ORIGINAL ARTICLE

Adverse Effects of Risperidone on Spatial Working Memory in First-Episode Schizophrenia

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Context: Working memory impairments are a central neurocognitive feature of schizophrenia. The nature of these impairments early in the course of illness and the impact of antipsychotic drug treatment on these deficits are not well understood. The oculomotor delayed response task is a translational spatial working memory paradigm used to characterize the neurophysiologic and neurochemical aspects of working memory in the primate brain.

Objective: To examine oculomotor delayed response task performance in patients with first-episode schizophrenia before and after antipsychotic drug treatment.

Design, Setting, and Participants: Twenty-five antipsychotic drug–naive, acutely ill patients with first-episode schizophrenia performed an oculomotor delayed response task at baseline before any drug treatment and again after 6 weeks of risperidone treatment. Twenty-five matched healthy controls were studied in parallel.

Main Outcome Measure: Accuracy for remembered spatial locations on an oculomotor delayed response task.

Results: Before treatment, patients demonstrated baseline impairment in the ability to maintain spatial location information in working memory at longer delay-period durations (8 seconds), when maintenance demands on working memory were greatest. After 6 weeks of risperidone treatment and significant clinical improvement, this pretreatment impairment worsened such that patients were uniformly impaired across all delay period durations (1-8 seconds). This occurred in the absence of any generalized adverse effect on oculomotor systems or significant extrapyramidal adverse effects.

Conclusions: Deficits in the maintenance of spatial information in working memory are present early in the course of illness. Risperidone treatment exacerbated these deficits, perhaps by impairing the encoding of information into working memory. Studies with nonhuman primates performing oculomotor delayed response tasks suggest that the apparent adverse effect of risperidone might result from treatment-related changes in modulatory functions of prefrontal D_1 receptor systems.

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COGNITIVE DYSFUNCTION represents a core feature of schizophrenia, and working memory deficits are a key component of this dysfunction.[1-3] Working memory impairments are prognostic indicators of relapse and social functioning[4-6] and may be endophenotypes for schizophrenia inasmuch as they are found among patients' unaffected first-degree relatives.[7-9]

Working memory is subserved primarily by the dorsolateral prefrontal cortex (DLPFC),[10,11] a region established by neuropsychologic, neurophysiologic, and neuroimaging studies to be disturbed in schizophrenia.[12-16] The oculomotor delayed response (ODR) task is a spatial working memory paradigm that has been used in studies of nonhuman primates to provide much of our current understanding of the neurophysiologic and neurochemical features of working memory systems.[17,18] This task requires individuals to remember a spatial location for a period of time, after which they make a saccadic eye movement to the remembered location guided only by information maintained in working memory. In nonhuman primates, spatially tuned neurons in the DLPFC (Brodmann areas 46/8a) code the location information via increased firing rates during delay periods, when location information is held in working memory.[19-21] Prefrontal dopaminergic D_1 receptor activation modulates the ability of these pyramidal cells to sustain increased firing rates during delay periods and, in turn, support behavioral performance on this task.[22-24] Given the role of dopaminergic abnormalities in schizophrenia[25-27] and the impact of antipsychotic medications on dopamine systems, this translational task has the potential to be an especially useful tool for understanding working memory deficits in schizophrenia and how they are affected by pharmacologic treatment.

Impairments in ODR task performance among unaffected relatives of patients with schizophrenia[7,8] suggest that spatial working memory deficits are probably present at illness onset. However, the nature and the magnitude of these deficits early in the

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Table. Demographic and Clinical Characteristics of Patients With Schizophrenia and Controls

	Controls (n = 25)	Patients (n = 25)		*P* Value
		Baseline	6 wk	
Baseline demographics				
Age, mean (SD), y*	25.1 (5.2)	24.6 (6.8)	NA	.76
IQ, mean (SD)*	98.2 (8.9)	95.4 (10.0)	NA	.29
Parental SES, mean (SD)†	2.2 (0.8)	2.7 (1.3)	NA	.24
Sex, M/F, No.‡	17/8	18/7	NA	.76
Handedness, right/left, No.‡	23/2	24/1	NA	.55
Clinical ratings and medication, mean (SD)§				
BPRS score	NA	51.4 (8.5)	40.4 (9.1)	<.001
SANS score	NA	15.0 (2.5)	13.0 (2.5)	<.001
SAPS score	NA	9.9 (3.2)	4.9 (3.2)	<.001
HAM-D score	NA	21.0 (11.9)	15.8 (7.6)	.06
Risperidone, mg/d	NA	0	4.0 (1.5)	NA
EPSE scale score (range, 0-35)	NA	NA	3.9 (4.5)	NA

Abbreviations: BPRS, Brief Psychiatric Rating Scale; EPSE, Extrapyramidal Side Effects[38]; HAM-D, Hamilton Depression Rating Scale (24 items); NA, not applicable; SANS, Schedule for the Assessment of Negative Symptoms; SAPS, Schedule for the Assessment of Positive Symptoms; SES, socioeconomic status.

*For age and IQ (Ammons Quick Test[39]), *P* values reflect the significance level for independent-sample *t* tests.

†The *P* value for parental SES (Hollingshead[40]) represents the significance level for a Mann-Whitney test.

‡*P* values for sex and handedness (Edinburgh Handedness Questionnaire[41]) reflect the significance level for a χ^2 test.

§*P* values for clinical ratings reflect significance levels for paired-sample *t* tests.

course of illness are not well characterized. More important, how these impairments are affected by antipsychotic drug treatments has yet to be directly investigated. Studies[28-33] documenting impaired ODR task performance among patients with schizophrenia have typically used medicated, chronically ill patients, which makes disentangling disease and medication effects difficult. The few studies[34-36] of untreated or never-treated patients are limited by the use of cross-sectional rather than longitudinal designs and by treatment with heterogeneous antipsychotic medications and adjunctive agents. Also, the effects of delay period duration have not been investigated systematically in these studies, so it remains unclear whether performance deficits reflect a problem initially encoding information into working memory or a faster rate of information decay once information is encoded.

In the present study, treatment-naive patients with first-episode schizophrenia performed an ODR task at baseline and again after 6 weeks of risperidone treatment. Matched controls were studied during a similar time frame. The delay period during which information was remembered varied between 1 and 8 seconds to determine whether patient performance changed as a function of increased temporal maintenance demands and whether treatment differentially affected performance across delay period durations. Subsets of both groups were available for additional assessments at 26- and 52-week follow-up.

