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Smooth pursuit and antisaccade performance evidence trait stability in schizophrenia patients and their relatives

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Abstract

Several forms of eye movement dysfunction (EMD) have been widely regarded as candidate endophenotypes of schizophrenia, ultimately capable of identifying individuals carrying schizophrenia susceptibility genes and elucidating the pathophysiology of schizophrenia. As an indication of their trait-like status, candidate endophenotypes optimally evidence stability over time. However, there have been few published reports of test–retest reliability of several forms of EMD in schizophrenia patients and their relatives. In the current investigation, schizophrenia patients and the first-degree biological relatives of schizophrenia patients ($n=15$) were administered by an eye movement battery including smooth pursuit, antisaccade and prosaccade tasks, and re-tested after an average of 1.82 years (range = 14–24 months). Adequate test–retest reliabilities of smooth pursuit closed-loop gain (Pearson $r=0.72$), antisaccade error rate ($r=0.73$), saccade reaction time to correct antisaccade responses ($r=0.73$), and prosaccade hypometria ($r=0.72$) were observed. Lower reliabilities were obtained for smooth pursuit open-loop gain ($r=0.52$) and prosaccade reaction time ($r=0.43$). The results are supportive of the trait-like characteristics of particular forms of EMD in schizophrenia families and of the candidacy of EMD as an endophenotypic marker of schizophrenia.

Keywords: Schizophrenia; Smooth pursuit; Antisaccade; Saccade; Endophenotype; Reliability

1. Smooth pursuit and antisaccade performance evidence trait stability in schizophrenia patients and their relatives

Eye movement dysfunction (EMD) is widely regarded as one of the most promising endophenotypic or biological markers of schizophrenia (Erlenmeyer-Kimling and Cornblatt, 1987; Holzman et al., 1987; Iacono, 1988, 1983, 1998; Iacono and Clementz, 1993; Siever and Coursey, 1985; Siever et al., 1982; Venables, 1991). Endophenotypes typically derive from genetically informed laboratory measures that are likely to reflect the action of genes pre-disposing an individual to a specific disorder even in the absence of diagnosable pathology. This characteristics, therefore, identifies gene carriers who have the disorder as well as those who do not demonstrate observable signs,

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and optimally will be useful as a tool in the search for schizophrenia susceptibility genes. If a candidate endophenotype is an enduring marker of genetic vulnerability reflective of the underlying pathology of schizophrenia, it should ideally exhibit trait-like properties, including temporal stability, in affected and at-risk individuals (Iacono, 1998).

Global smooth pursuit EMD, which is a deviation in the overall extent to which subject eye position is congruent with target position during a smooth pursuit task, has been described as evidencing stability over time periods as long as two years in schizophrenia patients (Clementz and Sweeney, 1990; Gooding et al., 1994; Iacono, 1985; Iacono and Clementz, 1993; Levy et al., 1993). However, there have been very few investigations of the temporal stability of more precise measures of smooth pursuit EMD or of other forms of EMD (e.g. antisaccade) in schizophrenia patients.

The integrity of the maintenance of smooth pursuit is reflected by closed-loop gain, which is an index of the temporal synchrony of the eye and the target during pursuit, estimated by the ratio of the eye velocity to target velocity. When eye velocity is unable to maintain target velocity, the ratio falls below 1.0, reflective of low gain pursuit, and suggestive of an abnormality somewhere in the smooth pursuit system. Numerous investigations have reported that schizophrenia patients evidence reduced closed loop gain (for narrative reviews see Clementz and Sweeney, 1990; Hutton and Kennard, 1998; Iacono and Clementz, 1993; Levy et al., 1993). Three investigations of test–retest reliability in schizophrenia patients have supported the trait stability of closed-loop gain deficits, reporting retest coefficients ranging from 0.57 to 0.84 over test–retest periods of 21 days to two years (Campion et al., 1992; Sweeney et al., 1994, 1998). In the only published investigation of EMD temporal stability in schizophrenia relatives, good stability of closed-loop gain was reported over an average of 1.1 years ($r=0.76$, O'Driscoll et al., 1999). In addition, high one-month retest stability has been reported in healthy participants ($r=0.97$) (Roy-Byrne et al., 1995).

