen, E.A., van den Bosch, R.J., den Boer, J.A., 2001. Does frontal normality exist in schizophrenia? A saccadic eye movement study. Psychiatry Res. 103, 167–178.

Broerse, A., Crawford, T.J., den Boer, J.A., 2002. Differential effects of olanzapine and risperidone on cognition in schizophrenia? A saccadic eye movement study. J. Neuropsychiatry Clin. Neurosci. 14, 454–460.

Brownstein, J., Krastoshevsky, O., McCollum, C., Kundamel, S., Matthysse, S., Mendell, N.R., Levy, D.L., 2003. Antisaccade performance is abnormal in schizophrenia patients but not in their biological relatives. Schizophr. Res. 63, 13–25.

Burke, J.G., Reveley, M.A., 2002. Improved antisaccade performance with risperidone in schizophrenia. J. Neurol. Neurosurg. Psychiatry 72, 449–454.

Butcher, J., Williams, C., 1992. Essentials of MMPI-2 and MMPI-A Interpretation. University of Minnesota Press, Minneapolis, MN.

Cadenhead, K.S., 2002. Vulnerability markers in the schizophrenia spectrum: implications for phenomenology, genetics, and the identification of the schizophrenia prodrome. Psychiatr. Clin. North Am. 25, 837–853.

Cadenhead, K.S., Light, G.A., Geyer, M.A., McDowell, J.E., Braff, D.L., 2002. Neurobiological measures of schizotypal personality disorder: defining an inhibitory endophenotype? Am. J. Psychiatr. 159, 869–871.

Calkins, M.E., Iacono, W.G., 2000. Eye movement dysfunction in schizophrenia: a heritable characteristic for enhancing phenotype definition. Am. J. Med. Genet. 97, 72–76.

Calkins, M.E., Katsanis, J., Hammer, M.A., Grove, W.M., Iacono, W.G., 2001. The misclassification of blinks as saccades: implications for investigations of eye movement dysfunction in schizophrenia. Psychophysiology 38, 761–767.

Calkins, M.E., Curtis, C.E., Grove, W.M., Iacono, W.G., 2003a. The multiple dimensions of schizotypy in the first-degree biological relatives of schizophrenia patients. Schizophr. Bull. (In Press).

Calkins, M.E., Iacono, W.G., Curtis, C.E., 2003b. Smooth pursuit and antisaccade performance evidence trait stability in schizophrenia patients and their relatives. Int. J. Psychophysiol. 49, 139–146.

Chaudhry, I.B., Soni, S.D., Hellewell, J.S., Deakin, J.F., 2002. Effects of the 5HT antagonist cyproheptadine on neuropsychological function in chronic schizophrenia. Schizophr. Res. 53, 17–24.

Clementz, B.A., 1998. Psychophysiological measures of (dis)inhibition as liability indicators for schizophrenia. Psychophysiology 35, 648–668.

Clementz, B.A., Grove, W., Iacono, W.G., Sweeney, J., 1992. Smooth pursuit eye movement dysfunction and liability for schizophrenia: implications for genetic modeling. J. Abnorm. Psychology 101, 117–129.

Clementz, B.A., McDowell, J.E., Zisook, S., 1994. Saccadic system functioning among schizophrenia patients and their first-degree biological relatives. J. Abnorm. Psychology 103, 277–286.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Lawrence Erlbaum, Hillsdale NJ.

Crawford, T.J., Haeger, B., Kennard, C., Reveley, M.A., Henderson, L., 1995a. Saccadic abnormalities in psychotic patients: I. Neuroleptic-free psychotic patients. Psychol. Med. 25, 461–471.

Crawford, T.J., Haeger, B., Kennard, C., Reveley, M.A., Henderson, L., 1995b. Saccadic abnormalities in psychotic patients: II. The role of neuroleptic treatment. Psychol. Med. 25, 473–483.