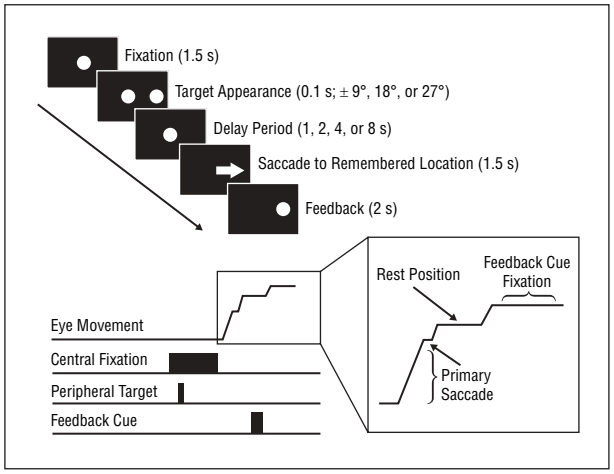

Figure 1. Oculomotor delayed response task paradigm. Participants fixate on the central location while a target briefly (0.1 seconds) appears 9°, 18°, or 27° to the right or left. Participants were instructed to remember the location of the peripheral target while maintaining central fixation for an unpredictable variable delay period (1, 2, 4, or 8 seconds) and then to shift their gaze to the remembered target location after the central light was extinguished. A correction light appeared after 1.5 seconds and remained illuminated for 2 seconds at the location where the peripheral target had been presented to provide participants with feedback about their performance on each trial.

METHODS

PARTICIPANTS

Twenty-five antipsychotic drug–naive patients (7 women and 18 men) met criteria for schizophrenia according to the Structured Clinical Interview for *DSM-III-R*[37] and additional information reviewed at consensus diagnosis meetings. Patients had experienced psychotic symptoms on average for 1 year before entering the study (median duration of untreated illness, 11.8 months). Twenty-five healthy individuals (8 women and 17 men) without any Axis I disorders according to the Structured Clinical Interview for *DSM-III-R* were recruited from the community. Groups were matched for age, IQ, sex, parental socioeconomic status, and handedness (**Table**). All the participants met the following criteria: (1) age 18 to 49 years, (2) no systemic or neurologic disease, (3) no electroconvulsive therapy, (4) no history of head trauma, (5) no lifetime history of substance dependence or history of substance abuse within 3 months, (6) no anticonvulsant drug therapy for 1 month or benzodiazepine use for 5 half-lives before testing, and (7) no caffeine intake or cigarette smoking 1 hour before testing. The study was approved by the University of Pittsburgh, Pittsburgh, Pa, institutional review board, and all the participants provided informed consent.

Patients' baseline ODR studies were conducted before treatment initiation, and follow-up testing occurred on average 6 weeks later. After the baseline evaluation, patients were treated with risperidone (mean ± SD dose = 4.0 ± 1.5 mg). Clinical psychologists and psychiatrists blind to ODR task performance completed clinical ratings in parallel with each testing using the Brief Psychiatric Rating Scale,[42] the Scales for the Assessment of Positive[43] and Negative[44] Symptoms, and the 24-item Hamilton Depression Rating Scale[45] (Table). Extrapyramidal adverse effects[38] were modest at the 6-week retesting (Table), but 5 patients were taking low-dose benztropine mesylate (1 or 2 mg).

ODR TASK

Participants were tested in a darkened room, and a technician in an adjacent room provided instructions via an intercom. Par-

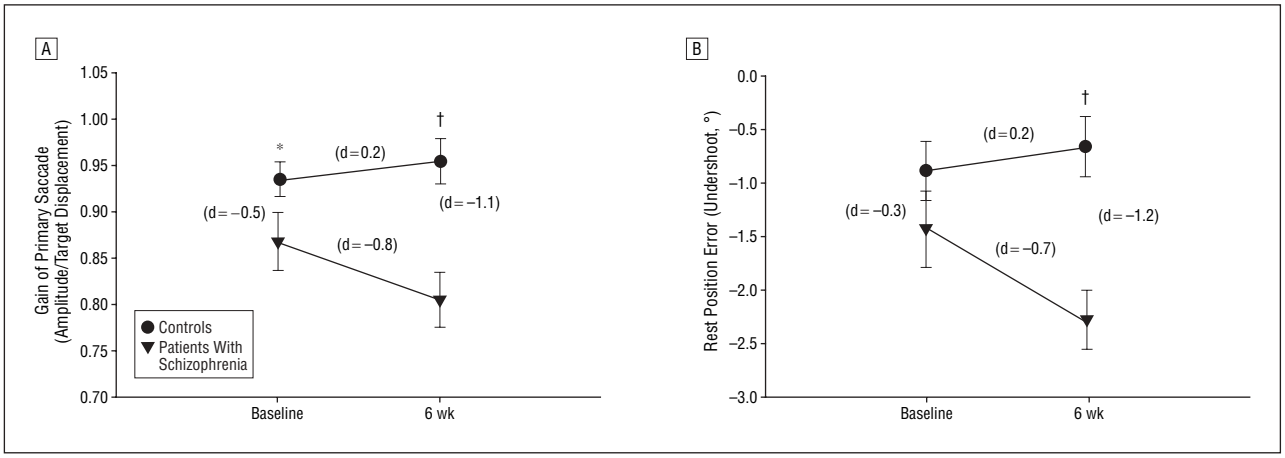

Figure 2. Mean gain of primary saccades (A) and error of resting eye position (B) for patients with schizophrenia and controls. Patients' primary saccades and resting eye position were significantly less accurate at 6-week follow-up relative to controls. The effect sizes (Cohen d) are for between-group comparisons at each study visit and within-group changes from baseline to 6-week follow-up. *P=.05 and †P<.001 for comparisons between patients and controls. Error bars represent SE.

ticipants sat facing a circular black arc with a 1-m radius and red light–emitting diodes subtending approximately 0.2° of visual angle in the horizontal plane at eye level. A chin and forehead rest minimized head movement.

