Effects of Second-Generation Antipsychotic Medication on Smooth Pursuit Performance in Antipsychotic-Naive Schizophrenia

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Context: Analyses of smooth pursuit eye movement parameters in patients with schizophrenia provide information about the integrity of neural networks mediating motion perception, sensorimotor transformation, and cognitive processes such as prediction. Although pursuit eye tracking deficits have been widely reported in schizophrenia, the integrity of discrete components of pursuit responses and the effect of second-generation antipsychotic medication on them are not well established.

Objective: To examine different components of smooth pursuit performance in antipsychotic-naive patients with schizophrenia before and after treatment with second-generation antipsychotic medication.

Design, Setting, and Participants: Thirty-three antipsychotic-naive patients with schizophrenia performed 3 different smooth pursuit paradigms designed to evaluate specific components of the pursuit response. All of the patients were retested after 6 weeks of treatment with risperidone or olanzapine. Testing was also performed with 39 matched healthy individuals. Thirteen patients and 21 healthy participants were retested after 26 and 52 weeks.

Main Outcome Measures: Pursuit initiation, maintenance gain (ratio of eye velocity over target velocity), and frequency of catch-up saccades during pursuit maintenance.

Results: Prior to treatment, pursuit gain when tracking less predictable ramp targets tended to be reduced, latency of pursuit initiation was speeded, and catch-up saccade frequency was increased during predictive pursuit. After antipsychotic treatment initiation, pursuit gain decreased with ramp targets, indicating treatment-emergent impairments in sensorimotor processing. No changes were observed for predictive pursuit. Exploratory analyses in the subgroup with follow-up to 1 year revealed that these effects continued through long-term follow-up with some partial normalization at 1 year. Deficits were unrelated to drug dosage and clinical ratings.

Conclusions: Impaired sensorimotor function was observed after initiation of second-generation antipsychotic medications, which may be explained by their serotonergic antagonism of brainstem sensorimotor systems. Predictive mechanisms supported by frontostriatal-cerebellar circuitry were not affected by treatment initiation and appear able to compensate for treatment-emergent sensorimotor impairments during predictive tracking.

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S

MOOTH PUSUIT EYE MOVE-

ments enable us to focus our

eyes on moving objects by

using well-established senso-
motor and cognitive mecha-
nisms. Pursuit deficits in schizophrenia

were first reported in 1908, making them

perhaps the oldest biological marker for

a major mental illness.1 Genetic linkage

studies indicate that pursuit deficits may

represent a useful intermediate pheno-
type for schizophrenia.2,3 Further, novel

quantitative smooth pursuit measure-
ments provide information about distur-
bances of distinct neurocognitive pro-
cesses, including visual motion processing,

sensorimotor transformation, and the use

of predictive mechanisms.4,5

The maintenance of smooth pursuit is
driven by a combination of the predic-
tion of target velocity and visual feed-
back about performance quality, with their
loadings depending on the extent of ex-
perience with the pattern of target mo-
tion and the predictability of the stimu-
lus.7,9 Small position errors due to slow
pursuit velocity are corrected by catch-up
saccades (CUS). Different pursuit tasks can
isolate distinct components of the pur-
suit response (Figure 1), such as visual
motion processing during pursuit initia-
tion after saccades (step ramps), pursuit
latency and maintenance when tracking
unpredictable target ramps (pure ramps),
and pursuit maintenance when tracking
predictable target patterns (oscillating tar-
guts). Pursuit maintenance in unpre-
dictable ramp tasks relies heavily on imme-
diate visual feedback rather than prediction
because of the unpredictability and brev-
ity of target movement. In contrast, main-
tenance velocity when tracking regularly
Oscillating targets depend primarily on prediction derived from learning a repetitive pattern.

Functional brain imaging and neurophysiological studies have defined the neural mechanisms subserving different components of smooth pursuit in humans. Extrastriatal area V5 is crucial for motion perception and processing, and the frontal eye fields generate oculomotor commands and contribute to predictive pursuit. The V5 lesions have especially pronounced effects on motion processing during pursuit initiation, whereas frontal eye field lesions slow pursuit initiation and impede motion processing but leave motion processing unimpaired. Other areas mediate sensorimotor, cognitive, and motor processes, including supplementary and parietal eye fields, anterior cingulate, dorsolateral prefrontal cortex, cerebellum, and basal ganglia. These areas directly or indirectly project to the dorsolateral pontine nuclei and the nucleus reticularis tegmenti pontis in the brainstem and then to the cerebellum.