Crawford, T.J., Puri, B., Nijran, K.S., Jones, B., Kennard, C., Lewis, S.W., 1996. Abnormal saccadic distractibility in patients with schizophrenia: a 99mTc-HMPAO SPET study. Psychol. Med. 26, 265–277.

Crawford, T.J., Sharma, T., Puri, B.K., Murray, R.M., Berridge, D.M., Lewis, S.W., 1998. Saccadic eye movements in families multiply affected with schizophrenia: the Maudsley family study. Am. J. Psychiatr. 155, 1703–1710.

Curtis, C.E., Calkins, M.E., Grove, W.M., Feil, K.J., Iacono, W.G., 2001a. Saccadic disinhibition in acute and remitted schizophrenia patients and their first-degree biological relatives. Am. J. Psychiatr. 158, 100–106.

Curtis, C.E., Calkins, M.E., Iacono, W.G., 2001b. Saccadic disinhibition in schizophrenia patients and their first-degree biological relatives: a parametric study of the effects of increasing inhibitory load. Exp. Brain Res. 137, 228–236.

Depatie, L., O'Driscoll, G.A., Holahan, A.-L.V., Atkinson, V., Thavundayil, J.X., Kin, N.N.Y., Lal, S., 2002. Nicotine and behavioral markers of risk for schizophrenia: a double-blind, placebo-controlled, cross-over study. Neuropsychopharmacology 27, 1056–1070.

Fukushima, J., Fukushima, K., Chiba, T., Tanaka, S., Yamashita, I., Kato, M., 1988. Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. Biol. Psychiatry 23, 670–677.

Fukushima, J., Fukushima, K., Morita, N., Yamashita, I., 1990. Further analysis of the control of voluntary saccadic eye movements in schizophrenic patients. Biol. Psychiatry 28, 943–958.

Fukushima, J., Fukushima, K., Morita, N., Yamashita, I., 1991. Disturbances in the control of saccadic eye movement and eye–head coordination in schizophrenics. J. Vestibular Res. Equilib. Orientat. 1, 171–180.

Fukushima, J., Fukushima, K., Miyasaka, K., Yamashita, I., 1994. Voluntary control of saccadic eye movement in patients with frontal cortical lesions and Parkinsonian patients in comparison with that in schizophrenics. Biol. Psychiatry 36, 21–30.

Gershon, E.S., 2000. Bipolar illness and schizophrenia as oligogenic diseases: implications for the future. Biol. Psychiatry 47, 240–244.

Gooding, D.C., 1999. Antisaccade task performance in questionnaire-identified schizotypes. Schizophr. Res., 35.

Gooding, D.C., Tallent, K.A., 2001. The association between antisaccade task and working memory task performance in schizophrenia and bipolar disorder. J. of Nerv. Ment. Dis. 189, 8–16.

Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiatr. 160, 1–10.

Hunter, J.E., Schmidt, F.L., 1990. Methods of Meta-Analysis: Correcting Error and Bias in Research Findings. Sage, Newbury Park, CA.

Hutton, S.B., Crawford, T.J., Puri, B.K., Duncan, L.J., Chapman, M., Kennard, C., Barnes, T.R., Joyce, E.M., 1998. Smooth pursuit and saccadic abnormalities in first-episode schizophrenia. Psychol. Med. 28, 685–692.

Hutton, S.B., Joyce, E.M., Barnes, T.R., Kennard, C., 2002. Saccadic distractibility in first-episode schizophrenia. Neuropsychologia 40, 1729–1736.

Iacono, W.G., 1998. Identifying genetic risk for psychopathology. In: Routh, D.K., DeRubeis, R.J. (Eds.), The Science of Clinical Psychology: Accomplishments and Future Directions. American Psychological Association, Washington, DC, pp. 3–22.

Jackson, D.N., 1984. Jackson Personality Research Form Manual. Research Psychologists Press, Port Huron, MI.

Karoumi, B., Ventre-Dominey, J., Vighetto, A., Dalery, J., d'Amato, T., 1998. Saccadic eye movements in schizophrenic patients. Psychiatry Res. 77, 9–19.

