

Adverse Effects of Risperidone on Eye Movement Activity: A Comparison of Risperidone and Haloperidol in Antipsychotic-Naive Schizophrenic Patients

John A. Sweeney, Ph.D., Kenneth S. Bauer, B.S., Matcheri S. Keshavan, M.D.,
Gretchen L. Haas, Ph.D., Nina R. Schooler, Ph.D., and Patricia D. Kroboth, Ph.D.

Risperidone is a novel and clinically effective atypical antipsychotic medication with a unique biochemical profile. To contrast the neurophysiological effects of this new medication with those of a typical antipsychotic medication, we performed quantitative measurements of saccadic eye movements in a series of antipsychotic-naïve schizophrenic patients treated with either risperidone or haloperidol. Patients were tested before and after 1 month of treatment, and a matched group of healthy subjects was tested twice over a similar time interval. Risperidone, but not

haloperidol, was associated with prolonged latency and decreased peak velocity and accuracy of saccadic eye movements that was detectable 4 weeks after treatment initiation. The adverse effects of risperidone may be due to the lack of development of acute tolerance to its powerful serotonergic (5-HT_{2A}) antagonism, which could be responsible for the disruption of brainstem physiology in regions controlling saccadic eye movements. © 1997 American College of Neuropsychopharmacology [Neuropsychopharmacology 16:217–228, 1997]

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Risperidone is a novel benzisoxazole derivative with demonstrated clinical efficacy as an antipsychotic agent in the treatment of schizophrenia (Chouinard et al. 1993; Marder and Meibach 1994; Schooler 1994). Receptor binding studies in rodents and human PET studies have demonstrated that risperidone is a potent 5-HT_{2A} antagonist at low dosages and a potent D₂ antagonist at

higher doses (Nyberg et al. 1993; Sumiyoshi et al. 1994). Its affinity is approximately 20 times higher for 5-HT_{2A} than D₂ receptors, and among serotonergic receptor subtypes the effects are highly selective for 5-HT_{2A} receptors (Janssen and Awouters 1994; Leysen et al. 1994). Risperidone possesses an affinity for D₂ receptors that is approximately two to three times less than haloperidol and a lower affinity at H₁ and muscarinic receptors than the atypical antipsychotic clozapine (Leysen et al. 1994).

Clinical trials suggest that risperidone may have therapeutic advantages relative to the typical antipsychotics haloperidol (Borison et al. 1992; Chouinard and Arnott 1993; Marder and Meibach 1994; Owens 1994; Schooler 1994) and perphenazine (Hoyberg et al. 1993), including greater efficacy in reducing negative symptoms, less frequent extrapyramidal side effects, and perhaps a faster onset of action. Clinically significant hematological and cardiovascular side effects are uncommon during treatment with risperidone (Mesotten

From the Departments of Psychiatry (JAS, MSK, GLH, NRS) and Neurology (JAS), Neurobehavioral Studies Program, University of Pittsburgh School of Medicine; and the Department of Pharmacy and Therapeutics (KSB, PDK), University of Pittsburgh School of Pharmacy, Pittsburgh, PA.

Address correspondence to: John A. Sweeney, Ph.D., Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213.

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et al. 1989). Sedation has been reported as an adverse effect in some studies (Hoyberg et al. 1993; Heinrich et al. 1994), as has been described for the atypical antipsychotic clozapine (Lieberman and Safferman 1992; Centorrino et al. 1994). To date, clinical studies of the efficacy and adverse effects of risperidone have been conducted almost exclusively with chronically ill schizophrenic patients and have utilized clinician- or observer-rated assessment of adverse effects. One quantitative EEG study reported that risperidone, in contrast to haloperidol, induces a widespread change in interhemispheric power asymmetry. These changes were seen in both the beta and theta bands and were attributed to serotonergic mechanisms (Czobor and Valavka 1993).

Previous research has demonstrated dose-related changes in saccadic eye movements in response to a variety of CNS-active medications and drugs of abuse. Saccades are brief rapid eye movements that shift the focus of gaze from one point to another in the visual field. Some drugs appear to disrupt all aspects of saccadic eye movements, including their latency, accuracy and peak velocity. Drugs that reduce alertness or have sedative effects, such as benzodiazepines (Bittencourt et al. 1981; Jurgens et al. 1981; Hommer et al. 1986; Roy-Byrne et al. 1993), barbiturates (Schalen et al. 1988), clonidine (Glue et al. 1991), nitrous oxide (Gao et al. 1991), the calcium channel blocker flunarizine (Tedeschi et al. 1992), methadone (Rothenberg et al. 1980), and alcohol (Baloh et al. 1979; Katoh 1988), all distort the latency, peak velocity, and accuracy of saccades. The anti-convulsant carbamazepine has been shown to disrupt saccade dynamics at lower doses than those required to cause clinically detectable sedation (Tedeschi et al. 1989).