The quantitative evaluation of pursuit performance on different pursuit tasks in antipsychotic-naive patients with schizophrenia can help unravel the complex sensorimotor and cognitive system deficits associated with the disorder, independent from potential medication confounds. Further, assessing the effect of antipsychotic medication on pursuit systems in previously untreated patients may be informative about drug effects on multiple brain systems subserving smooth pursuit. Previous comparisons of antipsychotic-naive or treatment-withdrawn patients and patients treated with mostly first-generation antipsychotics revealed few consistent differences in global eye tracking measures, maintenance velocity, or CUS frequency. Longitudinal studies found pursuit performance to be relatively unaffected by first-generation antipsychotic medication. Some studies with patients receiving first-generation antipsychotics reported greater deficits in treated than untreated chronically ill patients, but selection bias rather than drug effects may have accounted for those observations.

Investigations of saccadic eye movements indicate that oculomotor responses may be more affected by second-generation than first-generation antipsychotics, but the effects on pursuit have not been systematically studied. Some evidence indicates that clozapine impairs pursuit, but studies included only small sample sizes and examined only pursuit maintenance. Effects of second-generation antipsychotics on serotonergic as well as dopaminergic systems might account for this difference.

The aims of our study were to use several pursuit paradigms to assess sensorimotor and cognitive mechanisms involved in pursuit control in antipsychotic-naive patients with schizophrenia and to examine the differential effects of second-generation antipsychotic treatment on pursuit performance.

### METHODS

#### PARTICIPANTS

Thirty-three antipsychotic-naive patients (24 men, 9 women; mean [SD] age, 25.0 [7.0] years; mean [SD] premorbid IQ, 97.3 [8.1]) from inpatient and outpatient services met DSM-IV criteria for schizophrenia (n = 30), schizoaffective disorder, depressed subtype (n = 2), or schizoaffective disorder (n = 1). Diagnoses were confirmed at consensus conferences using all of the available clinical data, including responses on the Structured Clinical Interview for DSM-III-R. Time since the first psychotic symptom until testing was on average 1 year (median, 12.2 months). Thirty-nine healthy control participants (24 men, 15 women; mean [SD] age, 23.5 [4.3] years; mean [SD] premorbid IQ, 99.0 [6.3]) from inpatient and outpatient services met DSM-IV criteria for schizophrenia (n = 30), schizoaffective disorder, depressed subtype (n = 2), or schizoaffective disorder (n = 1). Diagnoses were confirmed at consensus conferences using all of the available clinical data, including responses on the Structured Clinical Interview for DSM-III-R and without any history of Axis I disorders (according to the Structured Clinical Interview for DSM-III-R) and without any known history of psychotic or mood disorder with psychotic features in their first-degree relatives (participant’s report) were recruited from the surrounding community via advertisements. Groups were matched on age (t = -1.13; P = .27) and premorbid IQ (t = 1.02; P = .31) estimated by vocabulary test performance. Inclusion criteria for both groups included the following: (1) age between 16 and 45 years; (2) premorbid IQ greater than 80; (3) no known systemic or neurological disease; (4) no history of head trauma with loss of consciousness for more than 10 minutes; (5) no lifetime history of substance dependence and no substance abuse for at least 3 months; (6) no alcohol (24 hours), coffee, tea, or cigarettes (1 hour) prior to testing according to self-report and clinical observation; (7) no lifetime exposure to lithium carbonate, lithium citrate, mood stabilizers, stimulants, or anticholinergics; and (8) no benzodiazepines or antidepressants...
(5 half-lives) before testing (as an exception, 1 patient was tested after 4 days [3.5 half-lives] of withdrawal from 50 mg of sertraline hydrochloride). Follow-up studies were conducted 6 weeks after baseline testing for all of the participants. Additionally, 13 patients and 21 control participants were retested after 26 and 52 weeks. The study was approved by the University of Pittsburgh Institutional Review Board, and all of the participants provided informed consent.

Clinical ratings were obtained for patients at each time of testing (Table): (1) the Brief Psychiatric Rating Scale; (2) the Schedule for the Assessment of Negative Symptoms; (3) the Schedule for the Assessment of Positive Symptoms; (4) the Extrapyramidal Side-Effects Scale; NA, not applicable; SANS, Schedule for the Assessment of Negative Symptoms; SAPS, Schedule for the Assessment of Positive Symptoms. Medication assignment was not randomized as treatment choice was guided by standard clinical practice. Medication dosages were stable in the week prior to each testing.

