INHIBITION AND MONITORING OF SACCADIC EYE MOVEMENTS IN SCHIZOPHRENIA

By

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CHAPTER I

INTRODUCTION

Flexible modification of behavior based on advance knowledge or feedback is essential to adaptive functioning in a dynamic environment. Schizophrenia is associated with impairments in a wide range of cognitive functions that underlie behavioral flexibility, including working memory (Lee & Park, 2005), attention (Braff, 1993), and cognitive control (Barch, 2005). Cognitive deficits in schizophrenia predict functional outcome better than do clinical symptoms (Green, 1996) and are major targets for pharmacotherapy. Further, a subset of these deficits has been identified as candidate endophenotypes, or biological markers, of the disorder. However, the precise cognitive profile of schizophrenia has yet to be defined, in part because of the paradigms used to study cognitive function in schizophrenia. Understanding the specific cognitive profile—the pattern of functions that are spared and impaired—in schizophrenia is important for development of new treatments and for potentially discovering cognitive markers of the disease that are present prior to onset. Although certain neuropsychological tasks are touted to probe specific aspects of cognition, they often place demands on a range of functions, making it difficult to draw precise conclusions about the nature of deficits. As such, it is still unclear whether deficits in multiple domains of cognitive functioning represent semi-independent impairments or are subsumed under one fundamental impairment. Indeed, Park, Goldman-Rakic and colleagues argue that the ability to guide

behavior by internal representation (i.e. working memory) is the core deficit (Goldman-Rakic, 1994; Park, Holzman, & Goldman-Rakic, 1995).

As an alternative to standard neuropsychological tests, a translational approach, in which paradigms are adapted from the animal literature, can be more valuable in describing specific cognitive deficits and making clear hypotheses about underlying abnormalities in brain function in schizophrenia. Further, the use of saccadic over manual tasks in schizophrenia has an added advantage. Slowing in manual response times (RTs) has been consistently reported in schizophrenia (Nuechterlein, 1977), but the latency of reflexive saccades is generally normal (Gale & Holzman, 2000; Levin, Holzman, Rothenberg, & Lipton, 1981). Thus, it has been argued that the use of saccadic tasks to study cognitive function in schizophrenia minimizes confounding effects due to impairments in the basic response system (Reuter & Kathmann, 2004).

The goal of the following series of experiments was to advance our understanding of two particular cognitive functions related to flexible behavior in schizophrenia, response inhibition and response monitoring, using two experimental paradigms that are firmly grounded in neurophysiology research and mathematical modeling. In the following introduction, I will discuss response inhibition and response monitoring in healthy human and non-human primates and discuss findings in schizophrenia. Then, I will focus on behavioral, neurophysiological, and computational modeling data from the countermanding and double-step paradigms, and argue that these tasks are well-suited for examining deficits in schizophrenia.

Response Monitoring

Response monitoring involves evaluation of actions via feedback to guide future actions. Although internal monitoring is a covert process, it can be measured via behavioral adjustments to ongoing or future actions, typically as a function of errors. That is, in healthy organisms, errors give rise to predictable adjustments, and these observable adjustments can serve as a measure of the integrity of the monitoring process. Response monitoring has been studied at two levels of analysis: online adjustment to current action plans and adjustments to future action plans based on performance history. It has been studied in the context of basic motor tasks as well as higher-level cognitive tasks, but there has been surprisingly little cross-talk between these fields.

Response monitoring is of interest in schizophrenia from two perspectives. Irwin Feinberg (1978) theorized that a deficit in the monitoring of self-generated action in schizophrenia gives rise to the positive symptoms of the disorder. This theory predicts that if internal feedback of the motor command to sensory areas permits the distinction between self-generated and environmentally-generated thoughts or actions, then absent or disordered internal feedback could induce various psychotic experiences. Frith formalized this idea (1987) and argued that information about volitional actions is not appropriately monitored in schizophrenia. He reasoned that since the role of the internal monitoring system in action production is to communicate that a thought or action will occur and indicate the source of this action, a breakdown in this internal monitor could lead to ambiguity in or misattribution of the source of an action. For example, auditory

hallucinations could arise because self-generated internal speech is misattributed externally, and delusions of being controlled by an outside force could occur because feedback from the internal monitor about the expected consequences of an action is absent.

Examination of response monitoring in schizophrenia is also relevant for cognitive control. The ability to monitor actions and use information indicating success or failure to guide future actions is purported to be necessary for efficient cognitive performance (Kok, Ridderinkhof, & Ullsperger, 2006). Patients with schizophrenia have consistently been shown to have pervasive deficits in executive functions, those cognitive abilities that are involved in the control of thought and action (see Barch, 2005 for review).

Response Monitoring in Healthy Organisms

Sensory and motor systems interact to form feedback and feed-forward mechanisms for monitoring and correcting motor plans. In feedback mechanisms, sensory units provide a feedback signal to a comparator, which then compares that signal to a reference signal that carries information about the desired motor output. The resulting error signal is sent to the controller to optimize the output of the motor system. Because transport of sensory signals to the central nervous system is relatively slow, feedback mechanisms are inefficient when fast movements are required. For example, Wolpert and Ghahramani (2000) cite the example of predicting the location of a tennis ball that one has just hit; if relying solely on the retinal location of the ball, the estimate

of its position would be delayed by approximately 100 ms. In such a case, mechanisms that provide advance information about the position or force of effector muscles are more effective, and feed-forward mechanisms provide just this.

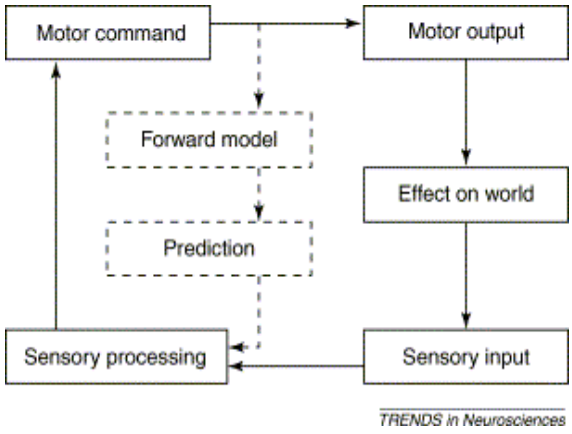

Figure 1. Schematic representation of a sensorimotor system with a forward model. The unbroken lines indicate the loop by which a motor command is translated into motor output, has some effect on the world and causes some sensory input, which the system can process to generate the next command. The forward model is an internal loop (broken lines) that takes the motor command and predicts the expected sensory input, which can be used to modulate the processing of the actual input. Reproduced from Webb (2004).

