Journal of Abnormal Psychology
2005, Vol. 114, No. 1, 75–84


0021-843X/05/$12.00 DOI: 10.1037/0021-843X.114.1.75

# What Is Perseverated in Schizophrenia? Evidence of Abnormal Response Plasticity in the Saccadic System

Jason J. S. Barton
Beth Israel Deaconess Medical Center, Harvard Medical School, and Boston University

Mariya V. Cherkasova and Kristen A. Lindgren
Beth Israel Deaconess Medical Center and Harvard Medical School

Donald C. Goff and Dara S. Manoach
Massachusetts General Hospital and Harvard Medical School

Although perseveration is sometimes attributed to defective set switching, the authors have recently shown that set-switching is normal in schizophrenia. In this article, the authors tested for persistent states of the saccadic response system, rather than set perseveration. Schizophrenic and healthy subjects performed antisaccades and prosaccades. The authors analyzed for 3 carry-over effects. First, whereas the latency of the current saccade correlated with that of the prior saccade in both groups, the correlations under mixed-task conditions declined in healthy but not in schizophrenic subjects. Second, antisaccades in penultimate trials delayed upcoming saccades in schizophrenic but not in healthy subjects. Third, schizophrenic subjects were more likely to erroneously perseverate the direction of a prior antisaccade but not a prior prosaccade. The authors concluded that, in schizophrenia, the effects of correct antisaccades are persistent not weak. Saccades in schizophrenia are characterized by perseveration of antisaccade-induced changes in the saccadic response system rather than failures to switch task set.

Perseveration is the contextually inappropriate and unintentional repetition of a response. Older taxonomies have drawn distinctions between different components of behavior that can be perseverated (Goldberg, 1986; Sandson & Albert, 1984). On the one hand, there can be a failure to change from one task set to another. Task sets are the sets of stimulus–response associations appropriate to a task and usually involve a rule that defines correct behavior. For example, the Stroop task set of color naming can be characterized as "given a written word, name the ink color." A subject might perseverate on the Stroop test by continuing to name the ink color after the task had changed to reading the word written in the ink. Such a person would be "stuck in set," and their perseveration would be attributed to defective switching of task sets. On the other hand, there can be unwanted repetition of a prior response, such as continuing to name the ink color in the prior trial. This would be an example of "feature/element" perseveration. This type of perseveration represents abnormal persistence of a specific state of the response system rather than defective set switching.

Perseveration is a classic abnormality in schizophrenia (Crider, 1997; Freeman & Gathercole, 1966; Sandson & Albert, 1984). In the past, some types of schizophrenic perseveration have been attributed to impaired set switching. Defective set switching has been blamed for the poor performance of schizophrenic subjects on neuropsychological instruments such as the trail making test or the Wisconsin Card Sort Test (Braff et al., 1991; Perry & Braff, 1998). However, these tests are multidimensional. That is, they depend on several cognitive functions for success. Poor performance on the Wisconsin Card Sort Test may reflect problems in not only set switching but also sustained attention, concept formation, and working memory, more general functions that are not intrinsic to the switch process (Cohen & Servan-Schreiber, 1992; Gold et al., 1997; Smith et al., 1998; Sullivan et al., 1993). The multidimensionality of these tests makes it impossible to attribute failure specifically to a set-switch deficit.

In the last few years, methods that isolate set-switch processes more effectively have been devised. Studies in healthy subjects have in turn revealed that set switching is itself a composite of several switch-related cognitive processes (Meiran, Chorev, & Sapir, 2000; Rushworth, Passingham, & Nobre, 2002). These include passive dissipation of inhibition from the alternate task set of the prior trial (Allport, Styles, & Hsieh, 1994; Meiran et al., 2000; Wylie & Allport, 2000), active reconfiguration of the system following the cue to switch (Meiran, 1996; Monsell, Yeung, & Azuma, 2000; Rogers & Monsell, 1995), effects of advance knowledge of the requirement to switch (Sohn & Carlson, 2000;

Jason J. S. Barton, Department of Neurology, Beth Israel Deaconess Medical Center; Department of Ophthalmology, Harvard Medical School; and Department of Bioengineering, Boston University. Mariya V. Cherkasova and Kristen A. Lindgren, Department of Neurology, Beth Israel Deaconess Medical Center, and Department of Neurology, Harvard Medical School. Donald C. Goff, Department of Psychiatry, Massachusetts General Hospital, and Department of Psychiatry, Harvard Medical School. Dara S. Manoach, Department of Psychiatry, Massachusetts General Hospital, and Athinoula A. Martinos Center for Biomedical Imaging, Harvard Medical School.

This work was supported by National Institute of Mental Health Grants K23MH10829 and R01 MH67720 to Dara S. Manoach and National Institute of Neurological Disorders and Stroke Grant K08NS01920 to Jason J. S. Barton.

Correspondence concerning this article should be addressed to Jason J. S. Barton, who is now at Neuro-opthalmology Section D, VGH Eye Center, 2550 Willow Street, Vancouver, British Columbia, Canada V5Z 3N9. E-mail: jbarton@caregroup.harvard.edu

Tornay & Milan, 2001), and even effects related to the nature of the cue indicating the new task set (Arbuthnott & Frank, 2000; Arbuthnott & Woodward, 2002).

Two recent studies have used these new protocols to isolate and test the integrity of set-switch effects in schizophrenia (Manoach et al., 2002; Meiran, Levine, & Henik, 2000). One examined simple stimulus-response remappings (i.e., the subject switches between different responses to the same stimulus) by using manual responses to visual stimuli (Meiran, Levine, & Henik, 2000). Although schizophrenic subjects had elevated reaction times in general, the proportional increase of latency induced by switching did not differ from healthy subjects. The other study (Manoach et al., 2002) also used stimulus-response re-mappings, switching between prosaccades (gaze shifts toward a suddenly appearing target) and antisaccades (gaze shifts away from the target). The effects of set switching on latency and accuracy were similar in schizophrenic and healthy subjects not just relatively, but absolutely.

These two studies question the assumption that perseveration in schizophrenia is due to difficulty switching between task sets. However, the results do not exclude the possibility that other elements of behavior are perseverated in schizophrenia. In particular, perseveration at the level of the response system rather than the task set must be considered given the taxonomies of perseveration initially discussed. In this article, we present the second part of our analysis of the data from Manoach et al. (2002). That report established that schizophrenic subjects have no difficulty switching saccadic task sets. In this work, we examine the same data to see if abnormal perseveration of the state of the saccadic response system is present in schizophrenia. If so, this might provide a modern ocular motor parallel to older concepts of feature/element perseveration in schizophrenia.

