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Temporal stability of saccadic task performance in schizophrenia and bipolar patients

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ABSTRACT

Background. Identifying endophenotypes of schizophrenia will assist in the identification of individuals who are at heightened risk for the disorder. Investigators have proposed antisaccade task deficits as an endophenotypic marker of schizophrenia. However, the diagnostic specificity and the temporal stability of the task deficit are unresolved issues. To date, there are few published reports of test–retest stability of antisaccade task performance in psychiatric patients.

Method. Twenty-three schizophrenia out-patients and 10 bipolar out-patients were administered two saccadic (antisaccade and refixation) tasks at two separate assessments, with an average test–retest interval of 33 months.

Results. The schizophrenia patients displayed high test–retest reliabilities of antisaccade task accuracy, despite changes in medication and clinical status. Additionally, the schizophrenia group's saccadic reaction times for antisaccade correct responses and task errors were moderately stable over time. In contrast, the bipolar patients did not show temporal stability in their antisaccade task accuracy or in their response latencies to either correct or incorrect antisaccade responses.

Conclusions. The results are supportive of the trait-like characteristics of antisaccade task deficits in schizophrenia patients. These findings also suggest that antisaccade task deficits may serve as an endophenotypic marker of schizophrenia.

INTRODUCTION

Endophenotypes are useful tools in psychiatry and psychopathology research because they provide an intermediate link between the genetic diathesis, the disease process and the phenotype of clinical disorder (Gottesman & Shields, 1972; Gottesman & Gould, 2003). In order to serve as an endophenotype, several criteria must be met: the characteristic must have a relatively low base rate in the general population, have a heritable component, and show temporal stability (Iacono, 1985). The trait-like characteristic must precede the onset of the disorder in affected persons, be present in affected individuals during symptom remission as well as symptom exacerbation, and segregate with the illness in affected relatives. Such a vulnerability indicator, if found in affected family members, would also be expected to be present at a higher rate among non-affected family members compared to the general population (Iacono, 1985; Gottesman & Gould, 2003). In order to serve as a genetic marker of risk for schizophrenia as opposed to being a risk marker for psychosis in general, the indicator would be expected to have relative specificity for schizophrenia.

One of the most promising candidate markers of a schizophrenic diathesis is ocular motor dysfunction (cf. Iacono, 1985; Erlenmeyer-Kimling & Cornblatt, 1987; Clementz & Sweeney, 1990; Levy *et al.* 1993 for reviews). Ocular motor

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abnormalities are among the most robust abnormalities observed in the psychophysiological study of schizophrenia. Calkins & Iacono (2000) assert that abnormal smooth pursuit eye tracking and antisaccade task deficits may serve as two independent endophenotypic markers of schizophrenia. In contrast to the considerable empirical support for considering deviant pursuit tracking a marker of increased liability for schizophrenia, there is much less research concerning the candidate marker status of volitional saccade abnormalities.

Refixation tasks and antisaccade tasks are typically used to elicit volitional saccadic eye movements. In a saccadic refixation task, a visual target typically elicits a reflexive saccade. Overall, schizophrenia patients display normal saccadic responses to peripherally presented visual cues that follow a central fixation point (Iacono *et al*. 1981; Clementz *et al*. 1994; Gooding *et al*. 1997; Hutton *et al*. 1998; Klein *et al*. 2000; Mahlberg *et al*. 2001; Hutton *et al*. 2002). However, some reports (Crawford *et al*. 1995; Arolt *et al*. 1998) indicate that schizophrenia patients may show increased error rates on these saccadic refixation tasks. It is noteworthy that in the Crawford *et al*. (1995) study, the schizophrenia patients were unmedicated, which may have accounted for less accurate responses. In general, however, schizophrenia patients perform normally on visually guided reflexive saccade tasks.

The retest stability of prosaccade parameters has been demonstrated in healthy controls. In normal adults, saccadic reaction times for reflexive saccades has been reportedly high, with test–retest correlations ranging from 0·61 to 0·69 for up to 2 weeks (Roy-Byrne *et al*. 1995), and from 0·77 to 0·90 for periods up to 3 months (Crevits *et al*. 2000; Klein & Berg, 2001; Ettinger *et al*. 2003). Iacono & Lykken (1981) reported test–retest correlations from 0·54 to 0·56 after a 2-year follow-up interval. To date, there has been one study of retest stability in a patient sample. Calkins *et al*. (2003) reported moderately high ($r = 0{\cdot}72$) test–retest reliability for error rates, though not for saccadic reaction times to prosaccade responses ($r = 0{\cdot}41$) in a heterogeneous sample retested after an average of 1·8 years.