Feed-forward mechanisms (*Figure 1*) use information about the current state of the system to make predictions about sensory consequences of motor commands (see Wolpert & Ghahramani, 2000 for review). These mechanisms allow organisms to make fast adjustments to motor programs. They also allow mobile organisms to distinguish between self-generated and externally generated actions. The term corollary discharge refers to those motor signals that send information to sensory areas and allow for prediction of sensory states. Along with maintaining visual stability and providing a

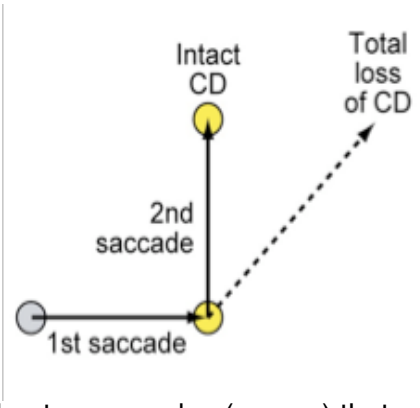

Figure 2. The pattern of double-step saccades (arrows) that would be expected with intact corollary discharge vs. a total loss of corollary discharge. Replicated from Sommer and Wurtz (2008).

means to distinguish externally versus internally generated actions, an important function of corollary discharge is fast corrections and adjustments of movements.

Psychophysical evidence for corollary discharge in the saccade system has been obtained using the double-step task (e.g. Aslin & Shea, 1987; Becker & Jurgens, 1979; Camalier et al., 2007; Hallett & Lightstone, 1976; Komoda, Festinger, Phillips, Duckman, & Young, 1973; Lisberger, Fuchs, King, & Evinger, 1975; Murthy et al., 2007). In this task, two targets are flashed sequentially, and subjects are instructed to make a saccade to the remembered locations of the first then to the second target. Since saccades are made in darkness and fixation points and targets are removed following presentation, the use of visual feedback is impossible and proprioception appears to provide little extraretinal information in making sequential saccades (Lewis, Zee, Hayman, & Tamargo, 2001; Steinbach, 1987). In this task, the measure of interest is the accuracy of the second saccade. A second saccade that lands on the correct target location implies intact corollary discharge. A vector that deviates from the target location, due to not compensating for the first saccade, implies impairments in corollary

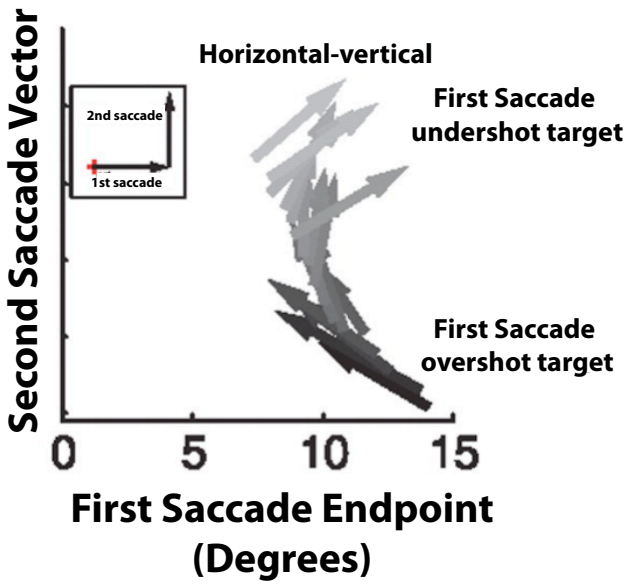

Figure 3. Adapted from Joiner et al. (2010)

discharge (*Figure 2*). Monkeys and humans can accurately compensate for the first saccade, and make an accurate second saccade to the remembered location, even when the intersaccadic interval between first and second saccade is very brief (Becker & Jurgens, 1979; Camalier, et al., 2007; Levy-Schoen & Blanc-Garin, 1974). Further, the second saccade can compensate for variations in the amplitude of the first saccade (*Figure 3*). That is, despite making a hypometric or hypermetric saccade to the first target, an accurate saccade to the second target can be executed (Joiner, FitzGibbon, & Wurtz, 2010).

Rapid correction of erroneous movements also lends psychophysical support to corollary discharge mechanisms. Hypometric saccades are corrected with a much shorter latency than would be predicted if relying on visual feedback (Becker & Jurgens, 1979; Kalesnykas & Hallett, 1987). Corollary discharge mechanisms are also

hypothesized to play a role in smooth pursuit eye movements, those that allow tracking of moving objects. If the eye does not keep up with the target motion, discrepancies in target and foveal location (position error) and velocity (retinal slip) lead to catch-up saccades being made to realign the eye to the target (de Brouwer, Yuksel, Blohm, Missal, & Lefevre, 2002). In contrast to saccades to stationary targets, catch-up saccades must take into account the velocity of the eye relative to the target velocity in order to be accurate; otherwise, the saccade would fall short of the moving target, and corollary discharge mechanisms are purported to play a role in these corrections.

Despite strong psychophysical evidence for corollary discharge and its role in the rapid monitoring of erroneous motor output, how it is instantiated in the primate brain is still poorly understood. However, potential sources and pathways of corollary discharge have been observed in the primate brain, in particular the pathway from superior colliculus (SC) in the brainstem to frontal eye fields (FEF) via the medial dorsal nucleus of the thalamus (SC-MD-FEF). Work by Sommer and Wurtz (2002) has provided evidence that MD relay neurons carry corollary discharge signals. They found that although inactivating MD relay neurons did not affect saccade execution in a simple visually guided saccade task, which did not rely on corollary discharge for accurate performance, MD inactivation disrupted performance on the double-step saccade task that did rely on corollary discharge signals.