In contrast to closed-loop gain, which assesses the maintenance of pursuit, open-loop gain is the average acceleration during the first 100 ms of pursuit initiation. It is termed open-loop as visual feedback does not occur during this epoch; because the pursuit system cannot be updated about its performance, eye movements that occur during pursuit initiation are controlled solely by sensory input of visual motion signals (Sweeney et al., 1999). Only one investigation of retest reliability of open-loop performance in schizophrenia patients has been reported. Sweeney et al. (1998) assessed the proportion of trials in which pursuit was initiated prior to the first catch-up saccade and found low ($r<0.27$) two-year test–retest reliability. However, this index of open-loop gain is different from the acceleration index that has been reported to be impaired in schizophrenia patients (Clementz and McDowell, 1994; Levin et al., 1988) and their relatives (Clementz et al., 1995). In contrast, using open-loop acceleration, Roy-Byrne et al. (1995) reported adequate one-month retest stability in healthy participants (range of *r*'s for two targets = 0.76–0.83). Thus, despite the suggestion of trait stability of open loop acceleration in healthy participants, its status in schizophrenia patients and their relatives remains unknown.

Increased reflexive errors on the antisaccade task, which requires the participant to generate a saccade in the direction opposite of target motion, have been reported in schizophrenia patients (e.g. Crawford et al., 1995; Curtis et al., 2001a,b; McDowell and Clementz, 1997; McDowell et al., 1999) and their relatives (e.g. Curtis et al., 2001a,b; McDowell and Clementz, 1997; 1999). Increased saccadic reaction time (SRT) to correct responses, but not to error responses, has also been described in schizophrenia patients (e.g. Curtis et al., 2001a, McDowell and Clementz, 1997, Sereno and Holzman, 1995). Only two investigations have reported test–retest reliabilities of antisaccade measures in samples that include schizophrenia patients. Thaker et al. reported high 1-year test–retest correlations of antisaccade error rate ($r>0.75$) and latency ($r>0.75$) in a group of psychiatric patients, not otherwise delineated (Thaker et al., 1989). In a later investigation, this research group reported a high one-week test–retest reliability ($r=0.9$) of antisaccade error rate

in a combined sample of schizophrenia patients without tardive dyskinesia, schizophrenia patients with tardive dyskinesia, and healthy participants (Thaker et al., 1990). Thus, though supportive of the trait-like status of antisaccade performance in general, neither of these two investigations disentangled the performance of schizophrenia patients from that of other participants. In healthy participants, Roy-Byrne et al. reported a low 1-month test–retest reliability ($r=0.15$) of reflexive saccades, possibly due to the infrequent reflexive errors generated by this participant group (Roy-Byrne et al., 1995). Response latencies evidenced adequate test–retest stability in that investigation ($r=0.62$). Although there is other evidence supportive of the trait-like status of antisaccade deficits in schizophrenia (e.g. presence in remitted patients, Curtis et al., 2001a, high heritability in normal twins, Malone and Iacono, 2002), together, the results of these three investigations render the test–retest stability of antisaccade parameters in schizophrenia patients unclear. Moreover, previous investigations have not differentiated SRT to correct responses from SRT to error responses in the antisaccade paradigm, despite that these variables appear to differ in their discrimination of schizophrenia patients from controls.

The latency and accuracy of reflexive visually guided saccades, as elicited by regular visually guided saccade paradigms, have generally been viewed as normal in schizophrenia patients (e.g. Clementz, 1998, Hutton and Kennard, 1998, McDowell et al., 2002). However, reports in which prosaccades are normal are not ubiquitous; several studies have suggested that decreased accuracy of visually guided reflexive saccades may occur in at least a subset of patients (e.g. Arolt et al., 1998; Crawford et al., 1995). To our knowledge, no published reports have examined the test–retest stability of visually guided saccade hypometria in schizophrenia patients and their relatives. Adequate one-year test–retest reliability of prosaccade SRT ($r>0.75$) has been reported in the mixed sample of Thaker et al. (1989), but no studies have been reported in a more homogeneous group of patients and relatives.

