Schizophrenic Subjects Show Deficient Inhibition but Intact Task Switching on Saccadic Tasks

Dara S. Manoach, Kristen A. Lindgren, Mariya V. Cherkasova, Donald C. Goff, Elkan F. Halpern, James Intriligator, and Jason J.S. Barton

Background: *Schizophrenic patients have executive function deficits, presumably on the basis of prefrontal cortex dysfunction. Although they consistently show impaired inhibition, the evidence of a task switching deficit is less consistent and is often based on performance of neuropsychological tests that require several cognitive processes (e.g., the Wisconsin Card Sort Test [WCST]). We investigated inhibition and task switching using saccadic tasks to determine whether schizophrenic patients have selective impairments of these executive functions.*

Methods: *Sixteen normal and 21 schizophrenic subjects performed blocks of randomly mixed prosaccade and antisaccade trials. This gave rise to four trial types: prosaccades and antisaccades that were either repeated or switched. Response accuracy and latency were measured. Schizophrenic subjects also performed the WCST.*

Results: *Schizophrenic subjects showed abnormal antisaccade and WCST performance. In contrast, task switching was normal and unrelated to either antisaccade or WCST performance.*

Conclusions: *The finding of intact task switching performance that is unrelated to other measures of executive function demonstrates selective rather than general impairments of executive functions in schizophrenia. The findings also suggest that abnormal WCST performance is unlikely to be a consequence of deficient task switching. We hypothesize that inhibition and task switching are mediated by distinct neural networks, only one of which is dysfunctional in schizophrenia.* Biol Psychiatry 2002;51: 816–826 © *2002 Society of Biological Psychiatry*

Key Words: Antisaccades, schizophrenia, prefrontal cortex, executive function, task switching, inhibition

Introduction

Executive functions are cognitive abilities that enable flexible rather than reflexive responses to the environment. They play a critical role in normal adaptive human behavior. The prefrontal cortex is thought to play a pivotal role in mediating executive functions on the bases of studies of subjects with frontal brain damage (Stuss and Benson 1984) and of neuroimaging studies (Carter et al 2000; Dove et al 2000; Garavan et al 2000; MacDonald et al 2000). Prefrontal cortex dysfunction likely contributes to the executive function deficits found in schizophrenia.

Within the prefrontal cortex, it is not clear whether all executive functions are mediated by a single supervisory attentional system (Norman and Shallice 1986) or by multiple distinct anatomical networks (Stuss et al 1995). If executive functions are discretely organized within the prefrontal cortex, they may be differentially affected by diseases such as schizophrenia. Conversely, finding selective impairments of executive function in schizophrenia would argue against a single supervisory attentional system. In addition, the pattern of dysfunction in schizophrenia may implicate specific neural circuitry and aid investigations of neuropathology.

In the present article, we investigated two different executive functions—inhibition and task switching—to determine whether schizophrenic subjects show selective impairments. Inhibition is the ability to suppress automatic or prepotent responses. Schizophrenic subjects consistently show deficits on tasks requiring inhibition, such as the Stroop interference paradigm (Barch et al 1999) and the antisaccade task (Levy et al 1998).

Task switching refers to moving flexibly from one behavior to another in response to changing environmental contingencies. Clinical observations of perseveration suggest that schizophrenics have deficient task switching function, but the presence of a task switching deficit is not well-established empirically. Although one recent study failed to find deficits (Cools et al 2000), several studies showed defective task switching (Elliott et al 1995; Smith et al 1998). Defective task switching is also presumed on the basis of performance of standard neuropsychological

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instruments, such as the Wisconsin Card Sort Test (WCST; Braff et al 1991; Perry and Braff 1998), the most commonly used measure of executive function in schizophrenia (Green 1998). Neuropsychological instruments are, however, often multidimensional; they require more than one cognitive process for successful performance. Poor performance on the WCST, for example, can reflect problems in sustained attention, concept formation, or working memory as well as task switching (Gold et al 1997; Smith et al 1998; Sullivan et al 1993). Therefore, poor performance cannot be definitively attributed to a task switching deficit.

We measured task switching and inhibition during saccadic tasks to determine whether schizophrenic subjects show selective impairments in executive function. Schizophrenic and normal comparison subjects performed trials requiring either prosaccades or antisaccades. During prosaccade trials subjects were instructed to look toward a suddenly appearing target. During antisaccade trials subjects they were instructed to look in the opposite direction. Whereas prosaccades are a prepotent, relatively automatic response, antisaccades require inhibition of the prosaccade and the generation of the novel behavior of looking *away* from a target.

In addition to presenting blocks of trials of a single task, as most antisaccade studies do, we presented prosaccade and antisaccade trials in a randomly mixed sequence. These mixed blocks resulted in two types of trials for each task: those that were repeated, in other words preceded by the same task (e.g., an antisaccade preceded by an antisaccade) and those that were switched or preceded by the other task (e.g., an antisaccade preceded by a prosaccade). Because both inhibition and task switching were measured during the same task blocks, the demands on other nonspecific functions, such as sustained attention, were equal. In addition, the stimuli (with the exception of the task prompt) and required motor responses were identical for all trial types (repeated and switched, prosaccades and antisaccades). This design allowed us to isolate the costs of antisaccade, task switching, and also of combining both functions for a single response (switched antisaccade). Our dependent measures were directional accuracy and the latencies of correct saccades.

We expected that our findings would replicate the numerous reports of antisaccade deficits in schizophrenia (Levy et al 1998). Our primary goal was to determine whether schizophrenic subjects also have task switching deficits, a point that is less well established. We had three additional goals.

First, we examined the interaction of inhibition and task switching when both functions were combined for a single response. If the two functions are independent, their combined effect on accuracy should be multiplicative. That is, the probability of success on a combined trial should be the product of the probabilities of a correct response for each function alone (Schweickert 1985). (Consider a coin toss, where the probability of obtaining heads twice ($p = .25$) equals the product of the probability of getting heads on each of the two single tosses [0.5×0.5].) This is the result we obtained in a prior study of normal subjects (Cherkasova et al, in press). For latency, if the functions are performed serially, the latency cost when the two tasks are combined should equal the sum of the latency costs of each process performed alone (Schweickert 1985). We hypothesized that prefrontal dysfunction in schizophrenia might reduce the processing resources available to coordinate the performance of two executive functions for a single response and cause disproportionate increases in accuracy and latency costs relative to normal subjects (Granholm et al 1991).