In an antisaccade task, a reflexive saccade must be inhibited and a saccade in the opposite direction has to be generated. Increasingly, investigators have turned their research focus to antisaccade task performance, in part due to the neuroanatomic specificity associated with the task. Antisaccade task performance appears sensitive to frontal lobe dysfunction, particularly, the dorsolateral aspects of the frontal cortex (Guitton *et al*. 1985; Pierrot-Deseilligny *et al*. 1991; Fukushima *et al*. 1994). Antisaccade task performance is relatively spared in neurological patients with non-frontal lesions (Guitton *et al*. 1985; Gooding *et al*. 1997). Compared to non-patient controls, schizophrenia patients produce significantly more reflexive saccade errors on antisaccade tasks, regardless of the specific antisaccade paradigm used (e.g. Fukushima *et al*. 1988, 1990; Thaker *et al*. 1990; Clementz *et al*. 1994; Sereno & Holzman, 1995; Allen *et al*. 1996; Gooding *et al*. 1997; Crawford *et al*. 1998; McDowell *et al*. 1999; Klein *et al*. 2000; Curtis *et al*. 2001; Gooding & Tallent, 2001; Hutton *et al*. 2002). Additionally, some investigators (Fukushima *et al*. 1990; Thaker *et al*. 1990; Sereno & Holzman, 1995; Crawford *et al*. 1998; Karoumi *et al*. 1998; Klein *et al*. 2000) have reported that schizophrenia patients display increased saccadic latency to correct antisaccade task responses, though this is not a consistent finding. It is noteworthy that Curtis *et al*. (2001) observed that acutely ill schizophrenia patients, though not remitted patients, showed significantly increased latencies on correct antisaccade trials.

The more robust observation that schizophrenia patients make more directional errors on antisaccade tasks compared to non-psychiatric controls does not appear attributable to effects of antipsychotic medication or chronicity. The first-degree relatives of schizophrenia patients also display increased antisaccade error rates (Clementz *et al*. 1994; Katsanis *et al*. 1997; Crawford *et al*. 1998; Ross *et al*. 1998; McDowell *et al*. 1999; Curtis *et al*. 2001; Karoumi *et al*. 2001). In addition to increased antisaccade error rates being familial, they also show heritability (Malone & Iacono, 2002). However, some studies of antisaccade task performance have indicated that abnormally high rates of antisaccade task error may not be specific to schizophrenia. Patients with bipolar disorder (Sereno & Holzman, 1995; Tien *et al*. 1996; Katsanis *et al*. 1997; McDowell & Clementz, 1997; Curtis *et al*. 2001; Gooding

& Tallent, 2001) and major depression (Sweeney *et al*. 1998; Curtis *et al*. 2001) have also displayed aberrantly high error rates on antisaccade tasks. The relative lack of diagnostic specificity has led some to question the viability of antisaccade task deficits as an indicator of a schizophrenic diathesis.

Another unresolved issue concerns the temporal stability of antisaccade task deficits. In healthy non-patient subjects, reports of test–retest correlations of antisaccade accuracy have ranged from 0·58 to 0·67 for up to 1 month (Crevits *et al*. 2000), with correlations as high as 0·89 for average test–retest intervals of two months (Ettinger *et al*. 2003). Two studies of healthy controls have reported retest correlations for antisaccade task accuracy that were low and/or non-significant [intra-class correlations (ICCs; Bartko & Carpenter, 1976; Bartko, 1991) ranging from 0·22 to −0·30, Roy-Byrne *et al*. 1995; $r_{tt} = 0{\cdot}44$, Klein & Berg, 2001], perhaps due to the relative infrequency of task errors produced by their samples. The test–retest reliability of saccadic response latency for antisaccade tasks has ranged from 0·78 to 0·80 for up to 2 weeks (Roy-Byrne *et al*. 1995) and ranged from 0·65 to 0·90 for retest intervals up to 3 months (Crevits *et al*. 2000; Klein & Berg, 2001; Ettinger *et al*. 2003). Typically, investigators have relied upon Pearson *r* correlations. More recent studies have reported similarly high test–retest correlations while relying upon a more stringent statistical measure of stability that takes into account within-subjects variance as well as between-subject variance, namely ICCs. Altogether, studies indicate that antisaccade task performance shows moderately high test–retest stability in the normal population.

Although the temporal stability of antisaccade task performance has been investigated fairly well in normal individuals, its stability in psychiatric patients has been much less studied. Thaker *et al*. (1990) found that schizophrenia patients showed high test–retest reliability for antisaccade errors ($r = 0{\cdot}90$) and latency ($r = 0{\cdot}89$) after a 1 week interval. In a second study, Thaker *et al*. (1990) reported that schizophrenia patients showed a high test–retest reliability ($r = 0{\cdot}75$) for antisaccade errors after a 1 year interval. However, both of these studies were based on small samples ($n = 14$ and $n = 8$ respectively). Another study of antisaccade task performance (Hutton, 2001) indicated that schizophrenia patients display test–retest reliability ($r = 0{\cdot}74$) over a 1 year period. In a mixed group of schizophrenia patients ($n = 7$) and first-degree relatives ($n = 8$), Calkins *et al*. (2003) reported moderately high ($r = 0{\cdot}73$) test–retest reliability for antisaccade error rates and reaction time to correct antisaccade responses over test periods ranging from 14 to 24 months. They reported low reliability for saccadic reaction times to antisaccade errors ($r = 0{\cdot}38$). Although these findings suggest that antisaccade task performance is stable in schizophrenia patients, these studies have been based on small samples of schizophrenia patients and/or mixed psychiatric samples. To date, there has been no report of the temporal stability of antisaccade task deficits in bipolar patients.