Thus, the contribution of the current investigation was to assess the long-term test–retest stability of EMD in schizophrenia patients and their relatives using a battery of eye movement tasks. The participants were fifteen individuals from a larger family study of psychophysiological, neuropsychological and behavioral indices of risk for schizophrenia who were re-tested after an average of 1.82 years (range = 14–28 months). Methods of participant recruitment and data collection are provided in detail in Curtis et al. (2001a). Briefly, schizophrenia patients ($n=7$; 86% male; mean age = 32.13, S.D. = 6.44) were recruited from acute-care units of a regional metropolitan hospital. All patients met Diagnostic and Statistical Manual for Mental Disorders–Fourth edition (American Psychiatric Association, 1994) criteria for schizophrenia (schizophrenia subtypes: undifferentiated $n=3$, paranoid $n=3$, disorganized $n=1$), as determined by the Structured Clinical Interview for DSM-IV (First et al., 1995) and chart review. First-degree biological relatives ($n=8$; 25% male; mean age = 41.88, S.D. = 14.60) of schizophrenia patients were recruited through written correspondence followed by phone contact.

Oculomotor recordings were obtained in a quiet, darkened room, using both infrared (IROG) and electro-oculographic (EOG) recording techniques. Eye movements were assessed monocularly (right eye) using an Applied Science Laboratories (Eyetrac Model 210) infrared monitor mounted on eyeglass frames. Sensors were positioned according to manufacturer specifications (Applied Sciences Laboratory, 1984). Participants' heads were stabilized throughout the procedure by a dental bite bar to minimize head movement artifact. Contact lenses, if worn, were removed prior to each session in order to minimize artifact and eye dryness. The vertical electro-oculography (VEOG) recordings were 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 cut-off 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. VEOG recordings were, however, used to aid in the identification and removal of blinks from the IROG record as we

have previously demonstrated that without the aid of VEOG, blinks can masquerade as saccades (Calkins et al., 2001). All stimuli (0.5° yellow circle, within which there was a small dot subtending a few minutes of visual arc) were presented on a darkened high-resolution flat-surface color monitor positioned 48 cm from the eyes of the participant. None of the participant reported their difficulty in seeing the stimuli.

Closed-loop gain was obtained from a step-sweep task. In this task, the target began 10° to the left or right of central fixation. The target jumped to 12.5° (the step) and then immediately began moving in the opposite direction at a constant velocity of 16 deg/s (the sweep) for 20° of visual angle. It paused at the extreme for 1.5 s prior to the next step, which signaled the beginning of the next trial. One block of 10 trials alternating leftward (five trials) and rightward (five trials) was administered. After the removal of blinks, saccades (650 deg/s^2 acceleration criteria), and other artifacts, closed-loop gain (eye velocity/target velocity) was derived.

Open-loop gain was assessed by a step-ramp task. In this task, the target began at central fixation. Following a 2–3 s pseudorandom interval, the target jumped either left or rightward either 2.5 or 4.0° (the step) and then immediately began moving in the opposite direction (the ramp) at a constant velocity of 12 or 24 deg/s. The target then returned to central fixation for the start of the next trial. This type of ramp task provided for the analysis of pursuit initiation prior to the first saccade that is generated with the onset of ramp motion (Rashbass, 1961). One block was administered composed of 12 trials, which were pseudorandomly distributed so as to be unpredictable in both direction (six trials right, six trials left) and velocity (six trials at each velocity). Thus, unlike the sweep task, the ramp task is unpredictable and described as optimal for obtaining open-loop gain (Clementz et al., 1994). Immediately following the target step, pursuit is initiated in the direction of target motion. Open-loop gain was the mean acceleration during the first 100 ms following pursuit initiation (i.e. the point at which eye acceleration exceeded zero) but prior to any saccades. Where a saccade occurred in response to the step and prior to pursuit initiation, the trial was omitted, as were trials in which a blink occurred contemporaneously with the initiation of pursuit.

Antisaccade error and SRT were obtained from a step-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 the task). SRT to correct and error trials were scored separately.

Reflexive visually guided saccade hypometria and SRT were derived from a prosaccade task, which required that the participant generate a series of saccades to visual stimuli that appeared suddenly, in unpredictable locations 5 ($n=7$), 10 ($n=11$), 15 ($n=2$) and 20 ($n=3$) degrees of visual angle to the left (11 trials) or right (12 trials) of a fixation stimulus. The percentage of trials on which a hypometric saccade ($>0.5°$ undershoot of target, i.e. greater than target size of 0.5°) was tabulated to obtain an index of hypometric error.