Second, we examined the relations of inhibition and task switching costs when each function was performed independently. In schizophrenia, correlated deficiencies in inhibition and task switching would be consistent with a single dysfunctional control system mediating both executive functions. In contrast, selectively impaired and uncorrelated performance would suggest separate executive control systems.

Third, to relate our results to previous studies that suggested task switching deficits on the basis of standard neuropsychological tests, we compared task switching costs to WCST performance in the schizophrenic group. If deficient task switching is responsible for poor performance on the WCST, WCST parameters should correlate with our task-switch costs.

Methods and Materials

Subjects

Schizophrenic outpatients were recruited from an urban mental health center. They had been maintained on stable doses of antipsychotic medications for at least 6 weeks (15 subjects on atypical and 6 on conventional agents). Diagnoses were confirmed with Structured Clinical Interviews for DSM-IV (First et al 1997). Clinical status was characterized with the Positive and Negative Syndrome Scale (PANSS; Kay et al 1987) and the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). Movement abnormalities were characterized with the Abnormal Involuntary Movement Scale (National Institute of Mental Health 1974) and the Simpson-Angus Rating Scale (Simpson and Angus 1970). Healthy control subjects, without a history of psychiatric illness, were recruited from the hospital community. All subjects were screened to exclude substance abuse or dependence within the preceding 6 months and any independent conditions that might affect brain function. Two schizophrenic and four normal subjects did not complete the protocol, because they could not tolerate the contact lens. The data from one

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

Subject characteristics	Normal subjects (n = 16)	Schizophrenic subjects (n = 21)	t	p	Level of severity
Age (y)	40.3 ± 8.7	43.7 ± 8.0	1.22	.23	—
Gender (M/F)	11M/5F	17M/4F	Phi = .14	.46	—
Laterality score (handedness)	63.8 ± 57.2	71.0 ± 52.6	.40	.69	—
Education (y)	18.3 ± 4.3	12.4 ± 2.9	5.03	<.0001[a]	—
Estimated verbal IQ	108.2 ± 13.3	98.4 ± 14.8	2.06	.05[a]	—
Parental SES[b]	2.1 ± 1.3	2.8 ± 1.3	z = 1.43	.15	—
Age of onset (y)	—	27.7 ± 9.3	—	—	—
Length of illness (y)	—	16.1 ± 10.3	—	—	—
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

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.

IQ, intelligence quotient; SES, socioeconomic status; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Symptom Scale; SANS, Scale for the Assessment of Negative Symptoms; AIMS, Abnormal Involuntary Movement Scale.

[a]Significant at $p \leq .05$.

[b]A lower score denotes higher status.

schizophrenic subject who completed the protocol were excluded owing to a greater than 50% error rate on blocked antisaccade trials, which limited the data available to calculate latency effects. The final sample size was 21 schizophrenic subjects and 16 normal control subjects (Table 1). Seventeen schizophrenic and 11 normal subjects were strongly right-handed, as determined by a laterality score of 70 or above on the modified Edinburgh Handedness Inventory (White and Ashton 1976). Subject groups did not differ in age, gender, handedness or parental socioeconomic status as determined by the Hollingshead Index (Hollingshead 1965). Normal subjects had significantly more years of education and higher verbal intelligence quotient estimates, based on a test of single-word reading (American National Adult Reading Test; Blair and Spreen 1989). The study was approved by the Committee on Clinical Investigations of Beth Isreal Deaconess Medical Center. All subjects gave written informed consent after the experimental procedures had been fully explained.

Eye Movement Apparatus and Protocol

We recorded eye movements with a magnetic search coil technique, using a scleral contact lens and a 3-foot field coil (Crist Instruments, Bethesda, MD). The subject's head was secured in a chin rest with the cornea 81 cm away from a tangent screen. Displays were generated by a Power Macintosh 9600/233 (Apple, Cupertino, CA), using programs written in C++ on the Vision Shell PPC (Watertown, MA) programming platform (available at www.kagi.com/visionshell), and back-projected with an Eiki LC-7000 units LCD-projector (Eiki International Inc., Lake Forest, CA). The lens was placed in the left eye. The system was calibrated by having the subject sequentially fixate nine targets in a square grid spanning 50 degrees. Twelve data points were collected at each of the target locations, and a regression method was used to find the best linear fit. Eye position was digitized at 500 samples/sec. A five-point central difference algorithm (Bahill and McDonald 1983) was used to derive velocity from eye position.

The initial stimulus presentation display consisted of a dark background with a white fixation ring at center, of 1.0° diameter and luminance of 20 candela (cd)/M^2 (see Figure 1). The fixation ring was flanked by two dots of 0.7° diameter and equal luminance placed 20° right and left of center. These two peripheral dots were visible in each trial until obscured by a

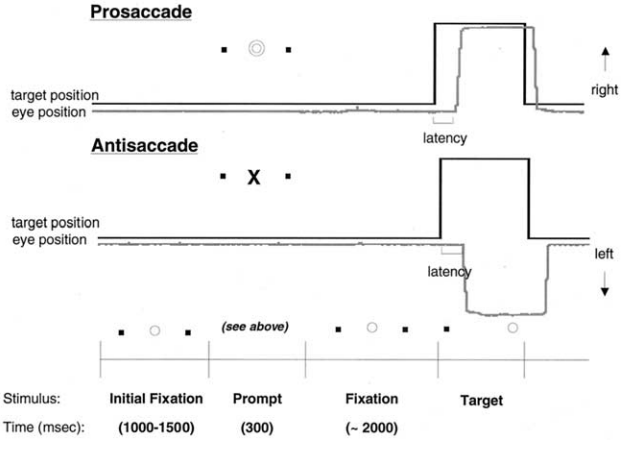

Figure 1. Saccadic tasks. Illustration of target position and eye position during correct performance of the prosaccade and antisaccade tasks. A central fixation ring is flanked by two peripheral dots that remain visible until obscured by a target. This is followed by the appearance of a prompt that indicates the task type (yellow "O" for prosaccades, blue "X" for antisaccades). Following a second fixation phase, the central ring disappears and appears as the target on either the right or left side. When the subject's eye reaches the correct position, the ring returns to the center. The next trial begins when the subject refixates the central ring.

target. The subject was required to look at the central fixation point and each trial began when a subject's eye fell within 3 degrees of the fixation point. After a period randomly varying between 1 and 1.5 sec, the fixation point was replaced by one of two symbols. A yellow "O" with a surrounding ring of 4.5° diameter was the prompt for a prosaccade, and a blue "X" spanning 4.5° was the prompt for an antisaccade. Prompts lasted 300 msec and were then replaced by the white fixation ring. After a mean interval of 2 sec the fixation ring disappeared, and a similar ring appeared around one of the two peripheral dots, the side randomly determined. This was the cue for the subject to make their saccade as quickly and accurately as possible. The white ring remained in the peripheral location until either the subject's eye had fallen within 3° of the desired end position or 10 sec had passed, at which time it returned to the central fixation point for the next trial.