Investigation of the temporal stability of antisaccade task deficits in both schizophrenia and non-schizophrenia patients is essential to the status of antisaccade task deficits as an endophenotype of schizophrenia liability. The purpose of the present study was to assess the temporal stability of antisaccade task performance in two patient groups, namely, schizophrenia patients and bipolar patients. Based upon observations of antisaccade deficits in both acutely ill as well as remitted patients, we predicted that schizophrenia patients would display temporally stable antisaccade task performance. Given the inconsistent findings regarding the antisaccade task performance of bipolar patients, as well as their greater impulsivity and disinhibition while acutely symptomatic, we predicted that the bipolar patients' antisaccade task performance would not be temporally stable. That is, we hypothesized that in schizophrenia patients, antisaccade deficits may be trait-related, whereas in patients with mood disorders, the deficits may be state-dependent.

METHOD

Participants

The sample included 23 DSM-IV schizophrenia (14 male, 9 female) patients and 10 DSM-IV bipolar I (5 male, 5 female) patients. All of the patients in the present investigation were outpatients who had previously participated in a

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cross-sectional investigation of antisaccade task performance (cf. Gooding & Tallent, 2001). At each assessment, the patients underwent a semi-structured clinical interview including Mood and Psychotic Symptoms modules from the patient version of the Structured Clinical Interview for DSM-IV (Spitzer *et al.* 1996). The interviews were administered by trained Masters- and doctoral-level interviewers. A consensus diagnosis was made by two experienced clinical researchers (including a psychiatrist) after the patient information gleaned from the interviews as well as from medical records was reviewed. The inter-rater agreement of the best overall diagnosis (in which the longitudinal course of the illness was considered) was high (kappa coefficient = 0·92).

The schizophrenia group included patients with the paranoid subtype ($n = 11$), the undifferentiated subtype ($n = 8$), and the residual subtype ($n = 4$). In the bipolar group 80% (8 of 10) reported a history of psychotic symptoms. The mean test–retest interval for these participants was nearly 3 years (range, 30–47 months). The schizophrenia patients' mean retest interval (mean = 33·2 months, S.D. = 3·6) did not differ significantly from that of the bipolar patients (mean = 33·5, S.D. = 3·6). At the time of retesting, the mean age of the sample was 44 (range, 24–64 years); the two groups did not differ in terms of age [$t(31) = 0{\cdot}21$, $p = 0{\cdot}84$]. Overall, while both patient groups are considered representative of the outpatient population at large, the patients who returned for the follow-up assessment were more likely to be higher functioning than those who were not reassessed. It should be noted that the original sample included 34 schizophrenia patients and 20 bipolar patients. By the time of the follow-up assessment, 5 (3 schizophrenia, 2 bipolar) patients were deceased, 1 (schizophrenia) patient was too paranoid to return for reassessment, 3 (1 schizophrenia, 2 bipolar) patients repeatedly failed to keep their return appointments, and the remaining (6 schizophrenia, 6 bipolar) patients could not be located. The groups did not differ significantly in terms of their attrition rates [$\chi^2(1) = 1{\cdot}65$, N.S.].

In order to be eligible for study inclusion, the participants had to be free of current substance abuse or dependence. Exclusion criteria consisted of a medical history of the following: organic cerebral illness, mental retardation, and any known oculomotor dysfunction. All of the patients were medicated, and none showed any signs of tardive dyskinesia, as assessed by their primary mental health professional. All patients were required to have had their medications stabilized for at least 7 days prior to psychophysiological assessment. After the study was explained, the participants signed written, informed consent as approved by the Institutional Review Board of the University of Wisconsin-Madison. All participants were paid a modest honorarium.

Eye movement tasks

Testing took place in a quiet, dimly illuminated room. A three-point calibration task ($+12^\circ$, 0°, -12°; each stimulus duration = 900 ms) was carried out before each task. The target, a small white circle (approximately 2 mm) of light presented against a darkened computer screen, moved ± 4, 8, or 12 degrees from the center, in a non-predictable pattern. There were 8 practice trials, each of which was followed by verbal feedback from the experimenter. Following the practice trials, there were 2 sets of 24 test trials. The stimuli were presented in an identical pseudorandom order to all subjects, at a rate that was paced by the subject (typically 1 trial every 2 s). Only the responses made during the 48 test trials were included in subsequent analyses. Subjects were allowed to rest (typically for 2 min) between tasks.

Two types of saccadic tasks were administered. In the saccadic inhibition task (hereafter referred to as the 'antisaccade task'), a central fixation point was presented for approximately 600 ms. Subjects were instructed to look in the opposite direction from a laterally displaced target (either to the left or right of the center). After the target appeared in the new location, it remained there for approximately 900 ms. Finally the circle of light returned to the center location for another trial.