The simplest manifestation of abnormal persistence of the state of the saccadic response system would be a repetition of the specific saccade made in the prior trial. However, there may also be other, more subtle reflections of the state of the saccadic response system in the prior trial. Consider one important finding of our investigations of set switching between prosaccades and antisaccades (Cherkasova, Manoach, Intriligator, & Barton, 2002; Manoach et al., 2002). As expected, switched prosaccades had longer latencies than did repeated prosaccades. However, the latencies of switched antisaccades were shorter than those of repeated antisaccades. This paradoxical set-switch benefit for antisaccades does not fit with current models of set switching. These all predict that switching to a new set would always generate longer latencies than would repeating the set of the prior trial. For example, the model of "task-set inertia" suggests that differences in latency between switched and repeated trials are due to persisting inhibition from the prior task set on the new task set (Allport et al., 1994; Wylie & Allport, 2000; see Figure 1A). Switching to the other set requires more time to overcome this inhibition. This would be true for both prosaccades and antisaccades, even though the effect would be greater for switching away from antisaccades because to generate these requires a large degree of inhibition of the more reflexive prosaccade.

To explain why switching reduces antisaccadic latencies, we suggested an alternative model. It may be that the persisting inhibition from antisaccades is not directed at the prosaccade task set but at the saccadic response system itself (see Figure 1B). If so,

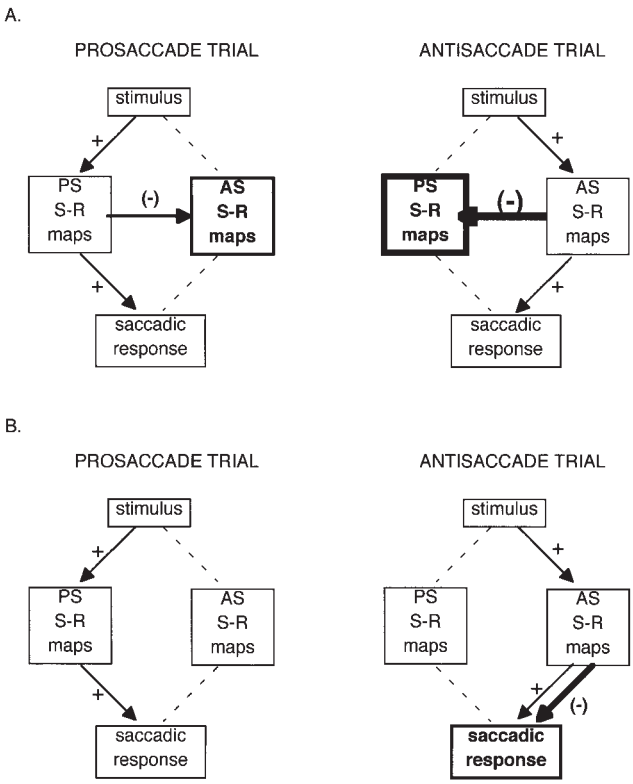


*Figure 1.* Models of the hypothetical sources of persistent inhibition in a saccadic-switching paradigm. Each of the four diagrams depicts the activation patterns in the prior trial and the inhibition that is then carried over into the subsequent trial. Arrows with a "+" indicate activation, thick arrows with a "−" indicate inhibition. Dashed lines indicate inactive pathways. Bold type and boxes indicate sites of inhibition that persist into the next trial. A: Task-set inertia model. With a prosaccade (left diagram), the target stimulus activates the prosaccade stimulus-response (S-R) map, which not only selects the appropriate response but also weakly inhibits the alternative antisaccade S-R map, which is overcome easily if the next trial calls for a switch to an antisaccade. An antisaccade (right diagram) requires strong inhibition of the prosaccade S-R map. If the next trial is a prosaccade, overcoming this will markedly delay latency. Thus, although asymmetric, switching in either direction will increase latency because of the need to overcome residual inhibition of S-R maps. B: Response-system plasticity model. Activity in the antisaccade S-R map (right diagram) not only activates a specific directional response but inhibits the response component of the system in general. Persistence of this inhibition delays saccades in the next trial regardless of whether a pro- or antisaccade is required, explaining why repeated antisaccades take longer than switched antisaccades.

recent execution of an antisaccade would prolong latencies in the next response whether prosaccade or antisaccade. Such generalized inhibition of the saccadic response system by antisaccades has been documented in the monkey physiology literature. In the frontal eye field and superior colliculus, antisaccades depress neuronal activity in a directionally nonselective manner during the interval prior to the appearance of the target (Everling, Dorris, Klein, & Munoz, 1999; Everling & Munoz, 2000). This pre-target neural activity reflects a preparatory state and is correlated with behavioral measures (Dorris & Munoz, 1998). The lower the

pre-target activity, the longer it takes to boost the firing rate past the threshold that triggers a saccade and hence the longer the saccadic latency.

Could this antisaccadic inhibition persist into the pre-target activity of the next trial? Although this has not yet been demonstrated, other prior-trial effects on pre-target activity have been shown. For example, a saccade into the response field of a neuron increases the pre-target activity of that neuron in the subsequent trial (Dorris, Paré, & Munoz, 2000). The result is that saccades in the same direction as a prior saccade have shorter latencies than they do when they are in the opposite direction. The fact that neural activity is altered by behavior in preceding trials led the authors to name this phenomenon *immediate neural plasticity*. If the direction of the prior response can affect subsequent pre-target activity, it seems plausible that the powerful inhibition generated by a prior antisaccade can also persist in the saccadic system as another type of *response-system plasticity*.

As can be seen in Figure 1, the main difference between the models of response-system plasticity and task-set inertia is the component that is inhibited. For task-set inertia, it is the competing set of stimulus-response maps. This type of inhibition always predicts longer latencies for switched responses. For response-system plasticity, it is the response system that is inhibited by the novel antisaccade task. Here the key aspect of the prior trial that generates increased latency is an antisaccade not a switch.

In the present analysis, we made three predictions on the basis of a response-system plasticity model. Our goal was to determine if these three effects would show that schizophrenic subjects had more carry-over of patterns of response-related activity from previous saccades. If so, this would support the hypothesis that it is the state of the response system rather than the prevailing task set that is abnormally persistent in this condition.

First, because the pretarget activity in ocular motor regions is correlated with saccadic latency (Dorris & Munoz, 1998; Everling, Dorris, Klein, & Munoz, 1999; Everling & Munoz, 2000), a relation between current and prior pretarget activity should translate into a correlation between current and prior saccadic latencies. Though the degree of pretarget activity will vary between prosaccades and antisaccades (Everling et al., 1999; Everling & Munoz, 2000), and with directional congruency (Dorris et al., 2000), when these factors are controlled we should find that the latency of one trial is a function of the latency of the prior trial. If the state of the response system in the prior trial has an abnormally persistent influence on the next trial, these correlations should be excessive. We predicted that this would be one manifestation of saccadic response perseveration in schizophrenia.

Second, antisaccades in trials more distant than the immediately preceding trial might also affect saccadic latency. Prior studies of task switching suggested that inhibitory effects attributed to task-set inertia are still visible several trials later (Allport et al., 1994). We wished to discover if antisaccadic inhibition of the saccadic response system, which we proposed to account for the paradoxical set-switch benefit of antisaccades, also persisted over more than one trial. Hence, we analyzed the data to see if an antisaccade in the penultimate trial also delayed saccadic responses. Similar "two-back" analyses have been performed in other studies of set-switching (Monsell et al., 2000) or saccadic directional congruency (Dorris et al., 2000). We predicted that another manifestation of response-system perseveration in schizophrenia would be greater delay of saccadic latencies by antisaccades in the more remote penultimate trial.

