Response Inhibition and Response Monitoring in a Saccadic Countermanding Task in Schizophrenia

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Background: Cognitive control deficits are pervasive in individuals with schizophrenia (SZ) and are reliable predictors of functional outcome, but the specificity of these deficits and their underlying neural mechanisms have not been fully elucidated. The objective of the present study was to determine the nature of response inhibition and response monitoring deficits in SZ and their relationship to symptoms and social and occupational functioning with a behavioral paradigm that provides a translational approach to investigating cognitive control.

Methods: Seventeen patients with SZ and 16 demographically matched healthy control subjects participated in a saccadic countermanding task. Performance on this task is approximated as a race between movement generation and inhibition processes; this race model provides an estimate of the time needed to cancel a planned movement. Response monitoring can be assessed by reaction time adjustments on the basis of trial history.

Results: Saccadic reaction time was normal, but patients required more time to inhibit a planned saccade. The latency of the inhibitory process was associated with the severity of negative symptoms and poorer occupational functioning. Both groups slowed down significantly after correctly cancelled and erroneously noncancelled stop signal trials, but patients slowed down more than control subjects after correctly inhibited saccades.

Conclusions: These results suggest that SZ is associated with a difficulty in inhibiting planned movements and an inflated response adjustment effect after inhibiting a saccade. Furthermore, behavioral results are consistent with potential abnormalities in frontal and supplementary eye fields in patients with SZ.

Key Words: Cognitive control, inhibition, response monitoring, saccades, schizophrenia, stop signal

Executive control and flexible modification of behavior on the basis of feedback are essential to adaptive functioning in a dynamic environment. Schizophrenia (SZ) is associated with impairments in a range of cognitive functions that underlie behavioral flexibility, including working memory (WM) (1), attention (2), and cognitive control (3). Cognitive deficits in SZ predict functional outcome better than clinical symptoms (4) and are major targets for pharmacotherapy (5). The saccade countermanding paradigm (6) is an ideal measure of cognition in treatment studies, because it measures two key components of cognitive control, inhibition, and response monitoring that have been studied in humans and nonhuman primates under similar experimental conditions. Thus, it provides a translational bridge for understanding deficits in SZ.

Response inhibition is the ability to deliberately inhibit actions (7). Although inhibitory deficits have been described in SZ (8,9), inhibition is not a unitary construct (10). Furthermore, correlations among performance measures on tasks of response inhibition are typically low (7,11,12). Thus, there is utility in investigating patient performance on a variety of inhibition-related tasks. The present research focuses on inhibition in the saccadic countermanding task.

Response monitoring involves evaluation of actions via feedback to guide future performance and is commonly indexed by error detection and response time (RT) adjustments as a function of trial history. There is mixed evidence for deficits in immediate error-related performance adjustments in patients with SZ (13–16).

The countermanding paradigm is used to investigate the ability to control the execution of a response (17,18). In the saccadic countermanding task, subjects are instructed to make a saccade to a visual target, unless a "stop signal" appears at some delay after target presentation. On these trials, subjects are instructed to withhold the saccade. The time needed to cancel a movement, the stop signal reaction time (SSRT), can be estimated from the distribution of RTs on "no-stop signal" trials and the probability of making a saccade given that a stop signal occurred; it is hypothesized to be based on a race between independent processes that generate (GO) and inhibit (STOP) the movement (19). Neural activity in the frontal eye fields (FEF) (20,21) and the superior colliculus (SC) (22) is necessary for saccadic preparation and inhibition. In contrast, neurons in the medial frontal cortex generate performance monitoring signals associated with errors, reward, and conflict (23,24), which might contribute to specific behavioral adjustments on the basis of trial history (25).

The countermanding task was included in a testing battery, resulting from a recent National Institutes of Health initiative, for evaluating changes in cognition in clinical trials (26). However, few studies have examined countermanding performance in SZ. Both longer (27,28) and equal (29) SSRTs have been reported in SZ from the manual countermanding task. Discrepant findings are potentially due to task-specific factors that affect estimation of SSRT (30). The present study is the first investigation of stopping behavior and RT adjustments on the basis of trial history with the saccadic countermanding task in SZ. There are several advantages to using the oculomotor version of this task. A substantial body of work has investigated neurophysiological mechanisms instantiating the inhibition and monitoring of saccades in nonhuman primates performing this task (31). In addition, a formal mathematical model was developed that accounts for behavior (19), and it has recently been elaborated to account for activity in single neurons during saccade

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countermanding (32). Accordingly, this paradigm allows us to make clear assumptions about what is being inhibited and monitored, to estimate when inhibition is occurring, and to understand how inhibition and monitoring of saccades is being supported in the brain. In this way, this task permits specific hypotheses to be drawn about the nature of putative deficits in response inhibition and monitoring. The use of saccadic versus manual tasks in SZ has an additional advantage. Slowing in manual RT has been consistently reported in SZ (33), but the latency of reflexive saccades is generally normal (34,35). Thus it is argued that saccadic tasks of cognitive control in SZ minimize confounding effects of impairments in the basic response system (36).

