RESPONSE INHIBITION AND MONITORING IN SCHIZOPHRENIA: EVIDENCE FROM COUNTERMANDING SACCADES

By

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Thesis

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

MASTER OF ARTS

In

Psychology

August, 2008

Nashville, Tennessee

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ACKNOWLEDGEMENTS

This work was financially supported by NIH grants F32-EY016679, P30-EY08126, Ingram Chair in Neuroscience, and NARSAD. I would like to thank Drs. Sohee Park and Jeffrey Schall for their mentorship, and Dr. Leanne Boucher and Erik Emeric for their assistance with stimulus presentation and data analysis.

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CHAPTER I

INTRODUCTION

Control of action in schizophrenia

Executive function refers to the diverse cognitive abilities, largely subserved by frontal cortex, involved in the control of thought and action. Patients with schizophrenia have consistently been shown to have profound executive dysfunction (for review see, Barch, 2005). Although cognitive functioning is one of the most reliable predictors of functional outcome (Green, 1996), typical neuroleptic drugs used to treat schizophrenia do little to improve these deficits. As a group, atypical antipsychotics appear to be an improvement over typical neuroleptics, and there is evidence that different atypical antipsychotic drugs have different effects on specific cognitive functions (Meltzer & McGurk, 1999). This underscores the importance of investigating the specificity of executive dysfunction in schizophrenia in order to guide targeted interventions. Moreover, executive dysfunction appears to be present in both early in the course of illness (e.g. Chan, Chen, & Law, 2006) and in first-degree relatives (e.g. Park, Holzman, & Goldman-Rakic, 1995), indicating that executive dysfunction is a possible endophenotype, a trait marker of genetic liability, of the disease.

Two executive functions critically involved in the control of action are response inhibition and performance monitoring (Kok, et al., 2006). Response inhibition is defined as the ability to *deliberately* inhibit actions (Rabbitt, 1997). Patients with schizophrenia perform poorly on tasks that rely on response inhibition, such as the

Stroop task (eg., Brazo et al., 2002; Donohoe, Corvin, & Robertson, 2006) and antisaccade tasks (eg., Curtis, Calkins, & Iacono, 2001; Manoach et al., 2002). Results using the Go/No-Go task, in which subjects are required to respond to one stimulus (Go) but not to the other (NoGo), are mixed. Some studies have found that patients make more false-alarm errors to NoGo stimuli (Kiehl, Smith, Hare, & Liddle, 2000; Weisbrod, Kiefer, Marzinzik, & Spitzer, 2000), whereas others have not (Rubia et al., 2001). One study found that patients made fewer false-alarm errors than controls, likely due to the patients establishing less of a prepotent stimulus-response mapping to the Go stimuli (Ford et al., 2004). Correlations of task performance with symptoms have suggested an association with negative (Donohoe, Corvin, & Robertson, 2006; Mahurin, Velligan, & Miller, 1998) and disorganized symptoms (Brazo et al., 2002; Leeson, Simpson, McKenna, & Laws, 2005). Although the data are mixed (Brownstein et al., 2003), deficits in response inhibition have also been found in unaffected relatives of patients (Curtis, Calkins, & Iacono, 2001; Kumari, Ettinger, Crawford, Zachariah, & Sharma, 2005).

Performance monitoring involves the ability to evaluate actions and use feedback signaling success or failure to guide future performance. Performance monitoring is commonly indexed by error detection on a cognitive task and subsequent response time (RT) adjustments. Error detection is thought to be accompanied by ACC activation; this region is purported to be the generator of the error-related negativity (ERN), an event-related potential that follows 80-180 ms following an error (Dehaene, Posner, & Tucker, 1994; Gehring, Goss, Coles, Meyer, & Donchin, 1993; Van Veen & Carter, 2002).

Frith (1992) has posited a theory that positive symptoms are the result of a failure to effectively self-monitor, such that internally generated thoughts and actions are attributed externally, and there has been empirical support for this claim including impaired error correction (Frith & Done, 1989; Malenka, Angel, Hampton, & Berger, 1982) and misattribution of the source of self-generated speech (Brebion et al., 2000; Cahill, 1996). However, evidence for deficits in immediate error-related performance adjustments, such as post-error slowing and error correction, in patients with schizophrenia is mixed. Some studies have found intact post-error adjustments (Kopp & Rist, 1994, 1999; Laurens, Ngan, Bates, Kiehl, & Liddle, 2003; Mathalon et al., 2002; Polli et al., 2006). Others have reported impairments in trial-by-trial performance adjustments (Carter, MacDonald, Ross, & Stenger, 2001; Malenka, Angel, Hampton, & Berger, 1982; Malenka, Angel, Thiemann, Weitz, & Berger, 1986; Turken, Vuilleumier, Mathalon, Swick, & Ford, 2003). In contrast, patients consistently show reduced ERN amplitude following errors (Alain, McNeely, He, Christensen, & West, 2002; Kopp & Rist, 1999; Mathalon et al., 2002), and reduced ACC hemodynamic activity during error trials using event-related fMRI (Carter, MacDonald, Ross, & Stenger, 2001; Laurens, Ngan, Bates, Kiehl, & Liddle, 2003).