Trials began with a brief tone concurrent with the appearance of a central fixation cue (**Figure 1**). After the participant maintained central fixation for 1.5 seconds, a target appeared for 0.1 seconds unpredictably at 9°, 18°, or 27° of visual angle to the right or left of center. The central cue was sustained during and after this target presentation, and the participant was instructed not to look at the peripheral target but to remember its location. After an unpredictable delay of 1, 2, 4, or 8 seconds, during which central fixation was maintained, the central light was extinguished, cueing the participant to look to the location where the target had appeared. After 1.5 seconds during which the participant could make 1 or more saccadic movements to the remembered location, the correct target location was illuminated for 2 seconds to provide feedback regarding performance accuracy. Twenty-four trials were administered. Eye movements were recorded using electro-oculography. Recordings for each trial were calibrated and measured as described elsewhere.[46]

Two primary measurements of performance accuracy were obtained: (1) gain (amplitude of saccade/target displacement) of the primary saccade, which reflects the accuracy of the initial movement to the remembered target location, and (2) error of final resting eye position (in degrees of visual angle from target) after any additional saccades were made to position the eyes at the desired location before appearance of the feedback light. The first of these measures can be affected by problems with initiating voluntary behavior without sensory guidance, and the second can be more sensitive to problems with maintaining spatial location information in working memory because participants have the opportunity to correct for error in initial motor commands.[47] The percentage of trials during which participants incorrectly looked immediately toward to-be-remembered targets (prosaccade errors) was monitored. Latency, peak velocity, and duration of primary saccades were also measured. The latter 2 measures did not differ between patients and controls at any study point and therefore are not reported.

STATISTICAL ANALYSES

Data from identical trials were averaged before statistical analyses. Data for each participant were pooled across the 3 peripheral target positions because there were no significant group × target position interactions. Repeated-measures analysis of variance was used to compare patients with schizophrenia and controls (between-subject factor), with time (baseline and 6-week follow-up), direction (rightward and leftward trials), and delay period (1, 2, 4, and 8 seconds) as within-subject factors. Effect sizes[48] are reported for within- and between-subject effects. Secondary analyses were conducted in the subset of participants available for retesting at 26- and 52-week follow-up to examine the longer-term stability of effects.

RESULTS

ACCURACY OF PRIMARY SACCADES AND FINAL RESTING EYE POSITION

Gain of patients' primary saccades to remembered target locations was reduced relative to that of controls ($F_{1,48}$=9.75; P=.003). The magnitude of this group effect was greater at 6-week follow-up than at baseline ($F_{1,48}$=9.73; P=.003), reflecting a significant worsening of patients' saccade gain after treatment initiation (t_{24}=4.00; P=.001; Cohen d=–0.8) (**Figure 2**A). In contrast, there was no significant change in gain over time among controls (t_{24}=–0.92; P=.37; Cohen d=0.2). Patients also demonstrated progressively poorer gain relative to controls as a function of increased delay period ($F_{3,46}$=4.47; P=.008). At baseline, patients were impaired relative to controls at the 8-second delay period (t_{48}=3.05; P=.004; Cohen d=–0.9) but not at the shorter delay periods. In contrast, at 6-week follow-up, patients were impaired relative to controls at all delay periods (P<.01 for all; Cohen d≤–0.8 for all) (**Figure 3**A). Finally, patients' primary saccades were less accurate when remembered target locations were to the right of center fixation before and after treatment ($F_{1,48}$=5.39; P=.03) (**Figure 4**A).

Patients' performance remained inaccurate compared with that of controls after making additional saccades to correct for any initial motor programming error ($F_{1,48}$=7.91; P=.007). The magnitude of this group difference was greater at 6-week follow-up than at baseline ($F_{1,48}$=8.84; P=.005), reflecting a significant worsening of patients' error in final resting eye position after treatment initiation (t_{24}=3.27; P=.003; Cohen

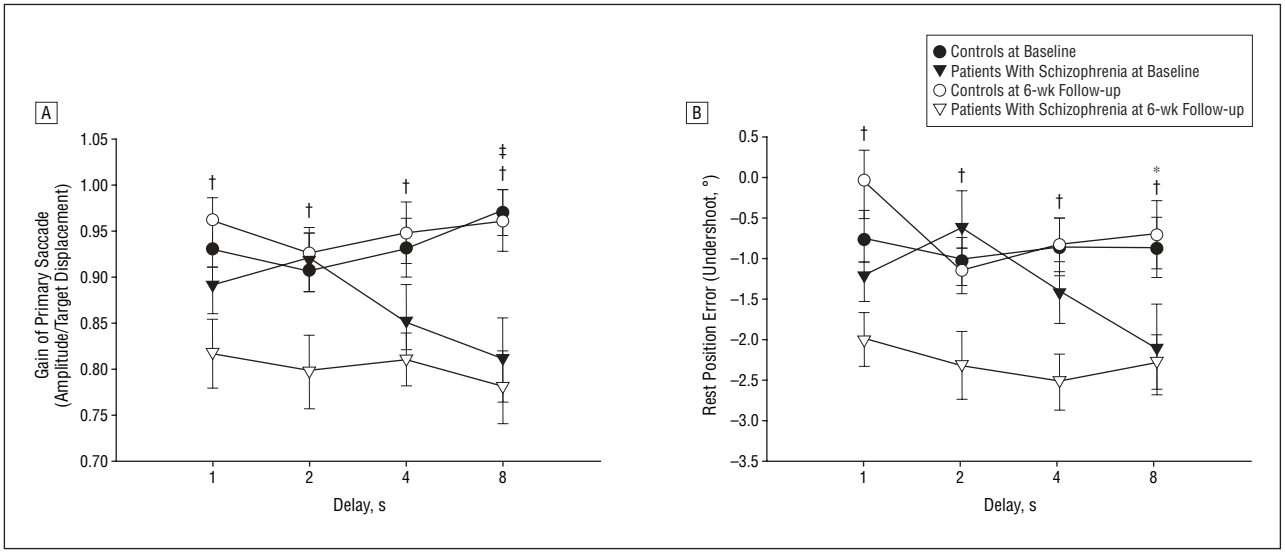

Figure 3. Mean gain of primary saccades (A) and error of resting eye position (B) for patients with schizophrenia and controls at baseline and 6-week follow-up. Patients' accuracy of primary saccades and final resting eye position were decreased only at the longer delay period at the baseline evaluation but across all delay periods at 6-week follow-up compared with controls. *P=.07 and ‡P=.004 for comparisons between patients and controls at baseline. †$P \leq .02$ for all comparisons between patients and controls at follow-up. Error bars represent SE.

