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Effects of Risperidone on Procedural Learning in Antipsychotic-Naive First-Episode Schizophrenia

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Studies of procedural learning in medicated schizophrenia patients using predictive saccade paradigms have consistently demonstrated hypometric predictive responses. Findings from antipsychotic-naive schizophrenia patients indicate fewer or no deficits. This pattern of findings suggests that antipsychotic medications might adversely affect frontostriatal systems supporting procedural learning on this task. The accuracy and latency of predictive saccades were assessed in 25 antipsychotic-naive first-episode schizophrenia patients and 22 matched healthy individuals. Patients were retested after 6 weeks of treatment with risperidone. Healthy individuals were reevaluated after a similar time period. The ability to learn to time response initiation in anticipation of target appearance (target prediction) was not impaired in patients before or after treatment. In contrast, although no deficits were evident before treatment initiation, after treatment patients showed a marked decrease in the accuracy of predictive but not sensory-guided responses. The findings from pretreatment testing indicate that procedural learning is a relatively unaffected cognitive domain in antipsychotic-naive first-episode schizophrenia. Although treatment-emergent extrapyramidal symptoms were minimal, these data suggest that D2 antagonism in striatum after risperidone treatment was sufficiently robust to disrupt the generation of planned volitional behavior guided by internalized representations.

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INTRODUCTION

Cognitive dysfunction has long been established as a cardinal feature of schizophrenia (Bleuler, 1952; Kraepelin, 1925). Oculomotor studies are a promising approach for investigating these neurocognitive deficits and the effects of pharmacotherapy on their respective functional brain systems. The neural systems involved in the cognitive control of eye movements are well characterized through studies with nonhuman primates (Everling and Munoz, 2000), clinical studies of patients with focal lesions (Guitton *et al*, 1985; Pierrot-Deseilligny, 1994), and functional neuroimaging studies (Sweeney *et al*, 1996).

The predictive saccade paradigm examines 'anticipatory' behaviors, which are responses guided by learned internal representations about predictable environmental events (Simo *et al*, 2005). In this paradigm, a target stimulus typically shifts back and forth between two locations at a constant time interval as participants track the target with saccadic eye movements. The predictive saccade paradigm is thus a serial reaction time task assessing procedural learning, which is the ability to acquire a motor routine via repeated exposure to a task governed by invariant rules (Cohen *et al*, 1985).

In contrast to many procedural learning tasks that take hours or days to train participants to peak performance, healthy individuals begin to initiate predictive eye movements in anticipation of target appearance after only a few trials (ie after less than 10 s) and approach peak performance within 1 min. Thus, the task provides an efficient approach for evaluating procedural learning in clinical studies.

Using fMRI, we previously demonstrated that predictive saccades rely upon frontostriatal circuitry including dorsolateral prefrontal cortex (PFC), dorsomedial thalamus, and dorsal striatum, as well as the hippocampus and anterior cingulate cortex, in contrast to visually guided saccades that rely on sensorimotor systems (Simo *et al*, 2005). Because dorsal-striatal systems are affected by the D2 blockade associated with antipsychotic medications, studying predictive saccades can be informative about systems level effects of antipsychotic treatments.

Previous studies investigating predictive saccades in schizophrenia all documented hypometric (ie undershooting) predictive saccades in medicated, typically chronic

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schizophrenia patients (Crawford *et al*, 1995a; Hommer *et al*, 1991; McDowell *et al*, 1996; Thaker *et al*, 1996). Findings with regard to the ability to learn to accurately time predictive saccades in relation to stimulus appearance have been less consistent. McDowell *et al* (1996) reported faster response latencies, Thaker *et al* (1996) reported slower latencies, and Crawford *et al* (1995a) found no latency differences between schizophrenia and healthy groups. In a combined group of antipsychotic-free and antipsychotic-naive schizophrenia patients, Krebs *et al* (2001) reported hypometric predictive saccades, as did Hutton *et al* (2001) in a group of never-medicated patients. In contrast, Crawford *et al* (1995b) and Hommer *et al* (1991) reported no reductions in saccade accuracy in previously treated but medication-free patients. Thus, although medicated patients have consistently been shown to produce hypometric predictive saccades, the findings have been less consistent in medication-free patients.