The vast literature on executive function in schizophrenia gives rise to the question of whether deficits in multiple domains (i.e. inhibition, response monitoring, working memory, etc.) represent semi-independent deficits or are subsumed under a fundamental impairment. Goldman-Rakic and colleagues (Goldman-Rakic, 1994; Park, Holzman, & Goldman-Rakic, 1995) have argued that the ability to guide behavior by working memory is the core deficit. In a similar vein, Barch and colleagues have

suggested that the ability to represent and maintain context information is impaired in schizophrenia (Barch et al., 2001; Braver, Barch, & Cohen, 1999; Braver & Cohen, 1999). This idea is similar to the idea of *goal neglect* put forth by Duncan (1996), a failure to active a target state that is necessary to fulfill current task requirements and echos Frith's (1992) theory that schizophrenia can be characterized as a "disorder of willed action".

Saccade countermanding paradigm

An important consideration in these studies of executive function in schizophrenia is the variety of instruments used; measurements of inhibition and performance monitoring might be confounded by the involvement of other cognitive processes. The stop signal, or countermanding, task has been used to investigate the ability to control initiation of a response (Lappin & Eriksen, 1966). In the oculomotor version of the task, a target appears in the periphery, and the subject is instructed to make a saccade to that target (*no-stop signal* trial) unless a subsequent stop signal appears (*signal* trial); in which case, the subject is instructed to withhold the prepotent response. Signal trials in which the subject is able to withhold the saccade are labeled *cancelled*, and signal trials in which the subject is not able to withhold the saccade to the target are labeled *noncancelled*. Subjects become less able to cancel a saccade as the stop signal delay (SSD), latency between the initial appearance of the peripheral target and the stop signal, increases. The inhibition function plots the proportion of noncancelled trials at each stop signal delay. Flatter inhibition slopes could indicate

poor capability for response inhibition or less sensitivity to the stop signal due to impairments in stimulus-response mappings.

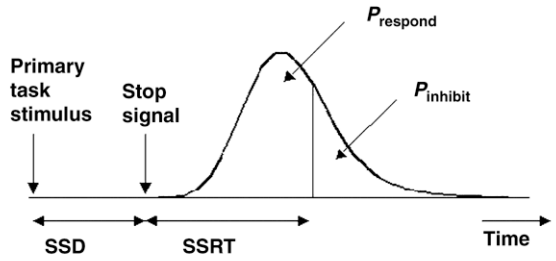

Figure 1. Race-model estimation of SSRT. A distribution of no-stop signal RTs is shown beneath the curve. SSD is the delay between target presentation and stop signal. The stop signal divides the no-stop signal RT distribution into two probabilities: a left part consisting of responses fast enough to escape inhibition ($P_{respond}$) and a right part corresponding to $P_{inhibit}$.

Performance in the stop signal task can be accounted for by a model based on a race between STOP and GO processes with independent stochastic finishing times (Figure 1; Logan & Cowan, 1984). Depending on whether the GO or STOP process 'wins', the response is executed or inhibited, respectively. This model provides an estimate of the time needed to respond to the stop signal and cancel the movement, the stop signal reaction time (SSRT), calculated using the distribution of RTs on no-stop signal trials and the probability of responding given a stop signal occurred. It has an advantage over other measures of inhibition in that, along with measuring the ability to inhibit a pre-potent response, it provides a measure of the time to cancel a planned action that is not confounded with group differences in mean and variability of GO trial RT.

Specific performance adjustments according to trial history have also been reported in this task. RTs on no-stop signal trials are significantly longer when they were preceded by correctly cancelled stop signal trials but less so following incorrect, noncancelled stop signal trials (Cabel, Armstrong, Reingold, & Munoz, 2000; Emeric et al., 2007; Kornylo, Dill, Saenz, & Krauzlis, 2003). In other words, no significant post-error slowing was observed. Emeric et al. (2007) suggest that the absence of post-error slowing may be due to high incidence and low cost of errors in this task. They also suggest that the increase in RT following cancelled trials may be due to compensatory adjustments in control due to response conflict between the mutually incompatible STOP process, identified with the activity of fixation neurons in the frontal eye fields (FEF), and the GO process, identified with presaccadic movement neurons in the FEF and superior colliculus (Schall & Boucher, 2007). The FEF is a brain region located in premotor cortex and implicated in the initiation of goal-directed saccades (Paus, 1996). This interpretation that trial-by-trial RT adjustments are due to conflict is supported by the discovery that single neurons in the supplementary eye field (SEF) signal conflict (Stuphorn, Taylor, & Schall, 2000), and that subthreshold microstimulation of SEF improves performance on the countermanding task by delaying saccade initiation (Stuphorn & Schall, 2006). Thus, there is an identifiable neural mechanism by which conflict is detected and subsequent RT adjustments are made.