A significant reduction of psychopathological symptoms was observed after introduction of antipsychotic medication, and this persisted at 26 and 52 weeks (Table).

### Table. Clinical Ratings and Antipsychotic Medication for Patients With Schizophrenia at Baseline and 6-, 26-, and 52-Week Follow-up

<table>
<thead>
<tr>
<th>Scale and Medication</th>
<th>Baseline</th>
<th>6 wk</th>
<th>26 wk</th>
<th>52 wk</th>
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<tr>
<td></td>
<td>(n=33)</td>
<td>(n=33)</td>
<td>(n=13)</td>
<td>(n=13)</td>
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<tr>
<td>Scale score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS</td>
<td>49.0 (8.6)</td>
<td>41.5 (8.1)</td>
<td>38.4 (9.9)</td>
<td>34.1 (9.4)</td>
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<td>SANS</td>
<td>14.2 (3.1)</td>
<td>13.0 (3.2)</td>
<td>13.0 (3.2)</td>
<td>11.8 (3.1)</td>
</tr>
<tr>
<td>SAPS</td>
<td>9.1 (3.4)</td>
<td>5.5 (3.2)</td>
<td>4.4 (3.5)</td>
<td>3.9 (3.2)</td>
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<tr>
<td>EPS</td>
<td>NA</td>
<td>3.0 (2.2)</td>
<td>3.0 (2.2)</td>
<td>3.1 (2.9)</td>
</tr>
<tr>
<td>Risperidone</td>
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<td>3.9 (2.1)</td>
<td>3.2 (1.1)</td>
<td>3.2 (1.7)</td>
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<tr>
<td>Olanzapine</td>
<td>NA</td>
<td>(n=6)</td>
<td>(n=2)</td>
<td>(n=2)</td>
</tr>
<tr>
<td>Dose, mg</td>
<td>NA</td>
<td>11.25 (6.3)</td>
<td>15.00 (7.1)</td>
<td>15.00 (7.1)</td>
</tr>
</tbody>
</table>

Abbreviations: BPRS, Brief Psychiatric Rating Scale; EPS, Extrapyramidal Side-Effects Scale; NA, not applicable; SANS, Schedule for the Assessment of Negative Symptoms; SAPS, Schedule for the Assessment of Positive Symptoms.

### STIMULUS PRESENTATION AND ASSESSMENT OF EYE MOVEMENTS

Visual acuity testing assured a minimum of 20/40 far acuity, and visual acuity was corrected to that threshold if necessary. Eye movement studies were performed in a darkened black room. Subjects were seated at the center of a circular black arc (1-m radius) with their head immobilized by a chin rest and forehead and occipital restraints. The visual stimulus was a laser spot (3 mm) projected by a mirror and mounted on a rotary stage platform that moved the target across the display arc under computer control (New England Affiliated Technolo-
gies, Lawrence, Massachusetts). Subjects were instructed via intercom to always follow the moving target with their eyes as precisely as possible. Eye movement data were inspected online during testing, and re-alerting instructions were given if subjects became inattentive. Eye movement recording was performed using infrared sensors mounted on spectacle frames (model 210; Applied Science Laboratories, Inc, Bedford, Mass.

### PURE RAMP TASK

In the pure ramp task, subjects tracked targets that moved at an unpredictable time, duration, and speed from center fixation to assess pursuit initiation latency and tracking of less predictable targets (Figure 1B). Each trial started with an initial central fixation for 2 to 4 seconds before targets moved at a constant speed to either the left or the right at 1 of 5 target speeds (4°/s, 8°/s, 16°/s, 24°/s, or 32°/s) between ±12° included 13, 15, 23, and 31 trials, respectively. The primary parameter of interest was maintenance gain between ±10° of target sweeps (b in Figure 1A). We further determined the frequency of CUS and mean CUS amplitudes during this epoch (a in Figure 1A).