Single-task blocks had 26 trials, either all prosaccades or all antisaccades. Mixed-task blocks consisted of 52 trials of prosaccades and antisaccades presented in random order. The trials from mixed-task blocks were classified as either repeated or switched trials (e.g., preceded by the same type of task or not). Each block was repeated four times, generating about 104 trials of each of six trial types: Blocked (from single-task blocks), Repeated, and Switched trials of both prosaccades and antisaccades. A second division of mixed-task trials is also possible, based upon not only what was required but also what was actually performed in the preceding trial. In this analysis we included only those trials that were preceded by trials with directionally correct responses. Our results with this second type of analysis were similar to those of the first analysis. Only the data from the first analysis are described in the results.

Before testing, the tasks were explained to each subject, and they were informed that they would receive a monetary bonus for each correct response. The incentive was intended to mitigate potential motivational deficits in the schizophrenic subjects. Subjects performed practice blocks of 20 trials for each of the three different types of blocks (prosaccade only, antisaccade only, and mixed-task). Experimental blocks were presented in a counterbalanced order to mitigate the effects of learning and fatigue. All subjects began with one single-task block—half began with prosaccades, half with antisaccades—followed by the other type of single-task block, followed by one mixed-task block. The order of the three tasks was then reversed. The entire sequence of six blocks was repeated for a total of 12 blocks. Short rests were provided between blocks.

Scoring of Eye Movement Protocols

We identified saccades as eye movements with velocities exceeding 46.9°/sec. The onset of a saccade was defined as the point at which the velocity of the eye first exceeded 31.3°/sec, and the end of a saccade was the point where the eye's velocity fell below this baseline. For each saccade, we recorded directional accuracy with respect to the required response and latency from target onset for the directionally correct responses only. The first saccade of each block was eliminated from analysis.

Wisconsin Card Sort Test

Schizophrenic subjects were tested with a standardized computerized administration of 128 cards of the WCST (© 1991 by CyberMetrics Testing Services, Riderwood, MD). One subject was missing data. The WCST requires subjects to match each card in a deck to one of four target cards, on the basis of one of three sorting rules (color, shape, or number). Subjects are not told how to match the cards, but must figure out the sorting rule on the basis of feedback. After ten consecutive correct sorts, the sorting rule changes without warning and the new rule must be learned. To succeed on the task, the subject must *attain* the concept (sorting rule), *maintain* this concept for 10 sorts, and then *switch* the concept when the rule changes (Green 1998). The test yielded 11 possible interrelated outcome variables for each subject (Heaton et al 1993). We characterized performance as total errors, which is the number of responses that do not match the sorting principle in effect, and perseverative errors, which are those in which the subject persists in responding to the previously reinforced but incorrect sorting principle (e.g., a failure to switch). Perseverative errors on the WCST are characteristic of individuals with frontal lobe lesions and schizophrenia and most clearly discriminate schizophrenic subjects from normal subjects (Blanchard and Neale 1994; Sullivan et al 1993).

Data Analysis

ACCURACY AND LATENCY. Because most studies present prosaccade and antisaccade trials in single-task blocks, we first investigated whether the randomized presentation of prosaccade and antisaccade trials during mixed-task blocks resulted in increased errors and latencies. One might expect this to be the case on the basis of increased requirements for vigilance and working memory (Rogers and Monsell 1995). We compared trials from the single-task blocks to repeated trials of the same task from the mixed-task blocks (i.e., "mixed-list cost" [Meiran 2000]). We analyzed percent errors with repeated measures analysis of variance (ANOVA) with a between-group factor (normal vs. schizophrenia) and Task (prosaccade vs. antisaccade) and Block Type (single-task vs. mixed-task, repeated trials) as repeated measures. Latencies for correct trials were analyzed with randomized block ANOVA with Group, Task, and Block Type as factors and with subjects nested within group as the random factor. Pairwise comparisons were evaluated with contrasts.

Our primary goal was to investigate the effects of antisaccades and task switching on percent errors and latencies. These analyses were based on the trials from the mixed-task blocks. They were identical to those described above but simply substituted the factor Condition (repeated vs. switched) for Block Type.

INTERACTIONS OF ANTISACCADE AND TASK-SWITCHING. We first examined the effects of combining an antisaccade and task-switch on accuracy rates. If antisaccades and task switching are independent, the probability of a correct response when both are performed in a single trial (switched antisaccade) should equal the product of the probabilities of correct perfor-

Table 2. Formulas Used in the Analyses Examining the Interactions and Relations of Antisaccade and Task Switching Performance

Condition	Task: PS	Task: AS
Repeated	PS_R	AS_R
Switched	PS_S	AS_S

Logarithms of accuracy rates: Combined AS & T-S:	Error and latency costs: Combined AS & T-S:
$\log (AS_S/PS_R)$	$AS_S - PS_R$
Antisaccade alone:	Antisaccade alone:
$\log (AS_R/PS_R)$	$AS_R - PS_R$
Task switch alone:	Task switch alone:
$\log (PS_S/PS_R)$	$PS_S - PS_R$
	(Task switch cost for AS: $AS_S - AS_R$)

Baseline: PS_R.
PS, prosaccade; AS, antisaccade; T-S, task switch; R, repeated, S, switched.

mance of each alone (a multiplicative relation). To isolate the effects of each executive function, the baseline accuracy rate must be removed. We used the accuracy rate of repeated prosaccades as the baseline, because they require neither an antisaccade nor a task-switch. The simplest expression of this hypothesized multiplicative relation is in terms of the logarithms of the accuracy rates: log (switched antisaccade/repeated prosaccade) = log (repeated antisaccade/repeated prosaccade) + log (switched prosaccade/repeated prosaccade) (Schweickert 1985) (Table 2). We examined how well the predicted value for switched antisaccades matched the observed value to determine if accuracy obeyed a multiplicative rule. We first compared the means of the logs of observed values to those of the predicted values using *t* tests. We also used linear regression with the log of the combined accuracy rate as the dependent variable and the sum of the logs of the antisaccade and task switch accuracy rates as the independent variable and tested for departures from an intercept of zero and a slope of one.