Eye movement scoring procedures were identical for Time 1 and Time 2 data using semi-automated interactive software. All schizophrenia patients were tested and re-tested during inpatient hospitalizations, and all were receiving antipsychotic medication on both test occasions. In our larger sample, antipsychotic medication has been found to be unrelated to performance on the oculomotor variables reported here (Calkins, 2002; Curtis et al., 2001a). Examination of distributions of the oculomotor variables indicated no significant departures from normality in this subsample of participants from our larger study (all Kolmogorov-Smirnov P values >0.05); therefore,

Table 1
Paired *t*-test of means of eye movement measures at Time 1 and Time 2

Eye movement measure	*n*	Means		Paired *t*
		Time 1 mean (S.D.)	Time 2 mean (S.D.)	
Smooth pursuit				
Open-loop gain (deg/s^2)	12	70.20 (23.74)	62.15 (29.76)	1.04
Closed-loop gain (eye vel/target vel)	15	0.84 (0.13)	0.84 (0.20)	−0.16
Antisaccade				
Error (% error responses)	15	48.93 (18.86)	44.67 (28.56)	0.84
Saccade reaction time-correct (ms)	14	352.54 (73.31)	364.89 (68.57)	−0.88
Saccade reaction time-error (ms)	14	226.34 (37.73)	250.50 (43.46)	−1.99
Prosaccade				
Hypometria (% hypometric responses)	14	46.45 (23.97)	59.74 (23.81)	−2.79*
Saccade reaction time (ms)	14	218.92 (32.44)	236.29 (30.29)	−1.91

Note: Paired $t = t$ test of mean difference between values at Time 1 and Time 2. Except for prosaccade hypometria, all P's > 0.05.
* $P < 0.05$.

untransformed values were used in the present analyses. Paired *t*-tests of means of eye movement variables at Time 1 and Time 2 were conducted to determine whether there were any consistent differences between scores at the two test sessions. Most researchers have reported Pearson correlations of test–retest values of EMD variables, however, it has been argued that the intraclass correlation coefficient is a more appropriate analytic technique for this purpose (e.g. Roy-Byrne et al., 1995), particularly with small samples. To address this concern but to enhance interpretations and comparisons with past reports, we report both Pearson and intraclass correlation coefficients as indices of test–retest reliability.

Paired *t*-tests of means of eye movement data at Time 1 and Time 2 are presented in Table 1. With the exception of prosaccade hypometria, the paired *t*-test of means were not significant, indicating that there were few changes in mean eye movement scores over time (see Table 1). Fig. 1 presents scatterplots and test–retest reliabilities of eye movement data at Time 1 and Time 2. As seen in Fig. 1, the closed-loop gain, antisaccade error rate, antisaccade correct SRT and prosaccade hypometria evidence adequate test–retest reliabilities. Lower reliabilities were obtained for open-loop gain, prosaccade SRT and antisaccade error SRT. Intraclass correlations tended to yield somewhat lower coefficients than Pearson correlations, but did not affect the pattern of significant and non-significant results.

Thus, closed-loop gain and antisaccade error, which have been reported as impaired in schizophrenia patients and their relatives, evidenced adequate test–retest stability over test periods ranging from 14 to 24 months. As indicative of the trait-like status of these characteristics, the results are consistent with reports that patients with remitted schizophrenia exhibit global smooth pursuit impairment (Iacono et al., 1981) and antisaccade deficits (Curtis et al., 2001a). Thus, these forms of EMD appear to be particularly promising endophenotypes of schizophrenia. In contrast, less salient aspects of eye movement functioning, including prosaccade SRT and antisaccade error SRT, did not evidence high reliability. The relatively greater retest stability of antisaccade correct SRT than error SRT is consistent with the suggestion that because schizophrenia patients and relatives experience difficulty in inhibiting unwanted reflexive saccades to the target, their responses during correct trials evidence compensatory, and trait-like, slowing (Curtis et al., 2001a).

Further investigations of open-loop acceleration will be needed to clarify its standing as an endophenotypic marker in view of its lower stability. Conversely, the relatively high retest stability of