Third, another feature of the state of the response system during an antisaccade trial is the generation of a positive response, an actual saccade in a specific direction. If the generalized, nondirectional inhibitory effects of an antisaccade persist, might the excitation related to making the antisaccade eye movement do the same? If so, there may be a tendency to perseverate the direction of the prior trial in the next trial, creating more perseverative errors when the current trial calls for a saccade in the opposite direction from the prior one. This would reflect persistently enhanced pre-target activity in neurons coding for the direction of the prior saccade (Dorris et al., 2000). Increased pre-target activity has been shown to correlate not only with reduced latencies but also with increased error rates for saccades (Everling & Munoz, 2000). If there is a directional selectivity for this effect, errors may be more likely to occur when the error is in the same direction as the prior saccade. If schizophrenia is characterized by response perseveration, these subjects should show an exaggeration of this directional effect in errors.

## Method

### *Subjects*

Our patient group (see Table 1) consisted of 21 schizophrenic outpatients maintained on stable doses of antipsychotic drugs for at least 6 weeks (15 subjects on atypical and 6 subjects on conventional agents). Diagnoses were confirmed with the Structured Clinical Interview for *DSM–IV* (First, Spitzer, Gibbon, & Williams, 1997). Clinical status was characterized with the Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987) and the Brief Psychiatric Rating Scale (Overall & Gorham, 1962). All subjects were screened to exclude substance abuse in the preceding 6 months or neurologic conditions that might impair cerebral function. Sixteen healthy individuals matched for age, sex, handedness, and parental socioeconomic status (Hollingshead, 1965) served as control subjects.

### *Apparatus and Eye Movement Protocol*

We recorded eye movements with a magnetic search coil technique (Crist Instruments, Bethesda, MD). Displays were generated by a Power Macintosh 9600/233, with programs written in C++ on the Vision Shell programming platform and back-projected with an Eiki LC-7000U projector. Eye position was digitized at 500 samples/s and a five-point central difference algorithm (Bahill & McDonald, 1983) derived velocity from eye position. Saccades were identified by a velocity criteria, as eye movements exceeding 47°/s. The onset of a saccade was taken as the point at which eye velocity exceeded 31°/s.

The initial display had a dark background with a white 1° fixation ring at center. The fixation ring was flanked by two 0.7° white dots at 20° right and left. Trials started when the subject's eye was within 3° of center. After 1 to 1.5 s, the fixation point was replaced by one of two prompts—a yellow *O* of 4.5° diameter for prosaccade trials, or a blue *X* spanning 4.5° for antisaccade trials. Prompts were replaced after 300 ms by the white fixation ring. After a mean interval of 2 s, the ring target shifted to one of the two peripheral dots where it remained until either the subject fixated the desired position or 10 s had passed, after which the next trial began. No feedback about accuracy was otherwise given.

Single-task blocks had 26 trials consisting of either all prosaccades or all antisaccades. Mixed-task blocks had 52 trials consisting of a random mix of prosaccades and antisaccades. Each block was repeated four times, generating 104 trials of each type. In the mixed-task blocks, about half required similar (repeated) and half required different (switched) responses

Table 1
*Means, Standard Deviations, and Group Comparisons of Demographic Data and Rating Scale Scores*

| | Healthy subjects ($n$ = 16) | | | Schizophrenic subjects ($n$ = 21) | | | | |
|---|---|---|---|---|---|---|---|---|
| Characteristics | *M* | *SD* | *n* | *M* | *SD* | *n* | *t* | *p* |
| Age | 40.3 | 8.7 | | 43.7 | 8.0 | | 1.22 | .23 |
| Gender | | | | | | | $\phi$ = 0.14 | .46 |
| Male | | | 11 | | | 17 | | |
| Female | | | 5 | | | 4 | | |
| Laterality score (handedness) | 63.8 | 57.2 | | 71.0 | 52.6 | | 0.40 | .69 |
| Education (years) | 18.3 | 4.3 | | 12.4 | 2.9 | | 5.03 | < .0001* |
| Estimated verbal IQ | 108.2 | 13.3 | | 98.4 | 14.8 | | 2.06 | .05* |
| Parental SES[a] | 2.1 | 1.3 | | 2.8 | 1.3 | | $z$ = 1.43 | .15 |
| Age of onset | | | | 27.7 | 9.3 | | | |
| Length of illness (years) | | | | 16.1 | 10.3 | | | |

| Scale | *M* | *SD* | Severity |
|---|---|---|---|
| BPRS | 17.0 | 5.6 | minimal |
| PANSS positive | 11.8 | 4.0 | minimal to mild |
| PANSS negative | 19.3 | 5.7 | mild to moderate |
| SANS | 41.0 | 16.6 | minimal to mild |
| AIMS | 3.0 | 4.3 | none to minimal |
| Simpson—Angus | 3.8 | 4.1 | none to minimal |

*Note.* The phi value is the result of a Fisher's exact test. The $z$ value is the result of a nonparametric Mann-Whitney U comparison. SES = socioeconomic status; BPRS = Brief Psychiatry Rating Scale; PANSS = Positive and Negative Symptoms Scale; SANS = Assessment of Negative Symptoms; AIMS = abnormal involuntary movement scale.
[a] A lower score denotes higher status.
* $p \leq .05$.

from the previous trial. Blocks were given in a counterbalanced order to mitigate against effects of learning and fatigue. (To check for this, we divided the data into those obtained from the first half and those from the last half of the session. We performed an analysis of variance [ANOVA] including subject group, saccade type, switch context, and session half. Session half had no significant main effect or interaction with the other variables, indicating no drift in performance in either group.) In total there were 12 blocks, between which short rests were provided. All subjects performed a practice session of 20 trials of each of the three different blocks.

## *Analyses*

The analyses focused mainly on the data from the mixed-task blocks, except for the prior latency effect, where we also examined the data from single-task blocks for comparison. The first trial of each block was eliminated from analysis as it lacked any immediate historical influences. Saccadic response was classified by directional accuracy (correct or incorrect). Latency was calculated from target onset to saccade onset. Trials in which the latency of the first saccade was less than 130 ms were excluded as anticipatory guesses rather than responses to the target stimulus. Trials in which the latency was longer than 800 ms (about four standard deviations above the normal overall saccadic latency) were also excluded as too delayed. Thus, responses were classified as correct, error, or ineligible. Ineligible responses constituted 2% of trials in healthy subjects and 5% of trials in schizophrenic subjects. The following analyses were based only on trials that were preceded by trials with correct responses. Although this reduced the number of responses for statistical analysis, the remaining data were more likely to reflect the true influences of prior responses.