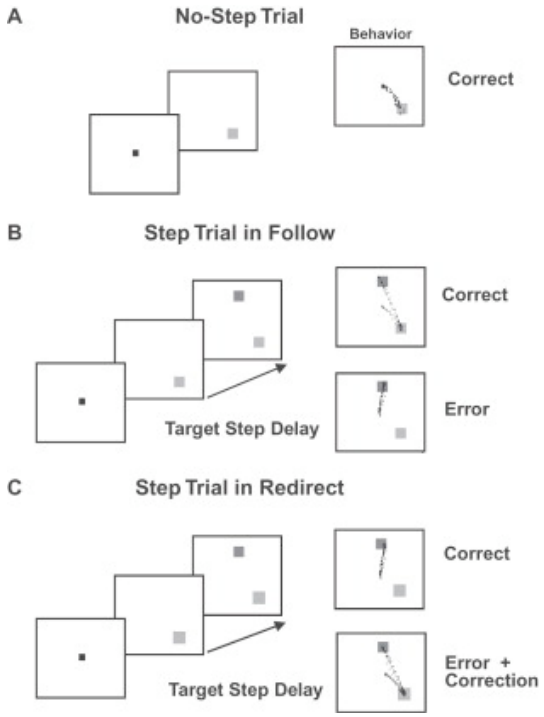

Figure 4. Schematic representation of events in different trial types in the FOLLOW and REDIRECT conditions. (A) No-step trial. Subject instructed to make saccade to target. (B) Step trial in the FOLLOW condition. Subject instructed to make saccade to first target, then second target. (C) Step trial in REDIRECT condition. Subject instructed to cancel response to first target and look directly at the second target. In correct trials, subjects made saccade only to second target. In incorrect trials, response consisted of initial incorrect response to first target and corrective saccade to final target. Adapted from Ray, et al. (2004)

There is also clear evidence from more complex cognitive tasks that the brain monitors performance, detects errors, corrects them, and uses internally or externally generated error feedback to adjust future performance. Research on error corrections has indicated that corrective movements can be planned before the error response has even been executed (Coles, Gratton, Bashore, Eriksen, & Donchin, 1985; Maylor & Rabbitt, 1987; Maylor & Rabbitt, 1989; Murthy, et al., 2007; Rabbitt, 1966a, 1966b, 1990, 2002; Rabbitt & Rodgers, 1977; Ray, Schall, & Murthy, 2004; Sharika, Ramakrishnan, & Murthy, 2008). Although, in some cases these error-correcting

movements have been construed as delayed correct responses (e.g. Coles, et al., 1985), there is evidence from oculomotor studies that there is more to the story.

Ray, Schall, and Murthy (2004; Figure 4) devised a modified version of the double-step task, which was performed under two separate sets of instructions, to explore the role of cognitive control in programming sequential saccades. In this experiment, the majority of trials were *no-step* trials, in which the subject was instructed to make a saccade to a single target. The remaining trials were *step* trials; in these trials, a second target appeared at some delay following the first target. In the *step* trials of the FOLLOW instruction block, subjects were instructed to make two successive saccades to the targets in the order of their presentation. In *step* trials of the REDIRECT condition, subjects were instructed to inhibit their saccade to the first target and, instead, redirect gaze to the second target. As the delay between the first and second target presentation becomes longer, subjects are more likely to fail to inhibit their response to the first target. On those error trials, subjects would look at the first target, then make a corrective saccade to the second target. So, for both incorrect *step* trials of the REDIRECT condition and correct *step* trials of the FOLLOW condition, a sequence of two saccades was executed. However, in the REDIRECT condition, the second saccade was a corrective response, whereas in the FOLLOW condition it was the correct response. The authors found that saccades to the second target were faster when they were error-correcting versus correct; that is, second saccades for incorrect trials of the REDIRECT condition were faster than correct trials of the FOLLOW condition. The inter-saccadic interval was also shorter in the REDIRECT versus FOLLOW condition.

Further, they found that processing rates for programming concurrent saccades were faster in the REDIRECT condition. These results support the conclusion that cognitive control processes that occur during error correction facilitate processing of the corrective saccade.

In an elaboration of these findings, Shakira, Ramakrishnan, and Murthy (2008) used a variant on the REDIRECT condition of the paradigm described above. As well as step trials, they included target-shift step trials in which the second target shifted location during the execution of the first saccade to test whether motor preparation for the corrective saccade can occur in parallel with the initial incorrect saccade. They observed error step trials in which the corrective saccade was made to the old, pre-shifted location of the final target, and concluded that preparation of the corrective saccade can begin concurrently with preparation of the erroneous saccade. Using a rise-to-threshold model (Carpenter & Williams, 1995), they estimated that 97% of corrective saccades were prepared before or during the erroneous saccade, before sensory feedback was available. Finally, they found that as the probability of making an erroneous response increased (i.e. as the *target step delay* increased), the onset latency of the corrective saccade decreased, which they interpreted as existence of predictive control. That is, error correction arises, in part, due to the brain estimating the likelihood of an error as it is trying to execute the correct response (in this case, inhibiting a saccade).

The effect of response monitoring can also be measured on future task performance. Slowing down on the trial following an error is a robust finding (e.g.

Jentzsch & Dudschig, 2009; Laming, 1979; Rabbitt, 1966b; Rabbitt & Rodgers, 1977; Verbruggen, Logan, Liefooghe, & Vandierendonck, 2008); however, there is some debate as to whether post-error reflects the workings of a cognitive control mechanism, or simply a result of error trials lengthening the psychological refractory period (Jentzsch & Dudschig, 2009). These hypotheses are not mutually exclusive (Rabbitt & Rodgers, 1977). A more recent theory supposes that the mechanism supporting post-error slowing is not specific to errors, but extends to rare events. That is, slowing arises due to attention being oriented away from current task demands by infrequent events (Notebaert et al., 2009).

The neural events associated with response monitoring have been of recent interest in cognitive neuroscience. Notably, a response-locked waveform that peaks soon after an error in speeded response tasks, the error-related negativity (ERN), has been described (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993). The ERN is typically localized to the anterior cingulate cortex (ACC; Dehaene, Posner, & Tucker, 1994; Van Veen & Carter, 2002). Functional MRI studies have also found increased BOLD activity in the ACC during error trials (e.g. Carter et al., 1998; Hester, Fassbender, & Garavan, 2004; Kiehl, Liddle, & Hopfinger, 2000; Menon, Adleman, White, Glover, & Reiss, 2001; Polli et al., 2006; Ullsperger & von Cramon, 2001; Ullsperger & von Cramon, 2003), cells responsive to errors have been found in monkey ACC (Amiez, Joseph, & Procyk, 2005; Ito, Stuphorn, Brown, & Schall, 2003; Niki & Watanabe, 1979), and lesions to ACC result in an attenuated ERN (Swick & Turken, 2002). A waveform similar in scalp distribution and latency is observed

following error feedback, the feedback-related negativity (FRN; Miltner, Baum, & Coles, 1997), and sometimes can be seen in reduced amplitude following correct responses, the CRN (Gehring & Knight, 2000; Luu, Flaisch, & Tucker, 2000; Scheffers & Coles, 2000). The CRN has been interpreted to be a result of some degree of error processing, either subthreshold error activity or uncertainty in response accuracy. The error positivity (Pe) is a slow positive-going potential with a centroparietal distribution that follows errors and peaks later than the ERN (Falkenstein, et al., 1991).