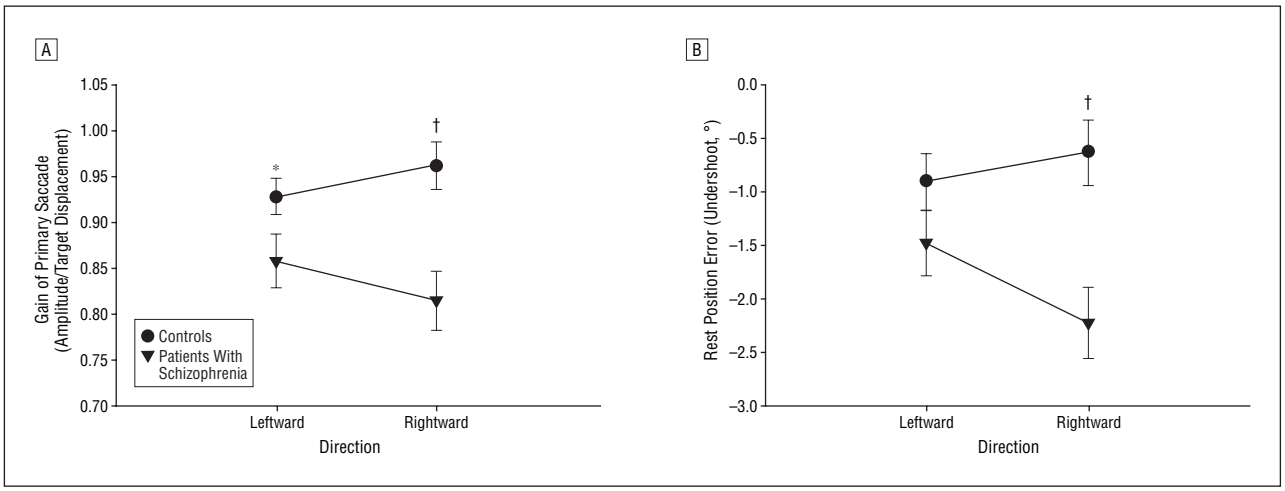

Figure 4. Mean gain of primary saccades (A) and error of resting eye position (B) for patients and controls. Primary saccades and final resting eye positions for target locations in the right hemifield were less accurate for patients than were their responses to left hemifield targets. *P=.05 and †$P<.001$ for comparisons between patients and controls. Error bars represent SE.

d=–0.7) (Figure 2B). This change over time was not seen among controls (t_{24}=–0.90; P=.38; Cohen d=0.2). Patients' inaccuracy of final resting eye positions was also greater than that of controls as a function of increased delay-period duration ($F_{3,46}$=3.07; P=.04). Patients' baseline inaccuracy tended to be greatest at only the 8-second delay period (t_{48}=1.87; P=.07; Cohen d=–0.5), whereas at 6-week follow-up they differed significantly from controls at all delay periods ($P<.02$ for all; Cohen d≤–0.7 for all) (Figure 3B). Patients' final resting eye positions were significantly less accurate for locations in the right hemifield compared with controls at both times ($F_{1,48}$=7.65; P=.008) (Figure 4B).

LATENCY AND PROSACCADE ERRORS

Patients were slower than controls in initiating primary saccades to remembered locations ($F_{1,48}$=10.24; P=.002). This effect did not change after treatment and did not vary as a function of delay period or response direction.

At each time point, patients committed more prosaccade errors than controls ($F_{1,48}$=8.32; P=.01). Both groups showed a comparable decline in errors from baseline (12% for patients vs 8% for controls) to 6-week follow-up (9% for patients vs 3% for controls).

DURATION OF UNTREATED ILLNESS, CLINICAL RATINGS, AND MEDICATION DOSE

The duration of untreated psychosis was unrelated to baseline ODR task performance or to changes in performance from baseline to 6-week follow-up. Improvement in clinical symptom ratings was unrelated to changes in ODR task performance from baseline to 6-week follow-up. Extrapyramidal adverse effect ratings and medica-

tion doses at 6-week testing were uncorrelated with changes in task performance from baseline to follow-up, although doses were in a relatively narrow range. Exclusion of the 5 patients taking benztropine at 6-week follow-up did not change any findings.

PERFORMANCE AT THE 26- AND 52-WEEK FOLLOW-UP EVALUATIONS

The stability of the present findings was examined in secondary analyses of a demographically matched subset of patients (n=13) and controls (n=18) who completed additional follow-up testing at both 26 and 52 weeks. These subgroups did not differ from participants in their respective larger groups in demographic characteristics or task performance at baseline or 6-week follow-up. The patient subgroup did not differ from the complete patient group in clinical ratings at baseline, risperidone dose at 6 weeks, or degree of clinical improvement at 6 weeks. Mean±SD risperidone doses at 26-week (3.6±1.4 mg) and 52-week (3.5±1.6 mg) follow-up were consistent with that at 6 weeks. One patient was taking benztropine (1 mg) at both later time points.

Throughout the 1-year follow-up period, patients remained significantly less accurate than controls in primary saccade gain ($F_{1,29}=10.90$; $P=.003$; Cohen d=–0.9) and final resting eye position ($F_{1,29}=11.80$; $P=.002$; Cohen d=–1.0). Neither accuracy measure at later time points differed from that at 6 weeks for patients or controls.

COMMENT

Antipsychotic drug–naive patients with first-episode schizophrenia performed an ODR task before and 6 weeks after initiation of risperidone treatment. Before treatment, patients demonstrated impairment in spatial working memory reflected by reduced accuracy of both primary saccade gain and final resting eye position. This impairment was evident only when patients were required to maintain information over the longer delay periods (8 seconds). In contrast, after 6 weeks of risperidone treatment, patients' baseline impairment was exacerbated such that they were uniformly inaccurate at all delay periods, including very brief delays (1 second). This decline in performance occurred in the absence of significant extrapyramidal adverse effects. Furthermore, these impairments persisted to the 1-year follow-up testing, indicating that patients did not habituate to apparent adverse effects of risperidone. Patients also had longer response latencies and committed more prosaccade inhibitory errors compared with controls. These performance variables did not change differentially in patients after treatment.