*Relation between current and prior trial latencies.* To determine if the latency of the prior response had a significant effect on the current response's latency, we performed analysis of covariance (ANCOVA) with JMP 4.0 software (http://www.jmp.com). This tested if current latency covaried with prior latency, with main effects of group (schizophrenic/healthy), current saccade type (prosaccade/antisaccade), prior saccade type, and directional congruency (same vs. different from prior to current trial). Subjects nested within group was the random factor. To determine whether prior latency effects were affected by the addition of a cognitive element like set switching, we also performed the same analysis on the data from blocks of pure antisaccades and pure prosaccades (except without a main effect of prior saccade type). Last, we examined the correlation of current response latency against prior response latency with linear regression within each saccadic subgroup (as defined by the main effects in the ANCOVA).

*Two-back (penultimate trial) analysis.* We classified all responses by whether they were preceded by a correct antisaccade or a correct prosaccade in both the prior trial and the penultimate trial. This requirement for three correct saccades in a row reduced the total number of eligible trials to 2,008 in the schizophrenic group, (a mean of 95 out of a possible 200 trials per subject), and 2,106 in the control group (a mean of 131 trials per subject). The analysis divided trials into eight possible sequences: AAA, PAA, APA, PPA, AAP, PAP, APP, PPP (where "A" is an antisaccade and "P" is a prosaccade). The minimum number of trials per group for a sequence was 191 for the AAA sequence in schizophrenic subjects and 242 for the AAP sequence in healthy subjects. We performed an ANOVA with group (schizophrenic/healthy), current saccade type (prosaccade/antisaccade), prior saccade type, and penultimate saccade type as the four main factors and subjects nested within group as a random effect. We also

repeated the ANOVA, but this time we replaced prior and penultimate saccade types by prior and penultimate switch condition (repeated vs. switched). If the effects are related to the prior response rather than to a prior switch, significant statistical differences should be apparent with the ANOVA that classified prior responses by response type (A or P) rather than with the ANOVA that classified prior responses by the presence of a switch.

*Effect of trial history on directional errors.* We analyzed trials in which the direction of the first saccade after target appearance was incorrect. Only trials preceded by trials with correct responses were included. We performed two different analyses. First, for each subject we determined the number of errors for each of the four different types of set sequence between the prior and current trial (PP, AP, PA, AA). Of these, we calculated the frequency of directional perseveration—that is, how many of these errors repeated the direction of the preceding correct saccade. We then performed an ANOVA with repeated measures, with group, current saccade type, and prior saccade type as the main factors and with subjects nested within group as a random effect. We were also interested in whether the frequency of directional perseveration was greater than chance, so for the group mean for each set sequence we used *t* tests to determine whether the mean frequency differed significantly from 0.5, the expected frequency if the prior saccade's direction had no effect on errors.

A second analysis examined the frequency of directional perseveration within the pooled data for each group rather than by subject. Although this ignores the contribution of the individual subject, which the first method takes into account, pooling has other advantages for infrequent events like errors (especially prosaccadic errors) and is a useful check on the first method. Again, we calculated the proportion of errors that repeated the direction of the prior correct saccade for each of the four possible set sequences (PP, AP, PA, AA). Binomial proportions were used for each result to test for the likelihood that the proportion deviated from 0.5.

## Results

### *The Relation Between Current and Prior Trial Latencies*

In the mixed-task blocks, current response latency varied significantly with prior response latency, $F(1, 36) = 34.2$, $p < .0001$. There was a significant interaction of prior latency with subject group, $F(1, 36) = 8.42$, $p < .004$: Schizophrenic subjects showed higher correlations between prior and current latency than did healthy subjects (see Table 2). There was no significant interaction of prior latency with current saccade type: Hence, the prior saccade's latency affected upcoming prosaccades and antisaccades equally. However, there was an interaction of prior latency with prior saccade type, $F(1, 36) = 3.93$, $p = .048$: Upcoming saccadic latencies were more strongly correlated with the latencies of prior prosaccades than of prior antisaccades. These findings are consistent with the proposition that carry-over latency correlations are passive effects, which are derived more from the previous response than from the current response.

The linear regressions of current versus prior latency clarified the origins of the interaction effects between prior latency and subject group. The average slope of the regressions across saccadic subgroups in schizophrenia was 0.50 ($SD = 0.06$), whereas in healthy subjects it was 0.42 ($SD = 0.06$). Thus, the interaction of

Table 2
*Prior Latency Effects for Saccades With Latencies Between 130 and 300 ms*

| | Schizophrenic subjects | | | Control subjects | | |
|---|---|---|---|---|---|---|
| Saccade type and sequence | slope | $R^2$ | residual $M^2$ | slope | $R^2$ | residual $M^2$ |
| **Mixed-Task blocks** | | | | | | |
| Prosaccade | | | | | | |
| P–P (repeated) | | | | | | |
| same direction | 0.31 | .33 | 1,393 | 0.33 | .34 | 1,475 |
| other direction | 0.41 | .40 | 1,477 | 0.36 | .34 | 1,509 |
| A–P (switched) | | | | | | |
| same direction | 0.12 | .13 | 1,157 | 0.08 | .07 | 1,758 |
| other direction | 0.39 | .40 | 1,276 | 0.23 | .19 | 1,785 |
| Antisaccade | | | | | | |
| A–A (repeated) | | | | | | |
| same direction | 0.39 | .38 | 1,358 | 0.21 | .21 | 881 |
| other direction | 0.38 | .35 | 1,258 | 0.31 | .28 | 1,170 |
| P–A (switched) | | | | | | |
| same direction | 0.35 | .33 | 1,367 | 0.32 | .37 | 1,061 |
| other direction | 0.40 | .44 | 1,106 | 0.23 | .30 | 940 |
| Total average | 0.34 | .35 | 1,299 | 0.26 | .26 | 1,323 |
| **Single-Task blocks** | | | | | | |
| Prosaccade | | | | | | |
| same direction | 0.37 | .36 | 1,334 | 0.34 | .25 | 2,696 |
| other direction | 0.44 | .42 | 1,402 | 0.32 | .33 | 1,218 |
| Antisaccade | | | | | | |
| same direction | 0.15 | .15 | 1,457 | 0.40 | .39 | 1,041 |
| other direction | 0.43 | .39 | 1,134 | 0.21 | .21 | 1,134 |
| Total average | 0.34 | .33 | 1,332 | 0.32 | .30 | 1,522 |

*Note.* P = prosaccade; A = antisaccade.

subject group with prior latency is because current latencies are more affected by prior latencies in schizophrenic subjects.

However, schizophrenic subjects also had a greater range of saccadic latencies than did control subjects. Outliers could artifactually affect the comparison of slopes and *R*-squares. Repeating the linear regression analysis on data in the range under 300 ms, where saccadic variance was equivalent for the two subject groups, still showed a group difference with the slopes for schizophrenic subjects being 0.35 ($SD = 0.10$) on average, compared to 0.26 ($SD = 0.10$) for control subjects.