Other drugs appear to affect only the initiation of saccades, but not the actual dynamics of these eye movements (such as their peak velocity and duration). Scopolamine reduces nystagmus after vestibular challenge (Pykko et al. 1985), reflecting cholinergic modulation of the vestibular nuclei. The NMDA receptor antagonist ketamine disrupts gaze maintenance but not the dynamics of saccades (e.g., peak velocity and accuracy) (Godaux et al. 1990). Parkinsonism associated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is most consistently associated with prolonged saccade latency rather than altered saccade dynamics, although disturbances in saccade dynamics are seen in some cases (Brooks et al. 1986; Schultz et al. 1989). Disturbances in saccade dynamics are most clearly related to altered function in the superior colliculus and its target projections in the brainstem and in the cerebellum (Keller 1989), as these regions code the dynamics of saccadic eye movements (Waitzman et al. 1991).

Oculomotor measurements offer several significant advantages relative to self- or observer-ratings of drug effect. First, the measurements are objective and quantitative, and are not dependent on the accuracy of patient

self-report or clinician ratings. Second, although subjects can voluntarily control the initiation and target for saccades, the dynamics of these eye movements are not under voluntary control and are therefore minimally influenced by intentional motivational factors. Third, saccades are known to be highly sensitive to variations in fatigue and alertness (Becker 1989). Fourth, the brain systems that control eye movements are relatively well understood both anatomically and biochemically, based on behavioral and single-cell electrophysiological studies in alert behaving monkeys (Fischer 1987; Sawaguchi et al. 1989; Sawaguchi and Goldman-Rakic 1991; Goldman-Rakic et al. 1992) and human functional neuroimaging studies (Fox et al. 1985; Sweeney et al. 1996), making this an ideal system for studying pharmacological effects on brain systems.

Disturbances of pursuit eye movements are well established in schizophrenia, including studies establishing the presence of reduced pursuit gain in never-treated patients (Holzman et al. 1974; Sweeney et al. 1994a; Friedman et al. 1995). The pursuit system does not appear to be affected by typical neuroleptic medications, at least not after 1 month of treatment (Friedman et al. 1991; Sweeney et al. 1994b). The effects of the atypical antipsychotic clozapine on pursuit eye movements remain controversial (Friedman et al. 1991; Litman et al. 1994).

In contrast to the consistent finding of pursuit disturbances in schizophrenia, reflexive saccadic eye movements have not been found to be impaired in most studies of schizophrenic patients (Fukushima et al. 1990; Abel et al. 1992; Clementz et al. 1994). Some studies have reported saccade abnormalities (Cegalis et al. 1982; Moser et al. 1990), but these effects were subtle and observed in chronically ill patients taking typical antipsychotic medications. Because of the motor system disturbances sometimes associated with neuroleptic treatment and reports indicating that acute doses of both remoxipride and chlorpromazine impair saccades in healthy subjects (King et al. 1995), studies of untreated patients are needed to determine whether there are disturbances in brain regions subserving saccadic eye movements in schizophrenia. At present, fewer data are available regarding the integrity of saccadic eye movements in treatment-naïve schizophrenic patients or about the effects of typical or atypical antipsychotic medications on saccadic eye movements in the clinical setting. In the present study, we compared the effects of risperidone and haloperidol on several quantitative indices of saccadic eye movement activity in antipsychotic-naïve first-episode schizophrenic patients.

METHODS

The study was conducted as part of the University of Pittsburgh First Episode Project, an ongoing prospec-

tive study of the early course of schizophrenia. The patient sample was comprised of 20 antipsychotic-naïve patients with a DSM-III-R diagnosis of schizophrenia ($n = 15$) or schizoaffective ($n = 5$) disorder. Diagnoses were based on Structured Clinical Interview for DSM-III-R (SCID) diagnoses (Spitzer et al. 1987) and all other available information that were reviewed at a consensus diagnosis meeting by senior investigators and clinical staff. Follow-up evaluations were conducted to confirm diagnoses. Matched healthy comparison subjects were recruited ($n = 10$) from the surrounding community and verified to have no Axis I disorder by SCID interview. The healthy comparison group was selected to match the patient sample on age, sex, and parental socioeconomic status. All subjects met the following criteria: (1) age between 18 and 45 years; (2) no known systemic or neurological illness; (3) no prior treatment with electroconvulsive therapy (ECT); (4) no history of head trauma with loss of consciousness; (5) no lifetime history of substance dependence or of substance abuse in the 2 months preceding hospitalization; (6) no anticonvulsant or other benzodiazepines for 1 month; and (7) no coffee, tea, or cigarettes for 1 hour before eye movement testing. Patient reports of prior treatment history were confirmed by family members and treating physicians. Table 1 summarizes the demographic and clinical information for the three subject groups (risperidone, haloperidol, and healthy comparison; $n = 10$ in each group). There were no significant group differences in age ($F = 0.44$, $df = 2,27$, NS), sex ratio ($\chi^2 = 2.39$, $df = 2$,

NS), or IQ as assessed using the Ammon's Quick Test (Ammons and Ammons 1962) ($F = 1.99$, $df = 2,27$, NS).

Patients were administered a battery of psychopathology rating instruments at the time of each eye movement testing by clinicians having no knowledge of findings from eye movement studies. The battery included the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) and the Schedules for the Assessment of Positive (SAPS; Andreasen 1984a) and Negative (Andreasen 1984b) Symptoms. At the time of the first eye movement testing, there were no significant differences between the two schizophrenic patient groups on any clinical measure (Table 1).