Only a few studies of response inhibition in schizophrenia using the stop signal task have been conducted, and results have been mixed. Badcock et al. (2002) found equal SSRT but decreased slope of the inhibition function; as mentioned above, this could arise from poorer capability for response inhibition or less sensitivity to the stop

signal. They interpreted this finding as a deficit in control and planning of stop processes, rather than slowing of the stop processes. However, another group (Bellgrove et al., 2006) found increased SSRT in an early-onset schizophrenia sample, but only for left hand responses. Both of these studies used manual responses. Since slowed manual response time is a very consistent finding in patients (see Nuechterlein, 1977), it is difficult to distinguish whether inhibitory difficulties are occurring at a more executive or peripheral level.

There are a few major benefits to using an oculomotor versus manual version of the stop signal task in schizophrenia. Reuter and Kathmann (2004) argue for the advantage of using saccade tasks in studying cognitive deficits since they seem to show greater sensitivity in detecting subtle neuropsychological impairments (Broerse, Holthausen, van den Bosch, & den Boer, 2001). They also contend that because of the simple nature of saccade tasks, they have the potential to be used in analyzing specific components of executive dysfunction. Additionally, slowed RT for manual but not saccadic eye movements in schizophrenia is a consistent finding in the literature (Gale & Holzman, 2000; Nuechterlein, 1977), implying that the circuitry underlying basic visually guided saccades is intact. Using saccade tasks potentially reduces confounding effects that are not due to additional cognitive demands, like low-level motor function differences. Importantly, the neural circuitry of the oculomotor system is very well mapped, and using an oculomotor version of the task allows more direct applications of spatially and temporally precise intracranial recordings in non-human primates in order to build translational links to models of schizophrenia.

To summarize, the oculomotor stop signal task provides a precise measure of the inhibitory process by permitting both a measurement of the estimated time needed to inhibit a response, as well as a measurement of control over these inhibitory processes. Moreover, we can derive measures of response monitoring by examining RT adjustments based on performance in the prior trial. In the present study, we hypothesize that: 1) the speed of inhibitory processes is intact in patients, but the inhibitory response is triggered less often, suggesting a failure of goal updating; 2) healthy subjects will show significant elevation of response time following stop signal trials versus no-stop signal trials, particularly following cancelled trials, and schizophrenic subjects will exhibit idiosyncratic variability in the magnitude of these adjustments; 3) indices of response monitoring will be associated with decreased positive symptomology such that patients scoring lower on positive symptoms will exhibit increased post-error and post-cancelled slowing

CHAPTER II

METHODS

Participants

Nine schizophrenia patients and six healthy controls completed the experiment. Notably, one patient was excluded because he could not inhibit his responses at any of the SSDs. Patients that met *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV) criteria were recruited from an outpatient treatment facility in Nashville,TN, and diagnoses were confirmed from the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995). All patients were on a stable dose of atypical antipsychotic medication at the time of the experiment, on a mean chlorpromazine dose equivalent of 328 mg. Clinical symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), the Scale for Assessment of Positive Symptom (SAPS; Andreasen & Olsen, 1982), and the Scale for Assessment of Negative Symptom (SANS; Andreasen & Olsen, 1982). Control participants with no history of mental illness, confirmed with the SCID, were recruited from the community. Exclusion criteria were as follows: a history of substance dependence, neurological trauma or mental retardation. Patients and controls were matched for age, sex, and full scale IQ on the Wechsler Abbreviated Scale of Intelligence (See *Table 1* for demographic data).

Table 1. Means, standard deviations and group comparisons of demographic data and symptom rating scores. The Phi value is the result of a Fisher's Exact Test.

	Healthy Controls (n=6)	Schizophrenia Patients (n=8)	t	p
Age	35.6±3.5	37.3±3.1	.33	.74
Sex	4F/2M	3F/5M	Phi=.06	.59
WASI FSIQ	103±7	99±6	.51	.62
SAPS (min: 0, max: 175)		15.8±7.1		
SANS (min: 0, max: 125)		28.8±6.7		
BPRS (min: 0, max: 144)		13.4±4.0		
Mean Duration of illness (yrs)		14.7 years		
Mean CPZ dosage (mg)		328		

Countermanding task

Apparatus and Stimuli

Eye position was monitored through pupil tracking using the EyeLink II eye tracker (SR Research, Canada) at a sampling rate of 250 Hz with average gaze position error <0.5°, noise limited to <0.01° RMS. Saccades were detected on-line using a velocity criterion (35°/sec). Subjects were seated 57 cm from the computer monitor that delivered the visual stimuli, with their head in a chinrest. The fixation and targets subtended 1.0° and were light gray squares on a darker gray background.