### OSCILLATING TASK

The oscillating task assessed sustained smooth pursuit of predictable target motion (Figure 1A). The paradigm was similar to an oscillating sinusoidal waveform except that across the center of the display screen the target moved at a constant speed. This was done for 2 reasons. First, it facilitated measurement of maintenance gain by allowing comparison of average pursuit velocity with a constant stimulus velocity. Second, it eliminated demands during the constant velocity epochs for ongoing dynamic adjustment of pursuit velocity as is required when tracking sinusoidal target motion. We presented predictable oscillating targets moving back and forth across the display arc covering ±17° in total. Beyond the positions of ±12°, target speed gradually decelerated to reverse its direction at ±17°, at which point it immediately accelerated again until it reached a constant speed at ±12°. One trial consisted of 1 full sweep of the target from ±17° to the opposing 17°. Blocks of target oscillation with a particular constant target speed (8°/s, 16°/s, 24°/s, or 32°/s) between ±12° included 13, 15, 23, and 31 trials, respectively. The primary parameter of interest was maintenance gain between ±10° of target sweeps (b in Figure 1A). We further determined the frequency of CUS and mean CUS amplitudes during this epoch (a in Figure 1A).
### FOVEOFUGAL STEP RAMP TASK

The foveofugal step ramp task was similar to the pure ramp task except that after initial central fixation for 2 to 4 seconds, the target stepped 3° to the left or right before continuing in that direction at 4°/s, 8°/s, 16°/s, or 24°/s (Figure 1C). This task assessed the use of visual motion information in the “open-loop period” before visual feedback could influence performance. As in the pure ramp task, each ramp moved 15° from central fixation. The task consisted of 32 trials (4 repetitions × 4 speeds × 2 directions) presented in a fixed pseudorandom order. Parameters of interest were the position error of the initial CUS (f in Figure 1C) and pursuit initiation gain during the first 100 milliseconds after the initial CUS (g in Figure 1C). These parameters together provide data regarding how the pursuit movement uses visual motion information. Maintenance gain in the remaining interval after the 100-millisecond “open-loop period” (b in Figure 1C) and the latency of the initial CUS following the target step (c in Figure 1C) were also measured.

### RESULTS

#### OSCILLATING TASK

**Baseline**

Maintenance gain in the oscillating task did not differ between antipsychotic-naive patients and control participants (Figure 2A). Patients exhibited higher CUS rates than control participants ($F_{1,70}[\text{group}] = 6.09; P = .02$) (Figure 3), and group differences increased with higher target speeds ($F_{3,60}[\text{speed} \times \text{group}] = 4.37; P = .007$).

**Short-term Follow-up**

There was no change in maintenance gain or CUS rate after treatment initiation in patients compared with control.
participants (Figure 2A). Elevated CUS rates in patients persisted during the short-term follow-up ($F_{1,70}[\text{group}]=8.92; P=.004$), as did the increased group difference with higher target speeds ($F_{3,68}[\text{speed} \times \text{group}]=5.34; P=.002$) (Figure 3).

**Long-term Follow-up**

The CUS rates in patients increased from the 6- to 52-week follow-up but remained the same in control participants ($F_{1,72}[\text{time} \times \text{group}]=3.57; P=.03$) (Figure 3). There were no significant changes in maintenance gain.

For the CUS amplitudes (overall mean [SD], 1.53° [0.30°] in patients and 1.54° [0.24°] in control participants), no effects were found at baseline, short-term follow-up, or long-term follow-up.

**PURE RAMP TASK**

**Baseline**

During the less predictable ramp task, there was a trend for patients' maintenance gain to be lower than that of control participants ($F_{1,70}[\text{group}]=3.85; P=.05$) (Figure 2B). Patients initiated pursuit faster than control participants ($F_{1,68}[\text{group}]=5.56; P=.02$) (Figure 4).

**Short-term Follow-up**

Maintenance gain was decreased in patients compared with control participants ($F_{1,70}[\text{group}]=8.07; P=.008$), an effect that occurred from baseline to 6-week follow-up ($F_{1,70}[\text{time} \times \text{group}]=5.52; P=.02$). The gain decrease in patients tended to be greater at higher target speeds ($F_{3,67}[\text{speed} \times \text{time} \times \text{group}]=2.50; P=.05$) (Figure 2B). During the 6-week follow-up, pursuit initiation latencies slowed in patients relative to control participants ($F_{1,41}[\text{time} \times \text{group}]=9.54; P=.004$), eliminating group differences observed at baseline (Figure 4).