The first eye movement testing was conducted within 7 days prior to treatment initiation. Patients were retested after they had taken antipsychotic medication for approximately 4 weeks with the last 7 days on a stable dose, and healthy comparison subjects were retested after a similar time interval. The first series of 10 study-eligible consenting patients admitted for inpatient care to the Western Psychiatric Institute and Clinic were treated with haloperidol. Shortly after risperidone received FDA approval for the treatment of schizophrenia in December 1993, we began to treat the next series of 10 study-eligible patients with risperidone. Both medications were administered at relatively low doses to minimize adverse side effects, and because low-dose treatment is clinically effective in the treatment of many schizophrenic patients early in the course of illness (Van Putten et al. 1990; McEvoy et al. 1991). Eight of the

Table 1. Demographic and Clinical Characteristics of Schizophrenic Patients Treated with Risperidone or Haloperidol with Healthy Comparison Subjects

	Haloperidol-Treated Patients	Risperidone-Treated Patients	Healthy Comparison Subjects
Age	24.5 ± 9.3	28.2 ± 9.9	25.5 ± 8.0
Gender (M/F)	6/4	9/1	7/3
Laterality ^a	9.3 ± 3.1	8.2 ± 6.5	9.7 ± 2.7
IQ	99.7 ± 15.3	94.8 ± 10.2	106.9 ± 14.9
SAPS			
Pretreatment	8.6 ± 3.9	8.6 ± 4.3	
Posttreatment	4.3 ± 2.7**	1.1 ± 1.7***	
SANS			
Pretreatment	10.9 ± 1.7	11.7 ± 3.6	
Posttreatment	8.8 ± 2.1*	10.0 ± 1.7	
BPRS			
Pretreatment	49.1 ± 9.1	49.4 ± 12.7	
Posttreatment	36.8 ± 9.0**	30.2 ± 5.5***	
Treatment duration (days)	31.4 ± 7.1	30.5 ± 5.9	
Antipsychotic dose	2.9 ± 1.3	4.2 ± 2.3	
Benzotropine ^b	1.7 ± 1.2	1.0	
	($n = 8$)	($n = 1$)	

^aScore on the Modified Edinburgh Handedness Inventory (Raczkowski and Kalat 1974).

^bAverage daily dose for patients receiving the medication.

* $p < .05$; ** $p < .01$; *** $p < .001$ from paired t -tests comparing pre- and posttreatment scores. Data presented are mean ± standard deviation.

patients receiving haloperidol and one risperidone-treated patient also were treated with the anticholinergic medication benztropine.

Saccadic Eye Movement Task

Tasks were designed to elicit "reflexive" saccades to temporally and spatially unpredictable targets. These tasks are simple and straightforward; subjects were instructed to look quickly to visual targets wherever they appeared. EOG recordings were obtained (Grass Neurodata 12 Acquisition System, Astro-Med, Inc., West Warwick, RI) to assess visuomotor functions across a large range of the horizontal visual field. Trials began with a center fixation target that remained illuminated for 1.5 to 2.5 s (average 2.0 s) before peripheral targets were presented to the left or right in the horizontal plane. Peripheral targets (target steps) were presented for 1.5 s at ± 10 , 20, or 30 degrees from center fixation. A total of 54 trials were presented. Targets were presented on a circular arc 1 m from subjects using individually addressable light-emitting diodes that subtended approximately 0.2 degrees of visual angle. Blinks were monitored using electrodes placed above and below the left eye. Data were digitized on-line at 500 Hz (Model DI-210 14-bit A/D converter, DATAQ Instruments, Akron, OH).

Subjects were tested alone in a completely dark room to prevent distraction from extraneous information that can influence eye movements. A chin rest, with forehead and occipital restraints and a head strap, was used to maintain head stability. Instructions were given by a technician via intercom from an adjacent room. The technician monitored eye movements during task performance to provide instructions and realerting commands when necessary. When the central fixation point

was presented at the beginning of each trial, a brief tone sounded behind the central fixation light to help subjects quickly refixate the central fixation cue (Konrad et al. 1989).

Eye Movement Analysis

Eye movement recordings were analyzed off-line using custom software written in this laboratory. Before any processing of the eye movement data took place, the data were smoothed with a finite-impulse response filter, a low-pass filter with a passband of 0 to 16 Hz, a smooth transition band of 16 to 70 Hz, and a stop band for frequencies 70 Hz and up. The filter was chosen empirically to reduce noise artifacts with a minimum of signal distortion.

Eye movement recordings from each trial were presented graphically to a technician for analysis. Eye position recordings were calibrated (i.e., converted from raw voltage data to eye movement in degrees of visual angle) for each trial independently using data from the time subjects fixated the central cue and the peripheral target. This "within-trial" calibration was performed to minimize artifacts resulting from drift in DC-EOG signals that can occur over the course of a study. Saccades were identified as beginning when eye velocity rose above 30 degrees/s and continuing until eye velocity returned below that level. The latency, peak velocity, and accuracy of the primary saccade on each trial were recorded.