Saccadic countermanding paradigm

Subjects performed the saccadic version of the countermanding task (Figure 2; Hanes & Carpenter, 1999; Hanes & Schall, 1995; Logan & Irwin, 2000). Seventy percent of the trials were no-stop signal trials. These required the subject to maintain

central gaze on the fixation spot until it disappeared (after a uniformly random delay of 200-600 msec) and an eccentric target appeared at one of 2 pseudo-randomly selected locations equidistant (8.5°) from the central fixation spot. Subjects were instructed to shift gaze as quickly as possible to the appearance of the target. The other 30% of trials were stop signal trials. On these trials, the fixation spot re-illuminated after a delay (SSD), cuing subjects that the response they were to make needs to be inhibited. Stop signal trials were labeled cancelled or noncancelled based on whether the planned saccade was inhibited or not inhibited, respectively.

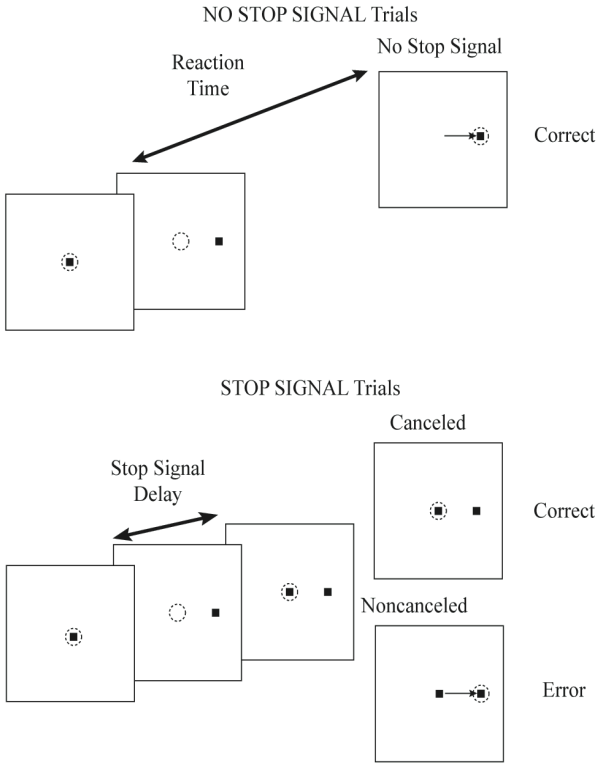

Figure 2. The saccade countermanding task. Dotted circles represent current gaze position.

A 1-up/1-down staircase procedure was used to determine the SSD on each stop signal trial. The delay was adjusted in increments of 50 ms based on performance in the prior stop signal trial. If the participant failed to cancel a saccade in a given trial, the SSD was reduced by 50 ms on the next stop signal trial. Likewise, if the participant successfully cancelled a saccade, the SSD was increased by 50 ms on the next stop signal trial. This procedure was used to ensure that approximately half of the stop signal trials were successfully inhibited.

Saccade initiation and termination were defined as the beginning and end of monotonic changes in eye position before and after the high velocity gaze shift. Trials during which the subject was fixating on the initial central target, the saccade was initiated only after presentation of the peripheral target, and the saccade terminated on the peripheral target will be classified as valid trials. For each valid trial, response time is the interval from target presentation to saccade initiation. The mean response time for each subject is the mean of session means.

Behavioral performance was evaluated through measurements of saccadic RTs on no-stop signal and noncancelled trials, and the probability of not canceling the eye movement as a function of SSD (the inhibition function). A linear regression will be fit to the inhibition function, and the slope was calculated.

As mentioned previously, performance in the stop signal task can be accounted for through a race model (Logan & Cowan, 1984). This model provides an estimate of the time needed to respond to the stop signal and cancel the movement, the stop signal reaction time (SSRT). With the integration method, the finish time of the STOP process is assumed to be constant. Although surely not so, violations of this assumption have

little effect on the validity of this estimate of SSRT (Band, van der Molen, & Logan, 2003; Logan, Cowan, & Davis, 1984). For each stop signal delay, SSRT is defined as the RT at which the integral of the no-stop signal RT distribution equals the proportion of noncancelled trials at that stop signal delay minus the stop signal delay. With the difference method, the finish time of the STOP process is assumed to be a random variable. The probability of responding given a stop signal at a given delay is described by the inhibition function. The difference method treats the inhibition function as a cumulative distribution. Mathematical analysis shows that the mean of this distribution equals the mean of the finish time for the GO process minus SSRT. Consequently, mean SSRT can be calculated by subtracting the mean of the inhibition function from the mean RT on no-stop signal trials. Difference in the values calculated by the two methods is typically small, so an overall SSRT estimate was taken as the average of the SSRT using both methods.