The present study was designed to assess procedural learning in antipsychotic-naive schizophrenia patients, and the early effects of antipsychotic treatment on task performance, by administering the predictive saccade task to antipsychotic-naive first-episode patients before and 6 weeks after treatment with the second-generation antipsychotic risperidone. On the basis of results of existing studies with untreated and medicated schizophrenia patients, and the D2 receptor antagonism in the striatum associated with risperidone treatment, we predicted a significant decline in accurate predictive behavior in patients after treatment initiation.

MATERIALS AND METHODS

Participants

Written informed consent for all study procedures was obtained from 25 antipsychotic-naive adult in- and outpatients meeting DSM-IV criteria for schizophrenia according to the Structured Clinical Interview (SCID; First *et al*, 1995), and collateral clinical data were reviewed at consensus diagnosis meetings. Diagnoses were confirmed at 6-month follow-up visits as part of the prospective longitudinal study of first-episode psychoses in Pittsburgh. All patients were experiencing their first lifetime psychotic episode and had never been treated with antipsychotic medication. Any such patient presenting to the inpatient or outpatient services of the University of Pittsburgh Medical Center was informed of the study by a clinician. Of the 43 patients who were screened, 3 (7.0%) refused participation, 1 (2.3%) was too psychotic/agitated to provide consent, and 7 (16.3%) met exclusion criteria (1 had a prior treatment history with antipsychotic medication, 1 did not meet diagnostic criteria, and 5 presented with current substance use problems). Of the remaining 32 patients who consented to study participation, 3 patients were judged by clinicians to be too psychotic to participate and to require immediate medication treatment, 3 patients refused participation after giving informed consent, and 1 patient later admitted to cannabis abuse. The remaining 25 patients participated in the study. The study protocol was approved by the Institutional Review Board of the University of Pittsburgh. All study participants gave written informed consent for all study procedures.

Clinical ratings were obtained by raters without knowledge of task performance. Ratings included the Brief Psychiatric Rating Scale (Overall and Gorham, 1962), the Schedule for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984a), the Schedule for the Assessment of Negative Symptoms (SANS; Andreasen, 1984b), the 24-item Hamilton Depression Rating Scale (Hamilton, 1960), and the Extrapyramidal Side Effects scale (EPSEs; McEvoy *et al*, 1991). A total of 22 healthy individuals, who did not meet criteria for any present or past Axis I disorder according to SCID interviews, were recruited from the surrounding community via advertisements. This group matched the patient group on age, gender, and estimated intellectual potential using a test of vocabulary knowledge (Ammons' Quick Test; Ammons and Ammons, 1962; Table 1).

All participants met the following criteria: (1) age between 18 and 45 years; (2) no known systemic or neurologic disease, including seizures; (3) no history of head trauma with loss of consciousness; (4) no lifetime history of substance dependence or substance abuse within 3 months prior to study participation; (5) no benzodiazepines (five half-lives) prior to testing; (6) no prior treatment with electroconvulsive therapy; and (7) no coffee, tea, or cigarettes 1 h prior to testing.

Patients' baseline eye movement studies and neuropsychological testing were conducted prior to treatment initiation. Treatment with the second-generation antipsychotic risperidone was started following baseline assessments, and follow-up testing was performed approximately 6 weeks after treatment initiation. Extrapyramidal side effects (EPS) were modest at the 6-week retesting (Table 1), but were sufficient in five patients to require low-dose (1–3 mg) benztropine. In addition, four patients also received antidepressant medication and one patient received lithium at the 6-week follow-up, including three of the benztropine-treated patients. No other medications were administered during the study period. Healthy individuals were studied over a similar interval.

Eye Movement Studies

Participants were seated in a darkened black room free from extraneous stimuli facing a circular black arc with a 1 m radius containing red light-emitting diodes (LEDs) embedded in the horizontal plane at eye level. The LEDs subtended approximately 0.2° of visual angle and were not visible unless illuminated. A chin and forehead rest minimized head movement. Participants were given no instructions to indicate that the stimulus sequence was predictable and were told only to look to the lights as they appeared.

Saccades were recorded using DC electrooculography (EOG; Grass Neurodata 12 Acquisition System, Astro-Med Inc., West Warwick, RI), and blinks were monitored using electrodes placed above and below the left eye. All recordings were digitized at 500 Hz (DI-210 14-bit A/D, DATAQ Instruments) and stored for offline analyses. Recordings were analyzed using custom software developed in our laboratory.