In the single-task blocks, current response latency still varied with prior response latency, $F(1, 36) = 67.8$, $p < .0001$, and there was still a significant interaction of prior latency with prior saccade type, $F(1, 36) = 12.2$, $p < .0005$, which was again the result of steeper slopes with prior prosaccades than with prior antisaccades. However, unlike the mixed-task blocks, the subject groups did not differ in these effects: Subject group did not interact with prior latency.

This suggests that, compared with healthy controls, schizophrenic subjects have elevated latency–latency correlations in mixed-task blocks but not single-task blocks. To ensure that this was not the result of some unexpected effect in switched trials, we repeated the ANCOVA on only the repeated trials from the mixed-task blocks. This may be a more appropriate comparison because all trials in single-task blocks are repetitions. The significant interaction between group and prior latency remained in this reanalysis of the mixed-task data, $F(1, 36) = 13.55$, $p < .0002$.

As another validation of the difference between single-task and mixed-task blocks in our subject groups, we combined the data from both the single-task blocks and the repeated trials of the mixed-task blocks for a third ANCOVA analysis. This examined main effects of subject group, saccade type, directional congruence, prior latency, and now also block type (mixed task vs. single task). The key confirmatory result was a significant three-way interaction between block type, subject group, and prior latency, $F(1, 36) = 7.19$, $p < .008$. All other interactions with prior latency were not significant. The slopes for the linear regressions showed that the two groups were equivalent for single-task blocks (0.32 for healthy subjects, 0.33 for schizophrenia), but the shift to mixed-task blocks reduced the average slope for healthy subjects (0.26) but did not change that of schizophrenic subjects (0.35, see Table 2).

To summarize, current latency varied significantly with prior latency in both groups. The effects were greater for prosaccades than antisaccades in the prior trial but did not vary with the type of saccade in the current trial, observations consistent with the proposal that these reflected carry-over effects from the prior trial. Schizophrenic subjects were no different from healthy subjects in the single-task blocks, but the increased task complexity in the mixed-task blocks was associated with decreased effects from prior-trial latency in healthy subjects only, not in schizophrenic subjects.

### *Two-Back (Penultimate Trial) Analysis*

This analysis determined whether the saccadic task set two trials back (the penultimate trial) had persistent effects on the latency of the response in the current trial. There were significant main effects for current saccade type, $F(1, 36) = 206.8$, $p < .0001$; prior saccade type, $F(1, 36) = 9.07$, $p < .0026$; and saccade type in the penultimate trial, $F(1, 36) = 6.51$, $p < .012$; all of which were due to longer latencies with antisaccades (see Figure 2). There was a significant interaction between subject group and current saccade type, $F(1, 36) = 23.5$, $p < .0001$, with an exaggerated difference between prosaccades and antisaccades in schizophrenia. As we reported previously (Manoach et al., 2002), there was no interaction between subject group and prior saccade type: Schizophrenic and healthy subjects are similar in the effect of the prior response on the current one, and hence there is no group difference in set switching. However, there was a significant interaction between subject group and penultimate saccade type, $F(1, 36) = 5.79$, $p < .016$. Contrasts showed that this interaction was due to prolongation of the latency in current trials by an antisaccade in the penultimate trial, for schizophrenic ($p < .0006$) but not control subjects.

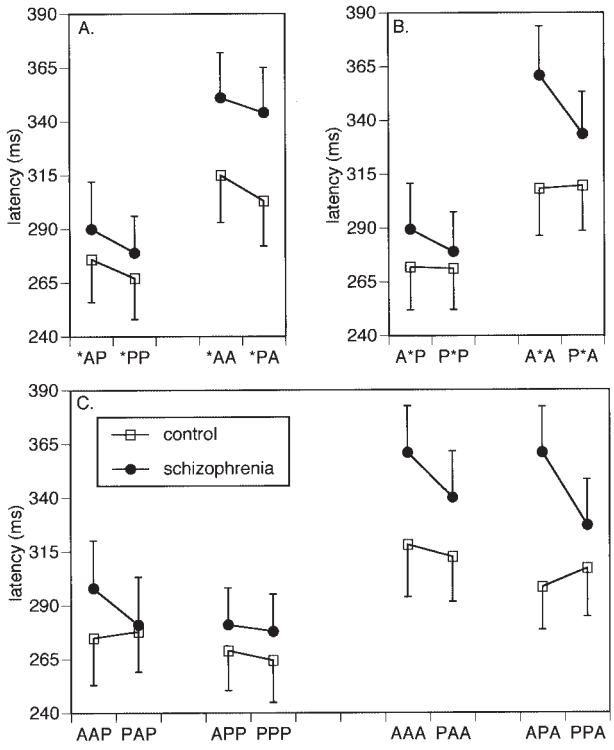


*Figure 2.* Two-back analysis. A: The type of saccade in the preceding trial influences the latency of the saccade in the current trial (regardless of what occurred in the penultimate trial, which is indicated by an asterisk). For example, the data for *AP and *PP indicate that for a current prosaccade, latencies are longer when preceded by an antisaccade (*AP) then when they are preceded by a prosaccade (*PP), for both healthy (open squares) and schizophrenic subjects (solid circles). The same pattern holds for current antisaccades (*AA has longer latencies than *PA). B: The type of saccade in the penultimate trial influences the latency of the saccade in the current trial (regardless of what occurred in the immediately preceding trial, which is indicated by an asterisk). Here an antisaccade in the penultimate trial elevates current prosaccade and antisaccade latencies in schizophrenia only. C: The data from Panels A and B separated into all eight possible saccadic sequences (in a sequence the last, right-most letter indicates the current saccade type). P = prosaccade; A = antisaccade.

Additional findings were a significant interaction between prior saccade type and penultimate saccade type, $F(1, 36) = 28.0$, $p < .0001$, and a three-way interaction between group and prior and penultimate saccade types, $F(1, 36) = 25.6$, $p < .0001$. This appeared to reflect that in schizophrenic subjects, the delay induced by an antisaccade in the penultimate trial was apparent for all sequences except for when it was followed by two prosaccades: a P–P–P sequence did not differ from an A–P–P one. Hence, as long as the system is perturbed by an antisaccade in either the current or prior trial, a delaying effect of a penultimate trial antisaccade emerges in schizophrenic subjects.

In contrast, the ANOVA with group, current saccade type, prior switch, and penultimate switch as factors did not show significant main effects of prior switch or penultimate switch, or a significant interaction of penultimate switch with subject group. Thus the persistent effects of both prior and penultimate trials do not reflect the costs of switching saccadic task sets. Rather, they reflect a persistent effect from recent performance of an antisaccade.