To examine behavioral indices of performance monitoring, saccade RTs on no-stop signal trials were sorted based on performance history and examined as a function of whether the preceding stop signal trial was cancelled or noncancelled or was a no-stop signal trial. Post-cancelled slowing was defined as the difference between mean RT of no-stop signal trials preceded by a cancelled trial and mean RT of no-stop signal trials preceded by a no-stop-signal trial. Post-error slowing was defined as the difference between the mean RT of no-stop signal trials preceded by a noncancelled trial and the mean RT of no-stop signal trials preceded by a no-stop-signal trial

To examine the relationship between symptomatology and measures of response inhibition and performance monitoring, Pearson product-moment correlations will be

calculated between measures of task performance and performance monitoring, outlined above, and positive and negative symptoms derived from the BPRS, SANS, and SAPS.

CHAPTER III

RESULTS

No-stop signal and noncancelled RTs

A repeated measures ANOVA was conducted on saccadic RTs with trial type (no-stop signal, noncancelled) entered as a within-subject factor and group entered as a between subjects factor (Figure 3). There was a main effect of trial type ($F(1,12)=41.7$, $p<.0001$) with no-stop signal RTs (251±40 ms) being slower than noncancelled RTs (206±36 ms). There was also a nonsignificant trend for patients to be slower than healthy controls (patients: 243±44 ms, healthy controls: 210±36 ms; $F(1,12)=3.7$, $p=.08$), but no group by trial type interaction ($F(1,12)=.0004$, $p=.98$).

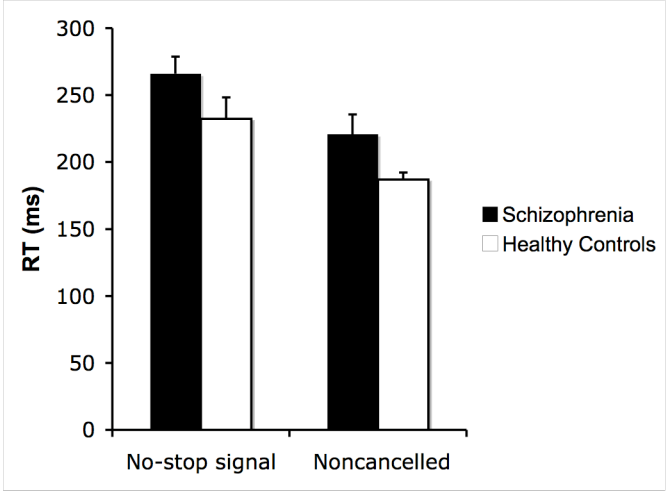

Figure 3. Bar graph of no-stop signal and noncancelled RT in milliseconds for schizophrenia patients and controls with standard error bars.

Stop signal reaction time

An independent t-test was conducted to evaluate group differences in SSRT, and no significant difference was found (Figure 4; controls: 132±39, patients: 135±52; t(12)=.09, p=.93). Thus, schizophrenia patients in this sample did not need more time to stop a planned movement.

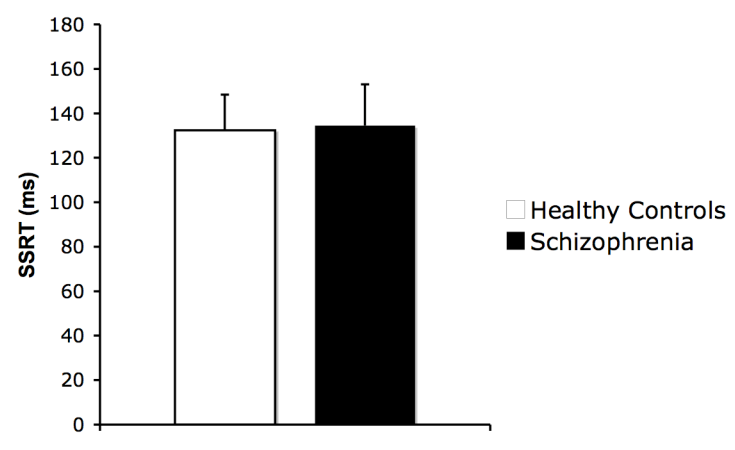

Figure 4. Bar graph of stop signal reaction time in milliseconds for schizophrenia patients and healthy controls with standard error bars.

Slope of inhibition function

An independent t-test was conducted to evaluate group differences in the linear slope of the inhibition function. Patients tended, non-significantly, to have a shallower slope than healthy controls (Figure 5; patients: 1.7±.90, controls: 2.9±1.3; t(12)=2.07, p=.06). Since a flatter inhibition function could result from either variability in the GO or STOP process (Logan, 1994), within-subject variability in no-stop signal RTs was compared across groups. Patients and controls did not differ in the amount of variability (t(12)=1.3, p=.21).