Table 1 Demographic Information and Clinical Ratings

	Healthy ($n = 22$)	Patients ($n = 25$)	*p*-value
Age (years)	23.1 (4.2)	25.4 (7.6)	NS
IQ	98.1 (5.5)	94.4 (7.3)	NS
Gender (M/F)	14/8	18/7	NS
	Baseline	**6 weeks**	
BPRS	50.0 (8.9)	41.0 (9.2)	<0.001
SANS	14.5 (3.3)	13.8 (3.3)	NS
SAPS	9.3 (4.1)	5.5 (3.8)	<0.001
HAM-D	19.3 (9.3)	16.8 (8.6)	NS
EPSEs (range 0–35)	NA	3.6 (2.8)	
Risperidone (mg per day)	NA	3.9 (1.5)	

Abbreviations: BPRS, Brief Psychiatric Rating Scale; SANS, Schedule for the Assessment of Negative Symptoms; SAPS, Schedule for the Assessment of Positive Symptoms; HAM-D, 24-item Hamilton Depression Rating Scale; EPSEs, Extrapyramidal Side Effects Scale; M, male; F, female; NS, not significant; NA, not applicable; IQ, intelligence quotient.
Data presented are mean (SD).
IQ was estimated with the Ammons' Quick Test.

Predictive Saccade Task

The predictive saccade paradigm is a simple serial reaction time task in which individuals shift gaze between two target positions sequentially illuminated at a fixed temporal interval. Participants very quickly learn to anticipate target appearance, so that an increasing percentage of saccades are made close to target appearance on the basis of internally generated predictions about target appearance rather than actual visual stimulus appearance. For this study, participants looked toward visual targets alternating between two locations at 7.5° of visual angle to the left and right of central fixation. The target shifted between the two locations every 1.5 s (0.33 Hz) 10 times (ie 20 target presentations). There was no gap or overlap as new targets appeared contemporaneously as previous targets were extinguished. The latency (time from appearance of target to response initiation) and gain (proportion of distance moved to the target location) of primary saccades toward target locations were measured. To avoid confusion with small saccades made during ongoing fixation of targets, we defined the primary saccade as the first saccade toward the next target with a gain of at least 0.2 (ie a saccade on the order of 3° of visual angle).

Eye Data Analysis

Eye position recordings obtained during fixation of targets during each trial were used to convert voltage recordings to eye position in degrees of visual angle. This minimized artifacts resulting from EOG signal drift over the course of testing. Recordings from each trial were reviewed to identify primary saccades, artifacts (eg blinks and signal clipping), and occasional failures of software algorithms to correctly identify saccades that were then marked manually. Before analysis, digitized eye movement signals were smoothed using linear phase, finite impulse response low-pass filters.

Neuropsychological Assessments

All participants also underwent comprehensive neuropsychological testing in parallel with eye movement testing, as described in detail elsewhere (Hill *et al*, 2004). For the purposes of the present study, measures of psychomotor abilities, specifically finger tapping and grooved pegboard test scores, were examined in relation to predictive saccade performance (Table 2).

Statistical Analyses

There were no significant saccade by direction effects or group by direction interaction effects. Therefore, data from leftward and rightward saccades were pooled for analyses. To examine the change in saccade latency over the course of the task, primary saccades in the 19 trials (response to the first unpredictable target displacement was excluded) were collapsed into three blocks (block 1, trials 1–6; block 2, trials 7–12; and block 3, trials 13–19).

Performance on this task has both quantitative (eg response latency and accuracy) and qualitative dimensions (internally generated predictive responses *vs* sensory-driven visually elicited responses). To examine the qualitative aspects of performance, each primary saccade was classified as follows: sensory-guided saccades (eg visually elicited saccades) with latencies greater than 140 ms; predictive saccades with latencies less than 90 ms; and an indeterminate/intermediate group of speeded saccades with latencies between 90 and 140 ms. The rationale for this classification is threefold. First, sensory-guided (or visually elicited) saccades in no-gap paradigms (old target extinguishes contemporaneously with new target appearance) such as the one used in this study very rarely occur with latencies shorter than 140 ms (Becker, 1989; Fischer *et al*, 1993). Second, oculomotor studies generally classify saccades with latencies less than 100 ms as predictive because this reflects the minimal time necessary for perceiving a visual stimulus