Our aim in the current study was to examine inhibition and monitoring of saccades in healthy individuals and patients with SZ. We also examined WM deficits (1) in relation to potential countermanding deficits. Thus, we sought to expand our understanding of the specific nature of cognitive control deficits in SZ.

Methods and Materials

Participants

Individuals who met the DSM-IV criteria for SZ were recruited from outpatient psychiatric facilities in Nashville, Tennessee. Diagnoses were confirmed with structured clinical interviews (SCID-IV) (37). All patients were taking atypical antipsychotic medications, with the exception of one patient, who was taking Depakote. Healthy, unmedicated control subjects (HC) without a personal and family history of DSM-IV Axis I disorders were recruited from the same community by advertisements.

Clinical symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS) (38), the Scale for the Assessment of Positive Symptoms (SAPS) (39), and the Scale for the Assessment of Negative Symptoms (SANS) (40). Social and occupational functioning was assessed by the Social Functioning Scale (SFS) (41). The Adult North American Reading Test (42,43) or Wechsler Abbreviated Scale of Intelligence (44) was used to assess IQ. Although mean IQ and education were lower in SZ subjects compared with HC subjects, their mean IQ was in the normal range, and the average SZ subject had achieved a high school education. Moreover, IQ has not been found to be related to response inhibition (10,17) or to the RT cost of task-switching (10). Handedness was assessed with the Modified Edinburgh Handedness Inventory (45).

All participants were screened to exclude substance use, neurological disorders, history of head injury, inability to fixate, and excessive sleepiness. All subjects had normal or corrected-to-normal vision. Two SZ subjects were excluded on the basis of countermanding task performance, as outlined in the Statistical Methods section. Analyses were conducted on the remaining 17 SZ subjects and 16 HC subjects. The SZ and HC subjects were matched for age, gender, and handedness; demographic data are presented in Table 1. All subjects gave written informed consent approved by the Vanderbilt Institutional Review Board and were paid.

Apparatus and Stimuli

Eye position was monitored with the EyeLink II eye tracker (SR Research, Mississauga, Ontario, Canada) at a sampling rate of 250 Hz with average gaze position error $<.5°$, noise limited to $<.01°$ root mean square. Saccades were detected online with a velocity criterion (35°/sec). Subjects were seated 57 cm from the computer monitor with their head in a chin rest. The fixation and targets subtended 1° and were light gray (34 cd/m^2) on a darker gray (18 cd/m^2) background.

Table 1. Demographic Characteristics of Patient and Control Groups

	Patients Mean (SD)	Control Subjects Mean (SD)	*t*	*p*
Age	36.0 (7.7)	34.9 (7.9)	.4	.70
Gender	6 F/11 M	7 F/9 M	$\Phi = .2$	.73
Edinburgh Handedness	51.5 (54.9)	56.7 (67.7)	.4	.70
Yrs of Education	13.4 (1.9)	16.2 (2.1)	4.0	.0003
IQ	102.6 (10.8)	110.5 (4.6)	2.7	.01
SAPS	13.8 (19.1)			
SANS	20.8 (16.7)			
BPRS	11.8 (7.1)			
SFS Total Score	132.3 (24.4)	156.8 (14.6)	3.4	.002
SFS Employment Score	5.2 (3.8)	9.7 (.7)	4.6	$<.0001$

The Φ value is the result of a Fisher exact test.

SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SFS, Social Functioning Scale; BPRS, Brief Psychiatric Rating Scale.