The technician reviewed the results of algorithm-based analyses on a trial-by-trial basis and made modifications or deleted trials when an artifact occurred that was not detected by software. If a blink began between 100 ms before presentation of a peripheral target and

Table 2. Peak Velocity of Saccades (in degrees/s \pm SD) to Target-Steps of $+/- 10$, 20, and 30 Degrees from Central Fixation in Antipsychotic-Naive Schizophrenic Patients before and after 1 Month of Treatment with Haloperidol or Risperidone and in Healthy Comparison Subjects

	Baseline	Second Testing	Change from Baseline
10-Degree target steps			
Haloperidol	317 \pm 42	298 \pm 63	-18 \pm 42
Risperidone	321 \pm 39	280 \pm 46	41 \pm 20***
Control	296 \pm 37	288 \pm 37	-8 \pm 22
20-Degree target steps			
Haloperidol	422 \pm 73	396 \pm 81	-26 \pm 58
Risperidone	444 \pm 65	389 \pm 83	-54 \pm 33***
Control	418 \pm 38	411 \pm 50	-7 \pm 33
30-Degree target steps			
Haloperidol	462 \pm 70	423 \pm 89	-38 \pm 66
Risperidone	512 \pm 87	416 \pm 97	-96 \pm 60***
Control	440 \pm 46	445 \pm 53	5 \pm 52

Data presented are mean \pm standard deviation. *** $p < .001$ from paired t -tests comparing pre- and post-treatment scores.

the end of the primary saccade, or if a saccade occurred within 100 ms before and 70 ms after peripheral target presentation, the trial was excluded from analyses. Data from the right eye were scored unless this was precluded by recording artifact (i.e., signal clipping, or considerably greater bioelectric noise than in the left eye recording).

Statistical Analysis

The primary data analyses involved repeated-measures analyses of variance (ANOVAs) performed to assess subject group and time of testing effects. Because there were no significant laterality effects on any eye movement parameter, data from leftward and rightward saccades were pooled for all analyses. Paired *t*-tests contrasting saccades at the first and second testings were used to clarify treatment effects. Exploratory correlational analyses were performed to assess the association between performance on eye movement tasks and clinical symptom ratings, medication dose, and demographic variables.

RESULTS

Comparisons of Patients and Healthy Comparison Subjects at Initial Testing

The integrity of visually guided saccadic eye movements in the schizophrenic patients prior to treatment was assessed by comparing the baseline performance of all patients with that of the healthy comparison subjects. There were no significant differences between the healthy comparison subjects and the schizophrenic patients in the peak velocity ($F = 1.83$, $df = 1,28$, NS), la-

tency ($F = 1.24$, $df = 1,28$, NS), or accuracy ($F = 3.71$, $df = 1,28$, NS) of saccades at the initial testing session when patients were untreated. Similar analyses comparing the pretreatment performance of the haloperidol- and risperidone-treated schizophrenic patients also failed to identify any significant differences in performance prior to the initiation of treatment.

Clinical Treatment Effects

Patients demonstrated a significant clinical improvement after 4 weeks of treatment with haloperidol and risperidone, as indicated in Table 1. This is reflected in the significantly reduced symptom ratings at the time of the second testing demonstrated using repeated measures analyses of variance: BPRS ($F = 34.65$, $df = 1,18$, $p < .001$), SAPS ($F = 41.83$, $df = 1,18$, $p < .001$), and SANS ($F = 9.77$, $df = 1,18$, $p < .01$). There were no significant differences in the magnitude of clinical change following treatment with risperidone or haloperidol on any of these measures (all p 's $> .10$).

Medication Effects on Eye Movements

Peak velocity, latency, and accuracy of saccades from the two testing sessions are presented in Tables 2, 3, and 4. Figures 1 and 2 show data from individual subjects for peak velocity and latency of saccades, respectively, in response to target displacements of 30 degrees of visual angle from center fixation. Differential changes between the first and second testing session were observed in the peak velocity ($F = 5.87$, $df = 2,27$, $p < .01$), latency ($F = 4.21$, $df = 2,27$, $p < .03$), and spatial error ($F = 4.75$, $df = 2,27$, $p < .02$) of saccades in the three subject groups. This differential effect was greater for

Table 3. Mean Latency (ms \pm SD) to Initiate Saccades to Target-Steps of ± 10 , 20, and 30 Degrees from Central Fixation in Antipsychotic-Naive Schizophrenic Patients before and after 1 Month of Treatment with Haloperidol or Risperidone and in Healthy Comparison Subjects

	Baseline	Second Testing	Change from Baseline
10-Degree target steps			
Haloperidol	179 \pm 29	183 \pm 26	3 \pm 16
Risperidone	205 \pm 37	221 \pm 55	16 \pm 31
Control	215 \pm 27	219 \pm 41	4 \pm 24
20-Degree target steps			
Haloperidol	196 \pm 35	199 \pm 21	3 \pm 27
Risperidone	221 \pm 40	251 \pm 39	30 \pm 26**
Control	224 \pm 29	227 \pm 35	3 \pm 21
30-Degree target steps			
Haloperidol	221 \pm 47	214 \pm 32	-7 \pm 45
Risperidone	258 \pm 44	289 \pm 58	31 \pm 26**
Control	246 \pm 24	244 \pm 32	-2 \pm 16

Data presented are mean \pm standard deviation. ** $p < .01$ from paired *t*-tests comparing pre- and post-treatment scores.