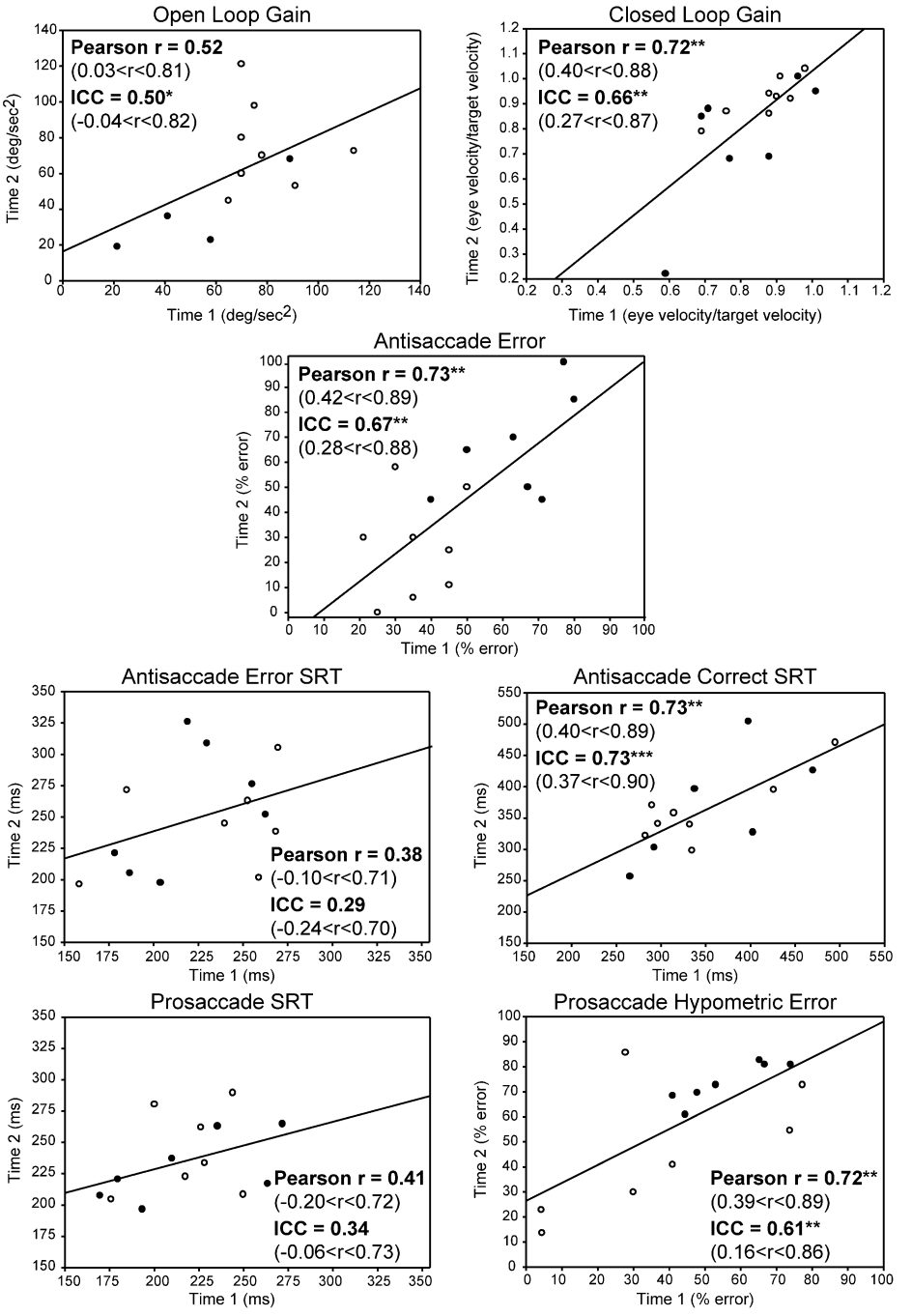

Fig. 1. Scatterplots of eye movement data and test–retest reliabilities at Time 1 and Time 2 (mean inter-test interval = 1.82 years). Filled circles represent schizophrenia patients; open circles are relatives of schizophrenia patients. Values in parentheses are the 95% confidence intervals of the preceding correlation. ICC = Intraclass correlation coefficient. Deg/s^2 = acceleration. ms = milliseconds. SRT = saccade reaction time. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

prosaccade hypometric error warrants further explorations of the extent to which hypometric error is characteristic of the performance of even a subgroup of schizophrenia patients. Although our investigation is the first to report test–retest reliabilities in relatives, our ability to discretely analyze trait stability in relatives is hampered by our small sample. Future studies should include a larger sample of relatives, so they can be analyzed as a separate group. Nonetheless, the results of the current investigation are supportive of the trait-like characteristics of particular forms of EMD in schizophrenia families and of the candidacy of EMD as an endophenotypic marker of schizophrenia.

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