Table 2 Neuropsychological Measures

	Baseline			6 weeks		
	Healthy	**Patients**	***p*-value**	**Healthy**	**Patients**	***p*-value**
Finger-tapping score (dominant hand)	49.7 (5.9)	50.2 (7.3)	NS	51.7 (7.2)	48.1 (7.6)	NS
Finger-tapping score (nondominant hand)	46.1 (5.8)	46.2 (8.5)	NS	48.1 (6.4)	44.6 (7.9)	NS
Grooved Pegboard time (dominant hand)	59.0 (8.2)	70.4 (17.2)	0.006	57.5 (7.2)	73.5 (20.3)	0.002
Grooved Pegboard time (nondominant hand)	66.8 (6.3)	77.2 (20.1)	0.03	69.5 (9.3)	81.8 (18.3)	0.01

Abbreviation: NS, not significant.
Data presented are mean (SD).
P-values reflect significance levels for group comparisons via independent *t*-tests. Finger-tapping scores reflect average taps in 10 s over 5 trials. Grooved Pegboard values reflect time in seconds for inserting 25 pegs into the board.

and performing sensorimotor transformations needed to initiate a motor response (Becker, 1989; Wenban-Smith and Findlay, 1991). We classified eye movements with latencies less than 90 ms as anticipatory movements. Third, whether saccades with latencies between 90 and 140 ms were predictive or not is difficult to determine, so they were considered separately as an indeterminate/intermediate group.

RESULTS

Latency of Saccades

At baseline, patients and healthy individuals demonstrated a significant reduction in saccade latencies across the three blocks of trials as they performed the predictive saccade task, reflecting an ability to learn the response sequence and to initiate saccades based on predictions about future target appearance ($F(2, 44) = 6.28$, $p < 0.01$). Also, the rate of learning to anticipate target appearance over trials, reflected in saccade latency reductions, did not differ between patients and healthy individuals ($F(2, 44) = 0.55$, $p = 0.58$; Figures 1 and 2a). Furthermore, treatment did not alter patients' capacity to learn to time the initiation of saccades in anticipation of target appearance, as reflected in similar reduction in response latencies across blocks of trials from baseline to follow-up for patients and healthy individuals ($F(2, 44) = 0.27$, $p = 0.76$; Figure 2b).

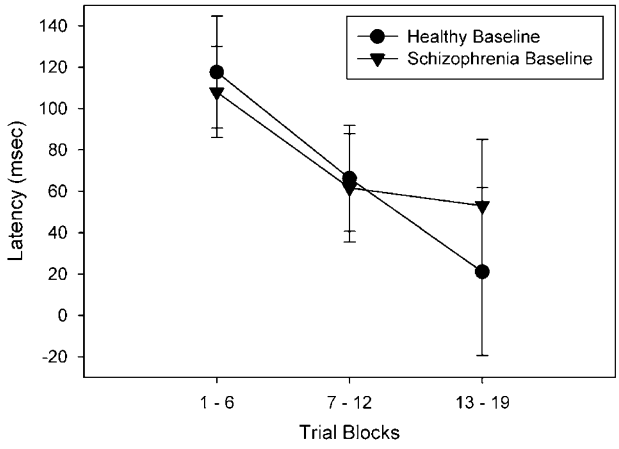

Figure 1 Mean (SE) latencies at baseline for schizophrenia patients and healthy individuals across blocks of trials. Both groups showed a comparable decline in saccade latencies over the course of the task. This decline was not altered in either participant group at the 6-week testing.

Accuracy of Saccades

The accuracy of patients' sensory-guided saccades (latencies > 140 ms) was comparable to that of healthy individuals ($F(1, 43) = 1.04$, $p = 0.32$; Figure 3a), and there was no group difference in change between baseline and follow-up testing in these responses ($F(1, 43) = 0.32$, $p = 0.57$). Findings were the same for speeded saccades (latencies between 90 and 140 ms) ($F(1, 36) = 2.06$, $p = 0.16$; Figure 3b for group differences) and ($F(1, 36) = 1.46$, $p = 0.23$ for differential change over time between groups). The accuracy of patients' predictive saccades (latencies < 90 ms), however, was significantly reduced after treatment relative to healthy individuals ($F(1, 34) = 10.98$, $p = 0.002$; Figure 3c). Although patients' predictive saccades were accurate at baseline ($t(40) = 0.43$, $p = 0.67$), they were significantly less accurate (ie more hypometric) than healthy individuals at the 6-week follow-up ($t(35) = 4.35$, $p < 0.001$). Relative to baseline, the gain of patients' saccades was reduced by 27% at follow-up ($t(18) = -5.43$, $p < 0.001$), but healthy individuals' saccade gain increased minimally by 8% from baseline to follow-up ($t(16) = 0.81$, $p = 0.43$). Exclusion of the five patients taking benztropine and the four patients taking antidepressants at the 6-week follow-up in secondary analyses did not change findings for saccade latencies or accuracy.