Design and Procedure

Countermanding Task. Subjects performed a saccadic countermanding task (Figure 1). Seventy percent of the trials were no-stop signal trials. These trials required subjects to fixate on a central spot until it disappeared (after a random delay between 500 and 1000 msec) and a peripheral target appeared at one of two randomly selected locations (left or right) equidistant (8.5°) from the central fixation spot. Subjects were instructed to look directly at the target as quickly as possible. The remaining 30% of trials were stop signal trials. These trials were initially identical to the no-stop signal trials, but the fixation spot was reilluminated after a variable delay (stop signal delay [SSD]) after target presentation, cuing subjects to inhibit a saccade to the target. Stop signal trials were labeled "cancelled" or "noncancelled" on the basis of whether subjects inhibited or failed to inhibit the saccade, respectively. Response inhibition becomes more difficult with increasing SSDs. The SSDs were dynamically adjusted with a 1-up/1-down tracking procedure, thereby ensuring successful inhibition on 50% of the stop signal trials (46). The initial SSD was set at 225 msec and increased or decreased by 47 msec when the subject succeeded or failed to inhibit, respectively. The testing session consisted of a practice block of 60 trials and four experimental blocks of 120 trials each.

Behavioral performance was evaluated through measurements of saccadic RT on no-stop signal and noncancelled trials and mean SSD. At each SSD, we quantified the proportion of trials in which a participant successfully inhibited a saccade. The proportion of cancelled trials at each delay is referred to as the "inhibition function."

Performance in the stop signal task can be accounted for by a mathematical model that assumes a race between independent processes that generate (GO) and inhibit (STOP) the movement (19). The response is executed if the GO process finishes first and inhibited if the STOP process finishes first. The latency of the GO process can be measured directly from the observable RTs, but the latency of the STOP process is estimated. The independent race model provides an estimate of the time needed to respond to the stop signal and cancel the movement, referred to as the SSRT (see Supplement 1 for description of SSRT calculation). The slope of the inhibition function is thought to reflect variability in the STOP and GO RT and the ability to trigger an inhibitory response. The slope can be corrected for variability in GO RT by applying a Z-transformation to the SSDs (47), which expresses them in terms of the latency relative to finish-

ing times of GO and STOP processes standardized with respect to variability in GO RT with the equation:

$$\text{ZRFT} = \frac{(\text{mean no} - \text{stop signal RT} - \text{SSD} - \text{SSRT})}{(\text{standard deviation of no} - \text{stop signal RT})}$$

RTs were examined as a function of trial history to index response monitoring. Mean RT was computed separately for no-stop signal trials before and after no-stop signal trials, correctly cancelled stop signal trials, and noncancelled stop signal trials (i.e., stop-task errors). The RTs on no-stop signal trials before and after two consecutive stop signal trials were included in this analysis only if the response on the two stop signal trials was the same. Post-cancelled slowing was calculated as the difference between mean RT for no-stop signal trials preceding and following a cancelled trial. Likewise, post-error slowing was calculated as the difference between mean RT for no-stop signal trials preceding and following a noncancelled trial.

Verbal and Spatial WM Tasks. Verbal working memory (VWM) was measured with the Letter Number Sequencing task (48) in which subjects were verbally presented a series of letters and numbers and asked to report the numbers in numerical order, followed by the letters in alphabetical order. The VWM scores were unavailable for one patient and one control subject.