We next examined the interaction of antisaccade and task switching latency costs. The costs of executive functions are usually measured as differences in error rate and latency. We isolated executive function costs by subtracting the baseline performance (repeated prosaccades) from each of the other trial types (Table 2). We isolated the antisaccade cost by subtracting the baseline from repeated antisaccades; the task switch cost by subtracting the baseline from switched prosaccades; and the combined cost by subtracting the baseline from switched antisaccades, which involve both an antisaccade and a task switch. If two tasks are performed serially, then the latency cost of combined performance should equal the sum of the latency costs of each task performed alone.

RELATIONS BETWEEN COSTS. Finally, Pearson correlations were used to describe the relations between performance costs (both accuracy, as measured by percent errors, and latency)

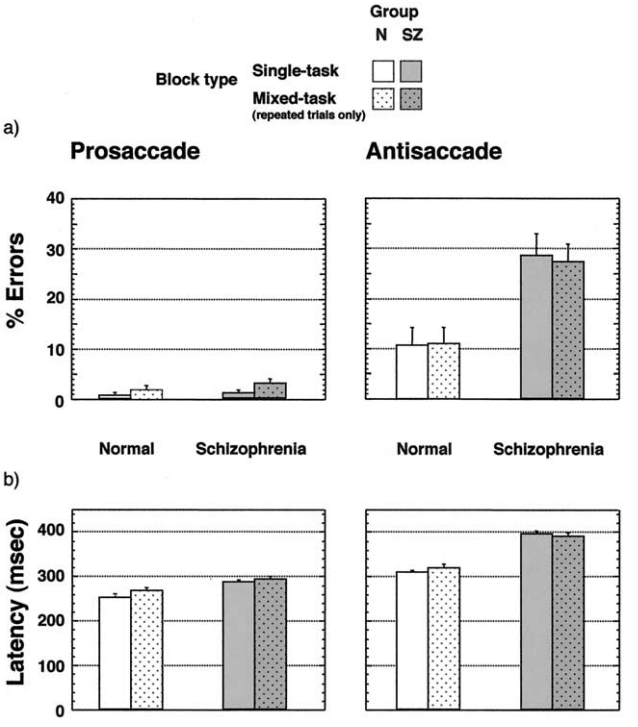

Figure 2. Bar graphs of performance in single-task versus mixed-task blocks (repeated trials), as measured by **(a)** percent errors and **(b)** latency with standard error bars. The graphs are divided by task, group, and block type (single-task vs. mixed-task). N, normal control subjects; SZ, schizophrenic patients.

when each executive function was performed independently. A statistic was considered to be significant if its exact two-tailed probability value was $\leq .05$.

Results

Mixed-List Costs: Single-Task versus Mixed-Task Repeated Trials

Subjects did not perform significantly worse on repeated trials in the mixed task blocks versus trials in the single-task blocks [main effect of Block Type: [accuracy $F(1,35) = .55$, $p = .46$; latency $F(1,35) = 2.26$, $p = .13$] (Figure 2). Block Type did not interact with Task [accuracy $F(1,35) = 2.14$, $p = .15$; latency $F(1,35) = 1.47$, $p = .23$], suggesting that it did not differentially affect performance for prosaccades and antisaccades. More importantly, the groups were not differentially affected by Block Type, as there were no significant interactions of Group with Block Type [accuracy $F(1,35) = .11$, $p = .75$; latency $F(1,35) = 1.70$, $p = .19$] or with Block Type and Task [accuracy $F(1,35) = .64$, $p = .43$; latency $F(1,35) = .08$, $p = .78$]. In summary, the presentation of trials in mixed versus single-task blocks did not significantly affect

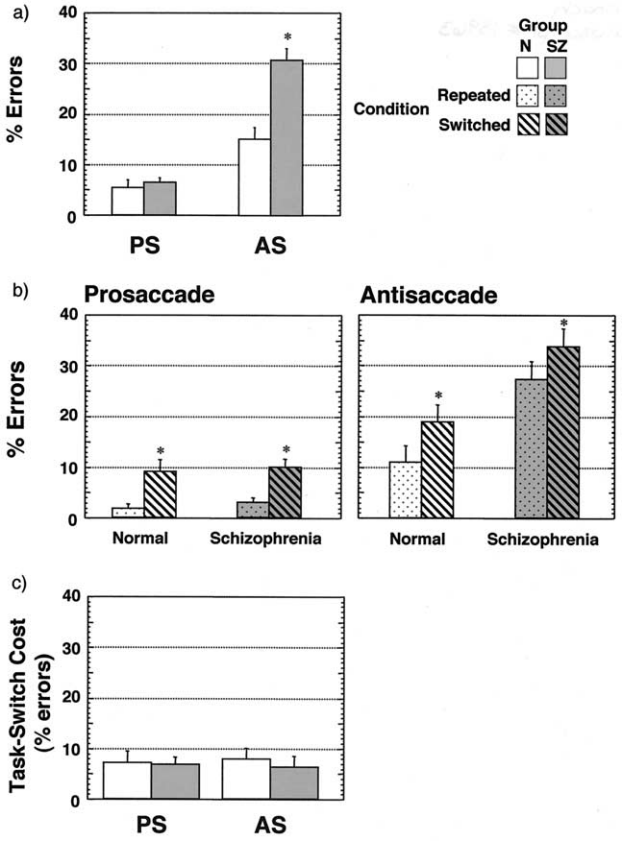

Figure 3. Bar graphs of accuracy, as measured by percent errors **(a)** collapsed across condition (repeated vs. switched) and **(b)** separated by condition; and **(c)** isolated task switch costs for prosaccades and antisaccades. An asterisk indicates that the comparison between adjacent bars is significant at $p \leq .05$. PS, prosaccade; AS, antisaccade; N, normal control subjects; SZ, schizophrenic patients.