Relationships with Clinical Ratings, Medication Dosage, and Neuropsychological Data

There were no significant associations between changes in the accuracy of sensory-guided, speeded or anticipatory saccades from baseline to 6-week follow-up and changes in clinical symptom ratings, risperidone dose, or EPS ratings. Associations between changes from baseline to follow-up of oculomotor and neuropsychological measures were minimal (Table 3).

DISCUSSION

The results of the present study demonstrate that antipsychotic-naive schizophrenia patients have the ability to use internal spatial and temporal representations to rapidly

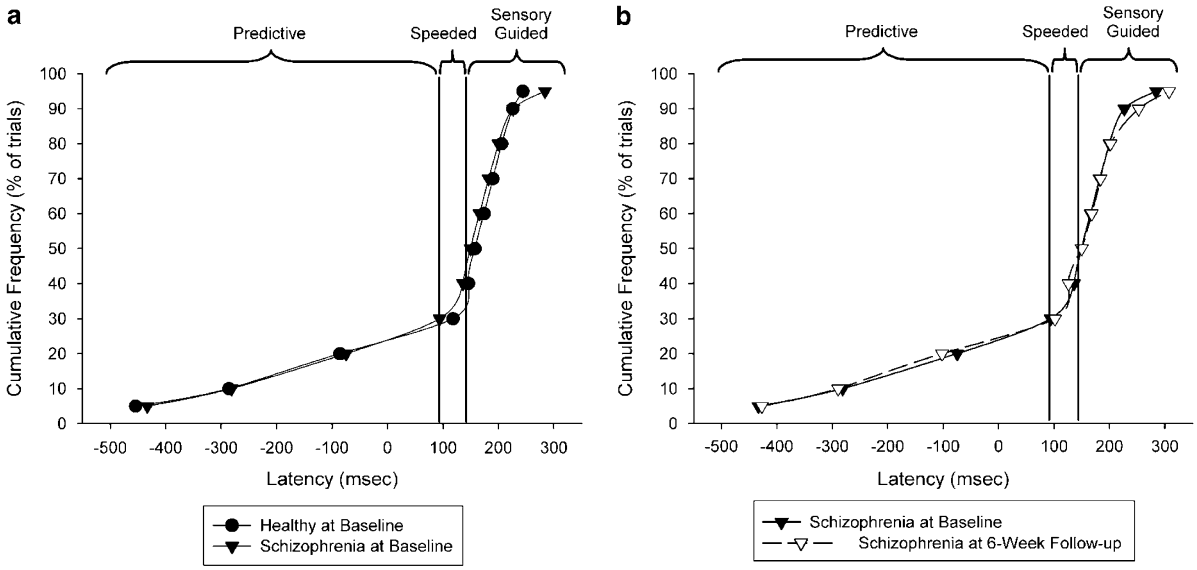

Figure 2 Cumulative percentage of trial-wise saccade latencies. (a) The comparison of patients (triangles) and healthy individuals (circles) at the baseline evaluation. Note the nearly overlapping distributions of the response latency data. (b) The stability of patients' response latencies from the baseline visit (solid line) to the 6-week follow-up. Predictive saccades had latencies less than 90 ms, speeded saccades had latencies between 90 and 140 ms, and sensory-guided saccades had latencies greater than 140 ms.