SPATIAL WORKING MEMORY IMPAIRMENT IN TREATMENT-NAIVE SCHIZOPHRENIA

The present study provides new evidence of impairment in spatial working memory during the early phase of untreated schizophrenia. To our knowledge, this is the first study to report a delay-dependent effect among treatment-naive patients with schizophrenia. This finding suggests that in the acute stages of recent-onset schizophrenia, spatial information is effectively encoded in working memory but that there is a faster rate of decay of spatial information from working memory systems under increased maintenance conditions.

At first glance, that patients in the current study did not demonstrate baseline ODR performance deficits at shorter delay periods may seem contrary to the notion that this is a core disease impairment also present among unaffected first-degree relatives of patients with schizophrenia.[7,8] Similar to previous investigations with patients, delay period duration was not parametrically varied in these family studies, so relatives' performance across a range of delay period durations is not known. The seminal study by Park et al,[9] which first demonstrated impaired ODR task performance in treated patients with schizophrenia and their relatives, used 10-second delay periods. This period approximates the delay interval at which baseline impairments were detected in the present study. It remains to be determined whether onset of the disorder increases preexisting deficits that are present before treatment initiation. However, the pretreatment findings suggest the possibility that the core spatial working memory deficit in schizophrenia involves a diminished ability to maintain information in working memory over time but not a reduced ability to encode information into working memory stores.

We also found greater impairment in patients when targets were presented in the right hemifield. This effect, which did not change after treatment, is consistent with previously reported findings[49] in which chronically ill, medicated patients with schizophrenia committed more errors when manually identifying the location of remembered targets presented in the right visual field. This laterality bias in the present untreated first-episode sample indicates that the observed hemifield-specific impairment is present at illness onset and thus is not accounted for by effects of treatment or progression of illness. This directional impairment does not reflect a failure to attend and accurately encode information presented in the right hemifield given that a previous study[46] showed comparable accuracy of visually guided saccades made to the left and right visual fields in this sample. In controls performing an ODR task, the contralateral prefrontal cortex has been shown to maintain spatial information of targets presented in the corresponding hemifield across delay periods.[50] Therefore, the present findings suggest greater disturbance in left prefrontal cortex systems, supporting the maintenance of information in spatial working memory in schizophrenia.

On the basis of neurophysiologic studies of nonhuman primates performing the ODR task, pharmacologic investigations of working memory in nonhuman primates and healthy human subjects, and receptor binding studies of medication-free patients with schizophrenia, one possible explanation for the present findings is that patients' baseline impairment in spatial working memory results from altered D_1 receptor activity or distribution in the DLPFC.[23] Studies of monkeys perform-

ing ODR tasks have established that the maintenance of spatial location information in working memory is modulated by D_1 receptor activity. Without sufficient D_1 stimulation, pyramidal neurons fail to sustain the firing rate needed to retain information in working memory systems over time, and performance deteriorates as a result. Microinjections of D_1, but not D_2, receptor antagonists into the nonhuman primate DLPFC reduce the accuracy of saccades to remembered targets but have no impact on saccades to visual targets.[51] Neurophysiologic studies have established that there is an optimal, but narrow, range of D_1 receptor activity of prefrontal neurons during the delay period when information has to be remembered on the ODR task, with either too much or too little receptor stimulation associated with working memory impairment.[24] This "inverted U"–shaped relationship between D_1 modulation and working memory is supported by behavioral studies demonstrating that D_1 agonists enhance working memory performance in dopamine-deficient monkeys,[52,53] whereas D_1 antagonists lead to a reversal of impairment in monkeys with experimentally induced dopamine elevation in the DLPFC.[54] Evidence of a similar D_1 receptor modulation of working memory performance in humans is provided by demonstrations of enhanced working memory after the administration of pergolide mesylate, a combined D_1 and D_2 agonist, but not the selective D_2 agonist bromocriptine mesylate.[55]

Alterations in prefrontal D_1 receptor activation in antipsychotic drug–free patients have been reported in some studies,[56,57] although the nature of this alteration is unclear, as both down-regulation and up-regulation have been observed. Using a selective D_1 ligand, Abi-Dargham et al[58] found increased D_1 receptor binding in antipsychotic drug–free patients with schizophrenia. Increased D_1 binding in patients predicted impairment on a verbal working memory task, particularly as task demands increased. This increased D_1 receptor availability may reflect a compensation, albeit functionally inadequate, for deficient mesocortical dopaminergic input.[58] Therefore, it is possible that suboptimal D_1 receptor function in the DLPFC could contribute to the poorer pretreatment performance of the patients on the ODR task, particularly when demands on D_1 activity to support working memory were greatest (ie, at the longest delay period).

ADVERSE EFFECTS OF RISPERIDONE ON SPATIAL WORKING MEMORY

To our knowledge, this is the first study to document a significant worsening of spatial working memory in patients with schizophrenia after initiating risperidone treatment. After 6 weeks of treatment, patients' performance declined beyond their initial baseline deficit, and impairment was seen across all delay period durations rather than just in high-maintenance demand conditions. The posttreatment deficits at even 1-second delay periods raise the possibility that encoding processes for working memory were adversely affected by treatment. This effect is striking in that the magnitude of change in patients' performance from baseline to follow-up is greater than that of the group difference between controls and patients before treatment (Figure 2). Patients' performance at baseline and 6-week follow-up was highly positively correlated, suggesting that an individual patient's relative performance within the group is maintained as the group average declines after treatment. This finding points to a consistent treatment effect. Impairments were maintained through 1-year follow-up, indicating that patients did not habituate to apparent treatment effects. The magnitude of the patients' deficits after treatment is highly consistent with those of a recently published meta-analysis[3] of 124 studies examining working memory in schizophrenia, most of which included medicated patients.