Table 4. Mean Error of Saccades (in Degrees of Visual Angle \pm SD) to Target-Steps of $+/-$ 10, 20, and 30 Degrees from Central Fixation in Antipsychotic-Naive Schizophrenic Patients before and after 1 Month of Treatment with Haloperidol or Risperidone and in Healthy Comparison Subjects

	Baseline	Second Testing	Change from Baseline
10-Degree target steps			
Haloperidol	-0.53 ± 0.55	-0.83 ± 1.10	$.31 \pm .76$
Risperidone	-0.34 ± 0.32	-0.70 ± 0.54	$.36 \pm .32^{**}$
Control	-0.39 ± 0.61	-0.52 ± 0.77	$.13 \pm .33$
20-Degree target steps			
Haloperidol	-2.07 ± 1.05	-1.79 ± 0.97	-0.28 ± 1.04
Risperidone	-1.25 ± 0.83	-2.01 ± 1.080	$.76 \pm .75^*$
Control	$-.98 \pm 0.75$	-0.98 ± 0.70	$0.0 \pm .53$
30-Degree target steps			
Haloperidol	-3.31 ± 2.27	-2.49 ± 1.53	-0.82 ± 2.11
Risperidone	-1.59 ± 1.05	-2.74 ± 1.85	1.14 ± 1.83
Control	-1.17 ± 0.85	-1.09 ± 0.33	$-.08 \pm .61$

Data presented are mean \pm standard deviation. $^*p < .05$; $^{**}p < .01$ from paired *t*-tests comparing pre- and posttreatment scores.

the peak velocity of larger saccades ($F = 3.90$, $df = 4,54$, $p < .01$), but the magnitude of group differences in saccade latency and accuracy did not differ significantly in relation to the amplitude of the target displacement.

In a series of paired *t*-tests comparing performance from the first and second testings on saccade parameters where significant effects had been demonstrated in repeated-measures ANOVAs, there were no significant changes in any dimension of saccadic eye movement activity for the healthy comparison subjects or the haloperidol-treated patients. In contrast, the risperidone-treated patients showed a deterioration in the dynamics of saccadic eye movements after treatment. Significant increases in saccade latency were evident in response to both the 20- and 30-degree target steps, and increases in saccade error were evident in response to both 10- and 20-degree target steps. Significant decreases in peak saccade velocity were evident in saccades to all three amplitudes of the target steps. To verify that the reduced peak saccade velocity in the risperidone-treated patients was not accounted for by a reduction in saccade amplitude (smaller saccades have lower velocity), we computed the ratio of saccade velocity over saccade amplitude for each saccade. Analyses of these "amplitude-corrected" velocity indices revealed significant reductions in saccade velocity to both 20-degree ($t = 3.00$, $df = 9$, $p < .02$) and 30-degree ($t = 4.04$, $df = 9$, $p < .003$) target steps, but reductions in saccade velocity for saccades to the 10-degree step were no longer significant ($t = 2.11$, $df = 9$, $p < .07$). These analyses indicate that the reduced peak saccade velocity in the risperidone-treated patients represents a true reduction in peak saccade velocity [i.e., not a velocity reduction resulting merely from smaller amplitude (hypometric) saccades]. The magnitude of drug effects was not significantly cor-

related with the oral dosage of antipsychotic medication or with changes on clinical ratings of symptom severity.

DISCUSSION

Treatment of antipsychotic-naive schizophrenic patients with risperidone led to significant clinical benefit, but also to adverse effects on saccadic eye movements that were evident after 4 weeks of treatment. These adverse effects were evident in the latency, peak velocity, and spatial error of visually guided "reflexive" saccades and suggest a treatment-related perturbation of brainstem physiology in regions that subserve saccadic eye movements.

In previous studies of the pharmacological effects of other CNS-active medications on saccadic eye movements, particularly benzodiazepines, acute tolerance to drug-induced effects on saccades develops quickly (on the order of hours; Kroboth et al. 1995). The effects of risperidone appear to be quite different. After 4 weeks of treatment, significant residual adverse drug effects were evident, which indicates, at the least, a very slow development of tolerance.

Saccades in Schizophrenia

There have been many demonstrations of abnormal pursuit eye movements in schizophrenia (Clementz and Sweeney 1990; Levy et al. 1994), but saccadic eye movements have been much less extensively investigated. To our knowledge, this is the first study to assess comprehensively multiple aspects of saccadic eye movements in a cohort of treatment-naive first-episode schizo-