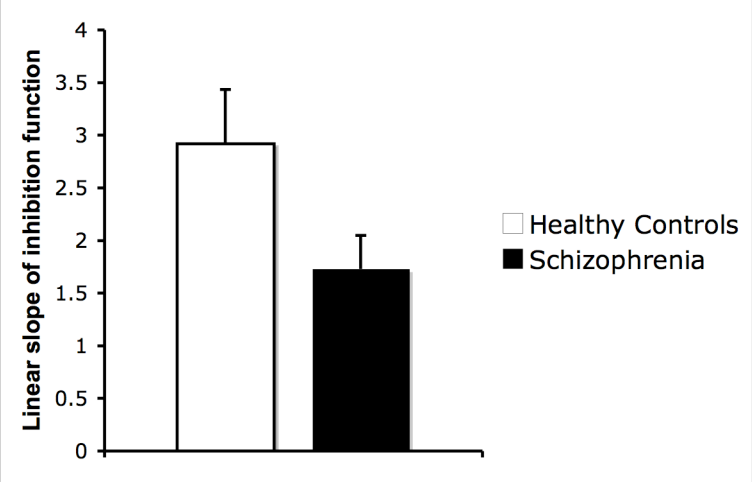

Figure 5. Bar graph with standard error bars of the mean linear slope of the inhibition function for schizophrenia patients and healthy controls.

Response monitoring

A repeated measures ANOVA was conducted on no-stop signal RTs with previous trial type (no-stop signal, noncancelled, cancelled) entered as a within subjects factor and group entered as a between subjects factor (Figure 6). There was a significant main effect of previous trial ($F(2,24)=43.5$, $p<.0001$). Pairwise comparisons revealed a significant difference in no-stop signal RTs between all of the previous trial types, with Tukey corrections for multiple comparisons (previous no-stop signal trial: 234±38 ms, previous cancelled trial: 323±68, previous noncancelled trial: 281±48). There was also a main effect of group ($F(1,12)=4.7$, $p=.05$), such that patients (301±64 ms) were slower than healthy controls (251±52 ms). Three planned contrasts were conducted to examine group differences in no-stop signal RTs preceded by each of the trial types. Patients were significantly slower than healthy controls on no-stop signal trials preceded by both cancelled (patients: 354±60 ms, controls: 281±57; $t(12)=2.4$, $p=.04$) and noncancelled (patients: 302±40 ms, controls: 253±45; $t(12)=2.2$, $p=.05$) stop

signal trials, but these differences failed to meet the Bonferroni-corrected pairwise alpha level (α=.017). However, there was no group difference in RTs preceded by no-stop signal trials (patients: 245±35 ms, controls: 220±39 m; t(12)=1.3, p=.23).

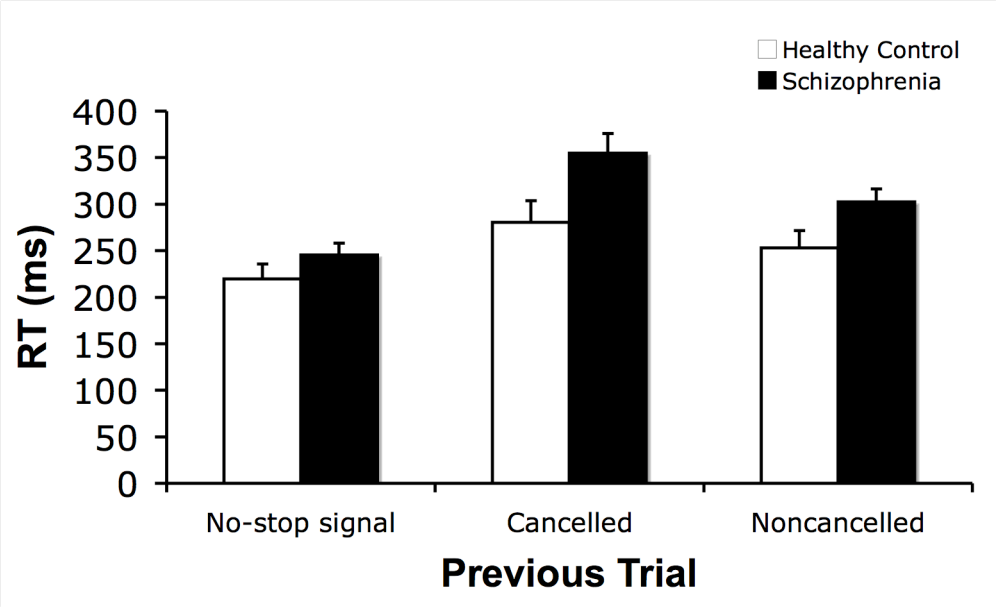

Figure 6. Bar graph with standard error bars of mean no-stop signal RT in milliseconds as a function of prior trial for schizophrenia patients and healthy controls.

Symptom correlations

There was a significant inverse correlation between SAPS score and amount of post-error slowing in patients with schizophrenia (r=-.76, z=2.2, p=.03). Greater positive symptom severity was associated with less slowing following an erroneously noncancelled stop signal trial (Figure 7). This correlation was not due to patients high on positive symptoms showing reduced post-error slowing compared to healthy controls. Rather, patients low on positive symptoms showed elevated post-error slowing compared to controls. There were no other significant correlations between symptom severity and measures of response inhibition and response monitoring.