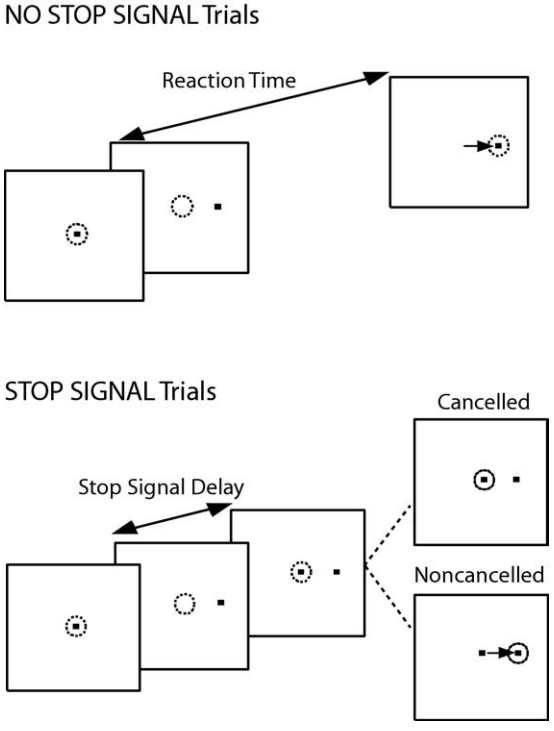

Figure 1. Saccade countermanding task. Dotted circles indicates gaze position, and the arrow indicates the direction of the saccade. All trials began with the presentation of a central fixation spot. After a variable fixation length, the fixation spot disappeared and, simultaneously, a target appeared at an eccentric location to the right or left of central fixation. On 30% of trials (stop signal trials), the fixation spot was reilluminated at some delay, referred to as stop signal delay, after target onset. Fixation reillumination was the cue for the subject to withhold a saccade to the target. Trials in which the subject was successful in maintaining fixation were referred to as cancelled trials, and trials in which the subject made a saccade to the eccentric target were referred to as noncancelled trials. For the remaining 70% of trials (no-stop signal trials), fixation was not reilluminated and the subject was instructed to make a saccade to the peripheral target.

Table 2. Performance Characteristics of Patient and Control Groups

	HC Mean (SD)	SZ Mean (SD)	*t*	*p*
Probability of Inhibition (%)	50.7 (4.2)	48.0 (4.6)	1.7	.09
NSS RT (msec)	273 (55)	283 (59)	.5	.60
Noncancelled RT(msec)	222 (40)	232 (44)	.7	.50
SSRT (msec)	124 (24)	147 (31)	2.5	.02
Post-Error Slowing (msec)	40 (22)	48 (38)	.7	.50
Post-Cancelled Slowing (msec)	24 (22)	51 (42)	2.3	.03

HC, healthy control subjects; SZ, schizophrenic patients; NSS, no-stop signal; RT, reaction time; SSRT, stop signal reaction time.

Spatial working memory (SWM) was assessed with a delayed-response task. Subjects fixated centrally. Then, a target (black circle subtending 2°) was presented for 300 msec at one of eight locations, 12° from the central fixation spot, followed by a delay of 8 sec. During the delay, numbers were presented centrally, in descending order in steps of four. Subjects were instructed to note any subtraction errors to prevent verbal rehearsal and maintain central fixation. After the delay, subjects were asked to indicate location of the target and then indicate whether they noticed a subtraction error with the keypad. There were 48 trials. The SWM scores were unavailable for two patients and one control subject.

Statistical Methods

All tests were two-tailed unless otherwise specified. Subjects were excluded from analyses if the adaptive tracking procedure in the stop signal task was ineffective, defined by a proportion of cancelled responses lying outside a 95% binomial confidence interval around $p = .5$.

Results

Table 2 shows stop signal performance and RT adjustments for SZ and HC subjects.

Probability of Inhibition

The dynamic tracking procedure was successful, and the mean proportion of noncancelled trials was 49%. The two groups did not differ in the proportion of noncancelled trials. For each subject, the estimated slope of the inhibition function plotted against ZRFT was

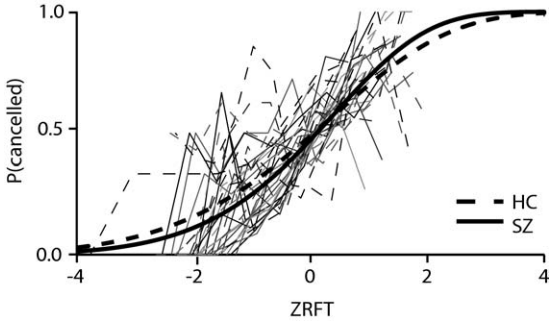

Figure 2. Individual normalized inhibition functions for healthy control subjects (HC) (dotted lines) and schizophrenia patients (SZ) (solid lines). Probability of inhibition is plotted as a function of a Z score that measures time relative to the finish time of the GO and STOP processes in SD units with the formula: ZRFT = (mean no-stop signal RT − SSD − SSRT)/SD of no-stop signal RT. Separate cumulative Weibull functions are fit to the normalized inhibition functions for patients and control subjects. SSRT, stop signal reaction time; RT, reaction time; SSD, stop signal delay.