**Long-term Follow-up**

Maintenance gain was reduced in patients compared with control participants during long-term follow-up ($F_{1,32}[\text{group}]=7.60; P=.01$), with different changes in patients than in control participants over time ($F_{1,31}[\text{time} \times \text{group}]=4.60; P=.02$) (Figure 2B). Maintenance gain in patients continued to be decreased from the 6-week follow-up to the 26-week follow-up but increased by 1 year ($F_{1,31}[\text{time}]=5.50; P=.04$), whereas in control participants it remained stable over time. These maintenance gain changes in patients were greater at higher target speeds ($F_{3,25}[\text{speed} \times \text{time} \times \text{group}]=2.96; P=.02$). For pursuit initiation latency, no group differences were observed during long-term follow-up (Figure 4).

**FOVEOFUGAL STEP RAMP TASK**

**Baseline**

Pursuit initiation gain (first 100 milliseconds) tended to be lower in antipsychotic-naive patients than control participants ($F_{1,69}[\text{group}]=3.26; P=.08$) (Figure 5A). The position error of the initial CUS (Figure 5B) and maintenance gain (Figure 2C) did not differ between groups, but patients tended to make their initial CUS faster than control participants ($F_{1,56}[\text{group}]=3.07; P=.08$) (Figure 5C).

**Short-term Follow-up**

Pursuit initiation gain in patients was decreased compared with control participants ($F_{1,67}[\text{group}]=6.55; P=.01$), an effect that tended to be more pronounced after treatment initiation ($F_{1,67}[\text{time} \times \text{group}]=3.15; P=.08$) (Figure 5A). The position error of the initial CUS (Figure 5B) did not change after treatment initiation. Latencies of initial CUS in patients increased during 6 weeks of treatment relative to control participants ($F_{1,70}[\text{time} \times \text{group}]=4.99; P=.003$), eliminating the pretreatment group difference (Figure 5C). During the 6-week follow-up, maintenance gain decreased in patients relative to control participants ($F_{1,70}[\text{time} \times \text{group}]=8.56; P=.005$) (Figure 2C) so that it was lower than in control participants ($F_{1,68}[\text{group}]=5.70; P=.02$). This effect parallels findings for initiation gain from the foveofugal step ramp task and for maintenance gain from the pure ramp task.

**Long-term Follow-up**

Pursuit initiation gain ($F_{1,31}[\text{group}]=11.76; P=.002$) (Figure 5A) and maintenance gain ($F_{1,32}[\text{group}]=10.87; P=.002$) (Figure 2C) were reduced in patients compared with control participants, representing persistence of short-term treatment-emergent effects. Changes in maintenance gain ($F_{1,31}[\text{time} \times \text{group}]=4.44; P=.02$) and a similar trend in initiation gain ($F_{1,30}[\text{time} \times \text{group}]=3.08; P=.06$) suggested some normalization of function by 52 weeks in patients. Analysis of position errors of the initial CUS revealed lower accuracy of saccades in patients ($F_{1,32}[\text{group}]=4.22; P=.048$) (Figure 5B). No changes in latencies of initial CUS were observed (Figure 5C).
Spearman rank correlations between the Schedule for the Assessment of Negative Symptoms, Schedule for the Assessment of Positive Symptoms, and Extrapyramidal Side-Effects Scale scores and oculomotor parameters did not reveal significant relationships between clinical ratings and eye movement parameters at any time. Duration of time since the onset of psychotic symptoms prior to testing was not correlated with any oculomotor parameter, making illness duration unlikely to be related to changes in smooth pursuit performance observed after treatment initiation. Because the group of patients treated with olanzapine was too small to conduct any medication-specific analysis, we performed analysis of eye movement data with risperidone-treated patients only. This yielded no different findings for any task compared with those reported for the whole sample. Although the medication dose range in patients receiving risperidone was rather narrow, it did not correlate with any oculomotor parameter.