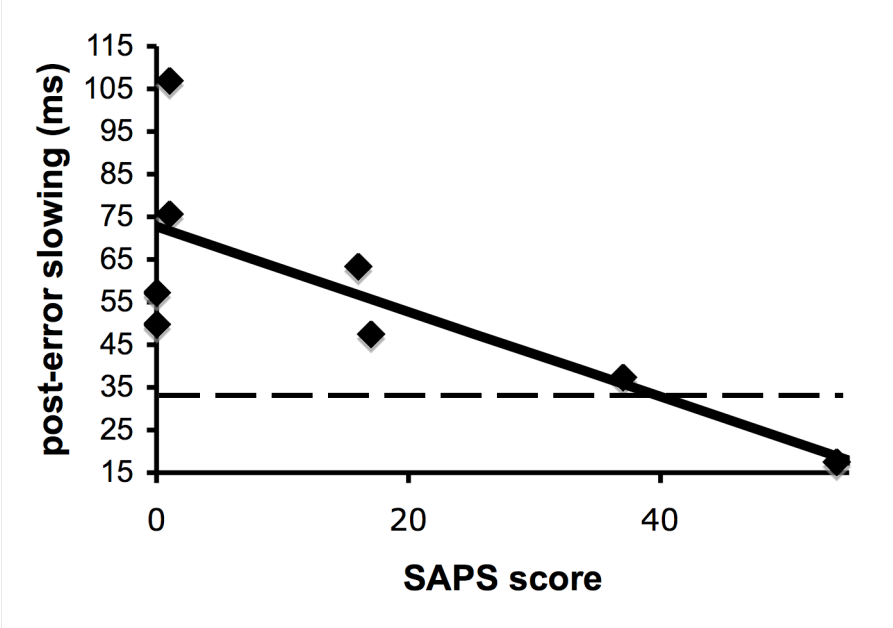

Figure 7. Linear regression of positive symptom severity on post-error slowing. Dotted line represents the mean post-error slowing for healthy controls (*SAPS*: Scale for Assessment of Positive Symptoms).

CHAPTER IV

DISCUSSION

Conformity to race model

Since this is the first study to examine performance of patients with schizophrenia on an oculomotor version of the stop signal task, it is important to note that all patients except one were able to comply with task instructions and tolerate the testing procedure. Notably, two important criteria for applying the race model to this data were fulfilled. First, their inhibition functions are generally increasing (i.e. as SSD increases, the proportion of noncancelled trials increases). Second, the mean RT for no-stop signal trials is greater than the mean RT for noncancelled stop signal trials, which follows from the race model assumption that the RT distribution on noncancelled trials amounts to the portion of the no-stop signal RT distribution that are less than the SSD plus the SSRT.

No-stop signal RT

Although patients with schizophrenia tended non-significantly to be slower on no-stop signal trials than healthy controls, this effect was only present for no-stop signal trials preceded by either cancelled or noncancelled stop signal trials; for no-stop signal trials preceded by no-stop signal trials, there was no group difference in RT. This is consistent with several other reports of normal latency of visually guided saccades in schizophrenia (Gale & Holzman, 2000; Nuechterlein, 1977).

Response Inhibition

In this sample, patients with schizophrenia do not show differences in the time needed to cancel a planned movement, evidenced by equal stop signal reaction time. Once the STOP process is initiated, it does not take any longer to complete than in healthy controls. However, patients tended to show a deficit in *triggering* the STOP processes, as evidenced by a reduced slope of the inhibition function, which is not accounted for by increased variability in no-stop signal reaction times (i.e. variability in the GO process). This is consistent with an earlier report of equal SSRT but reduced slope of the inhibition function (Badcock, Michie, Johnson, & Combrinck, 2002) using a manual version of the stop signal task.

The data also indicate that patients have a weaker stimulus-response mapping to the stop signal and a reduced sensitivity to the cue to inhibit, supporting the notion of a general impairment in using working memory to maintain representations of task-related goals underlying response inhibition deficits in schizophrenia. Based on a literature review and their own findings, Kane and Engle (2003) argue that action control, measured using the Stroop task, is sensitive to individual differences in working memory capacity and that interference of a prepotent response on an trial requiring inhibition in the context of a task with many trials that require a dominant response (e.g. the stop signal task) is due to a transient failure of goal maintenance in working memory. Further, several studies of inhibition in schizophrenia using the antisaccade task have argued for the relevance of working memory. Two studies have found negative correlations between working memory functions and proportion of reflexive saccades in

an antisaccade task (Gooding & Tallent, 2001; Nieman et al., 2000), and Hutton et al., (2002) found that patients with schizophrenia showed spared inhibition if the working memory demand of the task was low, and inhibition deficits that increased with the working memory demand.