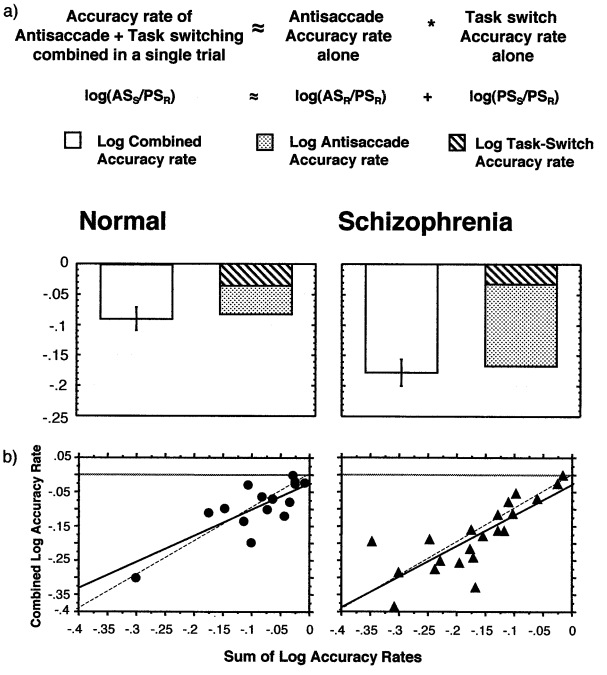

Figure 4. The interaction of antisaccade and task switch accuracy rates. (**a**) Bar graphs comparing the combined (switched antisaccade) log accuracy rate to the sum of the logs of antisaccade and task-switch accuracy rates in the normal and schizophrenic groups. Greater values indicate more accurate performance. AS_S, switched antisaccade; AS_R, repeated antisaccade; PS_R, repeated prosaccade; PS_S, switched prosaccade. (**b**) Linear regressions of accuracy rates. Scatter plots illustrating the relation of the logs of the combined and summed accuracy rates for the normal and schizophrenic groups. The slopes and intercepts of the regression lines do not differ significantly from the line of agreement, which is represented by a dotted line. Circles represent normal control subjects and triangles represent schizophrenic subjects.

performance. All subsequent analyses were conducted on trials from the mixed-task blocks only.

Accuracy (Mixed-Task Blocks)

ANTISACCADE. See Figure 3a. The performance of antisaccades was significantly less accurate than that of prosaccades [Task main effect: $F(1,35) = 58.49$, $p < .001$]. Schizophrenic subjects were less accurate than normal subjects [Group main effect: $F(1,35) = 10.73$, $p = .002$] and, as predicted, there was a significant Group-by-Task interaction [$F(1,35) = 11.06$, $p = .002$]. Schizophrenic subjects did not differ from normal subjects in the accuracy of prosaccades [$t(35) = .59$, $p = .56$] but made more errors on antisaccades [$t(35) = 4.57$, $p \leq .0001$].

TASK SWITCHING. See Figure 3b. Switched trials were significantly less accurate than repeated trials [Condition main effect: $F(1,35) = 34.81$, $p < .0001$]. The interaction of Task and Condition was not significant, suggesting that the task switching did not differentially affect the accuracy of prosaccades and antisaccades [$F(1,35) = .006$, $p = .94$]. Moreover, there were no group differences in the accuracy of task switching. Group did not interact with Condition [$F(1,35) = .04$, $p = .84$] or with Condition-by-Task [$F(1,35) = 2.14$, $p = .15$]. In summary, task switching error costs were similar for prosaccades and antisaccades and were approximately equal for both groups (Figure 3c).

INTERACTION OF ANTISACCADE AND TASK-SWITCHING ACCURACY RATES. We examined whether the effects of combining an antisaccade and task-switch in a single trial were multiplicative using the logarithms of the accuracy rates. The log of the accuracy rate for combining an antisaccade and task-switch in a single response did not differ from the sum of the logs of the

accuracy rates of performing an antisaccade and a task-switch independently for either group [normal: $t(15) = .49$, $p = .63$; schizophrenia: $t(20) = .79$, $p = .44$] (Figure 4a). Linear regressions showed that the log of the combined antisaccade and task-switch cost was strongly related to the sum of the logs of the antisaccade cost and the task-switch cost [normal $R^2 = .61$, $F(1,14) = 22.13$, $p = .0003$; schizophrenia $R^2 = .71$, $F(1,19) = 33.04$, $p < .0001$] (Figure 4b). Moreover, the slopes and intercepts of these regressions were not significantly different from the line of agreement [normal: slope $t(14) = 1.48$, $p = .16$, intercept $t(14) = 1.44$, $p = .17$; schizophrenia: slope $t(19) = .61$, $p = .55$, intercept $t(19) = .90$, $p = .38$]. This suggests that, for both subject groups, the accuracy of combining an antisaccade and a task-switch in a single response is well described by a multiplicative model.

RELATION OF ERROR COSTS. Antisaccade and task-switch error costs were not correlated in either group (normal: $r = -.11$, $p = .71$; schizophrenia: $r = -.16$, $p = .48$). In the normal group, the error costs of antisaccades and task switching were approximately equal [$t(15) = .47$, $p = .65$]. In the schizophrenia group, the error costs were significantly greater for antisaccades than task switching [$t(20) = 4.88$, $p < .0001$].

Latency

ANTISACCADE. See Figure 5a. Performance of antisaccades was significantly slower than that of prosaccades [Task main effect: $F(1,35) = 170.53$, $p < .0001$]. There was a Group-by-Task interaction [$F(1,35) = 9.25$ $p = .002$]. Although schizophrenic subjects had longer latencies than normal subjects on both tasks [prosaccade $t(35) = 3.33$, $p = .0009$; antisaccade $t(35) = 7.09$, $p = 1e^{-12}$], they were disproportionately slowed on antisaccade trials.

TASK SWITCHING. See Figure 5b. The main effect of Condition (repeated vs. switched) was not significant [$F(1,35) = .002$, $p = .97$]. This is because task switching affected the latency of prosaccades and antisaccades differently [Condition-by-Task interaction: $F(1,35) = 22.08$, $p < .0001$]. For prosaccades, switched trials were significantly slower than repeated trials [$t(35) = 3.52$, $p = .0004$], whereas the opposite was true for antisaccades [$t(35) = 3.15$, $p = .0017$]. Group did not interact with Condition [$F(1,35) = 1.28$, $p = .26$] or with Condition-by-Task [$F(1,35) = 1.58$, $p = .21$]. In summary, there were no significant group differences in task switching latency costs (Figure 5c). Paradoxically, performing an antisaccade and a task-switch within a single trial was actually faster than performing an antisaccade alone.