Exactly what these medial frontal negativities and ACC activity during errors represent has been up for contention amongst cognitive neuroscientists. The *Error Detection* hypothesis suggests that the ERN is a product of the process that compares motor output via corollary discharge from the movement command to a representation of the correct response; the mismatch between these two representations is reflected by the ERN (Falkenstein, et al., 1991; Gehring, et al., 1993). The *Conflict-Monitoring* theory (Botvinick, Cohen, & Carter, 2004; Carter, et al., 1998) posits that the ERN reflects conflict between competing responses. For example, a task that requires overcoming a prepotent response to a stimulus would engender conflict in the response system between the automatic, but inappropriate, response and the correct response. They argue that this response conflict signal, generated in the ACC, indicates the need for more cognitive control resources to be engaged. In the framework of this theory, ERN and increased BOLD activity in the ACC activity on error trials are argued to be the result of co-active response programs associated with the correct and erroneous response. Although the conflict-monitoring theory has had success explaining a wide

array of empirical phenomena, there are several findings that cannot be accounted for by this model (Ito, et al., 2003; Ridderinkhof et al., 2002; Swick & Turken, 2002). The *Reinforcement Learning Theory* of the ERN (Holroyd & Coles, 2002) supposes that a signal is generated in the basal ganglia upon failure to obtain a predicted reward. In the context of this theory, the monitoring mechanism responds to the earliest information signaling a failure to receive reward, resulting in a phasic decrease in dopaminergic activity. The mesencephalic dopamine system then sends the signal to the ACC, which conveys the need for cognitive control resources to be implemented. So, while stimulus-response-reward contingencies are being learned, this phasic decrease in dopaminergic activity occurs after external feedback that the response was incorrect. However, after learning these contingencies between rewards and S-R pairs, this signal propagates back in time and occurs after the response is made since external feedback is no longer necessary. Finally, the *affective/motivational theory* argues that the ERN represents not only evaluation of an error, but the affective response to the expectancy violation (Luu, Collins, & Tucker, 2000; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003). This theory does not present itself as an alternative to conflict or reinforcement learning hypotheses, but instead posits that errors or conflict gives rise to affective evaluations, which are represented by the ERN and ACC activity. Although the Pe has not been studied in as much detail as the ERN, its function has generally been conceptualized in terms of error significance (see Falkenstein, 2004 for review).

The neural basis of RT adjustments based on trial history is unclear. Functional MRI studies have suggested that ACC communicates with lateral PFC, which

implements these compensatory actions (see Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004 for review). However, lesions to lateral PFC did not affect post-error slowing (Gehring & Knight, 2000). Supplementary eye fields (SEF) in the medial frontal cortex can bias saccadic latency via connections to cortical and subcortical oculomotor regions (Schall & Boucher, 2007) and appears to be the basis of slowing following correctly inhibited saccades in a response inhibition task (Stuphorn & Schall, 2006). SEF and lateral PFC are connected anatomically (Munoz, 2002), and are also both connected to superior colliculus, brainstem, and cerebellum, but their functional relationship with regard to dynamic adjustments to performance based on trial history is yet to be investigated.

Response Monitoring in Schizophrenia

Although the literature is relatively sparse, there is evidence that patients with schizophrenia show some subtle deficits in the online monitoring of motor output, both in basic motor tasks as well as cognitive tasks. In the basic motor domain, the bulk of this work has been performed with oculomotor responses, specifically using smooth pursuit eye movement tasks. One of the most replicated findings in schizophrenia research is impaired smooth pursuit eye movements, with patients and their healthy relatives being less able to track the target and making more catch-up saccades to return the eyes to the target (see Levy, Holzman, Matthysse, & Mendell, 1993 for review). Although the dynamics of these corrective catch-up saccades has rarely been the focus of research, there is data to indicate that patients have a higher threshold for position and velocity

error during smooth pursuit tracking before correcting, as indexed by larger catch-up saccade amplitude (Abel, Friedman, Jesberger, Malki, & Meltzer, 1991; Litman, Hommer, Radant, Clem, & Pickar, 1994; Ross et al., 1997) and larger position (Fabisch et al., 2009) and velocity error (Radant & Hommer, 1992) prior to executing a catch-up saccade. Further, there is evidence that catch-up saccades are less accurate in patients (Ross, et al., 1997; Thaker et al., 1996). However, findings of increased catch-up saccade amplitude are not consistent, and several studies have failed to find significant differences in patients (Friedman, Jesberger, & Meltzer, 1991, 1992; Friedman, Kenny, Jesberger, Choy, & Meltzer, 1995; Lencer et al., 2008).

Few studies have been conducted on monitoring of motor errors outside the oculomotor domain; however one study found impaired monitoring of grip tension errors in patients (Rosen, Lockhart, Gants, & Westergaard, 1991). Additionally, analogous to smooth pursuit abnormalities, visuomotor tracking impairments in schizophrenia have also been reported (Gaebel & Ulrich, 1987; Silver, Shlomo, Schwartz, & Hocherman, 2002; Tigges et al., 2000) and, interestingly, have been related to positive symptomology (Gaebel & Ulrich, 1987). Although, to my knowledge, the dynamics of corrective movements in these visuomotor tracking tasks have not been described in detail, impaired manual tracking is likely related to impaired online monitoring of movement given the necessity of forward motor control for accurate, uninterrupted tracking. Further, in a visuomotor task that required subjects to indicate when they were no longer in control of the movement of the visual stimulus, increased latency to perceive the incongruence between the movement of their hands to control the stimulus

and the movements of the visual stimulus was related to positive symptomology (Schnell et al., 2008).