Response Monitoring

We found a pattern of RT adjustments based on the immediately preceding trial similar to previous studies (Cabel, Armstrong, Reingold, & Munoz, 2000; Emeric et al., 2007; Kornylo, Dill, Saenz, & Krauzlis, 2003), with significant RT elevation of no-stop signal trials preceded by both noncancelled and cancelled stop signal trials compared to those preceded by a no-stop signal trial and significant elevation of RT for no-stop signal trials preceded by successfully cancelled versus noncancelled trials. Interestingly, patients showed equal no-stop signal RTs for trials that were preceded by a no-stop signal trial, but they showed greater no-stop signal RTs compared to controls for trials preceded by either a noncancelled or cancelled stop signal trial, although this finding failed to meet correction for multiple comparisons. In short, patients seemed to show greater compensatory RT adjustments based on the presence of a stop signal in the prior trial.

There are a few theories regarding how these RT adjustments are instantiated, which are not necessarily incompatible. The error-monitoring hypothesis proposes RT adjustments arise from a comparison between the representations of the actual response and the correct response (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993). The reinforcement-feedback

hypotheses proposes that adjustments are elicited by feedback indicating error or punishment (Gehring & Willoughby, 2002; Miltner, Baum, & Coles, 1997). The conflict-monitoring hypothesis proposes the adjustments are due to detection of coactivation of incompatible responses, which recruit control processes (Botvinick, Braver, Barch, Carter, & Cohen, 2001). Although these data do not speak to the validity of the above theories, to our knowledge, there is no evidence in the literature to support patients with schizophrenia showing heightened error or conflict detection. To the contrary, the amplitude of ERP components thought to index error or conflict monitoring are generally found to be decreased in patients with schizophrenia (Alain, McNeely, He, Christensen, & West, 2002; Kopp & Rist, 1999; Mathalon et al., 2002; Weisbrod, Kiefer, Marzinzik, & Spitzer, 2000).

Another possible interpretation is that these increased trial-by-trial RT adjustments based on the immediately preceding trial in schizophrenia could be due to a working memory deficit. Previous studies have shown that as the proportion of stop signal trials is increased, mean RT on no-stop signal trials also increases (Logan & Burkell, 1986). Moreover, Emeric, et al. (2007) noted that nonhuman primates and humans were sensitive not only to the immediately preceding trial, but as the number of preceding consecutive no-stop signal trials increased, no-stop signal RT decreased. Likewise, as the number of preceding stop signal trials increased, stop signal RT increased. It is possible that patients with schizophrenia might be basing their estimated probability of a stop signal on the upcoming trial on a smaller number of preceding trials. Thus, their estimated probability of a stop signal trial might be more biased by the immediately preceding trial than healthy controls, causing a transient

increase in RT. Although there has been little work investigating probability estimation in patients with schizophrenia, recent work has suggested a link between working memory capacity and accurate estimation of the likelihood of an event, such that increased working memory capacity allows a greater number of alternative events to be considered and a more accurate probability judgment (Dougherty & Hunter, 2003; Dougherty & Hunter, 2003). There is robust evidence for a fundamental working memory impairment in schizophrenia (for meta-analysis see Lee & Park, 2005).

Symptom correlations

In the present sample, severity of positive symptoms was negatively correlated with the amount of slowing following a noncancelled stop signal trial. Thus, greater RT adjustments following an erroneous noncancelled trial was associated with decreased positive symptoms. Interestingly, patients low on positive symptoms showed relatively robust post-error slowing, which is unusual in this task. The amount of post-error slowing in patients high in positive symptoms was closer to the mean in healthy controls (Figure 7). The association of post-error slowing with positive symptoms is a potential explanation for mixed results among studies of behavioral indices of performance monitoring in schizophrenia, like error awareness and post-error slowing. Symptom profiles of patient samples could lead to differing results across studies. Moreover, this relationship might indicate that increased awareness and subsequent adjustments of behavior in schizophrenia might be a compensatory strategy for managing positive symptoms and, although highly speculative at this point, a possible avenue for targeted behavioral interventions.

Limitations

There are several limitations to the present study, the major limitation being the small sample size. Another potential concern in this study is the use of a tracking procedure to dynamically adjust the stop signal delay, and thereby dynamically adjusting the difficulty in canceling. The rationale behind using the tracking procedure was to ensure that error rates would be the same across groups and that the bulk of trials would be in the dynamic range of the inhibition function. However, the tracking procedure can also lead to transient periods of goal neglect or inattention being related to the stop signal delay and trial difficulty. Future replications of this study will also use fixed, random stop signal delays.

Another limitation in interpreting the correlation between post-error slowing and positive symptoms is the somewhat limited range of positive symptom scores. Most of the participants are relatively high-functioning and their symptoms are fairly well managed with neuroleptics. More subjects with high positive symptoms are needed to fully explore the relationship of task performance and response monitoring with symptomology.

Summary

To conclude, this is the first study investigating response inhibition in patients with schizophrenia using an oculomotor version of the stop signal task, and the first study in schizophrenia looking at RT adjustments based on trial history in the stop signal task. In our sample, we found no evidence for a slowing of the inhibitory process

in schizophrenia, but rather a deficit in triggering this process. Moreover, this deficit existed in spite of increased RT adjustments based on trial history.

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