Our observation of worsened impairment on an ODR task after treatment initiation in patients with schizophrenia may be best understood in the context of knowledge about risperidone's pharmacologic properties and recent neurochemical studies with nonhuman primates. In the dopamine system, risperidone strongly antagonizes dopamine D_2 and has relatively low affinity for D_1 receptors.[59] Antagonism of D_2 receptors in the PFC does not affect mnemonic performance on this task,[60] and thus, risperidone's effect on D_2 receptors is not likely to account for the treatment-related impairment report herein. However, exposure to either typical or atypical antipsychotic medications, including risperidone, induces a robust reduction of D_1 receptor expression in the PFC (an approximately two-thirds reduction for risperidone) but not in the striatum.[61]

Haloperidol administration to monkeys has been shown to result in impaired spatial working memory on an ODR task that was reversed with the administration of a selective full D_1 agonist.[53] Examination of risperidone's effects on working memory in monkeys has not been reported, but similar effects are expected given risperidone's somewhat greater prefrontal D_1 down-regulation compared with haloperidol.[61] It is thus possible that risperidone's apparent adverse effect on ODR performance observed in the present study could result, at least in part, from a treatment-related down-regulation of DLPFC D_1 receptors. In this case, a reduction in D_1 activity associated with risperidone treatment might further compromise a system that at baseline is already dysfunctional in its support of working memory processes.

Pharmacologic effects on neurotransmitter systems other than dopamine, such as antagonism of the serotonin 2A receptor, might also contribute to risperidone's effects on ODR performance. The role of this receptor in working memory has been examined, albeit to a lesser extent than dopamine receptors. Iontophoresis of a serotonin 2A antagonist on monkey prefrontal neurons, which were neurophysiologically determined to show memory field activity, diminished the activity of these neurons during delay periods of the ODR task.[62] This suggests that there may be deleterious effects on working memory associated with serotonin 2A antagonism. It is thus possible that the decline in patient performance after treatment may also result in part from antagonism of serotonin 2A receptors in the prefrontal cortex uniquely or in combination with D_1 receptor down-regulation.

Patients' worsening of performance on the ODR task is not likely to result from generalized adverse treat-

ment effects on oculomotor systems. First, the accuracy of both the primary saccade and final resting eye position declined after treatment, the latter of which relies less on the programming or execution of an initial precise motor response. Second, other saccade parameters, including peak velocity, latency, and duration, were not affected by treatment, and these are typically more sensitive indices of drug-induced changes in oculomotor systems.[63] Third, risperidone doses were not high enough to induce significant extrapyramidal adverse effects that could affect motor programming of saccades. Finally, in a previous study[46] of first-episode patients performing a visually guided saccade task, of which patients in the present study are a smaller subset, we reported a very mild decline in saccade accuracy after starting risperidone treatment. The average decline in memory-guided saccades was 4.5 times greater than that of saccades made in the presence of a visual target. Furthermore, the change in memory-guided saccade accuracy from baseline to 6-week follow-up was not related to changes in visually guided saccades.

The present findings of impaired ODR task performance after risperidone treatment stand in contrast to some recent neuropsychologic studies[64-67] that reported a modest improvement in working memory after treatment with atypical antipsychotic agents, including risperidone. Several factors may account for this apparent discrepancy. First, studies reporting neuropsychologic improvement with risperidone treatment have not followed treatment-naive patients over time and often report an advantage relative to a conventional antipsychotic drug rather than improvement per se. Second, the absence of a parallel healthy comparison group in larger clinical trials focused on cognitive outcomes, coupled with significant practice effects with many neuropsychologic tests, might exaggerate apparent procognitive treatment effects suggested by improved scores at retesting.[68] Third, and perhaps most important, working memory is a complex and variably defined construct that includes decidedly different cognitive components. Performance on traditional neuropsychologic measures, such as those used in most larger clinical trials,[64,65] is multifactorial and often requires maintenance, manipulation, and sequencing of information across trials. The ODR task taps a specific aspect of working memory: the maintenance of spatial information in short-term memory stores to guide future behavior. Because of its translational origins, the neurophysiologic basis and neurochemical regulation of this cognitive process is far more established than that of more complex processes required for most neuropsychologic measures of working memory. It is possible that subcomponents of working memory, and the brain systems that support them, may well be differentially affected by antipsychotic drug treatment. For example, complex problem solving and decision making might be enhanced, whereas the ability to maintain information online might be reduced. Differentiating how treatment affects the various aspects of working memory will require the development and use of paradigms that uniquely tap such subprocesses.

Certain limitations of this study require consideration. Without an untreated patient group followed in parallel with treated patients, the possible role of disease progression as a cause of worsening ODR task performance cannot be logically excluded. However, for several reasons, we believe that this is an unlikely explanation for the current findings. First, it is unlikely that patients who have been ill on average for a year before entering the study would have a sudden, stepwise, and consistent disease-related deterioration precisely at the time when medication treatment is initiated. Second, if the decline in task performance was somehow related to disease progression, then it is likely that the degree of impairment at baseline or the magnitude of decline after treatment would be associated with a greater length of untreated psychosis. This was not the case. Third, in the subset of patients who were available at the 26- and 52-week follow-up evaluations, there was no further deterioration in ODR task performance from the 6-week to the later follow-up visits. Whether the observed effects are specific to risperidone or to classes of antipsychotic drugs cannot be determined based on these findings. This question needs to be addressed in a future study using a randomized clinical trial design with a comparison drug.

We believe that the results of this study underscore the need for greater use and further development of translational tasks and biomarkers as an approach for advancing understanding of treatment effects on neurocognitive systems in schizophrenia. In another study[69] using an antisaccade task with these same patients, we reported improvement after risperidone treatment in the ability to suppress context-inappropriate responses and to more quickly plan and implement behavioral responses. These findings are in contrast to the adverse treatment effects on working memory reported herein. Such a dissociation of risperidone's effects on "executive" prefrontal abilities highlights the value of translational approaches that focus on discrete cognitive operations for parsing beneficial and adverse treatment-related changes in neural systems. Such differentiation of treatment effects on cognitive operations is rarely possible with standard neuropsychologic tests.[70] With increased clinical and scientific interest given to developing pharmacologic interventions targeting cognitive symptoms in schizophrenia, neurophysiologic testing that provides a translational bridge between pharmacologic studies with animal models and clinical studies may better clarify the nature of medication effects on cognition and thereby enhance the drug development process.