On cognitive tasks, the bulk of evidence suggests that patients with schizophrenia show intact online adjustments of erroneous responses in speeded RT tasks (Brownstein et al., 2003; Kopp & Rist, 1994, 1999; Morris, Yee, & Nuechterlein, 2006; Polli et al., 2008; Polli, et al., 2006; Reuter, Herzog, & Kathmann, 2006). Generally, those studies which have found impaired immediate behavioral adjustments following errors have used tasks with higher working memory demands (Malenka, Angel, Hampton, & Berger, 1982; Malenka, Angel, Thiemann, Weitz, & Berger, 1986; Turken, Vuilleumier, Mathalon, Swick, & Ford, 2003); thus, impaired behavioral adjustments can be explained by faulty representations of the correct response due to working memory impairments (Park & Holzman, 1992), rather than a deficit in a central monitoring system. However, there is some evidence that deficits in error correction are most evident in patients experiencing delusions of passivity (Frith & Done, 1989; Waters, Price, Dragovic, & Jablensky, 2009), but this is not a consistently reported finding. Further, there is evidence that patients with schizophrenia show abnormalities in correcting speech errors. In one study, Leudar, et al. (1992) found that patients *attempted* to correct their speech errors as frequently as controls, but that these corrections were more frequently inadequate. In a second study, the same authors found that speech error corrections in schizophrenia occur at a latency suggesting they are monitoring the acoustic feedback rather than the phonetic plan (Leudar, Thomas, & Johnston, 1994).

Current data also suggest intact behavioral adjustments of future performance based on trial history in schizophrenia during speeded response time tasks (Bates, Kiehl, Laurens, & Liddle, 2002; Laurens, Ngan, Bates, Kiehl, & Liddle, 2003; Mathalon et al., 2002; Morris, et al., 2006; Polli, et al., 2008; Polli, et al., 2006). Again, those studies that have reported impaired immediate behavioral adjustments following errors have used tasks with higher working memory demands (Alain, McNeely, He, Christensen, & West, 2002; Carter, MacDonald, Ross, & Stenger, 2001; Kerns et al., 2005); thus, impaired behavioral adjustments can be explained by faulty representations of the correct response due to working memory impairments, rather than a deficit in monitoring. On the other hand, there is evidence for more exaggerated latency adjustments following correctly performed antisaccades in patients with schizophrenia (Barton, Cherkasova, Lindgren, Goff, & Manoach, 2005; Barton, Goff, & Manoach, 2006; Franke, Reuter, Breddin, & Kathmann, 2009; Franke, Reuter, Schulz, & Kathmann, 2007); these effects are interpreted to reflect perseveration in the response system in schizophrenia.

In spite of mixed behavioral evidence for response monitoring impairments, attenuation of the ERN in patients with schizophrenia is a robust, well-replicated finding (Alain, et al., 2002; Bates, et al., 2002; Bates, Liddle, Kiehl, & Ngan, 2004; Kim et al., 2006; Kopp & Rist, 1999; Mathalon, et al., 2002; Mathalon, Jorgensen, Roach, & Ford, 2009; Morris, Heerey, Gold, & Holroyd, 2008). Moreover, reductions in fMRI activity in the ACC, the purported generator of the ERN, during error trials have also been noted in patients with schizophrenia (Carter, et al., 2001; Kerns, et al., 2005; Laurens, et al.,

2003; Polli, et al., 2008). Although there is evidence that reduction of ERN amplitude is more prominent in paranoid schizophrenia (Kopp & Rist, 1999) and increases as clinical state improves (Bates, et al., 2004), attenuation of the ERN is present even after symptoms have remitted (Bates, et al., 2004). Furthermore, although only investigated in one study, attenuation of the FRN has also been noted in patients with schizophrenia (Morris, et al., 2008). Additionally, correlations of ERN and FRN with task performance have suggested a diminished relationship between error- and feedback-related neural activity and task performance in patients with schizophrenia (Morris, et al., 2008).

Despite attenuation of the ERN in schizophrenia, larger CRN amplitude has been noted in some studies (Alain, et al., 2002; Kim, et al., 2006; Mathalon, et al., 2002; Morris, et al., 2006), but not others (Bates, et al., 2004; Mathalon, et al., 2009). This enhanced activity might reflect less certainty in the correct response, more partial errors, or longer persistence of response conflict, but no study has explicitly tested these hypotheses. To date, no study has observed group differences in the Pe (Alain, et al., 2002; Bates, et al., 2004; Kim, et al., 2006; Mathalon, et al., 2002; Morris, et al., 2006).

To summarize the existing response monitoring data in schizophrenia, studies of low-level motor error correction in schizophrenia are sparse, and with a few exceptions, examination of error adjustments has been secondary to a different primary question. As such, paradigms and analyses have not been optimized for studying errors and the dynamics of response-based adjustments. There is compelling evidence that patients with schizophrenia have a higher threshold for initiating corrective movements. That is, the criteria for what constitutes an error might be more lax in schizophrenia. However,

these measures are often indirect (i.e. catch-up saccade amplitude), and there is mixed evidence regarding the effect of antipsychotic medications on these measures (Friedman, et al., 1992; Lencer, et al., 2008; Litman, Hommer, Radant, Clem, & Pickar, 1994).

On the other hand, examination of error correction and post-error slowing during cognitive tasks indicates intact error-based adjustments in schizophrenia. Although there are discrepancies across studies, they are likely due to task-specific factors. However, it is possible that schizophrenia patients do show a deficit in correcting errors on cognitive tasks, but that measures of error correction ability are too crude to capture subtle deficits. Although post-error adjustments in cognitive tasks are generally intact in schizophrenia, the ERN, an electrophysiological correlate of error monitoring, is consistently reduced in schizophrenia. Further, fMRI activity in the ACC, the purported generator of the ERN, is also reduced in patients.

To date, no study has examined the specificity of putative response monitoring deficits (i.e. using a psychiatric control group) or whether similar deficits are found in first-degree relatives of patients with schizophrenia.