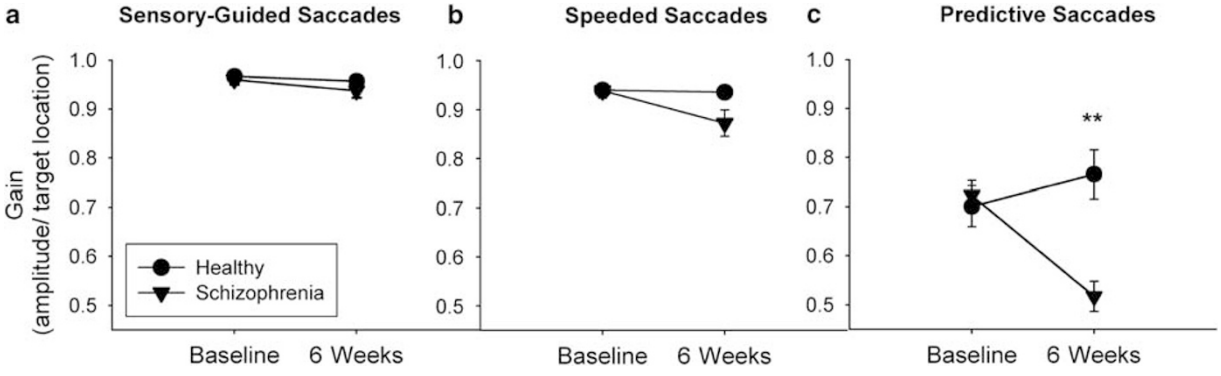

Figure 3 Mean (SE) error of saccade gain for patients and healthy individuals at baseline and 6-week follow-up. Patients' saccade gain of sensory-guided (a) and speeded saccades (b) were comparable to those of healthy participants at both time points. There was a substantial decline in the gain of patients' predictive saccades (c) at the 6-week follow-up relative to healthy individuals. $^{**}p < 0.001$.

learn to perform a simple procedural learning task. Before treatment, schizophrenia patients learned the invariant spatiotemporal characteristics of target positions, created a motor program based on internally generated predictions about the learned sequence, and executed anticipatory behavior as quickly and accurately as healthy individuals. After treatment with risperidone, the ability to time saccadic eye movements to predictable target appearance was unchanged. However, although the accuracy of sensory-guided responses remained unchanged, the accuracy of predictive saccades, voluntary saccades made before sensory input can be used to guide responses, was significantly reduced. Thus, although the temporal aspect of predicting target appearance remained unchanged, either spatial representational memory or the ability to use it to guide voluntary action was significantly impaired after 6 weeks of risperidone therapy. This effect was not related to minimal treatment-emergent EPS or to changes in manual motor control, suggesting that the ability to generate accurate behavioral responses based on internal representations without sensory feedback is a process adversely and selectively impacted by risperidone treatment.

The demonstration of reduced accuracy of predictive saccades after treatment is consistent with findings from prior studies with medicated patients (Crawford *et al*, 1995a; Hommer *et al*, 1991; McDowell *et al*, 1996; Thaker *et al*, 1996). However, the present findings are the first to document the onset of this robust deficit after the initiation of antipsychotic therapy. Our results are also important in documenting that antipsychotic-naive schizophrenia patients do not have deficits on this procedural learning task, which stands out as an area of intact neurocognitive function in the context of widespread neuropsychological (Bilder *et al*, 2000; Hill *et al*, 2004) and oculomotor deficits (Clementz *et al*, 1994; Harris *et al*, 2006; Lencer *et al*, 2000; Ross *et al*, 1997; Sweeney *et al*, 1998).

Notably, our oculomotor findings with regard to intact procedural learning prior to treatment stand in contrast to

Table 3 Associations Between Change Scores from Baseline to Follow-Up Testing of Oculomotor and Neuropsychological Parameters

	FT change score (dominant hand)		FT change score (nondominant hand)		GP time change score (dominant hand)		GP time change score (nondominant hand)	
	Healthy	**Patients**	**Healthy**	**Patients**	**Healthy**	**Patients**	**Healthy**	**Patients**
Sensory-guided saccade gain change score	0.000	0.183	0.122	0.288	0.043	−0.390	−0.049	−0.343
Speeded saccade gain change score	−0.106	0.156	−0.001	0.056	0.091	−0.091	−0.200	−0.262
Predictive saccade gain change score	0.406	0.070	0.114	−0.098	0.145	0.177	−0.286	0.169
Saccade latency change score[a]	−0.184	0.062	−0.151	−0.129	0.094	0.135	0.044	0.419*

Abbreviations: FT, Finger tapping; GP, Grooved Pegboard.
Data presented are Pearson's correlation coefficients (*r*) of change scores from baseline to 6-week testing of eye movement and neuropsychological parameters.
*$p < 0.05$.
[a]Latency change scores were calculated using data from trials 7 through 19 and excluding the initial response learning trials 1 through 6.

those from studies of manual serial reaction time tasks and manual pursuit rotor and mirror-drawing studies. On all of these tasks, schizophrenia patients were impaired even before antipsychotic drugs were available (Huston and Shakow, 1948). The basis of impaired procedural learning on manual but not oculomotor skills remains to be clarified. This could be due to the typically greater level of task difficulty in manual tasks used previously, or to differential perturbation of the functional brain systems supporting the intentional control of manual and eye movements. Regardless, the absence of deficits on oculomotor procedural learning tests indicates that the central processes associated with anticipation and prediction that are needed to support spatial representations and temporal interval timing for procedural learning on predictive saccade tasks do not appear to be impaired in the disorder.