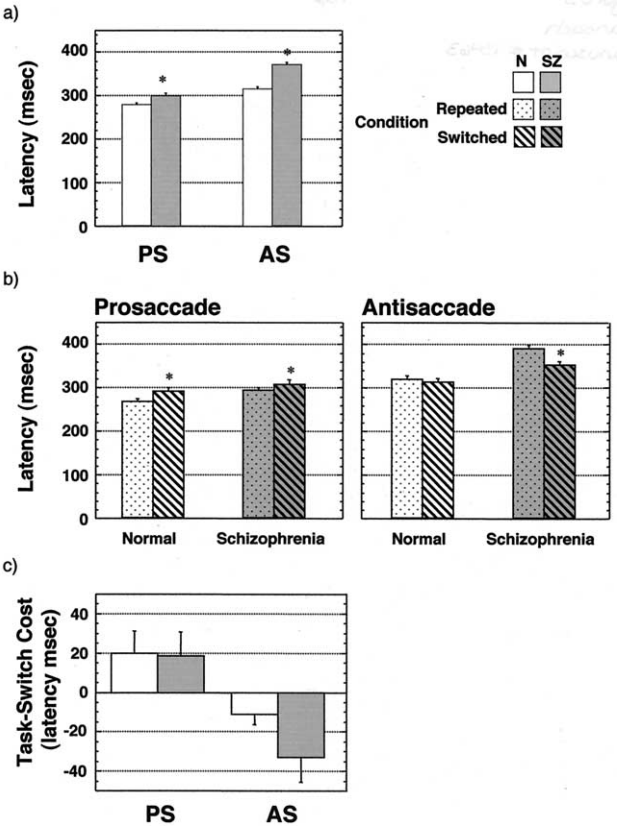

Figure 5. Bar graphs of latency **(a)** collapsed across condition (repeated vs. switched) and **(b)** separated by condition; and **(c)** isolated task switch costs for prosaccades and antisaccades. An asterisk indicates that the comparison between adjacent bars is significant at $p \leq .05$. N, normal control subjeects; SZ, schizophrenic patients; PS, prosaccade; AS, antisaccade.

INTERACTION OF INHIBITION AND TASK SWITCHING COSTS. Contrary to predictions from serial models, the latency costs of combining antisaccade and task switching within a single trial were not additive. Because both groups made more errors for switched antisaccades, one plausible explanation of the paradoxical reduction in latency is a speed–accuracy trade off. If this were the case, changes in latency from repeated to switched antisaccades should be inversely related to changes in errors; however, we found that task-switch effects on the latency of antisaccades were not correlated with task-switch effects on error rate in either group (normal: $r = -.22$, $p = .41$; schizophrenia: $r = 0.05$, $p = .82$). Another possibility is that latencies were slowed by having made an error in the previous trial. Given the increased error rate for antisaccades, this would elevate the latencies of repeated antisaccades and switched prosaccades for both groups, disproportionately so in the schizophrenia group; however, when we excluded trials for which the previous response was incorrect, the finding was unchanged.

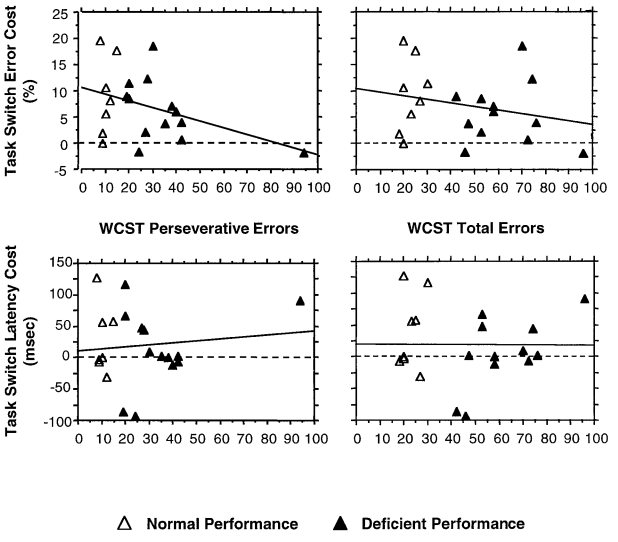

Figure 6. Relations between Wisconsin Card Sort Test (WCST) performance and saccadic task switch costs in schizophrenic subjects. Scatter plots illustrating the relation of task-switch error and latency costs (y axes) to WCST performance (x axes), as measured by the number of perseverative errors and total errors. Subjects are divided into those who performed average and above (normal performance) and those who performed in the below average to severely impaired range (deficient performance).

RELATION BETWEEN COSTS. In the normal group only, antisaccade and task switch costs were related (normal $r = .52$, $p = .04$; schizophrenia $r = .11$, $p = .64$). Latency costs were significantly greater for antisaccades than for task switching in both groups [normal: $t(15) = 3.11$, $p = .0072$; schizophrenia: $t(20) = 4.04$, $p = .0006$]. We also examined the relation of antisaccade costs to the change in latency for antisaccades when task switching was required (task switch cost for antisaccades). In the schizophrenic group only, antisaccade costs were directly related to the size of the paradoxical cost reduction (normal: $r = .23$, $p = .40$; schizophrenia: $r = .55$, $p = .001$).

WCST Performance and Task Switch Costs in Schizophrenia

We compared the WCST performance of our schizophrenic group to published age- and education-matched normative data (Heaton et al 1993). As a group, their mean standard score was in the mildly impaired range for total errors ($\mu = 82 \pm 16$) and for perseverative errors ($\mu = 83 \pm 18$). There was no relationship between either total or perseverative errors from the WCST and task switch costs as measured by either errors or latency (see Figure 6). Even schizophrenic subjects with abnormal WCST performance could have normal task switch costs.

Discussion

In this study, schizophrenic subjects showed normal task switching and deficient antisaccade performance, as determined by both accuracy and latency. Moreover, the costs of task switching and antisaccades were unrelated. These findings of intact task switching and abnormal inhibition demonstrate that schizophrenic patients have a selective impairment in executive functions.