Response Inhibition

Response inhibition refers to the ability to *deliberately* suppress inappropriate motor responses (Verbruggen & Logan, 2009a). At the phenomenological level, impairments in response inhibition have been linked to behavioral perseveration (Crider, 1997) and impulsivity (Logan, Schachar, & Tannock, 1997), although empirical support

for these ideas in schizophrenia is far from compelling. Further, given the traditional neuropsychological conception of inhibition as a frontal lobe task (e.g. Luria, Pribram, & Homskaya, 1964), the study of response inhibition has become relevant for understanding the location of underlying neuropathology in schizophrenia.

Response Inhibition in Healthy Organisms

In human subjects, response inhibition has been investigated using a range of experimental paradigms, and subjects are consistently slower and less accurate on speeded RT tasks when required to inhibit a prepotent response to a stimulus and make an alternate response. Widely used tasks of motor response inhibition include the go/no-go task, antisaccade task, and countermanding (or stop-signal) task. In the go/no-go task, a stimulus from two sets of stimuli is presented on the screen. One set indicates that a response should be made to the stimulus; the other set requires that the subject inhibit a response to the stimuli. The measure of interest is the number of commission errors (responses to no-go stimuli). The antisaccade task requires subjects to look in the opposite direction of a suddenly appearing visual target instead of making the prepotent response of fixating the target. The measure of interest is the number of erroneous prosaccades (eye movements towards the visual target). However, inhibition is not a unitary construct (Friedman & Miyake, 2004), and correlations among performance measures on tasks of response inhibition are typically low (Friedman & Miyake, 2004; Miyake et al., 2000; Rabbitt, 1997). The countermanding, or stop signal task, is argued to be a “purer” measure of inhibitory capacity. In this task, following a

signal to make a response, infrequently, a stop signal is presented that instructs participants to withhold that response. This task allows estimation of the latency of the inhibitory process, and is discussed in more detail in a following section.

The neural basis of response inhibition has been studied in both human and non-human primates, and has been most notably associated with frontal cortex, including ACC, premotor cortex, and dorsolateral prefrontal cortex (Braver, Barch, Gray, Molfese, & Snyder, 2001; Liddle, Kiehl, & Smith, 2001; Menon, et al., 2001; Rubia et al., 2001). Similarly, ERP components that are larger on trials when a response is inhibited have been localized to frontal cortex (Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004; Pfefferbaum, Ford, Weller, & Kopell, 1985; Ramautar, Kok, & Ridderinkhof, 2004; van Boxtel, van der Molen, Jennings, & Brunia, 2001). Event-related functional MRI during go/no-go and countermanding task performance has paid particular attention to increased activation during no-go and stop-signal trials in inferior frontal cortex (IFC), particularly in the right hemisphere (see Aron, Robbins, & Poldrack, 2004 for review).

Further, imaging studies have also indicated a role of the subthalamic nucleus (STN) in countermanding manual movements in healthy participants (Aron & Poldrack, 2006). Deep brain stimulation of STN in patients with Parkinson's disease improved inhibitory control and reduced time needed to inhibit a response (van den Wildenberg et al., 2006), and a subpopulation of neurons in STN was found to be active during inhibition of a saccade in an oculomotor go/no-go paradigm (Isoda & Hikosaka, 2008). In the antisaccade task, human fMRI studies have revealed increased activation in a cortical network of lateral, parietal and medial oculomotor regions during the preparation

period, including FEF, SEF, ACC, parietal eye fields, and DLPFC (e.g. Brown, Vilis, & Everling, 2007; Manoach et al., 2007). These findings have been supported by single-unit recording studies that have indicated decreased pre-target FEF and SC activity in preparation to execute an antisaccade (see Munoz & Everling, 2004 for review). Similarly, neurons that can control initiation and inhibition of a saccade during the countermanding task have been identified in FEF and SC (see Schall & Boucher, 2007 for review) and will be discussed in greater detail in the following section.

Response Inhibition in Schizophrenia

Individuals with schizophrenia typically perform poorly on traditional neuropsychological tests of response inhibition, such as the Stroop task and Wisconsin Card Sorting task (see Barch, 2005 for review). However, these tasks tap into a range of cognitive abilities. As far as basic motor inhibition, patients performing the antisaccade task have been found to make more errors by producing a prosaccade to the target and have longer antisaccade latency (see Clementz, 1998 for review). Consistent with evidence for generally intact error correction ability, patients correct nearly all of these errors (e.g. Levy, Mendell, & Holzman, 2004; Polli, et al., 2006). These deficits are present in neuroleptic-naïve patients, indicating that they are not due to medication effects (Harris, Reilly, Keshavan, & Sweeney, 2006).

In contrast, data from the go/no-go paradigm in schizophrenia are mixed. Some studies report an increased number of no-go commission errors (Kiehl, Smith, Hare, & Liddle, 2000; Weisbrod, Kiefer, Marzinzik, & Spitzer, 2000), whereas some find no

performance difference (Arce et al., 2006; Begre et al., 2008; Fallgatter, Bartsch, Zielasek, & Herrmann, 2003; Laurens, et al., 2003; Mathalon, et al., 2009; Woolard et al., 2010). In fact, Ford et al. (2004) found that patients made significantly *fewer* commission errors, which they argued was a result of reduced prepotency of the go stimulus in the schizophrenia group. Performance on the manual countermanding task is also mixed, and is discussed in detail in the following section.

Although both the antisaccade and go/no-go tasks claim to measure response inhibition, there are several potential explanations behind discrepant findings across tasks. Differences could potentially be task-specific; an antisaccade requires not only the inhibition of a response, but also replacement of the prepotent response with a competing response. The go/no-go task on the other hand requires only that the response be cancelled. Further, discrepancies between tasks could be related to effector. Additionally, as Ford et al. (2004) point out, normal commission error rate could be a result of intact inhibition ability or failure for the go stimulus to establish prepotency. That is, patients are able to stop because the impulse to go is weak. On the other hand, the antisaccade task requires inhibiting a much more prepotent visually guided saccade, which could potentially explain why this task captures deficits that the go/no-go task does not.