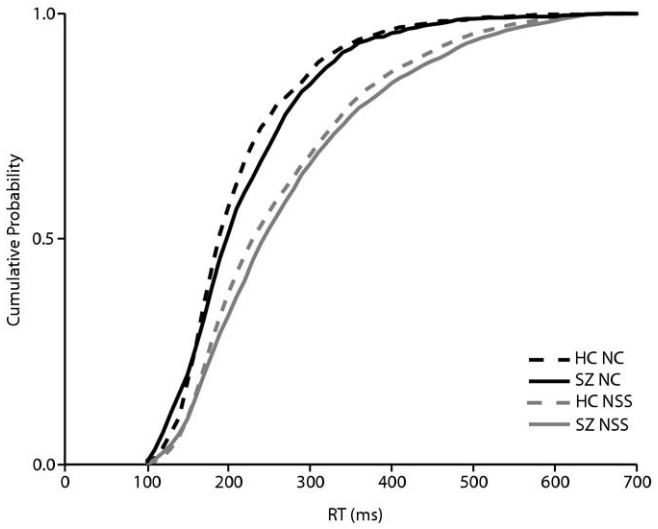

Figure 3. Cumulative distributions of saccade latencies in no-stop signal (gray) and noncancelled (black) trials for HC (dotted) and SZ (solid) groups. NSS, no-stop signal; NC, noncancelled; other abbreviations as in Figure 2.

calculated (Figure 2). There was no group difference in the slope of the Z-transformed inhibition function [$t(31) = 1.3, p = .20$], providing evidence for equal variability in the inhibitory process for both groups.

No-Stop Signal and Noncancelled RT

The effect of trial type (no-stop signal or noncancelled) on RT was assessed with a repeated-measures analysis of variance, with group as a between-subjects variable and trial type as a within-subjects variable. There was a significant effect of trial type [$F(1,31) = 106.7, p < .0001$], with no-stop signal trials being slower than noncancelled trials. There was no main effect of group [$F(1,31) = .38, p = .54$] or group × trial type interaction effect [$F(1,31) = .0003, p = .99$]. Cumulative RT distributions are presented in Figure 3.

SSRT

SSRT was significantly longer in SZ subjects [$t(31) = 2.5, p = .02$], who required more time to inhibit a saccade than HC subjects.

RT Adjustments Across Three Trials in Sequence

The RT adjustment effects are presented in Figure 4. To assess effects of trial history on the current no-stop signal trial, a repeated-measures analysis of variance was conducted on no-stop signal RTs with diagnostic group as a between-subjects variable and critical trial (no-stop signal, cancelled, noncancelled) and history (before or after critical trial) entered as within-subjects variables. There was a significant effect of history [$F(1,31) = 68.2, p < .0001$] and critical trial [$F(2,62) = 61.5, p < .0001$]. Notably, there was a significant history × critical trial interaction [$F(2,62) = 57.3, p < .0001$].

Planned contrasts revealed that RTs for no-stop signal trials were slower when they followed cancelled [$F(1,62) = 54.4, p < .0001$] and noncancelled [$F(1,62) = 74.0, p < .0001$] trials than when they preceded them. This suggests that presenting a stop signal increases saccadic RT on the subsequent trial, whether or not the saccade was cancelled. When three no-stop trials were presented in a row, participants got faster throughout [$F(1,62) = 25.8, p < .0001$]. Additionally, planned contrasts revealed significant differences between RTs of the trials preceding each of the critical trial types. Trials preceding cancelled trials were slower than those preceding both noncancelled [$F(1,62) = 30.7, p < .0001$] and no-stop signal trials [$F(1,62) = 5.9, p = .02$]. This suggests that when subjects are responding slower, they are more likely to be able to cancel a saccade on the subsequent trial. Trials preceding no-stop signal trials were slower than those preceding noncancelled trials [$F(1,62) = 9.7, p = .003$]. Likewise, this suggests that faster saccadic RT might result in subsequent failure to cancel a saccade.

There was no main effect of group [$F(1,31) = .32, p = .58$], but there was a significant group × history effect [$F(1,31) = 4.23, p = .05$]. Planned contrasts revealed slower performance in SZ subjects compared with HC subjects, and this difference was more pronounced after the critical trial [$F(1,31) = 26.0, p < .0001$] than before the critical trial [$F(1,31) = 4.8, p = .04$]. There was a trend toward a group × history × critical trial effect [$F(2,62) = 2.7, p = .07$]. Independent *t* tests were conducted to assess group differences in post-cancelled and post-error slowing and speeding after no-stop signal trials. The SZ subjects slowed down significantly more after cancelled trials than HC subjects [$t(31) = 2.3, p = .03$]. There were no group differences in post-error slowing [$t(31) = .7, p = .50$] or speeding after no-stop signal trials [$t(31) = 1.7. p = .10$].