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REFERENCES

1. Elvevag B, Goldberg TE. Cognitive impairment in schizophrenia is the core of the disorder. *Crit Rev Neurobiol*. 2000;14:1-21.
2. Goldman-Rakic PS. Working memory dysfunction in schizophrenia. *J Neuropsychiatry Clin Neurosci*. 1994;6:348-357.
3. Lee J, Park S. Working memory impairments in schizophrenia: a meta-analysis. *J Abnorm Psychol*. 2005;114:599-611.
4. Liddle PF. Cognitive impairment in schizophrenia: its impact on social functioning. *Acta Psychiatr Scand Suppl*. 2000;400:11-16.
5. Meltzer HY, Thompson PA, Lee MA, Ranjan R. Neuropsychologic deficits in schizophrenia: relation to social function and effect of antipsychotic drug treatment. *Neuropsychopharmacology*. 1996;14:27S-33S.
6. McGurk SR, Meltzer HY. The role of cognition in vocational functioning in schizophrenia. *Schizophr Res*. 2000;45:175-184.
7. Glahn DC, Therman S, Manninen M, Huttunen M, Kaprio J, Lonnqvist J, Cannon TD. Spatial working memory as an endophenotype for schizophrenia. *Biol Psychiatry*. 2003;53:624-626.
8. McDowell JE, Brenner CA, Myles-Worsley M, Coon H, Byerley W, Clementz BA. Ocular motor delayed-response task performance among patients with schizophrenia and their biological relatives. *Psychophysiology*. 2001;38:153-156.
9. Park S, Holzman PS, Goldman-Rakic PS. Spatial working memory deficits in the relatives of schizophrenic patients. *Arch Gen Psychiatry*. 1995;52:821-828.
10. Baddeley A. *Working Memory: Theory and Practice.* New York, NY: Oxford University Press; 1986.
11. Goldman-Rakic PS. Circuitry of primate prefrontal cortex and regulation of behavior by representational memory . In: Mountcastle VB, ed. *Handbook of Physiology, Section 1: The Nervous System Vol V: Higher Functions of the Brain, Part 1.* Bethesda, Md: American Physiology Society; 1987:373-417.
12. Barch DM, Carter CS, Braver TS, Sabb FW, MacDonald A III, Noll DC, Cohen JD. Selective deficits in prefrontal cortex function in medication-naive patients with schizophrenia. *Arch Gen Psychiatry*. 2001;58:280-288.
13. Callicott JH, Bertolino A, Mattay VS, Langheim FJP, Duyn J, Coppola R, Goldberg TE, Weinberger DR. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb Cortex*. 2000;10:1078-1092.
14. Goldberg TE, Hyde M, Kleinman JE, Weinberger DR. Course of schizophrenia: neuropsychological evidence for a static encephalopathy. *Schizophr Bull*. 1993;19:797-804.
15. Manoach DS, Gollub RL, Benson ES, Searl MM, Goff DC, Halpern E, Saper CB, Rauch SL. Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. *Biol Psychiatry*. 2000;48:99-109.
16. Weinberger DR, Berman KF, Zec RF. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia, I: regional cerebral blood flow evidence. *Arch Gen Psychiatry*. 1986;43:114-124.
17. Hikosaka O, Wurtz RH. Visual and oculomotor functions of monkey substantia nigra pars reticulata, III: memory-contingent visual and saccade responses. *J Neurophysiol*. 1983;49:1268-1284.
18. Goldman-Rakic PS. The physiological approach: functional architecture of working memory and disordered cognition in schizophrenia. *Biol Psychiatry*. 1999;46:650-661.
19. Funahashi S, Bruce CJ, Goldman-Rakic PS. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J Neurophysiol*. 1989;61:331-349.
20. Rao SG, Williams GV, Goldman-Rakic PS. Isodirectional tuning of adjacent interneurons and pyramidal cells during working memory: evidence for microcolumnar organization in PFC. *J Neurophysiol*. 1999;81:1903-1916.
21. Goldman-Rakic PS. Cellular basis of working memory. *Neuron*. 1995;14:477-485.
22. Sawaguchi T, Goldman-Rakic PS. D1 dopamine receptors in prefrontal cortex: involvement in working memory. *Science*. 1991;251:947-950.
23. Goldman-Rakic PS, Castner SA, Svensson TH, Siever LJ, Williams GV. Targeting the dopamine D1 receptor in schizophrenia: insights for cognitive dysfunction. *Psychopharmacology (Berl)*. 2004;174:3-16.
24. Williams GV, Goldman-Rakic PS. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature*. 1995;376:572-575.
25. Abi-Dargham A, Moore H. Prefrontal DA transmission at D1 receptors and the pathology of schizophrenia. *Neuroscientist*. 2003;9:404-416.
26. Davis KL, Kahn RS, Ko G, Davidson M. Dopamine in schizophrenia: a review and reconceptualization. *Am J Psychiatry*. 1991;148:1474-1486.
27. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry*. 1987;44:660-669.
28. Broerse A, Crawford TJ, Den Boer JA. Differential effects of olanzapine and risperidone on cognition in schizophrenia? a saccadic eye movement study. *J Neuropsychiatry Clin Neurosci*. 2002;14:454-460.
29. Karoumi B, Ventre-Dominey J, Vighetto A, Dalery J, d'Amato T. Saccadic eye movements in schizophrenic patients. *Psychiatry Res*. 1998;77:9-19.
30. McDowell JE, Clementz BA. Ocular-motor delayed-response task performance among schizophrenia patients. *Neuropsychobiology*. 1996;34:67-71.
31. Park S, Holzman PS. Schizophrenics show spatial working memory deficits. *Arch Gen Psychiatry*. 1992;49:975-982.
32. Park S, Holzman PS. Association of working memory deficit and eye tracking dysfunction in schizophrenia. *Schizophr Res*. 1993;11:55-61.
33. Ross RG, Harris JG, Olincy A, Radant A. Eye movement task measures inhibition and spatial working memory in adults with schizophrenia, ADHD, and a normal comparison group. *Psychiatry Res*. 2000;95:35-42.
34. Crawford TJ, Haeger B, Kennard C, Reveley MA, Henderson L. Saccadic abnormalities in psychotic patients, I: neuroleptic-free psychotic patients. *Psychol Med*. 1995;25:461-471.
35. Crawford TJ, Haeger B, Kennard C, Reveley MA, Henderson L. Saccadic abnormalities in psychotic patients, II: the role of neuroleptic treatment. *Psychol Med*. 1995;25:473-483.
36. Muller N, Riedel M, Eggert T, Straube A. Internally and externally guided voluntary saccades in unmedicated and medicated schizophrenic patients, part II: saccadic latency, gain, and fixation suppression errors. *Eur Arch Psychiatry Clin Neurosci*. 1999;249:7-14.
37. Spitzer RL, Williams JBW, Gibbons M, First M. Structured Clinical Interview for *DSM-III-R* (SCID). New York: New York State Psychiatric Institute; 1987.
38. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia: a controlled study of the neuroleptic threshold and higher haloperidol dose. *Arch Gen Psychiatry*. 1991;48:739-745.
39. Ammons CH, Ammons RB. The Quick Test (QT): provisional manual. *Psychol Rep*. 1962;11:111-161.
40. Hollingshead AB. *Four Factor Index of Social Status.* New Haven, Conn: Department of Sociology, Yale University; 1975.
41. Oldfield RC. The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia*. 1971;9:97-113.
42. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962;10:799-812.
43. Andreasen NC. *Scale for the Assessment of Positive Symptoms.* Iowa City: University of Iowa Press; 1984.
44. Andreasen NC. *Scale for the Assessment of Negative Symptoms.* Iowa City: University of Iowa Press; 1984.
45. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.
46. Reilly JL, Harris MS, Keshavan MS, Sweeney JA. Abnormalities in visually guided saccades suggest corticofugal dysregulation in never-treated schizophrenia. *Biol Psychiatry*. 2005;57:145-154.
47. Krappmann P, Everling S. Spatial accuracy of primary and secondary memory-guided saccades in schizophrenic patients. *Schizophr Res*. 1998;30:183-185.
48. Rosenthal R. *Meta-analytic Procedures for Social Research*. Newbury Park, Calif: Sage; 1991.
49. Park S. Hemispheric asymmetry of spatial working memory deficit in schizophrenia. *Int J Psychophysiol*. 1999;34:313-322.
50. Muri RM, Gaymard B, Rivaud S, Vermersch AI, Hess CW, Pierrot-Deseilligny C. Hemispheric asymmetry in cortical control of memory-guided saccades: a transcranial magnetic stimulation study. *Neuropsychologia*. 2000;38:1105-1111.
51. Sawaguchi T, Goldman-Rakic PS. The role of D1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. *J Neurophysiol*. 1994;71:515-528.
52. Arnsten AF, Cai JX, Murphy BL, Goldman-Rakic PS. Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. *Psychopharmacology (Berl)*. 1994;116:143-151.
53. Castner SA, Williams GV, Goldman-Rakic PS. Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. *Science*. 2000;287:2020-2022.
54. Arnsten AF, Goldman-Rakic PS. Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. *Arch Gen Psychiatry*. 1998;55:362-368.
55. Muller U, Von Cramon DY, Pollmann S. D1- versus D2-receptor modulation of visuospatial working memory in humans. *J Neurosci*. 1998;18:2720-2728.
56. Okubo Y, Suhara T, Kazutoshi S, Kobayashi K, Inoue O, Terasaki O, Someya Y,