Response inhibition deficits, specifically poor performance on the antisaccade task, are argued to be potential endophenotypic markers of schizophrenia (see Hutton & Ettinger, 2006 for review). As such, a handful of studies have attempted to investigate heritability and specificity of these deficits by assessing individuals with bipolar disorder

as a psychiatric control group and first-degree relatives of schizophrenic patients. Results have been mixed. For the most part, available evidence suggests that individuals with bipolar disorder are also less accurate on the antisaccade task (Curtis, Calkins, Grove, Feil, & Iacono, 2001; Harris, Reilly, Thase, Keshavan, & Sweeney, 2009; Katsanis, Kortenkamp, Iacono, & Grove, 1997; Martin et al., 2007; McDowell & Clementz, 1997; Tien, Ross, Pearlson, & Strauss, 1996), but there is evidence that antisaccade deficits are state-related in bipolar disorder (Gooding, Mohapatra, & Shea, 2004) and only occur during acute mood episodes. The lack of specificity of these deficits has brought into question their validity as endophenotypic markers. Further, findings of antisaccade deficits in first-degree relatives of schizophrenia relatives are also equivocal (see Levy et al., 2004 for review). Results from a recent meta-analysis indicate the variability amongst effect sizes can be accounted for by subject selection criteria (Levy, O'Driscoll, et al., 2004). Studies that found poorer antisaccade performance in relatives used more lenient inclusion criteria, in terms of personal psychopathology, for relatives versus control subjects. Likewise, those studies that found null effects used equivalent inclusion criteria for controls and relatives.

Studies have also investigated the relationship between response inhibition and schizotypy, which refers to the personality traits that are related to symptoms of schizophrenia and suggest vulnerability for the disorder (Raine et al., 1994). Response inhibition impairments on the antisaccade task have been found to be greater in those scoring high on self-report measures of schizotypy, particularly on the positive

syndrome (Gooding, 1999; Holahan & O'Driscoll, 2005; Larrison, Ferrante, Briand, & Sereno, 2000; O'Driscoll, Lenzenweger, & Holzman, 1998; Smyrnis et al., 2003).

There are relatively few fMRI studies investigating the neural basis of putative response inhibition deficits in schizophrenia. Further, several of these studies utilize a less-than-optimal block design, in which the hemodynamic response on single trials cannot be measured. Still these studies have described abnormal activity in wide network of prefrontal and subcortical areas (e.g. Raemaekers et al., 2002; Tu, Yang, Kuo, Hsieh, & Su, 2006).

Stopping and Stepping

An important consideration in these preceding studies of response inhibition and response monitoring in schizophrenia is the variety of instruments used; measurements of inhibition and monitoring might be confounded by the involvement of other cognitive processes. The countermanding task has been used to investigate the ability to control initiation of a response (*Figure 5*).

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 (*stop signal* trial); in which case, the subject is instructed to withhold the prepotent response. The delay between initial target onset and stop signal is referred to as the *stop signal delay* (SSD). Stop 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*.

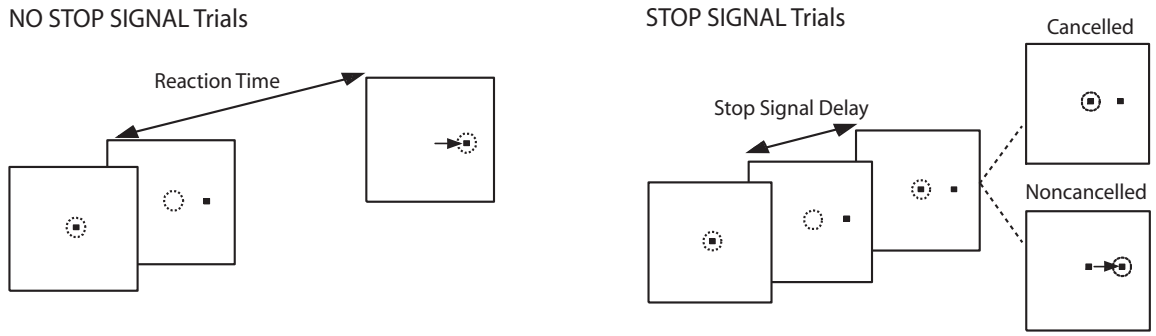

Figure 5. Saccadic countermanding task. Dotted circles indicate gaze position, and the arrow indicates the direction of the saccade. Trials begin with the presentation of a central fixation spot. After the fixation spot disappears, a target appears simultaneously at a non-central location. On stop signal trials, the fixation spot is reilluminated at some delay, referred to as stop signal delay (SSD), following target onset. Fixation reillumination is cue for the subject to withhold a saccade to the target. Trials in which the subject is successful in maintaining fixation are referred to as cancelled trials, and trials in which the subject makes a saccade to the target are referred to as noncancelled trials. For the remaining majority of trials (no-stop signal trials), fixation is not reilluminated, and the subject is instructed to make a saccade to the target.

Subjects become less able to cancel a saccade as the SSD increases. The inhibition function plots the proportion of noncancelled trials at each stop signal delay. A flatter inhibition function has been interpreted as increased failure to trigger the inhibition process or variability in the stopping process.

The time needed to cancel a movement, *stop signal reaction time* (SSRT), can be estimated from the distribution of RTs on no-stop signal trials and the probability of responding given a stop signal occurred; it is based on a race between STOP and GO processes with independent stochastic finishing times (Logan & Cowan, 1984). If the STOP process wins, the response is inhibited, and if the GO process wins, the response is executed (*Figure 6*). This model also accounts for experimental findings of shorter RTs on noncancelled trials than no-stop signal trials, since these noncancelled trials are being sampled from the fastest portion of the RT distribution—that is, they