### *Effect of Trial History on Directional Errors*

The variable in this analysis was the frequency of directional perseveration in erroneous responses (i.e., errors that repeat the same direction as the saccade in the prior trial). An ANOVA showed significant interactions between group and saccade type, $F(1, 36) = 5.4$, $p < .03$. Whereas healthy subjects were more likely to make a directionally perseverative error during prosaccade than antisaccade trials ($p < .006$), the likelihood of this type of error was similar for the two types of saccades in schizophrenics. A more significant interaction was between group and prior saccade type, $F(1, 36) = 15.5$, $p < .0002$. Whereas healthy subjects were more likely to perseverate the direction of a prior prosaccade than of a prior antisaccade ($p < .008$), schizophrenics had the opposite tendency, being more likely to perseverate the direction of a prior antisaccade than of a prior prosaccade ($p < .006$) (see Figure 3).

We determined whether the frequency of directional perseveration for any particular sequence of saccadic task sets differed significantly from chance. We first determined if the group means of this variable differed from 0.5. This showed that for healthy subjects, only the rare occurrence of a prosaccadic error following a correct prosaccade had a rate of directional perseveration greater than chance. In schizophrenia, a prior antisaccade caused significant directional perseveration for both prosaccadic and antisaccadic errors in the next trial (see Figure 3).

Our second method used pooled data and binomial proportions to determine whether the rate of directional perseveration in either group for a particular set sequence differed from the expected random rate of 0.5. The results were similar to those of the first method. In healthy subjects a prior prosaccade generated significant directional perseveration in current prosaccadic ($p < .003$) and antisaccadic errors ($p < .034$). In the schizophrenic group, a prior antisaccade generated directional perseveration for both prosaccadic ($p < .014$) and antisaccadic ($p < .002$) errors.

In summary, these data show that whereas healthy subjects tend to repeat the direction of a prior prosaccade in their few errors, schizophrenic subjects have an abnormal tendency to make errors in the direction of a prior antisaccade but not in the direction of a prior prosaccade.

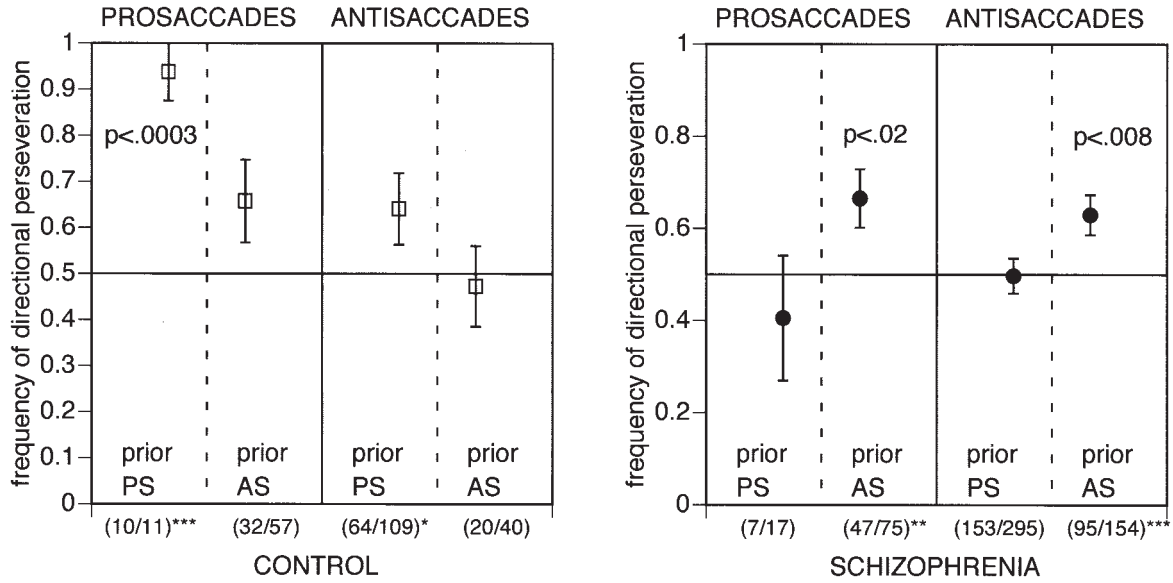


*Figure 3.* Directional perseveration. The mean frequency of directional perseveration (saccadic errors made in the same direction as the saccade in the prior, correctly performed trial) is plotted for each of the four different saccadic sequences. Error bars depict one standard error. Solid horizontal lines mark a frequency of .5, which would indicate no directional effect; *p* values mark means that are significantly different from a frequency of .5 (*t* tests). Numbers in parentheses indicate the number of directional perseverative errors divided by the total number of errors, pooled for each group. Data that are significantly different from .5 by binomial proportions are marked by asterisks. *$p < .05$. **$p < .02$. ***$p < .005$.

## Discussion

We found three significant effects of the prior trial on current saccadic behavior that differentiated schizophrenic from healthy subjects. First, the latency of a current saccade was highly influenced by that of a prior saccade, particularly a prior prosaccade. Whereas the relation between prior and current saccadic latencies was similar in the two subject groups when they performed blocks of all prosaccades or all antisaccades, the more difficult mixed-task blocks were associated with a decline in this correlation in healthy subjects but not in schizophrenic subjects. Second, although an antisaccade task set in the prior trial slowed both prosaccades and antisaccades equally in healthy and schizophrenia subjects (Manoach et al., 2002), only schizophrenic subjects showed a significant delay (≈24 ms) of a current saccadic response by an antisaccade occurring two trials before. Last, schizophrenic subjects were more likely to make errors in the direction of a prior antisaccade, which was not true in healthy subjects. In aggregate, these findings suggest that, although switching at the task-set level is intact in schizophrenic subjects (Barton et al., 2002; Manoach et al., 2002; Meiran, Levine, & Henik, 2000), there is abnormal persistence of the state of the response system, particularly when induced by recent antisaccades, and that this abnormal persistence contributes to perseveration in schizophrenia.

The robust correlations between the latencies of prior and current saccades likely indicate that the preparatory pre-target neural activity in the saccadic response system during one trial carries over into the next. When pre-target activity is greater, the pulse of neural activity generated by the appearance of the target more rapidly reaches the threshold for triggering a saccade, resulting in a shorter latency (Dorris & Munoz, 1998; Everling et al., 1999; Everling & Munoz, 2000). A correlation of prior and current latencies probably reflects an underlying correlation between the pre-target activity of prior and current trials, a form of "immediate neural plasticity" in the saccadic system (Dorris et al., 2000). Stronger latency correlations from prior prosaccades presumably indicate that prosaccades induce more plastic modulation of future pre-target activity than antisaccades.

The key finding from the analysis of the effect of prior-response latency was that the correlations in schizophrenic subjects were normal in single-task blocks but did not decline in the more demanding mixed-task blocks as they did in healthy subjects. Compared with single-task blocks, mixed-task blocks require greater vigilance and working memory (Rogers & Monsell, 1995). We speculate that the decreased correlation in healthy subjects implies that increased processing demands obscure the plastic effects induced by prior saccades. As latency reflects the contribution of multiple cognitive processes, the addition of more processes in a more complex task will lessen the contribution of any one factor. The net result is that any single factor, such as the modulation induced by prior trials, will have less impact on latency in a complex task, resulting in reduced correlations between prior and current latencies. However, schizophrenic subjects fail to show this reduction in correlation with mixed-task blocks. Hence, the plastic effects induced by prior responses in schizophrenia persist excessively in the face of increasing task complexity. Whether this reflects an additional failure to reflect the contingencies of more difficult tasks remains to be determined.