Karoumi, B., Saoud, M., d'Amato, T., Rosenfeld, F., Denise, P., Gutknecht, C., Gaveau, V., Beaulieu, F.E., Dalery, J., Rochet, T., 2001. Poor performance in smooth pursuit and antisaccadic eye-movement tasks in healthy siblings of patients with schizophrenia. Psychiatry Res. 101, 209–219.

Katsanis, J., Kortenkamp, S., Iacono, W.G., Grove, W.M., 1997. Antisaccade performance in patients with schizophrenia and affective disorder. J. Abnorm. Psychology 106, 468–472.

Kendler, K.S., 1985. Diagnostic approaches to schizotypal personality disorder: a historical perspective. Schizophr. Bull. 11, 538–553.

Kendler, K.S., McGuire, M., Gruenberg, A.M., O'Hare, A., Spellman, M., Walsh, D., 1993. The Roscommon Family Study: III. Schizophrenia-related personality disorders in relatives. Arch. Gen. Psychiatry 50, 781–788.

Kendler, K., Neale, M., Walsh, D., 1995. Evaluating the spectrum concept of schizophrenia in the Roscommon family study. Am. J. Psychiatr. 152, 749–754.

Klein, C., Heinks, T., Andresen, B., Berg, P., Moritz, S., 2000a. Impaired modulation of the saccadic contingent negative variation preceding antisaccades in schizophrenia. Biol. Psychiatry 47, 978–990.

Klein, C.H., Brugner, G., Foerster, F., Muller, W., Schweickhardt, A., 2000b. The gap effect in pro-saccades and anti-saccades in psychometric schizotypes. Biol. Psychol. 55, 25–39.

Larrison, A.L., Ferrante, C.F., Briand, K.A., Sereno, A.B., 2000. Schizotypal traits, attention and eye movements. Prog. Neuropsychopharmacol. Biol. Psychiatry 24, 357–372.

Levy, D.L., Mendell, N.R., LaVancher, C.A., Brownstein, J., Krastoshevsky, O., Teraspulsky, L., McManus, K.S., Lo, Y., Bloom, R., Matthysse, S., Holzman, P.S., 1998. Disinhibition in antisaccade performance in schizophrenia. In: Lenzenweger, M.F., Dworkin, R.H. (Eds.), Origins and Development of Schizophrenia: Advances in Experimental Psychopathology, pp. 185–210.

Malone, S.M., Iacono, W.G., 2002. Error rate on the antisaccade task: heritability and developmental change in performance among preadolescent and late-adolescent female twin youth. Psychophysiology 39, 664–673.

Manoach, D.S., Lindgren, K.A., Cherkasova, M.V., Goff, D.C., Halpern, E.F., Intriligator, J., Barton, J.J., 2002. Schizophrenic subjects show deficient inhibition but intact task switching on saccadic tasks. Biol. Psychiatry 51, 816–826.

Maruff, P., Danckert, J., Pantelis, C., Currie, J., 1998. Saccadic and attentional abnormalities in patients with schizophrenia. Psychol. Med. 28, 1091–1100.

Matsue, Y., Saito, H., Osakabe, K., Awata, S., Ueno, T., Matsuoka, H., Chiba, H., Fuse, Y., Sato, M., 1994. Smooth pursuit eye movements and voluntary control of saccades in the antisaccade task in schizophrenic patients. Jpn. J. Psychiatry Neurol. 48, 13–22.

McDowell, J.E., Clementz, B.A., 1997. The effect of fixation condition manipulations on antisaccade performance in schizophrenia: studies of diagnostic specificity. Exp. Brain Res. 115, 333–344.

McDowell, J.E., Myles-Worsley, M., Coon, H., Byerley, W., Clementz, B.A., 1999. Measuring liability for schizophrenia using optimized antisaccade stimulus parameters. Psychophysiology 36, 138–141.

McDowell, J.E., Brown, G.G., Paulus, M., Martinez, A., Stewart, S.E., Dubowitz, D.J., Braff, D.L., 2002. Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. Biol. Psychiatry 51, 216–223.