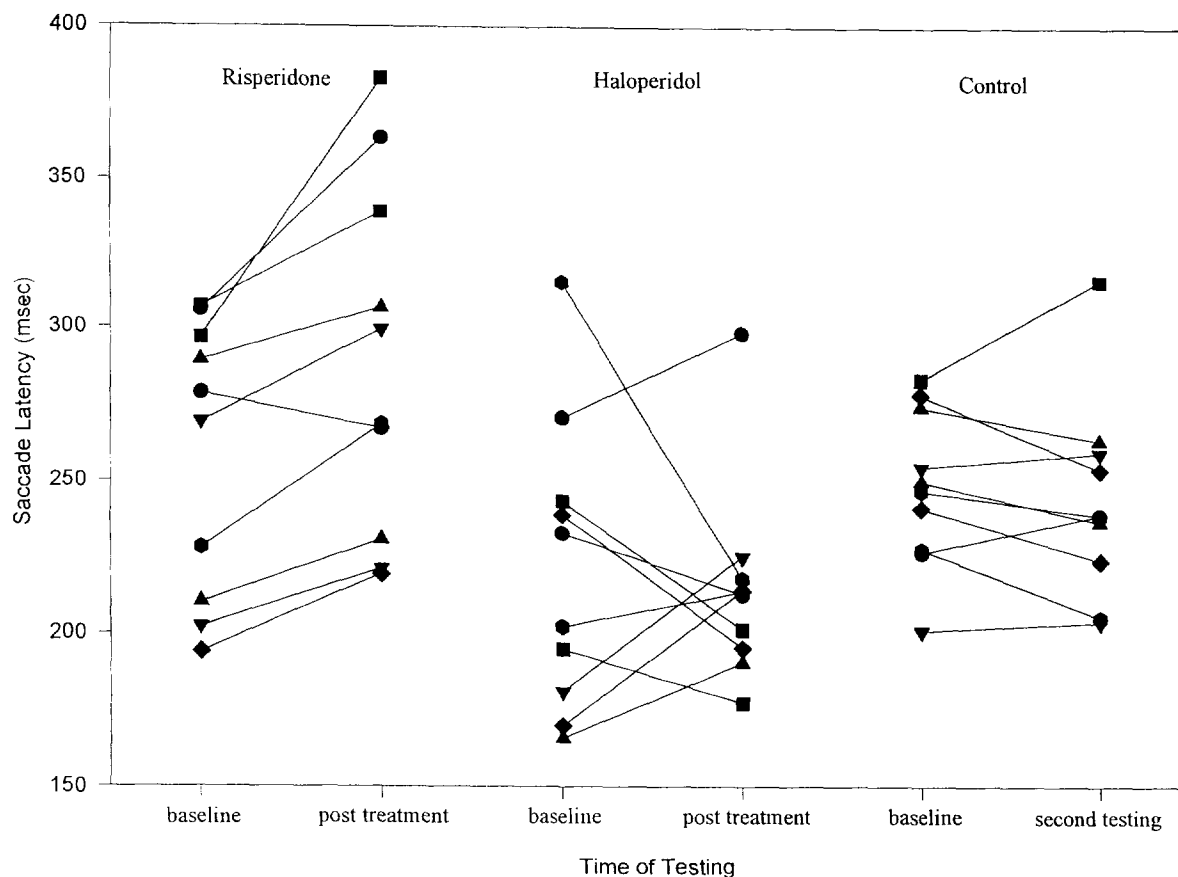


Figure 1. Individual subject data for average latency of saccadic eye movements to target-steps of ± 30 degrees of visual angle from central fixation in antipsychotic-naïve schizophrenic patients before and after one month of treatment with haloperidol or risperidone, and in healthy comparison subjects.

phrenic patients and to follow them over the early course of treatment with antipsychotic agents.

We did not identify any abnormalities in reflexive visually guided saccadic eye movements in these treatment-naïve schizophrenic patients prior to treatment initiation. This observation is similar to the findings of most previous studies of schizophrenic patients, even though patients in those studies were almost always taking typical antipsychotic medications at the time they were studied (Mather and Putchat 1982; Yee et al. 1987; Fukushima et al. 1990; Clementz et al. 1994; Crawford et al. 1995b). However, there have been reports of saccade disturbances in schizophrenic patients. A subtle, but significant, increase in saccade error (dysmetria) has been reported in some studies (Cegalis et al. 1982; Mather and Putchat 1982; Moser et al. 1990; Crawford et al. 1995b), an abnormality that is pronounced in patients with tardive dyskinesia (Oepen et al. 1990). One study has reported a pattern of normal latency, but hypometric saccades, in schizophrenic patients who had been untreated for at least 6 months (Crawford et al. 1995a). An increased latency of visually guided saccades also has been reported in some studies of schizophrenic patients (Yee et al. 1987), and one group has shown this

to be particularly pronounced in chronically ill patients with prominent negative symptoms (Mackert and Flechtner 1989). On the basis of the results of the present study, which indicate intact reflexive saccadic eye movements in schizophrenic patients prior to treatment initiation, previous reports of saccade abnormalities might represent adverse medication effects or pathophysiological changes associated with the course of illness.

Treatment Effects on Saccades

The results of the present study indicate significantly reduced peak velocity and accuracy of saccades and increased saccade latency in schizophrenic patients treated with relatively low doses of risperidone for approximately 1 month. Patients treated with haloperidol did not demonstrate these effects. The reduced peak velocity of saccades in risperidone-treated patients suggests a disturbance in brainstem physiology, because it implies a perturbation at the level of pontine burst cell input to oculomotor nuclei. The reduced saccade accuracy suggests a disturbance intrinsic to the brainstem or involving its cerebellar input, whereas the prolonged saccade latency is a less-specific finding suggesting