Similarly, the fact that an antisaccade delays saccades two trials later in schizophrenic but not in healthy subjects indicates abnormally persistent inhibition of the response system from even more remote trials. This "penultimate-trial effect" suggests that antisaccadic inhibition of the saccadic response system declines to zero two trials later in healthy subjects but persists in schizophrenic subjects. The result is counterintuitive, as the traditional view of antisaccade performance in schizophrenia is that it is weak, being error-prone and delayed (Broerse, Crawford, & den Boer, 2001). Here an antisaccade, *when correctly performed* (the analysis includes only trials in which the prior responses were correct) has abnormally persistent effects in schizophrenia.

Persistent antisaccade effects on the saccadic response system may also account for the abnormal directional perseveration of antisaccades in the errors of schizophrenic subjects. Whereas the penultimate-trial effect shows persistence of generalized inhibition from a prior antisaccade task set, directional perseveration suggests persistence of a directionally specific excitation at the level of the antisaccadic response. This may lead to elevated pre-target activity in the direction of the prior saccade and decreased pre-target activity in the other direction, an effect shown previously for prosaccades (Dorris et al., 2000). As shown in prior studies, elevated pre-target activity correlates with increased error rate (Everling & Munoz, 2000). In our case, this would result in congruent errors being more frequent than incongruent ones.

Our distinction between antisaccadic effects on the state of the response system (response-system plasticity) and effects on task sets echoes older taxonomies of perseverative behavior (Goldberg, 1986; Sandson & Albert, 1984). These distinguish between "stuck in set" or "activity" perseveration and "recurrent" or "feature/element" perseveration. In the feature/element perseveration there is an ". . .unintentional repetition, after cessation, of a previously emitted response to a subsequent stimulus" (Goldberg, 1986). This would be conceptually similar to our hypothesis that what persists excessively from trial to trial in schizophrenia is the state of the saccadic response system, not the inhibition between saccadic task sets. We include in these response-system effects not only directionally specific activation, accounting for the perseverated errors, but directionally nonspecific depression by antisaccades, accounting for the persistent prolongation of latencies following antisaccade trials.

The persistence of these effects from recent trials also is reminiscent of older theories of behavior in schizophrenia. The immediacy hypothesis postulated that schizophrenic subjects are more influenced by temporally contiguous events, and it was invoked to explain differences in schizophrenic speech, including the tendency to verbal perseveration (Salzinger, 1971). Others have pointed out that the same verbal data fit with the "neuronal trace model" (Zubin, 1975), which suggested that "facilitatory and inhibitory neural traces have greater duration in schizophrenics than normals" (Nuechterlein, 1977). The key data for the neural trace model came from switching studies in which subjects had to respond to either a light or a sound (Nuechterlein, 1977; Sutton, Hakerem, Zubin, & Portnoy, 1961; Waldbaum, Sutton, & Kerr, 1975). Unlike our work, in which stimuli are identical but the response must be switched, these involved a cross-modal (visual/auditory) switch between stimuli to which identical responses were made. These studies showed that schizophrenic subjects had a greater increase in reaction time (about 20 ms) than did healthy

subjects when stimuli changed across modalities. This was attributed to "summation of brief memory traces for prior *stimuli* [that] persist longer in the case of schizophrenics" (Zubin, 1975). In our study, where response mappings rather than stimuli are changed, we find that it is summation of brief memory traces for prior responses that is exaggerated in schizophrenia. As such, our work provides an ocular motor parallel to the older sensory switch studies, also indicating an abnormal persistence of prior neural activity.

Persistent antisaccadic latency and accuracy effects in schizophrenia also have implications for how psychologists conceptualize the antisaccadic defect in these subjects. The hallmarks of schizophrenic antisaccadic performance are increased error rates and prolonged latencies (e.g., Broerse et al., 2001; Manoach et al., 2002). These abnormalities cannot be explained as exaggeration of the effects of normal pre-target activity in areas like the frontal eye field and superior colliculus. Increases in such pre-target activity are associated with more errors but also with shorter antisaccade latencies (Everling et al., 1999; Everling & Munoz, 2000), hence providing a physiological basis for speed–accuracy trade-off. To account for both increased errors and increased latency in schizophrenia, one may postulate one of two hypothetical defects. One is weak generation of the novel antisaccade command. This would lead to prolonged latency, and this might provide more opportunity for an erroneous prosaccade signal to escape suppression and reach threshold, thereby increasing errors. The other is a failure to suppress reflexive errors. To overcome the reflex to look at the target, schizophrenics may need an overly strong antisaccadic response pattern, which would excessively depress pre-target activity and thus prolong the latencies of correct antisaccades. The enduring influences of recent antisaccades in the present study are consistent with the latter hypothesis. Because they have more trouble suppressing reflexive errors, schizophrenics need a very strong pattern of antisaccadic activity to make a correct antisaccade. Both the non-directional inhibition and the directionally specific activation in this pattern may then persist abnormally, with the former elevating saccadic latencies two trials later and the latter causing perseverative directional errors. A stronger carryover effect from prior trials makes it harder to respond to the demands of the current trial: hence the perseverative directional errors and also the higher latency–latency correlations when the difficult conditions of the mixed-task blocks should have weakened historical influences, as they do in healthy subjects.

In summary, instead of a deficit in switching between task sets, we find that schizophrenic subjects show abnormally persistent plasticity effects in the saccadic-response system. This is manifested in increased correlations between the latencies of prior and current trials and enduring inhibition from preceding antisaccadic task sets on future saccades of all types. We also found that the direction of a prior correct antisaccade tends to be abnormally perseverated when an error is made in the next trial, indicating perseveration of specific responses rather than perseveration of task sets. We believe that these findings may reflect a failure of current task demands to "overwrite" the plastic changes induced in the saccadic response system by prior trials, in particular allowing strong antisaccadic effects to continue to exert influence on saccadic responses.

## References


Allport, A., Styles, E., & Hsieh, S. (1994). Shifting intentional set: Exploring the dynamic control of tasks. In C. Umiltà & M. Moscovitch (Eds.), *Attention and Performance XV* (pp. 421–452). Hillsdale, NJ: Erlbaum.

Arbuthnott, K., & Frank, J. (2000). Executive control in set switching: Residual switch cost and task-set inhibition. *Canadian Journal of Experimental Psychology, 54,* 33–41.

Arbuthnott, K., & Woodward, T. S. (2002). The influence of cue-task association and location on switch cost and alternating-switch cost. *Canadian Journal of Experimental Psychology, 56,* 18–29.

Bahill, T., & McDonald, J. (1983). Frequency limitations and optimal step size for the two-point central difference derivative algorithm with applications to human eye movement data. *IEEE Transactions on Biomedical Engineering, 30,* 191–194.