It is unlikely that the finding of a selective impairment reflects reduced sensitivity of the task switching versus antisaccade measurements. In the normal group, error costs were equivalent for antisaccades and task switching and were not at ceiling. Although latency costs were substantially smaller for task switching than for antisaccades, both groups showed similar, significant task switching costs for prosaccades, indicating that the measurement was sensitive. In addition, although not significant, the direction of difference was toward smaller task switch costs in schizophrenic patients for both errors and latency, suggesting that inadequate statistical power does not explain the failure to find a task switching deficit.

The finding of normal task switch costs in schizophrenia contrasts with the literature that suggests that schizophrenic subjects are deficient in this function. A possible explanation for this discrepancy involves the nature of the task-switch requirement. Studies of task switching in schizophrenia frequently employ paradigms that involve a predictable sequence of trials (Smith et al 1998). In normal subjects, predictable task switch trials are associated with faster responses (Monsell et al 2000) and greater lateral prefrontal cortex activation (Brodmann's Areas 46/45) than unpredictable task switch trials (Sohn et al 2000). In addition, response speed for predictable task-switch trials correlates with the magnitude of lateral prefrontal cortex activation (Sohn et al 2000). These findings suggest that normal subjects use sequence information to predict and prepare for switched trials and thereby improve their performance. Using sequence information in this manner requires working memory. The subject must maintain and analyze the trial history "online" to learn the sequence and to anticipate the next trial. Because the lateral prefrontal cortex participates in working memory (McCarthy 1995), its association with the performance of predictable task-switches is not surprising.

Schizophrenic subjects, as a consequence of deficient working memory, may be inefficient at using sequence information to enhance their performance for predictable switches. If normal subjects use sequence information to enhance their performance on predictable switch trials and schizophrenic subjects do not, the schizophrenic subjects will appear to have a task switch deficit; however, their deficit will be present on the basis of poor working

memory rather than impaired task switching per se. Recent findings and interpretations of Meiran and colleagues, using a manual choice reaction time task, are consistent with those of the current study and isolate the source of apparent task switching deficits in schizophrenia to poor memory for task context information (Meiran et al 2000). In the current study, because the two tasks were presented in a random order, sequence information was not available to enhance the performance of either group. For this reason, the saccadic paradigms employed in this study provide relatively pure measurements of task switching that are less confounded by the effects of working memory.

Consistent with previous findings, schizophrenic subjects showed abnormal WCST performance (Braff et al 1991; Perry and Braff 1998); however, saccadic task switching costs were normal and unrelated to WCST performance. This strongly suggests that poor WCST performance was not a consequence of defective task switching. Rather, it likely reflects a deficit in one of the other cognitive processes required for performance. Just as working memory is required to benefit from predictability, correct performance of the WCST also requires subjects to maintain and analyze the trial history on-line to learn the sorting rule. Thus, deficient working memory may account for poor WCST performance, as has been suggested previously (Cohen and Servan-Schreiber 1992; Gold et al 1997).

In addition to the absence of a working memory component, the current task switching paradigm differs in other ways from many of those previously employed in schizophrenia. Unlike the WCST, there is no build up of an expected response over multiple trials; however, other neuropsychological instruments that are considered to be indices of task switching (e.g., Trail Making Tests) do not involve this sort of build up either. In addition, our findings demonstrate that the establishment of an expected response set is not necessary to obtain significant task switch costs. The requirement to disengage from an established response set, although often present in tasks that require task switching, may be a distinct process. Our saccadic paradigm measures task switching in relative isolation—it involves a fairly pure stimulus-response remapping. In addition, we studied "residual task switch costs (Rogers and Monsell 1995). Our prompt-to-target interval of two seconds gave ample time for advance reconfiguration of the new task set on switched trials. When studied in this manner, task switching is not deficient in schizophrenia. The deficiency in schizophrenia responsible for perseveration may be in a closely related process rather than the simple requirement to switch. Our findings challenge the long established notion of deficient task switching in schizophrenia. They suggest the need for finer discriminations in defining executive function deficits in schizophrenia.

Contrary to our expectations, schizophrenic subjects were not disproportionately affected by having to perform two executive functions for a single response. For both groups, the accuracy of combining executive functions was well described by a multiplicative model. Latency costs, in contrast, interacted in a nonlinear fashion. We found a paradoxical reduction of latency costs for combining executive functions in both groups, consistent with our finding in a prior study of younger normal subjects (Cherkasova et al, unpublished data). This reinforces the fact that accuracy and latency measurements reflect different processes for antisaccades and task switches.

Accurate performance indicates successful suppression of an incorrect response—the prior response for switched trials and a prosaccade for antisaccade trials. The suppression of a prior response is likely to be a different process than the inhibition of a prosaccade. The latter requires inhibiting a reflexive tendency that has been acquired over the course of a lifetime rather than in the previous trial. Both the multiplicative nature of accuracy rates for inhibiting reflexive responses and suppressing prior responses and the finding that only one of these functions is impaired in schizophrenia supports the notion that they are independent.

Whereas accuracy reflects suppression inhibition, latency reflects the processing time required to generate a novel or switched response. Combining these two functions had different effects on antisaccades than prosaccades. Superficially, this is consistent with prior assertions that switching from a dominant (i.e., prosaccade) to a nondominant task (i.e., antisaccade) has lesser latency costs than switching in the reverse direction (Allport et al 1994; Monsell et al 2000); however, the novel finding of a task switch *benefit* for antisaccades is not accounted for by current models of task switching, all of which assert that switching generates time *costs* (Meiran 2000; Monsell et al 2000; Wylie and Allport 2000). This reduction or benefit may be consistent with recent observations that an additional attention demanding task actually speeds up antisaccades (Kristjansson et al, 2001). The investigators proposed that the additional cognitive task (in the current study, the requirement to switch) interferes with the programming of reflexive prosaccades and, in so doing, frees the subject from having to actively inhibit the prosaccade during an antisaccade trial. One might expect, then, that subjects with greater antisaccade latency costs would show a larger benefit (e.g., latency cost reduction) when task switching was also required. This was the case only in the schizophrenic group. This relation may be more difficult to detect in the normal group, given their more limited range of antisaccade performance.