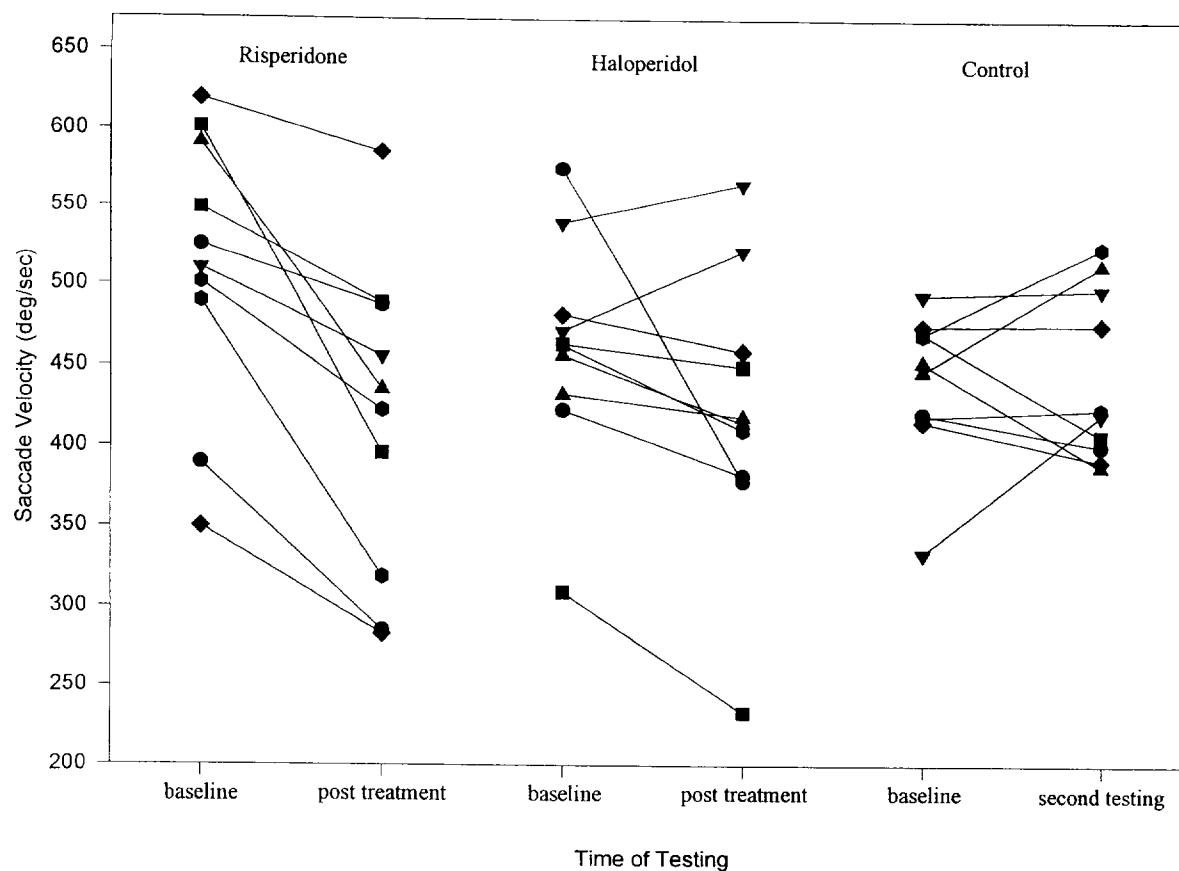


Figure 2. Individual subject data for average peak velocity of saccadic eye movements to target-steps of ± 30 degrees of visual angle from central fixation in antipsychotic-naïve schizophrenic patients before and after one month of treatment with haloperidol or risperidone, and in healthy comparison subjects.

slowed transmission of information in widely distributed visual sensorimotor systems. This pattern of generalized deficits in the saccade system is one associated with multiple CNS-active medications that reduce alertness or cause sedation, and thus it is possible that some reductions in alertness may be associated with risperidone treatment.

Mackert and Flechtner (1989), in the only published study of which we are aware investigating treatment effects on saccades in initially untreated schizophrenic patients, studied saccade latencies and reported no change after an average of 11.5 weeks of treatment with various typical neuroleptic medications. The results of the present study in haloperidol-treated patients replicate this effect in saccade latency and extend it by demonstrating that other parameters of saccade function, including peak velocity and accuracy, also appear not to be affected by the typical antipsychotic haloperidol.

The clinical relevance of our observations remain to be clarified, particularly in terms of whether risperidone-related changes in saccadic eye movements are associated with changes in the psychological alertness of patients. Investigation of linkages to patient reports of adverse effects and with neuropsychological studies

of attentional functions are needed to evaluate this possibility. Should risperidone treatment be found to be associated with reduced psychological alertness, it will be important to clarify the range of severity and dose dependence of this effect. Furthermore, it will be important to determine the duration of such effects to establish whether tolerance develops over longer courses of treatment than the 1-month period examined in this study. In this context, it is important to note that haloperidol might have induced dose-dependent perturbations of saccades earlier in the course of treatment but that tolerance to such effects developed prior to our second testing 1 month after treatment initiation. Efforts to characterize better the biochemical changes resulting from risperidone that alter brainstem physiology could be of clinical relevance, as they might suggest strategies for diminishing the impact of associated adverse effects when they are troubling for patients and dose reduction is undesirable.