The saccadic refixation task (hereafter referred to as the 'prosaccade task') was identical to the antisaccade task in terms of stimulus presentation and fixation duration. The prosaccade task differed from the antisaccade task in terms of the task requirements; in the prosaccade task, participants were instructed to look in the same direction as the laterally displaced target

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(either to the left or right of the center). However, participants were not instructed to match the distance of the target movements. As such, the presence and/or temporal stability of saccadic hypometria could not be assessed. Due to data storage error, Time 2 prosaccade data were not available for one of the participants.

Eye movement recording

Eye movements were recorded using a system (Eyelink) that has a temporal resolution of 4 ms and a spatial resolution of 0·25 degrees of visual angle. Eye position was recorded by an infrared reflection technique, in which eye cameras mounted on a headband worn by the subjects recorded the differential reflectivity between the iris and the sclera. Subjects' head movements were recorded by the headband's head camera that picked up phototransistor signals from four diode strips mounted to the computer. A 33-cm monitor located 53 cm from the subject's nasion was used to present the stimuli.

Eye movement analysis

Saccadic eye movements were identified using an interactive pattern recognition program (the Eyelink system), thereby permitting the identification and removal of blinks. Both saccadic tasks were scored in terms of accuracy (percentage of direction errors) and response latency [saccadic reaction time (SRT)]. Note that in the task instructions, experimenters emphasized the importance of making the saccadic eye movement in the appropriate direction (depending on the saccadic task); participants were not told that they had to match the distance of the target movement.

The first saccade of at least 2 degrees in amplitude made 100 ms after the target movement was scored as the response. For the antisaccade task, if the subject looked in the direction of the target, this constituted an error. For the prosaccade task, an error was defined as any failure to make a saccade in the same direction as the laterally displaced target. Saccadic latency was operationally defined as the time (in ms) from the beginning of the target movement to the initiation of the subsequent saccade. The data were scored by two independent raters who were naïve to group membership and the study hypotheses. Interrater reliability for 10 randomly selected antisaccade and 10 randomly selected prosaccade records was excellent (ICCs ranging from 0·95 to 0·99). Eye movement scoring procedures were identical for the initial (Time 1) and follow-up (Time 2) assessments.

Data analysis

Analyses were performed with raw data as well as with transformed values; the results did not differ. To facilitate comparison with prior research, descriptive statistics as well as results based upon untransformed values are presented. Paired t tests of means of saccadic parameters (i.e. accuracy, reaction time) at Time 1 and Time 2 were conducted to determine whether there were any consistent differences across time (Kirk, 1982). Estimates of test–retest stability were obtained by calculating ICCs for each measure of saccadic performance. Additionally, Pearson correlation coefficients were calculated in order to permit comparisons with earlier studies (e.g. Klein & Berg, 2001).

RESULTS

Temporal stability of saccadic performance

Antisaccade task performance

In both groups, participants' antisaccade correction rate at the initial testing and retesting was high, indicating that they understood the task requirements and were sufficiently motivated to perform the antisaccade task. However, these corrective saccades were not included in any of the analyses.

Paired t tests of means of saccadic eye movement data are provided in Table 1. Overall, the schizophrenia patients produced significantly fewer antisaccade task errors at the time of retesting [paired $t(22) = 2{\cdot}22$, $p < 0{\cdot}05$]. Despite showing improvement over time, the schizophrenia patients displayed the same relative performance from Time 1 to Time 2, thereby demonstrating high test–retest stability (Pearson's $r = 0{\cdot}87$, ICC $= 0{\cdot}85$, $p < 0{\cdot}001$). In contrast, the bipolar patients' antisaccade task accuracy was not characterized by a consistent difference from Time 1 to Time 2 [paired $t(9) = 0{\cdot}87$, $p = 0{\cdot}41$]. Moreover, the bipolar patients' antisaccade task performance showed considerable variability across sessions (Pearson's $r = 0{\cdot}21$, ICC $= 0{\cdot}22$, $p = 0{\cdot}56$). Between-group comparisons in terms of the strength of the Pearson r's, revealed a significant difference

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Table 1. *Saccadic eye movement performance*

	Schizophrenia patients						Bipolar patients					
		Test		Retest		Paired		Test		Retest		Paired
	n	M	(S.D.)	M	(S.D.)	*t*	*n*	M	(S.D.)	M	(S.D.)	*t*
Antisaccade task												
Accuracy (% errors)	23	0·55	(0·29)	0·48	(0·31)	2·22*	10	0·31	(0·22)	0·23	(0·25)	0·87
Reaction time												
Correct	23	288·30	(80·33)	276·78	(50·25)	0·79	10	283·35	(49·25)	264·62	(45·37)	1·10
Error	23	196·92	(35·35)	193·31	(38·18)	0·48	10	205·20	(48·31)	201·14	(77·70)	0·13
Prosaccade task												
Accuracy (% errors)	23	0·02	(0·03)	0·03	(0·07)	−0·63	9	0·01	(0·01)	0·01	(0·03)	−0·51
Reaction time												
Correct	23	191·06	(31·08)	189·17	(30·10)	0·28	9	188·80	(29·03)	187·26	(21·21)	−0·06

Raw values for saccadic eye movement parameters are presented. Paired *t* = *t* test of association between values at test and retest.
* $p < 0{\cdot}05$.