Muller, N., Riedel, M., Eggert, T., Straube, A., 1999. Internally and externally guided voluntary saccades in unmedicated and medicated schizophrenic patients: Part II. Saccadic latency, gain, and fixation suppression errors. Eur. Arch. Psychiatry Clin. Neurosci. 249, 7–14.

Nieman, D.H., Bour, L.J., Linszen, D.H., Goede, J., Koelman, J.H., Gersons, B.P., Ongerboer de Visser, B.W., 2000. Neuropsychological and clinical correlates of antisaccade task performance in schizophrenia. Neurology 54, 866–871.

Nkam, I., Thibaut, F., Denise, P., Van Der Elst, A., Segard, L., Brazo, P., Menard, J., Thery, S., Halbeck, I., Delamilleure, P., Vasse, T., Etard, O., Dollfus, S., Champion, D., Levillain, D., Petit, M., 2001. Saccadic and smooth-pursuit eye movements in deficit and non-deficit schizophrenia. Schizophr. Res. 48, 145–153.

O'Driscoll, G.A., Lenzenweger, M.F., Holzman, P.S., 1998. Antisaccade and smooth pursuit eye tracking and schizotypy. Arch. Gen. Psychiatry 55, 837–843.

Radant, A.D., Claypoole, K., Wingerson, D.K., Cowley, D.S., Roy-Byrne, P.P., 1997. Relationships between neuropsychological and oculomotor measures in schizophrenia patients and normal controls. Biol. Psychiatry 42, 797–805.

Raemaekers, M., Jansma, J.M., Cahn, W., Van der Geest, J.N., van der Linden, J.A., Kahn, R.S., Ramsey, N.F., 2002. Neuronal substrate of the saccadic disinhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. Arch. Gen. Psychiatry 59, 313–320.

Raine, A., 1991. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophr. Bull. 17, 555–564.

Ross, R.G., Harris, J.G., Olincy, A., Radant, A., Adler, L.E.,

Freedman, R., 1998. Familial transmission of two independent saccadic abnormalities in schizophrenia. Schizophr. Res. 30, 59–70.

Rosse, R.B., Schwartz, B.L., Kim, S.Y., Deutsch, S.I., 1993. Correlation between antisaccade and Wisconsin card sorting test performance in schizophrenia. Am. J. Psychiatr. 150, 333–335.

Sereno, A.B., Holzman, P.S., 1995. Antisaccades and smooth pursuit eye movements in schizophrenia. Biol. Psychiatry 37, 394–401.

Sweeney, J., Mintun, M., Kwee, S., Wiseman, M., Brown, D., Rosenberg, D., Carl, J., 1996. Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. J. Neurophysiol. 75, 454–468.

Thaker, G.K., Kirkpatrick, B., Buchanan, R.W., Ellsberry, R., Lahti, A., Tamminga, C., 1989. Oculomotor abnormalities and their clinical correlates in schizophrenia. Psychopharmacol. Bull. 25, 491–497.

Thaker, G., Buchanan, R., Kirkpatrick, B., Tamminga, C.A., 1990. Oculomotor performance in schizophrenia. In: Schulz, C.S., Tamminga, C.A. (Eds.), Schizophrenia: scientific progress, pp. 115–123.

Thaker, G.K., Cassady, S., Adami, H., Moran, M., Ross, D., 1996. Eye movements in spectrum personality disorder: comparison of community subjects and relatives of schizophrenic patients. Am. J. Psychiatr. 153, 362–368.

Thaker, G.K., Ross, D.E., Cassady, S.L., Adami, H.M., Medoff, D.R., Sherr, J., 2000. Saccadic eye movement abnormalities in relatives of patients with schizophrenia. Schizophr. Res. 45, 235–244.

Webb, C., Levinson, D., 1993. Schizotypal and paranoid personality disorder in the relatives of patients with schizophrenia and affective disorders: a review. Schizophr. Res. 11, 81–92.