Symptom and Social Functioning

Spearman rank-correlation coefficients were used to evaluate the association between the severity of psychiatric symptoms and behavioral measures in SZ subjects. The SANS score was positively correlated with SSRT ($r_s = .61, p = .009$); those with increased negative symptoms needed more time to inhibit saccades (Figure 5). The SANS score did not correlate with any of the other behavioral measures, and SAPS and BPRS scores were not correlated with any of the behavioral measures.

Because scores on the Employment subscale of the SFS were bimodally distributed in SZ subjects, a median split was performed

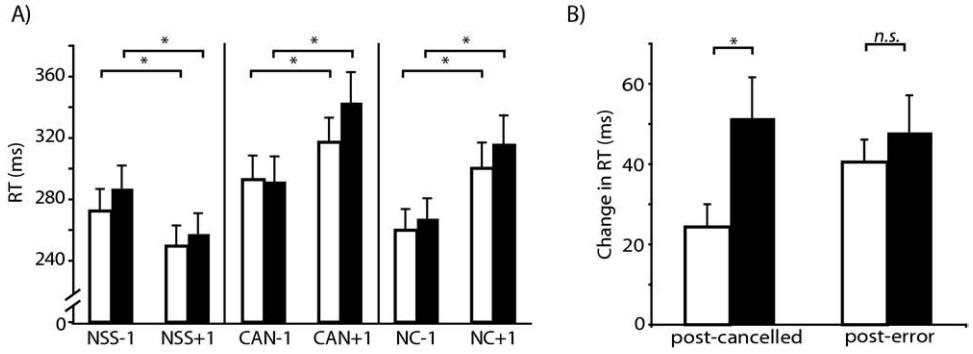

Figure 4. Mean NSS RT as a function of trial history. **(A)** Mean NSS RT (with SEM) for trials after (+1) and before (−1) NSS, cancelled (CAN), and noncancelled (NC) trials for HC subjects (empty bars) and SZ patients (filled bars). **(B)** Mean post-cancelled and post-error slowing. Other abbreviations as in Figure 2.

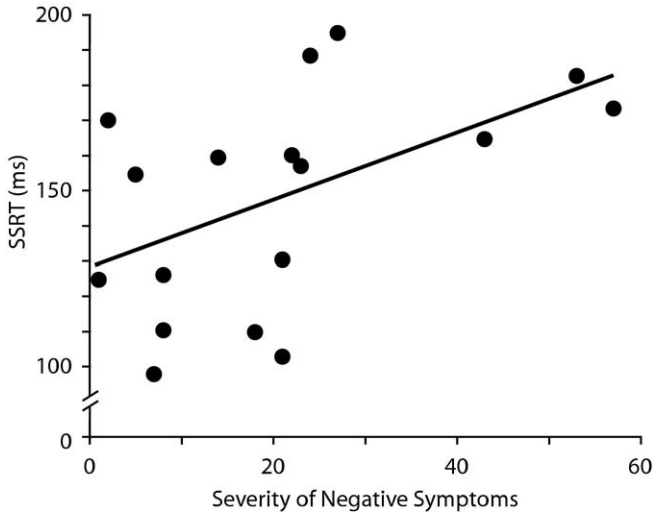

Figure 5. Relationship between stop signal reaction time (SSRT) and severity of negative symptoms, indexed by Scale for the Assessment of Negative Symptoms score, in schizophrenia patients. Greater Scale for the Assessment of Negative Symptoms scores represent more severe negative symptomatology.

on the scores, and independent *t* tests were conducted to compare behavioral measures in those scoring high and those scoring low on occupational functioning. SSRT was significantly longer in the low- compared with high-employment group [$t(14) = 2.8$, $p = .02$] (i.e., better occupational functioning was associated with less time needed to inhibit a planned movement in SZ subjects) (Figure 6). There was no significant difference in post-error or post-cancelled slowing between employment groups, and no significant relationship between SFS total score and countermanding task performance was observed.

Interestingly, both SZ participants who were excluded from analyses on the basis of performance indexes would have fallen into the low-employment group, and their SANS scores were above the group mean.

Working Memory

Because we had an a priori hypothesis of poorer WM performance in SZ subjects (1), one-tailed independent *t* tests were conducted to compare WM performance between groups. The SZ subjects had significantly fewer correct sequences (M = 13.6, SD = 3.5) on the VWM task [$t(28) = 1.9$, $p = .03$, one-tailed] than HC subjects (M = 15.7, SD = 2.4). Because variances were unequal, a Welch's *t* test was used to compare accuracy on the SWM task. The SZ subjects (M = 89.0%, SD = 10.9%) were less accurate than HC subjects (M = 96.8%, SD = 4.9%) [$t(19.4) = 2.5$, $p = .01$,one-tailed].