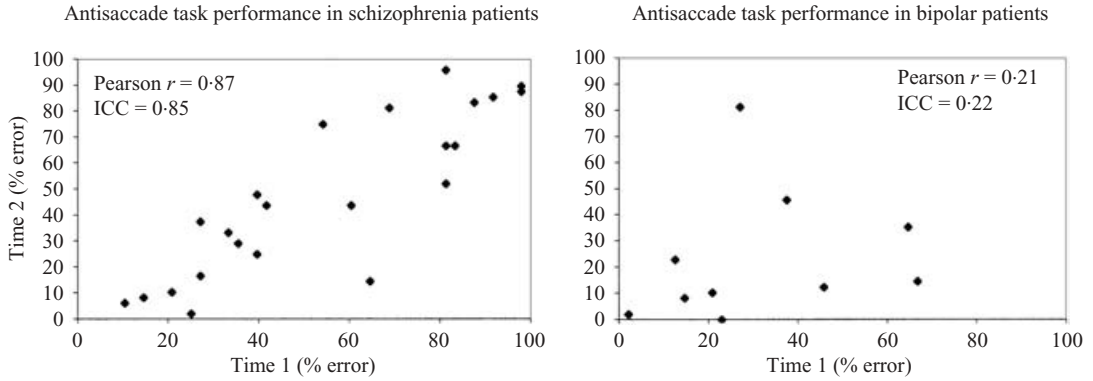

FIG. 1. Scatterplots of antisaccade task performance at Time 1 and Time 2 (mean inter-test interval = 2·78 years) for schizophrenia patients and bipolar patients. See the text for the values of the test–retest correlations.

($Z = 2{\cdot}56$, $p < 0{\cdot}01$). Fig. 1 provides the scatterplots of the patient groups' antisaccade error rates at the two assessments.

At both times, schizophrenia patients displayed significantly greater SRTs for correct antisaccade responses than incorrect saccadic responses [$t(22) = 5{\cdot}19$ and $6{\cdot}57$, $p < 0{\cdot}001$, for Time 1 and Time 2 respectively]. As shown in Table 1, the schizophrenia patients did not display a significant difference in terms of their mean SRTs for correct antisaccade responses at Time 1 or Time 2, nor did they display a significant difference in response latency for antisaccade task errors from Time 1 to Time 2. Fig. 2*a* shows that the schizophrenia group's latency for correct antisaccade task responses was moderately stable (Pearson's $r = 0{\cdot}64$, ICC = 0·56, $p < 0{\cdot}01$), as was their latency for antisaccade task errors (Pearson's $r = 0{\cdot}52$, ICC = 0·53, $p < 0{\cdot}05$).

Overall, the bipolar patients displayed significantly greater reaction times for correct antisaccade responses than incorrect saccadic responses [$t(9) = 5{\cdot}14$ and $2{\cdot}40$, $p < 0{\cdot}05$, for Time 1 and Time 2 respectively]. The bipolar patients did not display a significant difference in terms of their mean SRTs at Time 1 and Time 2 for either correct antisaccade responses or antisaccade errors (Table 1). The bipolar patients' SRTs for correct antisaccade responses showed relatively poor stability (Pearson's $r = 0{\cdot}35$, ICC = 0·34, $p = 0{\cdot}32$; see Fig. 2*b*). Similarly, the bipolar patients showed large within-subjects variance in terms of their latency for incorrect antisaccade responses (Pearson's $r = 0{\cdot}24$, ICC = 0·18, $p = 0{\cdot}50$).

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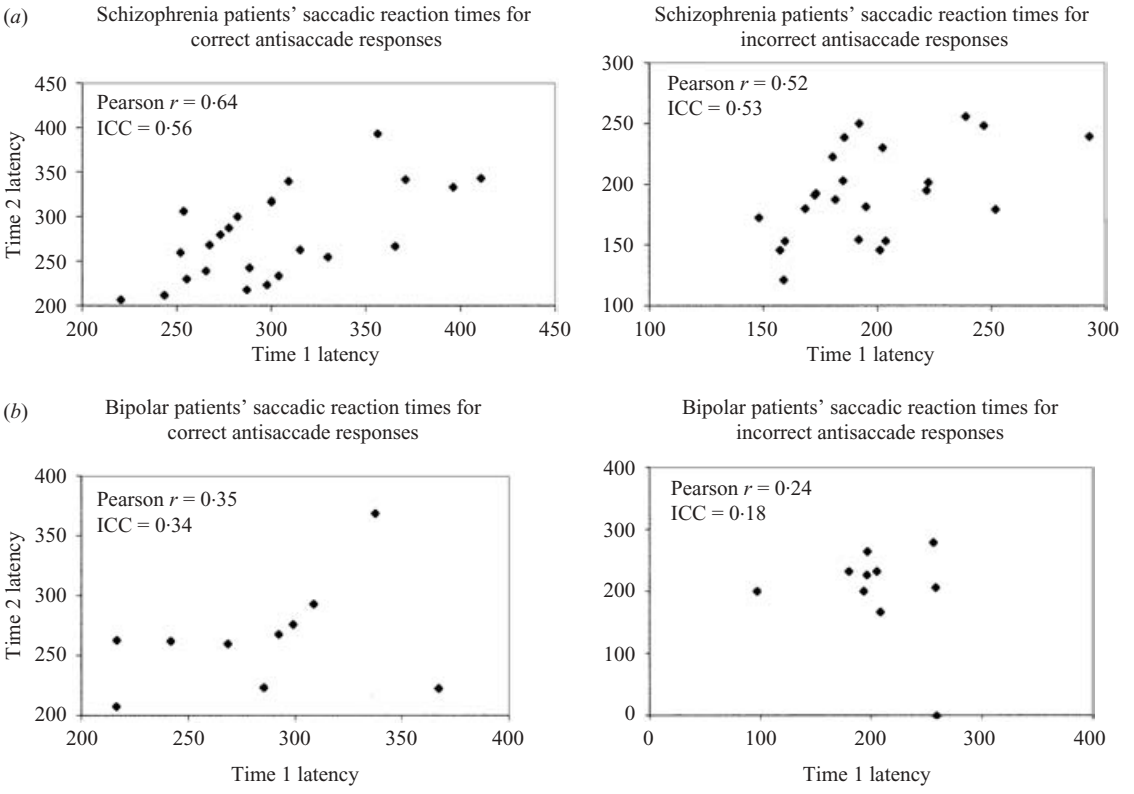