Some previous investigations have reported hypometric predictive saccades in untreated patients, such as Krebs *et al* (2001) who reported this finding in a combined group of medication-naive and medication-free patients. Our work differs from that study in that all of our patients were antipsychotic-naive at baseline, and thus were not affected by potential residual effects of prior antipsychotic treatment. Hutton *et al* (2001) reported hypometric saccades in drug-naive schizophrenia patients, which is not consistent with our observations. The reasons for the difference between the results are not clear, but methodological factors may be important. Hutton *et al* (2001) employed auditory as well as visual stimuli to cue shifts in target locations, and used a shorter interstimulus interval (1 s).

We propose three mechanisms that may account for the reduction in predictive saccade accuracy after treatment with risperidone: (1) a disruption in motor learning or voluntary motor control, (2) a disturbance of spatial working memory, and (3) a disruption in spatial mapping and memory.

Motor Learning and Control

Functional neuroimaging studies with healthy individuals indicate central roles for the striatum and frontal cortex in procedural learning (Krebs *et al*, 1998; Poldrack *et al*, 2005; Zedkova *et al*, 2007), consistent with human lesion and disease models (Salmon and Butters, 1995) and unit recording studies of behaving monkeys (Hikosaka *et al*, 1999). Kumari *et al* (2002) have shown reduced activation in frontostriatal circuitry in treated schizophrenia patients performing a procedural learning task. Further, Kumari *et al* (1997) reported an adverse effect of haloperidol and a facilitative effect of D-amphetamine on procedural learning in healthy participants, demonstrating a key role of dopamine in human procedural learning. Therefore, the impairments we observed in predictive saccade accuracy after antipsychotic treatment might be due to the effects of D2 antagonism in striatum or frontal cortex. Consistent with this hypothesis, Bedard *et al* (2000) and Purdon *et al* (2003) have reported adverse effects of risperidone treatment on procedural learning in schizophrenia. Kern *et al* (1998) did not observe a differential effect of risperidone *vs* haloperidol treatment on a manual sequence learning test, suggesting that drug induced changes in procedural learning may occur with both first- and second-generation antipsychotic medications.

In addition to planning and enacting motor responses without sensory guidance, the ability to estimate temporal intervals is also required to perform predictive saccade tasks. Mechanisms supporting temporal interval timing in the basal ganglia are also known to be dopamine dependent (Garraux *et al*, 2005; Hinton and Meck, 1997). Dopamine, via pars compacta projections to the striatum, modulates 'clock' speed of the striatal timing system (Hinton and Meck, 1997). Thus, the absence of treatment effects on the timing of responses, consistent with previous findings on a manual task (Green *et al*, 1997), suggests that timing systems in the striatum are not adversely affected by antipsychotic treatment. The ability to learn to time responses appropriately after treatment suggests that the treatment-emergent reduction in predictive saccade accuracy is not a result of disturbances in pars compacta input to the striatum, or in striatocerebellar circuits that are also important for response timing (Hikosaka *et al*, 1999). Rather, disturbances in frontostriatal integration may be a more likely mechanism of the treatment effect, as the striatum prepares behavioral plans under the direction of prefrontal and premotor systems (Kermadi and Joseph, 1995).

Because of the key role of frontostriatal systems in procedural learning, results from oculomotor studies of Parkinson's disease (PD) are relevant to our findings. PD has an established impact on cognitive abilities subserved by frontostriatal circuitry, including procedural learning

and working memory (Hodgson *et al*, 1999). Investigations of internally generated saccades in patients with PD using predictive and memory-guided saccade tasks have reported reduced accuracy of responses (Chan *et al*, 2005; Crawford *et al*, 1989; Kimmig *et al*, 2002). Hence, the dopaminergic effects of risperidone may in some ways be analogous to the effect of PD on the dopamine systems in striatum, with its consequent adverse effect on thalamocortical drive and therefore the ability of premotor cortex to initiate behavior without sensory guidance (Grafton, 2004).