This is the first longitudinal study evaluating sensorimotor and cognitive components of smooth pursuit initiation and maintenance in antipsychotic-naive patients with schizophrenia. Our findings document modest impairments of the pursuit system in these patients at baseline, including trends for reduced pursuit gain of less predictable ramp targets, speeded pursuit latency, and increased CUS rates during predictable pursuit. Initiation of second-generation antipsychotic medication consisting of risperidone or olanzapine yielded an effective reduction of psychotic symptoms after 6 weeks. Pursuit gain of less predictable targets decreased significantly during these first weeks of treatment and pursuit latency normalized, but tracking of predictable oscillating targets did not change. Exploratory long-term follow-up in a subset of participants indicated that these effects continued during the first 6 months of treatment with partial normalization by 1 year. There were no systematic correlations between oculomotor parameters and psychopathological symptoms or extrapyramidal side effects. The treatment-related changes with less predictable ramp tasks that require sensorimotor processing to a high extent document a selective effect of second-generation antipsychotic drugs on sensorimotor control of pursuit responses. This is in accordance with earlier reports of pursuit gain reduction associated with clozapine treatment and saccade latency prolongation with risperidone. Furthermore, the observation of unchanged pursuit of predictable oscillating targets relying heavily on prediction and rule-based learning but less on sensorimotor processing implies that high-order cognitive or predictive signals were not affected by treatment initiation. These findings provide novel information about the effect of second-generation antipsychotic drugs on functional brain systems in patients with schizophrenia.

**OCULOMOTOR PARAMETERS AND CLINICAL CHARACTERISTICS**

We observed trends for pursuit gain reductions with less predictable ramp targets prior to treatment, in accordance with previous studies of antipsychotic-naive patients with schizophrenia. Increased CUS rates in the predictive oscillating task are also consistent with earlier reports. Unimpaired initial CUS accuracy in the step ramp task suggests that CUS efficiently corrected for small position errors when tracking moving targets. The presence of increased CUS rates together with unimpaired maintenance gain in the oscillating task might be explained by an instability of the pursuit response, resulting in increased aggregate CUS rates due to brief periods of slow pursuit rather than consistently slowed pursuit maintenance velocity.
Differences in task demands in our oscillating target task, relative to previous studies using triangular or sinusoidal waveforms to evaluate pursuit, might explain why we did not observe maintenance gain impairment with that task. Patients with schizophrenia might have greater difficulty dynamically adjusting pursuit velocity and acceleration required for sinusoidal target tasks or have difficulty predicting abrupt reversals in target movement direction or motion onset as with triangular or trapzoidal waveforms. When these additional task demands were removed, patients with schizophrenia were able to match eye velocity to that of a predictable constant target similar to healthy subjects, even at high target speeds. This indicates that at least some cognitive predictive mechanisms for sustained pursuit are spared in schizophrenia even though the ability to initiate and maintain predictive pursuit with a combined reliance on temporal and velocity memory signals in the absence of a visual target may be impaired.

Normal saccadic CUS amplitude errors in the step ramp task before treatment imply sufficient integrity of visual motion information processing in extrastriatal area V5 although pursuit initiation gain also depending on visual motion signals tended to be impaired. Interestingly, we did find evidence for faster pursuit initiation in schizophrenia before treatment, indicating speeded sensorimotor processing. These results differ from our previous study where we did not find evidence for speeded pursuit latency. This discrepancy might be due to different stimulus presentation because in our previous study, pursuit was not driven by a continuously moving visual target such as in the present investigation but by a sequentially illuminated line of light-emitting diodes. Faster pursuit initiation as observed in the present investigation might be related to a reduction in top-down inhibitory prefrontal regulation of attentional processes that has been proposed to account for speeded latency of visually guided saccades in antipsychotic-naive patients. Consistent with this pattern, we found a trend for speeded initial CUS latencies with the step ramp task at baseline.

ADVERSE EFFECTS OF SECOND-GENERATION ANTIPSYCHOTIC MEDICATION ON SMOOTH PURSUIT OF LESS PREDICTABLE TARGETS

Ramp tasks impose a higher demand for online sensorimotor processing than sustained pursuit of oscillating targets, which is reflected in the dramatically lower maintenance gains for faster-moving ramp targets than oscillating targets (Figure 2). Significantly decreased gain for pursuit initiation and maintenance on ramp tasks at 6-week follow-up that continued during the first 6 months of treatment without a parallel effect on sustained predictive pursuit therefore implies an adverse influence of second-generation antipsychotic medication on sensorimotor systems rather than on cognitive or predictive pursuit control. Exploratory analyses suggest partial normalization by 1 year, which could be due to the development of partial tolerance to drug effects. Because we did not find significant changes in psychopathological symptoms or medication dosages during long-term follow-up, illness recovery or decreased medication dosages are unlikely to explain the partial normalization of sensorimotor function. However, the size of the follow-up sample was small, and blood drug-level measurements were not obtained to ensure that reduced treatment compliance did not account for reduced pursuit deficits at 1 year. Further studies are required to confirm the presence and time course of tolerance development. Consistent with the reported effects on sensorimotor systems when tracking less predictable targets, latencies of pursuit and saccade initiation increased after medication initiation, yielding posttreatment findings similar to those of previous studies with antipsychotic-treated patients.