FIG. 2. Scatterplots of saccadic reaction times for (*a*) schizophrenia patients and (*b*) bipolar patients. Latencies (in ms) are provided for correct antisaccade responses (left) and incorrect antisaccade responses (right-hand side of the figure).

Saccadic refixation task performance

As indicated in Table 1, the schizophrenia patients displayed no consistent change in their refixation task performance over time [paired $t(21) = 0{\cdot}63$, $p = 0{\cdot}54$]. Examination of the schizophrenia patients' prosaccade task performance revealed no test–retest stability, either in terms of accuracy (Pearson's $r = 0{\cdot}17$, ICC = 0·14) or response latency (Pearson's $r = 0{\cdot}13$, ICC = 0·15).

The bipolar patients' prosaccade performance was not consistently different from initial testing to retesting. Prosaccade task accuracy in the bipolar group was not temporally stable (Pearson's $r = 0{\cdot}31$, ICC = 0·30), though their saccadic reaction times appeared temporally stable (Pearson's $r = 0{\cdot}64$, ICC = 0·64). Moreover, comparisons of *z*-transformed correlation coefficients revealed that the schizophrenia and bipolar patients did not differ significantly from each other in terms of the relationships between their prosaccade performance (either accuracy or latency) at the initial and follow-up assessments.

Medication status changes over time

Medication status is provided in Table 2. All of the participants were medicated at both assessments. At the time of initial testing, nearly all (88%) of the patients were taking more than one medication concurrently. The schizophrenia group was significantly more likely to be treated with antipsychotic medications [$\chi^2(1) = 13{\cdot}55$, $p < 0{\cdot}001$] and antiParkinson agents [$\chi^2(1) = 4{\cdot}31$, $p < 0{\cdot}05$]. The bipolar group was more likely to be treated with mood stabilizers [$\chi^2(1) = 15{\cdot}39$, $p < 0{\cdot}001$].

At the follow-up assessment, the majority (79%) of the patients were being treated with more than one medication concurrently. Among the schizophrenia patients, nearly 70% (16 of 23) experienced a change in at least one medication from the time of initial testing to the

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Table 2. *Medication status at Time 1 (initial testing) and Time 2 (retesting)*

	Schizophrenia		Bipolar	
Medication type†	Time 1	Time 2	Time 1	Time 2
Antipsychotics				
Typical	22	26	10	20
Atypical	52	61	40	30
Both	26	13	0	0
Mood stabilizer	17	13	90	90
Antidepressant	57	57	40	50
Anxiolytic	30	39	20	20
AntiParkinson	48	35	10	0
GAF scores‡	59·26 (9·04)	56·87 (12·6)	64·10 (8·52)	62·30 (10·5)

† Percentage of schizophrenia ($n=23$) and bipolar ($n=10$) patients on each type of medication is provided.

‡ Group means and standard deviations (in parentheses) for Global Assessment of Functioning (GAF) ratings.

time of retesting, while 80% of the bipolar patients experienced a change in medication; the two groups did not differ significantly in terms of the proportion of patients whose medications changed over time [$\chi^2(1)=0{\cdot}38$, $p=0{\cdot}54$].

Clinical state over time

Overall, both groups were functioning more poorly at the follow-up assessment, relative to their initial clinical status. Among the schizophrenia patients, 57% reported acute psychotic symptoms (i.e. delusions or hallucinations) at Time 1, compared to 74% at Time 2. None of the bipolar patients reported psychotic symptoms at Time 1, though 40% were psychotic at Time 2. At the time of initial testing, the clinical status of the bipolar patients was mixed; three of the bipolar patients were depressed, two were euthymic and five (50%) were hypomanic. At the time of retest, nearly all (90%) were acutely symptomatic; six were depressed and three were hypomanic. The schizophrenia patients and bipolar patients were compared in terms of their proportion of patients whose clinical state had changed from the initial testing to the follow-up. Chi-squared analyses revealed that the groups did not differ significantly in terms of the proportion of patients whose clinical status changed [$\chi^2(1)=1{\cdot}38$, $p=0{\cdot}24$].