A Possible 5-HT Mechanism

The mechanism by which risperidone adversely impacts eye movement activity is unclear. One possibility

is suggested by the differences in receptor-binding affinity profiles between haloperidol and risperidone (Leysen et al. 1994), particularly the powerful serotonergic effect of risperidone (5-HT_{2A} receptor antagonism). Acute administration of the serotonin precursor L-tryptophan causes drowsiness, saccadic disinhibition, and hypometric saccades (Smith and Prockop 1962; Hodge et al. 1964; Baloh et al. 1982). Fluoxetine, a potent 5-HT reuptake inhibitor, has been shown to disinhibit saccadic activity during non-rapid eye movement sleep (Schenck et al. 1992). This effect is likely to result from a potentiation of serotonergic neurons that project from the dorsal raphe nucleus and inhibit "pause" neurons, a group of brainstem neurons that play a key role in saccade control. Pause neurons provide monosynaptic inhibitory input to the pontine burst cells that drive motoneurons to initiate saccades. Inhibitory input from pause cells is dramatically reduced during saccades and resumes immediately at the end of saccades. Thus, pause cells effectively "release" burst cells so that they can initiate saccades and prevent unintended saccades at other times. The inverse off-on patterns of neurophysiological activity in burst and pause cells are precisely integrated temporally, and disturbing this synchrony disrupts the velocity characteristics of saccades (Hepp et al. 1989). In animal models, iontophoretic application of serotonin onto pause neurons markedly decreases their firing rate and disinhibits burst cells (Ashikawa et al. 1991), and lesions of serotonergic dorsal raphe projections to pause neurons markedly lowers saccade peak velocity by removing inhibitory regulation of pause cells (Kaneko and Fuchs 1991).

Alterations of serotonergic tone in other brain regions might also contribute to the observed effects of risperidone (Figure 3). The effect could be at the level of the superior colliculus (Brandao et al. 1991), cerebellar regions that project to oculomotor nuclei (Gonzalo-Ruiz et al. 1990), or via disrupted modulation of GABA-ergic projections from the caudate nucleus to the substantia nigra (Nakada et al. 1984) and from the substantia nigra to the superior colliculus (Hikosaka 1989; Lavoie and Parent 1990) (Figure 1). Perturbation of serotonergic modulation of neuronal activity in some or all of these areas may contribute to the adverse effects of risperidone on saccadic eye movements. To our knowledge, studies of serotonergic regulation of saccades in healthy human subjects have not yet been conducted. However, one recent study in healthy human subjects demonstrated that the serotonin agonist MK-212 (6-chloro-2-[1-piperazinyl]-pyrazine) alters pursuit eye movements (Friedman et al. 1994), indicating a role for serotonin in the modulation of at least some forms of eye movement activity in humans.

Other biochemical effects of risperidone also might contribute to the pharmacological effects of risperidone treatment, such as histaminergic (H₁) and α_1 -adreno-

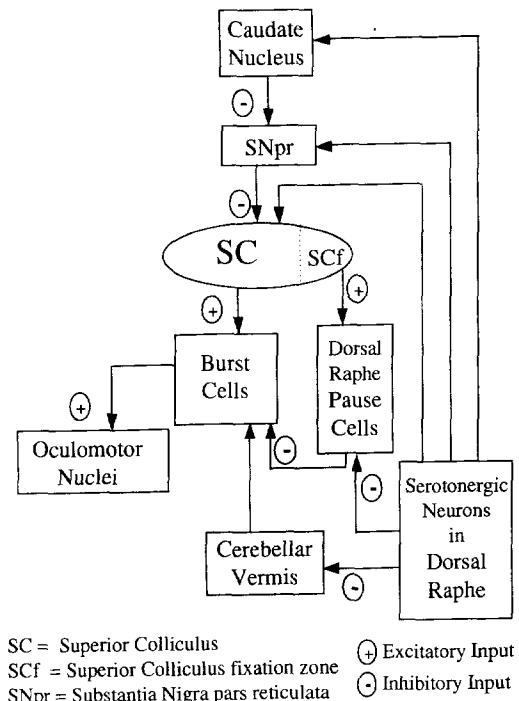


Figure 3. Serotonergic innervation of subcortical brain regions known to subserve saccadic eye movements. Pathways are marked as excitatory or inhibitory when direct modulatory effects on eye movement circuitry are established.

ceptor antagonism. Dopaminergic (D₂) blockade, on its own, is not likely to be the primary cause of the observed effects of risperidone on eye movement activity. Although dopaminergic manipulations in patients with parkinsonism alter eye movement activity (Rascol et al. 1989), we observed no such adverse effects in association with haloperidol, which has a considerably greater D₂ affinity than risperidone.

The observation of adverse effects of risperidone on saccadic eye movements raises an obvious methodological concern for studies of saccadic eye movements and visual information processing in schizophrenia. Based on our findings, some patients treated with risperidone and similar medications may show impairments of saccadic eye movements (and hence of visual target acquisition) because of their medication rather than (or in addition to) pathophysiological processes directly associated with their illness.

Aspects of the sampling and retesting of the subjects in the present study leave certain questions unanswered regarding the adverse effects of antipsychotic medications on saccadic eye movements. First, treatment assignment was consistent within two consecutive cohorts rather than randomly assigned, which raises some concern about the apparent differential drug effects. Although all patients were recruited in an identical fashion and displayed similar pretreatment

eye movement performance, the possibility of some unknown cohort-specific confound cannot be fully excluded. Second, neither the magnitude of the initial acute drug effect nor the dose-response curve of the effects can be determined based on data from this study. Future neurophysiological and neurobehavioral studies of the beneficial and adverse effects of risperidone and other atypical antipsychotic medications are needed to characterize further the pharmacodynamics of this rapidly growing group of newer antipsychotic medications.

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