Pearson product-moment correlation coefficients were used to evaluate the associations among WM performance and SSRT, post-error slowing, and post-cancelled slowing in HC and SZ subjects. One-tailed tests of significance were conducted to examine the strength of the correlation between WM and SSRT, given their purported relationship (49). In patients, the relationship between SSRT and VWM performance was significant ($r_s = -.45$, $p = .05$, one-tailed) (i.e., better VWM was associated with less time needed to cancel a planned saccade). There were no other significant correlations between WM performance and countermanding measures.

Discussion

Schizophrenia was associated with increased latency to inhibit a planned saccade. Longer SSRT was found in patients, despite patients having equal sensitivity to the stop signal and similar latencies to initiate a saccade. Furthermore, SSRT was related to increased negative symptoms and poorer occupational functioning, indicating the clinical relevance of these findings. In addition, patients made appropriate RT adjustments after errors but slowed down significantly more than control subjects after correctly inhibited saccades.

Importantly, the performance of both patients and control subjects satisfied two criteria for the race model to hold. First, the probability of successfully inhibiting decreased with longer SSDs. The slopes of the inhibition functions of the two groups were not statistically different, after normalizing the SSD of each individual with respect to their mean and variance of no-stop signal RT, suggesting equal variability in SSRT and probability that the inhibitory process was triggered. Second, RTs were shorter for noncancelled than no-stop signal trials, indicating that only the fastest GO processes were fast enough to escape inhibition. There was no group difference in the latency to initiate a saccade, consistent with prior findings (34,35).

For the most part, our data conform to the existing cognitive control literature in SZ. Increased SSRT in patients indicates that they needed more time to inhibit a saccade, consistent with mounting evidence for impaired response inhibition in SZ (see introductory section of text). We also found that patients had WM deficits, and poorer WM was related to longer SSRT. Further studies are necessary to investigate the degree to which increased SSRT might be due to inappropriate use of WM to trigger the stop process.

In our analysis of RT adjustments on the basis of trial history, we found that both groups were faster on no-stop signal trials when they were preceded by no-stop signal trials versus cancelled and noncancelled trials. Post-cancelled slowing has been observed in both humans and nonhuman primates performing this task ([25,50–52], but see [53]). Likewise, post-error slowing is commonly observed in speeded response tasks (54), including the manual (51,53) and saccadic ([55,56]; but see [25] for exception and [56] for methodological explanation for inconsistent post-error findings) countermanding tasks. There was no group difference in post-error

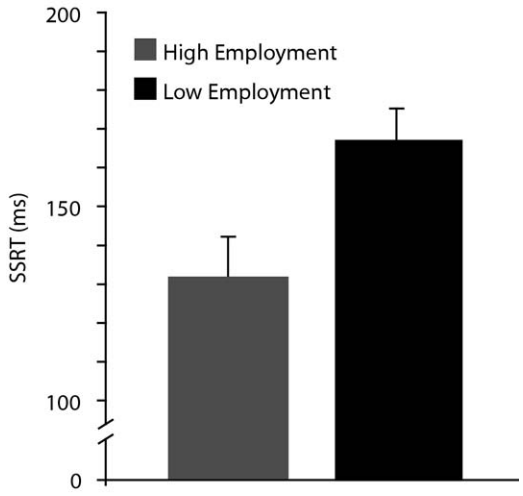

Figure 6. Stop signal reaction time (SSRT) (plus SEM) for schizophrenia patients scoring high (gray) and low (black) on the Social Functioning Scale employment subscale, defined by median split within patient group.

slowing, consistent with prior reports (14,16). These data suggest that the ability to evaluate performance and make appropriate short-term changes to response strategy is spared in SZ. Furthermore, we found no group difference in speeding after no-stop signal trials. However, patients slowed down significantly more than control subjects after inhibited saccades. This finding is in line with recent evidence of prolonged effects of prior antisaccades on saccadic latency in SZ (57–59), which are interpreted as abnormal perseveration in the saccadic response system (57). The degree to which increased post-cancelled slowing in patients represents a purposeful adjustment of response strategy is unclear. Although our findings partially replicate existing response inhibition and response monitoring data in SZ using other cognitive tasks, the advantage of using the saccadic countermanding paradigm is the leverage it gives us on understanding the neural mechanisms of these abnormalities. In the following sections, we relate our findings in SZ subjects to the extensive neurophysiology literature on this task.