Patients' Global Assessment of Functioning (GAF) ratings, based upon their clinical, psychosocial and occupational functioning, are provided at the bottom portion of Table 2. The schizophrenia patients did not differ significantly from the bipolar patients in terms of their GAF ratings at either Time 1 or Time 2 [t's(31) $=-1{\cdot}44$ and $-1{\cdot}19$, $p=0{\cdot}16$ and $0{\cdot}24$ respectively].

Relationship between clinical state and saccadic performance

To determine whether there was any relationship between patients' saccadic task performance and their overall functioning, we tested the association between direction errors and GAF scores. At the time of initial testing, neither the schizophrenia nor the bipolar patients displayed a significant association between their antisaccade performance and their GAF scores (r's $=-0{\cdot}32$ and $-0{\cdot}51$, $p=0{\cdot}07$ respectively); the two groups did not differ in terms of the strength of the association ($Z=0{\cdot}51$, $p=0{\cdot}31$). At the follow-up testing, the schizophrenia patients did not display a significant association between their antisaccade task errors and their GAF scores ($r=-0{\cdot}23$, $p=0{\cdot}14$), though the bipolar patients showed a significant association between the frequency of inhibition failures on the antisaccade task and their GAF scores ($r=-0{\cdot}61$, $p=0{\cdot}03$). Further analysis revealed that the two patient groups did not differ significantly in terms of the strength of the relationship between antisaccade task errors and overall functioning ($Z=1{\cdot}09$, $p=0{\cdot}14$). There was no significant relationship between prosaccade performance and GAF ratings at the time of the initial assessment or at retest (r's ranged from $-0{\cdot}05$ to $-0{\cdot}50$). The two groups did not differ significantly in terms of the strength of the correlations between prosaccade error rates and GAF scores at either time.

In order to further examine the association between patients' clinical status and their disinhibition on the antisaccade task, we compared the error rates of patients who were experiencing psychotic symptoms (i.e. delusions and/or hallucinations) with those patients who were not experiencing psychotic symptoms at the time of the follow-up testing. It should be noted that because none of the bipolar patients was experiencing psychosis at the initial testing, it was not possible to conduct comparable analyses for the Time 1 error rates.

In both patient groups, individuals who were experiencing psychotic symptoms produced

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more reflexive saccades (errors) on the antisaccade task than the patients who were not currently psychotic. However, the differences were not statistically significant for either the schizophrenia patients [$t(21) = 1{\cdot}31$, $p = 0{\cdot}17$] or the bipolar patients [$t(8) = 0{\cdot}86$, $p = 0{\cdot}42$].

DISCUSSION

Validating endophenotypes of schizophrenia will assist genetic studies of the disorder by providing a means of identifying individuals at heightened risk without relying upon the presence of clinical symptoms. One possible endophenotypic marker of schizophrenia liability is antisaccade task deficits. Unresolved questions regarding the status of antisaccade task deficits include issues regarding diagnostic specificity and temporal stability. Concern regarding the relative lack of diagnostic specificity is somewhat assuaged by recognition that current diagnostic criteria are imprecise and have varying criterion validity and reliability. One of the key requirements for an endophenotype is temporal stability. The findings from the present investigation provide suggestive evidence that antisaccade task deficits may serve as an endophenotype of a schizophrenic diathesis.

Research with non-patient samples has indicated that antisaccade task performance can be reliably assessed. While there has been suggestive evidence from prior studies of schizophrenia patients indicating that antisaccade deficits are stable in these patients, most of those studies have been hampered by small samples (i.e. less than 15 schizophrenia patients). With a larger sample, we have demonstrated high temporal stability of schizophrenia patients' antisaccade performance. The test–retest correlations obtained here for the schizophrenia patients' antisaccade task performance are consistent with previous reports in the literature. These findings add to the literature by demonstrating high temporal stability of antisaccade task deficits over a fairly long time span, namely, up to 3 years. This stability was observed despite changes in the schizophrenia patients' clinical and medication status.

In the present study, the schizophrenia patients showed significant improvement in their antisaccade task performance over time. However, despite their improvement, the schizophrenia patients with abnormal antisaccade task performance continued to show deficits at the follow-up assessment. Indeed, we observed evidence of excellent temporal stability of antisaccade task performance in schizophrenia patients, even when using a more conservative estimate, namely, the ICC coefficient. Also important in these data is the fact that consistent with prior reports, the schizophrenia patients displayed temporal stability of their antisaccade RTs. The test–retest reliability coefficients of antisaccade response latencies in the present study are more modest than those previously reported, perhaps reflecting our longer follow-up interval.