Sassa T, Sudo Y, Matsushima E, Iyo M, Tateno Y, Toru M. Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. *Nature.* 1997;385: 634-636.
57. Karlsson P, Farde L, Halldin C, Sedvall G. PET study of D(1) dopamine receptor binding in neuroleptic-naive patients with schizophrenia. *Am J Psychiatry.* 2002; 159:761-767.
58. Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, Hwang DR, Keilp J, Kochan L, Van Heertum R, Gorman JM, Laruelle M. Prefrontal dopamine D1 receptors and working memory in schizophrenia. *J Neurosci.* 2002; 22:3708-3719.
59. Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Mol Psychiatry.* 2005;10:79-104.
60. Wang M, Vijayraghavan S, Goldman-Rakic PS. Selective D2 receptor actions on the functional circuitry of working memory. *Science.* 2004;303:853-856.
61. Lidow MS, Elsworth JD, Goldman-Rakic PS. Down-regulation of the D1 and D5 dopamine receptors in the primate prefrontal cortex by chronic treatment with antipsychotic drugs. *J Pharmacol Exp Ther.* 1997;281:597-603.
62. Williams GV, Rao SG, Goldman-Rakic PS. The physiological role of 5-HT2A receptors in working memory. *J Neurosci.* 2002;22:2843-2854.
63. Kroboth PD, Folan MM, Bauer KS, Tullock W, Wright E, Sweeney JA. Do alprazolam-induced changes in saccadic eye movement and psychomotor function follow the same time course? *J Clin Pharmacol.* 1998;38:337-346.
64. Green MF, Marshall BD Jr, Wirshing WC, Ames D, Marder SR, McGurk S, Kern RS, Mintz J. Does risperidone improve verbal working memory in treatment-resistant schizophrenia? *Am J Psychiatry.* 1997;154:799-804.
65. Harvey PD, Green MF, McGurk SR, Meltzer HY. Changes in cognitive functioning with risperidone and olanzapine treatment: a large-scale, double-blind, randomized study. *Psychopharmacology (Berl).* 2003;169:404-411.
66. McGurk SR, Carter C, Goldman R, Green MF, Marder SR, Xie H, Schooler NR, Kane JM. The effects of clozapine and risperidone on spatial working memory in schizophrenia. *Am J Psychiatry.* 2005;162:1013-1016.
67. Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bull.* 1999;25:233-255.
68. Hill SK, Schuepbach D, Herbener ES, Keshavan MS, Sweeney JA. Pretreatment and longitudinal studies of neuropsychological deficits in antipsychotic-naive patients with schizophrenia. *Schizophr Res.* 2004;68:49-63.
69. Harris MS, Reilly JL, Keshavan MS, Sweeney JA. Longitudinal studies of antisaccades in antipsychotic-naive first-episode schizophrenia. *Psychol Med.* 2006; 36:485-494.
70. Reilly JL. Treatment effects of atypical antipsychotic medication on neurocognition in first-episode schizophrenia: differential sensitivity of neuropsychological and neurophysiological measures [abstract]. *J Int Neuropsychol Soc.* 2005; 11:196.