Worsening of pursuit after second-generation antipsychotic treatment with clozapine has been attributed to its antagonism of serotonin 2A receptors, a property shared by risperidone and olanzapine. Serotonergic effects on pursuit have only rarely been studied. A single dose of MK-212, a direct serotonin agonist, was reported to increase maintenance gain and reduce CUS frequency in 10 healthy subjects, suggesting that activation of some serotonin receptors facilitates pursuit, however, no effect was found in another study with sertraline, a serotonin reuptake inhibitor. In our previous study using ramp tasks with first-episode patients before and after treatment, first-generation antipsychotic medication did not impair sensorimotor aspects of pursuit control. This difference from the present study is consistent with an important role for serotonergic mechanisms in the sensorimotor changes reported here. Similarly, risperidone but not haloperidol has been reported to impair sensorimotor control of visually guided saccades to stationary targets. These latter effects have been attributed to serotonergic antagonism on saccade-regulating neurons in the brainstem, which are under inhibitory serotonergic regulation from the dorsal raphe nucleus. Altered serotonergic activity might result in a disturbance of the precisely temporally integrated synchronicity of these neurons, which could reduce saccadic velocities and slow latencies. Similar effects on the dorsolateral pontine nuclei and the nucleus reticularis tegmenti pontis in the brainstem that encode a variety of pursuit-related signals could potentially disrupt the pursuit system as well. More translational research is needed to investigate whether second-generation antipsychotic agents cause adverse treatment-emergent effects on visual sensorimotor systems via serotonin mechanisms.

MINIMAL EFFECTS OF SECOND-GENERATION ANTIPSYCHOTIC MEDICATION ON PREDICTIVE PURSUIT

The absence of treatment-induced maintenance gain impairment with oscillating targets suggests that cognitive or predictive mechanisms may be able to sufficiently compensate for treatment-emergent sensorimotor deficits during predictive pursuit. Recent studies support the hypothesis of a greater reliance on predictive signals during pursuit in patients with schizophrenia. Higher pursuit velocity in treated patients with schizophrenia compared with healthy sub-
jcts was reported after a target was switched off during predictable sinusoidal target movements, and patients showed closer adherence to predictive, repetitive target patterns as revealed with predictive saccade tasks. Predictive sustained pursuit requires motor learning mechanisms mediated by frontostriatal and cerebellar systems. Accordingly, a recent imaging study revealed greater activation during predictive pursuit in medicated patients with schizophrenia than in healthy control subjects in the dorsolateral prefrontal cortex, thalamus, and cerebellar hemispheres, a network that modulates planning and rule-based learning during pursuit. Furthermore, greater activation of the frontal eye fields and the anterior cingulate during pursuit was found in patients when pursuit had to be generated during intervals of target blanking, which is consistent with an increased reliance on predictive systems for pursuit control in schizophrenia. 

In conclusion, treatment with low to moderate dosages of second-generation antipsychotic agents such as risperidone and olanzapine led to treatment-emergent sensorimotor impairments in patients with schizophrenia. Exploratory analyses suggest that partial normalization may have developed to some of these sensorimotor effects by 1 year of treatment. In comparison, cognitive mechanisms such as prediction seemed sufficiently unaffected by treatment initiation to be able to provide compensation for these sensorimotor disturbances.

Because serotonin 2A antagonists may preserve striatal function and minimize extrapyramidal side effects, our findings imply that brainstem sensorimotor mechanisms under serotonergic control may be adversely affected. More studies are needed to further specify these effects with regard to potential differences between individual drugs and drug classes, their neuropharmacological mechanisms, and their time course. The effects of second-generation antipsychotics on pursuit systems, as previously established with saccade paradigms, as well as the modest pursuit disturbances evident prior to treatment using the specific paradigms in this study suggest that the severity of disorder-related impairment in pursuit tracking may be overestimated when patients treated with second-generation antipsychotic medication are assessed.

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21. MacAvoy MG, Gottlieb JP, Bruce CJ. Smooth pursuit eye movement represen-