This investigation is the first to report test–retest reliabilities in bipolar patients. The test–retest correlations for antisaccade error rates indicate that antisaccade task deficits are not temporally stable in bipolar patients. Low retest reliability coefficients in terms of bipolar patients' error rates suggests that their performance changed in different ways, so that some patients improved in performance over time, whereas in other patients, their antisaccade task performance worsened. One reason for lower reliability may be the relative infrequency of antisaccade errors, so that a small change in the number of errors has a great effect on the variability (i.e. reliability). Although this reason may account for lower reliability in healthy control samples, the bipolar patients in this investigation showed a relatively high frequency of erroneous saccades on the antisaccade task. Thus, the failure to observe a high test–retest reliability for antisaccade task performance in the bipolar group cannot be attributed to a restriction of range. Similarly, the bipolar patients' response latencies during the antisaccade task were not temporally stable. In contrast to the schizophrenia patients, the bipolar patients displayed poor temporal stability for saccadic latency while making either correct or incorrect responses during the antisaccade task.

Because this was a naturalistic study, patients' medications were changed. Not only did patients' medication status change over time, but for many, their symptomatic status also changed. It is noteworthy, however, that the two patient groups did not differ in terms of the proportion of patients who experienced such changes. Despite the changes in medication

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and/or symptoms, the antisaccade task performance of the schizophrenia patients remained stable over time.

We found few significant associations between patients' overall functioning, as measured by the GAF, and their saccadic performance. Although the difference was not statistically significant, we observed that in both groups, patients who were experiencing psychotic symptoms at the time of the follow-up testing produced more errors on the antisaccade task than the patients who were not acutely psychotic. Despite the apparent association between psychosis and accuracy on the antisaccade task, it is noteworthy that the bipolar patients with psychotic symptoms still performed better than the schizophrenia patients who were not experiencing any positive symptoms. We interpret this finding as indicating that although bipolar patients may also display antisaccade task deficits, the extent of their impairment is less than that of schizophrenia patients.

As demonstrated previously (Gooding & Tallent, 2001), working memory impairments as well as disinhibition are processes underlying schizophrenia patients' antisaccade task deficits. Further investigation is necessary to identify the underlying disease process that bipolar patients' antisaccade task defects reflect. Although disinhibition may be a common underlying problem in both schizophrenia and bipolar disorder, it remains to be seen whether the inhibitory failure that characterizes schizophrenia is tonic in nature, whereas the inhibitory failure seen in bipolar disorder is more phasic. It is possible that bipolar patients' phasic failure in inhibition might yield less consistent antisaccade task deficits, hence, their instability in task performance. Further research on bipolar patients who are tested over three phases of illness (e.g. depressive, euthymic and hypomanic/manic) would shed further insights regarding the nature of their antisaccade task performance.

Although some investigators (Green *et al.* 2000; Ettinger *et al.* 2003) have reported practice effects on antisaccade task performance in healthy non-patient samples, other investigators (Hallett & Adams, 1980) have not observed a significant decrease in antisaccade error rates with practice. Overall, greater improvements seem to occur for subjects with higher antisaccade error scores. As Crevits *et al.* (2000) noted, participants' reduction in anxiety about the experimental setting upon retesting may yield positive practice effects. Although such practice effects may have been present in our investigation, it is not known whether they exerted an equal effect across participant groups. However, it is noteworthy that the time interval between initial testing and follow-up was equivalent between the groups, and during each assessment, participants were provided an equal number of practice trials.

Unlike Calkins *et al.* (2003), we did not observe temporal stability of schizophrenia patients' prosaccade task performance. Similarly, we did not obtain evidence of temporal stability of saccadic refixation performance in the bipolar patient group. We attribute the low correlations to the relative infrequency of errors produced during the prosaccade task. Interestingly, in both patient groups, individuals who were experiencing psychotic symptoms at the time of testing were less accurate on the prosaccade task than the non-psychotic patients, though the differences did not reach statistical significance. The temporal stability of prosaccade task performance in psychiatric patients is clearly an issue that warrants further investigation.

Our ability to definitively clarify the potential of antisaccade task deficits as an endophenotypic marker of schizophrenia liability is limited by the small sample of non-schizophrenia patients. The size of our bipolar patient group precludes a definitive resolution of the issue of the effects of clinical state on antisaccade task performance in bipolar patients. Future studies should include a larger sample of bipolar patients. Other supportive data regarding the candidate status of antisaccade task deficits could be derived from studies of the antisaccade task performance of bipolar patients' biological relatives. If it appeared that the biological relatives of bipolar patients did not demonstrate higher rates of antisaccade task errors than the general population, this would suggest that antisaccade task deficits are indicators of a specific liability to schizophrenia.

Nonetheless, these data suggest that in contrast to the more persistent, trait-like performance deficits displayed by the schizophrenia patients, the bipolar patients' antisaccade task performance is variable over time. The significant test–retest reliability seen in schizophrenia

patients' antisaccade task accuracy is consistent with the considerable evidence for a genetic basis for the deficit, derived from both twin studies (Malone & Iacono, 2002) and from the increased incidence of antisaccade task deficits among relatives of schizophrenia patients. In summary, the results of the current investigation provide further evidence in support of the hypothesis that antisaccade task deficits may serve as an endophenotype of schizophrenia liability.

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