Barton, J., Cherkasova, M., Lindgren, K., Goff, D., Intriligator, J., & Manoach, D. (2002). Antisaccades and task-shifting: Studies of control processes in saccadic function in normal subjects and schizophrenia. *Annals of the New York Academy of Sciences, 956,* 250–263.

Braff, D. L., Heaton, R., Kuck, J., Cullum, M., Moranville, J., Grant, I., & Zisook, S. (1991). The generalized pattern of neuropsychological deficits in outpatients with chronic schizophrenia with heterogeneous Wisconsin Card Sorting Test results. *Archives of General Psychiatry, 48,* 891–898.

Broerse, A., Crawford, T., & den Boer, J. (2001). Parsing cognition in schizophrenia using saccadic eye movements: A selective overview. *Neuropsychologia, 39,* 742–756.

Cherkasova, M., Manoach, D., Intriligator, J., & Barton, J. (2002). Antisaccades and task-shifting: Interactions in controlled processing. *Experimental Brain Research, 144,* 528–537.

Cohen, J., & Servan-Schreiber, D. (1992). Context, cortex, and dopamine: A connectionist approach to behavior and biology in schizophrenia. *Psychology Review, 99,* 45–77.

Crider, A. (1997). Perseveration in schizophrenia. *Schizophrenia Bulletin, 23,* 63–74.

Dorris, M., & Munoz, D. (1998). Saccadic probability influences motor preparation signals and time to saccadic inhibition. *Journal of Neuroscience, 18,* 7015–7026.

Dorris, M., Paré, M., & Munoz, D. (2000). Immediate neural plasticity shapes motor performance. *Journal of Neuroscience, 20,* RC52.

Everling, S., Dorris, M. C., Klein, R. M., & Munoz, D. P. (1999). Role of primate superior colliculus in preparation and execution of antisaccades and prosaccades. *Journal of Neuroscience, 19,* 2740–2754.

Everling, S., & Munoz, D. P. (2000). Neuronal correlates for preparatory set associated with prosaccades and antisaccades in the primate frontal eye field. *Journal of Neuroscience, 20,* 387–400.

First, M., Spitzer, R., Gibbon, M., & Williams, J. (1997). *Structured Clinical Interview for DSM–IV Axis I Disorders, Research Version, Patient Edition with Psychotic Screen (SCID-I/P W/PSY SCREEN*). New York: Biometrics Research, New York State Psychiatric Institute.

Freeman, T., & Gathercole, C. (1966). Perseveration—the clinical symptoms—in chronic schizophrenia and organic dementia. *British Journal Psychiatry, 112,* 27–32.

Gold, J., Carpenter, C., Randolph, C., Goldberg, T. E., &Weinberger, D. R. (1997). Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Archives of General Psychiatry, 54,* 159–165.

Goldberg, E. (1986). Varieties of perseveration: A comparison of two taxonomies. *Journal of Clinical Experimental Neuropsychology, 8,* 710–726.

Hollingshead, A. (1965). *Two factor index of social position.* New Haven, CT: Yale University Press.

Kay, S., Fiszbein, A., & Opler, L. (1987). The positive and negative

syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13,* 261–276.

Manoach, D. S., Lindgren, K. A., Cherkasova, M. V., Goff, D. C., Halpern, E. F., Intriligator, J., & Barton, J. J. S. (2002). Schizophrenic subjects show deficient inhibition but intact task-switching on saccadic tasks. *Biological Psychiatry, 51,* 816–825.

Meiran, N. (1996). Reconfiguration of processing mode prior to task performance. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 22,* 1423–1442.

Meiran, N., Chorev, Z., & Sapir, A. (2000). Component processes in task switching. *Cognitive Psychology, 41,* 211–253.

Meiran, N., Levine, J., & Henik, A. (2000). Task set switching in schizophrenia. *Neuropsychology, 14,* 471–482.

Monsell, S., Yeung, N., & Azuma, R. (2000). Reconfiguration of task-set: Is it easier to switch to the weaker task? *Psychological Research, 63,* 250–264.

Nuechterlein, K. (1977). Reaction time and attention in schizophrenia: A critical evaluation of the data and theories. *Schizophrenia Bulletin, 3,* 27–35

Overall, J., & Gorham, D. (1962). The brief psychiatric rating scale. *Psychological Reports, 10,* 799–812.

Perry, W., & Braff, D. (1998). A multimethod approach to assessing perseverations in schizophrenia patients. *Schizophrenia Research, 33,* 69–77.

Rogers, X., & Monsell, S. (1995). Costs of a predictable switch between simple cognitive tasks. *Journal of Experimental Psychology: General, 124,* 207–231.

Rushworth, M., Passingham, R., & Nobre, A. (2002). Components of switching intentional set. *Journal of Cognitive Neuroscience, 14,* 1139–1150.

Salzinger, K. (1971). An hypothesis about schizophrenic behavior. *American Journal of Psychotherapy, 25,* 601–614.

Sandson, J., & Albert, M. (1984). Varieties of perseveration. *Neuropsychologia, 22,* 715–732.

Smith, G., Large, M., Kavanagh, D., Karayanidis, F., Barrett, N. A., Michie, P. T., & O'Sullivan, B. T. (1998). Further evidence for a deficit in switching attention in schizophrenia. *Journal of Abnormal Psychology, 107,* 390–398.

Sohn, M.-H., & Carlson, R. (2000). Effects of repetition and foreknowledge in task-set reconfiguration. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 26,* 1445–1460.

Sullivan, E. V., Mathalon, D. H., Zipursky, R. B., Kersteen-Tucker, Z., Knight, R. T., & Pfefferbaum, A. (1993). Factors of the Wisconsin Card Sorting Test as measures of frontal-lobe function in schizophrenia and in chronic alcoholism. *Psychiatry Research, 46,* 175–199.

Sutton, S., Hakerem, G., Zubin, J., & Portnoy, M. (1961). The effect of shift of sensory modality on serial reaction-time: A comparison of schizophrenics and normals. *American Journal of Psychology, 74,* 224–232.

Tornay, F. J., & Milan, E. G. (2001). A more complete task-set reconfiguration in random than in predictable task switch. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology, 54*(A), 785–803.

Waldbaum, J., Sutton, S., & Kerr, J. (1975). Shift of sensory modality and reaction time in schizophrenia. In M. Kietzman, S. Sutton, & J. Zubin (Eds.), *Experimental approaches to psychopathology* (pp. 167–176). New York: Academic Press.

Wylie, G., & Allport, A. (2000). Task switching and the measurement of "switch costs". *Psychological Research, 63,* 212–233.

Zubin, J. (1975). Problem of attention in schizophrenia. In M. Kietzman, S. Sutton, & J. Zubin (Eds.), *Experimental approaches to psychopathology* (pp. 139–165). New York: Academic Press.

Received October 8, 2003
Revision received April 1, 2004
Accepted April 2, 2004 ■