It is important to highlight that treatment-related change in predictive saccades was not a simple problem of motor control, as there was no abnormality in sensory-guided responses. Also, EPS ratings were low after treatment (Table 1), and the change in predictive saccade gain was not related to changes in manual motor abilities on neuropsychological tests that require sensory-guided responses as do sensory-guided saccades. The reductions in predictive saccade accuracy, in the context of minimal changes in sensory-guided saccades, manual visuomotor control, or EPS, suggest that the predictive saccade task may provide an especially sensitive biomarker of D2 blockade on frontostriatal systems.

Spatial Working Memory

Because performance of the predictive saccade task requires the maintenance and retrieval of spatiotemporal information to guide behavior, spatial working memory is important in facilitating procedural learning of spatially guided motor sequences. Patients with focal prefrontal lesions have working memory deficits and also procedural learning deficits on serial reaction time tasks (Gomez *et al*, 1999), and spatial working memory deficits are related to reduced saccade gain on the predictive saccade task in schizophrenia (Hutton *et al*, 2001).

The impact of antipsychotics on working memory systems remains somewhat ambiguous. Though some studies report a beneficial effect (McGurk *et al*, 2005), we previously reported in two independent samples a worsening of spatial working memory on an oculomotor-delayed response (ODR) task after risperidone treatment (Reilly *et al*, 2006, 2007). The ODR task places heavier demands on maintenance rather than manipulation aspects of working memory compared to most neuropsychological tests, and therefore it is more similar in cognitive demand to the requirements of the predictive saccade task.

Working memory relies on the activation of prefrontal cortical D1 receptors in PFC (Goldman-Rakic, 1999; Lidow *et al*, 1997). Destruction of dopamine terminals in the PFC disrupts the integrity of short-term working memory (Seamans *et al*, 1998), and direct injections of D1 antagonists into the dorsolateral PFC disrupt memory-guided but not sensory-guided saccades (Sawaguchi and Goldman-Rakic, 1994). Given that antipsychotic medication induces robust downregulation of prefrontal D1 receptors (Lidow *et al*, 1997) and, in turn, working memory impairments that can be reversed by short-term treatment with a D1 agonist (Castner *et al*, 2000), it is conceivable that reduced fidelity of internal spatial representations could be, at least in part, a cause of decreased predictive saccade accuracy after risperidone treatment. One caveat is that Lidow *et al* (1997) demonstrated D1 changes in monkeys after 6 months of antipsychotic drug administration, and whether they are present to a neurophysiologically significant level in humans after 6 weeks of treatment is not known.

Spatial Mapping and Memory

Several lines of evidence point to abnormal function and anatomy of the hippocampus in schizophrenia (Heckers, 2001). Wilkerson and Levin (1999) demonstrated that infusion of a D2 antagonist into the hippocampus significantly impaired spatial working memory in rats. Another animal study documented decreased local cerebral glucose utilization in the hippocampus following acute administration of risperidone (Huang *et al*, 1999). These findings suggest that the hippocampus is affected by risperidone, possibly in ways that could alter the ability of the hippocampus to encode spatial location information necessary for successful performance of the predictive saccade task (Simo *et al*, 2005).

CONCLUSION

Although there were no pretreatment abnormalities in procedural learning in antipsychotic-naive schizophrenia patients, reductions in the accuracy of predictive saccades were observed after risperidone treatment. The most parsimonious cause of this treatment effect is an alteration of dopamine regulation in striatum, which could reduce thalamocortical facilitation of premotor systems and thus lower the amplitude of voluntary motor actions initiated without sensory guidance. Effects of risperidone on spatial working memory or spatial mapping systems might also contribute to the observed treatment-related neurobehavioral changes.

Because there was no reduction in the accuracy of sensory-guided saccades after treatment, the deficit in predictive saccades was not due to a simple motor system disturbance. Rather, the problem was more cognitive in nature, involving the initiation of accurate responses based on internal spatial representations and behavioral plans. The observation of such an impairment, which is consistent with animal models of the effects of dopamine receptor blockade (Wang *et al*, 2004) and observations in PD (Hodgson *et al*, 1999), stands out by way of comparison with the pattern of generalized enhancement on neuropsychological tests reported in clinical trials with risperidone and other antipsychotic treatments (Harvey *et al*, 2005; Keefe *et al*, 2006; Woodward *et al*, 2005). Findings from the present study, and others (Reilly *et al*, 2006; Sweeney *et al*, 1997), suggest that translational oculomotor biomarkers may provide sensitive and specific tools for drug discovery and evaluation by parsing drug effects on discrete neurocognitive operations.

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DISCLOSURE/CONFLICTS OF INTEREST

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