Potential Neural Mechanisms Underlying Abnormal Saccade Countermanding in SZ

Neurophysiological research in nonhuman primates has identified neural mechanisms by which saccades are inhibited in the countermanding task in the FEF and SC where GO and STOP processes have been mapped onto saccade- and fixation-related neurons, respectively. On no-stop signal and noncancelled trials, activity in saccade-related neurons reaches a threshold, and the saccade is executed (60,61). On correctly cancelled trials, activity in saccade-related neurons begins to decay after the stop signal but before SSRT, whereas activity in fixation neurons begins to grow (21,22). Thus, activity in gaze-shifting and gaze-holding neurons in FEF and SC seems to play a crucial role in the control of saccades (see Supplement 1 for discussion of countermanding performance in SZ in the context of computational models of interacting neurons in FEF and SC).

Although not explored in nonhuman primates performing the saccadic countermanding task, other brain regions are thought to play a role in inhibition of eye movements. Data from single unit recordings in nonhuman primates (62,63) and human functional magnetic resonance imaging (fMRI) studies (64) point to a role of subthalamic nucleus in response inhibition. Additionally, deep brain stimulation of subthalamic nucleus in patients with Parkinson's disease improved inhibitory control and resulted in shorter manual SSRT (65). A role of the right inferior frontal gyrus in countermanding movements has also been described (66). Although there have not been any neuroimaging studies of the countermanding task in SZ, fMRI studies that have examined neural activity during the antisaccade task suggest abnormalities in frontostriatal–thalamo–cortical circuits (67,68).

Potential Neural Mechanisms Underlying Abnormal RT Adjustments Following Cancelled Saccades

Neural correlates of response monitoring and performance adjustments have also been investigated on a single-cell level in the saccadic countermanding task, with a focus on the role of medial frontal structures. Activity in a subpopulation of supplementary eye fields (SEF) neurons after correctly inhibited saccades is thought to reflect conflict between incompatible gaze-shifting and gaze-holding signals in FEF. The SEF can bias saccadic latency via connections to cortical and subcortical oculomotor regions (31) and seems to be the basis of slowing following cancelled saccades (69).

On the basis of these findings, a few potential hypotheses emerge regarding the mechanism of enhanced slowing after cancelled saccades in SZ. Because the inhibitory process might take longer to complete in SZ, as indexed by longer SSRT, the saccade could be cancelled at a longer delay after the rise of movement-related activity in FEF and SC, leading to more coactivation and subsequent conflict between gaze-holding and gaze-shifting neurons on correctly cancelled saccades. Alternatively, gaze-holding and gaze-shifting related neurons might be coactivated longer in patients with SZ, resulting in a longer period of conflict. SEF would signal longer conflict between mutually incompatible responses, resulting in prolonged RTs on subsequent trials. Finally, neurons in the SEF of patients with SZ could be more sensitive to conflict between mutually incompatible responses or exert more powerful biasing effects on structures directly implicated in saccade initiation. Although functional SEF abnormalities have been noted during smooth pursuit (70) and volitional saccade tasks (71,72) in SZ, findings of abnormal SEF activity are not consistent (67,68,73,74).

Limitations

A limitation of the present study is the unclear effect of neuroleptics in saccade inhibition and monitoring. However, previous studies suggest that atypical neuroleptics improve, but do not normalize antisaccade performance (75). If deficits in countermanding and antisaccade tasks reflect inhibition impairments, longer SSRT in SZ subjects is unlikely to be a result of neuroleptics. Furthermore, administration of haloperidol had no significant effect on post-error slowing in healthy individuals (76,77). Finally, in our study, chlorpromazine-equivalent dose was not related to any countermanding measures (Supplement 1).

Conclusions and Implications

We found that patients with SZ needed more time to inhibit a planned saccade, which was related to negative symptom severity and occupational functioning. Furthermore, patients exhibited more pronounced RT effects after saccade inhibition. These findings are consistent with functional abnormalities in FEF and SEF. Furthermore, these results indicate the potential of this task to measure improvements in cognitive functioning with psychopharmacological treatment and have implications for inclusion in cognitive remediation batteries, which have shown success in improving psychosocial functioning in patients with SZ (78,79).

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Supplementary material cited in this article is available online.

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