Finally, our finding of selectively impaired antisaccade performance that was unrelated to task switching performance in schizophrenia suggests that inhibition and task-switching are subserved by distinct anatomical networks, only one of which is dysfunctional in schizophrenia. Such behavioral findings can guide investigations of dysfunctional neural circuitry in schizophrenia. More generally, this study demonstrates that different types of executive functions and their interactions can be examined within a single paradigm and that the findings can constrain hypotheses regarding the systems of exercising such control in both normal and pathologic populations.

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References

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

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 Trans Biomed Eng* 30:191–194.

Barch DM, Carter CS, Hachten PC, et al (1999): The "benefits" of distractibility: Mechanisms underlying increased Stroop effects in schizophrenia. *Schizophr Bull* 25:749–762.

Blair JR, Spreen O (1989): Predicting premorbid IQ: A revision of the National Adult Reading Test. *Clin Neuropsychologist* 3:129–136.

Blanchard JJ, Neale JM (1994): The neuropsychological signature of schizophrenia: Generalized or differential deficit. *Am J Psychiatry* 151:40–48.

Braff DL, Heaton R, Kuck J, et al (1991): The generalized pattern of neuropsychological deficits in outpatients with chronic schizophrenia with heterogeneous Wisconsin Card Sorting Test results. *Arch Gen Psychiatry* 48:891–898.

Carter CS, Macdonald AM, Botvinick M, et al (2000): Parsing executive processes: Strategic vs. evaluative functions of the anterior cingulate cortex. *Proc Natl Acad Sci USA* 97:1944–1948.

Cherkasova ML, Manoach DS, Intriligator J, Barton JJS (in press): Antisaccades and task switching: Interactions in controlled processing. *Exp Brain Res.*

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

Cools R, Brouwer WH, de Jong R, Slooff C (2000): Flexibility, inhibition, and planning: Frontal dysfunctioning in schizophrenia. *Brain Cogn* 43:108–112.

Dove A, Pollmann S, Schubert T, et al (2000): Prefrontal cortex activation in task switching: An event-related fMRI study. *Brain Res Cogn Brain Res* 9:103–109.

Elliott R, McKenna PJ, Robbins TW, Sahakian BJ (1995): Neuropsychological evidence for frontostriatal dysfunction in schizophrenia. *Psychol Med* 25:619–630.

First MB, Spitzer RL, Gibbon M, Williams JBW (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.

Garavan H, Ross TJ, Li SJ, Stein EA (2000): A parametric manipulation of central executive functioning. *Cereb Cortex* 10:585–592.

Gold JM, Carpenter C, Randolph C, et al (1997): Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Arch Gen Psychiatry* 54:159–165.

Granholm E, Asarnow RF, Marder SR (1991): Controlled information processing resources and the development of automatic detection responses in schizophrenia. *J Abnorm Psychol* 100:22–30.

Green MF (1998): *Schizophrenia from a Neurocognitive Perspective*. Boston: Allyn and Bacon.

Heaton RK, Chelune GJ, Talley JL, et al (1993): *Wisconsin Card Sorting Test Manual Revised and Expanded*. Odessa, FL: Psychological Assessment Resources, Inc.

Hollingshead AB (1965): *Two Factor Index of Social Position*. New Haven, CT: Yale University Press.

Kay SR, Fiszbein A, Opler LA (1987): The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 13:261–276.

Kristjansson A, Chen Y, Nakayama K (2001): Less attention is more in the preparation of antisaccades, but not prosaccades. *Nat Neurosci* 10:1037–1042.

Levy DL, Mendell NR, LaVancher CA, et al (1998): Disinhibition in antisaccade performance in schizophrenia. In: Lenzenweger MF, Dworkin RH, editors. *Origins and Development of Schizophrenia*. Washington, DC: American Psychological Association, pp 185–210.

MacDonald AW III, Cohen JD, Stenger VA, Carter CS (2000): Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* 288:1835–1838.

McCarthy G (1995): Functional neuroimaging of memory. *Neuroscientist* 1:155–163.

Meiran N (2000): Modeling cognitive control in task-switching. *Psychol Res* 63:234–249.

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? *Psychol Res* 63:250–264.

National Institute of Mental Health (1974): *Abnormal Involuntary Movement Scale (AIMS)*. U.S. Public Health Service Publication. Washington, DC: U.S. Government Printing Office.

Norman DA, Shallice T (1986): Attention to action: Willed and automatic control of behavior. In: Davidson RJ, Schwartz GE, Shapiro D, editors. *Advances in Research and Theory*, Vol 4. New York: Plenum, pp 1–18.

Overall JE, Gorham DR (1962): The brief psychiatric rating scale. *Psychol Rep* 10:799–812.

Perry W, Braff DL (1998): A multimethod approach to assessing perseverations in schizophrenia patients. *Schizophr Res* 33: 69–77.

Rogers RD, Monsell S (1995): Costs of a predictable switch between simple cognitive tasks. *J Exp Psychol* 124:207–231.

Schweickert R (1985): Separable effects of factors on speed and accuracy: Memory scanning, lexical decision, and choice tasks. *Psychol Bull* 97:530–546.

Simpson GM, Angus JWS (1970): A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* 212:11–19.

Smith GL, Large MM, Kavanagh DJ, et al (1998): Further evidence for a deficit in switching attention in schizophrenia. *J Abnorm Psychol* 107:390–398.

Sohn MH, Ursu S, Anderson JR, et al (2000): The role of prefrontal cortex and posterior parietal cortex in task switching. *Proc Natl Acad Sci USA* 97:13448–13453.

Stuss DT, Benson DF (1984): Neuropsychological studies of the frontal lobes. *Psychol Bull* 95:3–28.

Stuss DT, Shallice T, Alexander MP, Picton TW (1995): A multidisciplinary approach to anterior attentional functions. *Ann N Y Acad Sci* 769:191–211.

Sullivan EV, Mathalon DH, Zipursky RB, et al (1993): Factors of the Wisconsin Card Sorting Test as measures of frontal-lobe function in schizophrenia and in chronic alcoholism. *Psychiatry Res* 46:175–199.

White K, Ashton R (1976): Handedness assessment inventory. *Neuropsychologia* 14:261–264.

Wylie G, Allport A (2000): Task switching and the measurement of "switch costs." *Psychol Res* 63:212–233.