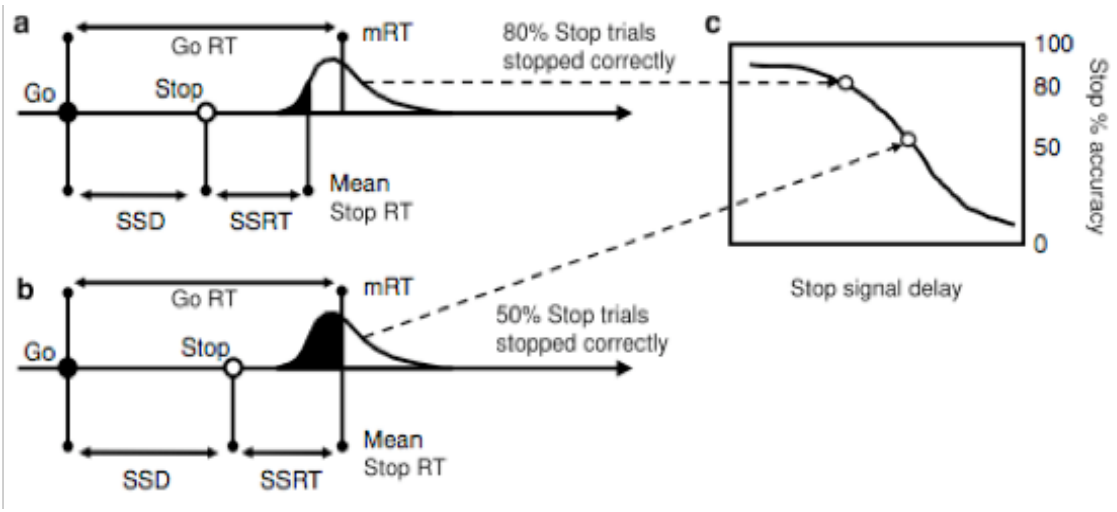

Figure 6. Assumptions and predictions of the race model, showing how the probability of inhibition (c) depends on the distribution of reaction times on Go (no-stop signal) trials and stop signal reaction time (SSRT). (a-b) The shaded part of the distribution represents the RTs that were fast enough to escape inhibition at a particular SSD. The empty parts of the distribution represent the RTs that were slow enough to be inhibited. Adapted from Eagle, et al. (2008).

were fast enough to escape inhibition. The countermanding task has an advantage over other measures of inhibition in that, along with measuring the ability to inhibit a prepotent response, it provides a measure the time to cancel a planned action that is not confounded with differences in mean and variability of GO RT.

Reliable latency adjustments according to trial history have also been reported in this task. Slowing following correctly cancelled saccades has been observed in both monkeys and humans (Cabel, Armstrong, Reingold, & Munoz, 2000; Emeric et al., 2007; Kornylo, Dill, Saenz, & Krauzlis, 2003). Although post-error slowing is commonly observed in choice manual response tasks (Rabbitt, 1966b), including the manual countermanding task (Rieger & Gauggel, 1999; Verbruggen, et al., 2008), it has not been consistently observed in the saccade countermanding task (Emeric, et al., 2007; Li

et al., 2008). Null findings regarding post-error slowing are potentially due to the analysis method. In most studies, only no-stop signal RTs immediately *following* the trial of interest were averaged without taking into account latency of the trial immediately *preceding* trial of interest. However, according to the race model, when subjects are going faster overall, they are more likely to fail to inhibit on stop signal trials, and non-independence of RTs across trials is commonly observed (Gilden, 2001; Welford, 1980). When no-stop signal RTs on trials following no-stop signal, cancelled and noncancelled trials are compared with the immediately preceding no-stop signal trial, in order to circumvent confounds created by local fluctuations in RT, post-error slowing is observed (Nelson, Boucher, Logan, Palmeri, & Schall, 2010).

The goal of a recent NIH-initiative, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS), was to improve measurements of cognition in treatment studies (Carter & Barch, 2007), and the countermanding task was included as part of this battery. However, little data examining countermanding performance exist in schizophrenia. Badcock et al. (2002) found equal SSRT but decreased slope of the inhibition function, which they interpreted as a deficit in control and planning of stop processes, rather than slowing of the stop processes. However, other groups have reported longer SSRT in schizophrenia using the manual countermanding task (Enticott, Ogloff, & Bradshaw, 2008; Huddy et al., 2009). Discrepant findings are potentially due to task-specific factors that affect estimation of SSRT (Band, van der Molen, & Logan, 2003). There are several major advantages to using an oculomotor version of the countermanding task in schizophrenia. Reuter and

Kathmann (2004) argue that saccade tasks show greater sensitivity in detecting cognitive deficits. Additionally, slowed RT for manual but not saccadic eye movements in schizophrenia is a consistent finding in the literature (Gale & Holzman, 2000; Nuechterlein, 1977). These results imply that the circuitry underlying the basic visually-guided saccadic response is intact, thereby reducing confounding effects that are not due to additional control demands.

Importantly, the neural circuitry of the oculomotor system is very well mapped, and a substantial body of work has investigated neurophysiological mechanisms instantiating the inhibition and monitoring of saccades in nonhuman primates (Schall & Boucher, 2007). Previous studies have identified neural mechanisms by which saccades are inhibited in the countermanding task, with a focus on gaze-shifting and gaze-holding neurons in the FEF and SC. Preceding a saccade, activity in saccade-related neurons in FEF and SC rises towards threshold for movement (Bruce & Goldberg, 1985; Hanes & Schall, 1996; Munoz & Wurtz, 1995) while activity in fixation-related neurons attenuates (Munoz & Wurtz, 1993; Segraves & Goldberg, 1987). On no-stop signal and noncancelled trials, activity reaches the threshold for movement, and the saccade is executed. However, on correctly cancelled trials, activity in saccade-related neurons begins to decay following the stop signal but before SSRT while activity in fixation neurons begins to rise (Hanes, Patterson, & Schall, 1998; Paré & Hanes, 2003). Thus, activity in gaze-shifting and gaze-holding neurons in FEF and SC appear to play a crucial role in the control of saccades.

Neural correlates of response monitoring and performance adjustments have also been investigated by recording single-cell and intracranial local field potentials in macaque monkeys performing the countermanding task, with a focus on the role of medial frontal structures. Activity in a subpopulation of SEF neurons following correctly inhibited saccades is thought to reflect conflict between incompatible gaze-shifting and gaze-holding signals in FEF (Emeric, Leslie, Pouget, & Schall, 2010; Stuphorn, Taylor, & Schall, 2000). SEF can bias latency of saccade production via connections to cortical and subcortical oculomotor regions (Schall & Boucher, 2007), and appears to be the basis of slowing following cancelled saccades in this task. Stuphorn and Schall (2006) found that microstimulation of the SEF improved performance on the countermanding task by delaying saccade initiation. However, this stimulation did not prolong latency on a simple visually-guided saccade task. Further, although neurons in ACC were not found to carry conflict signals, they modulate following errors and feedback (Emeric et al., 2008; Ito, et al., 2003). Activity in SEF was also found to modulate following errors (Emeric, et al., 2010; Stuphorn, et al., 2000).

A significant advantage to this task is that a formal mathematical model was developed that accounts for behavior in both saccadic and manual versions (Logan & Cowan, 1984), and it has recently been elaborated to also account for activity in single neurons during saccade countermanding (Boucher, Palmeri, Logan, & Schall, 2007). 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

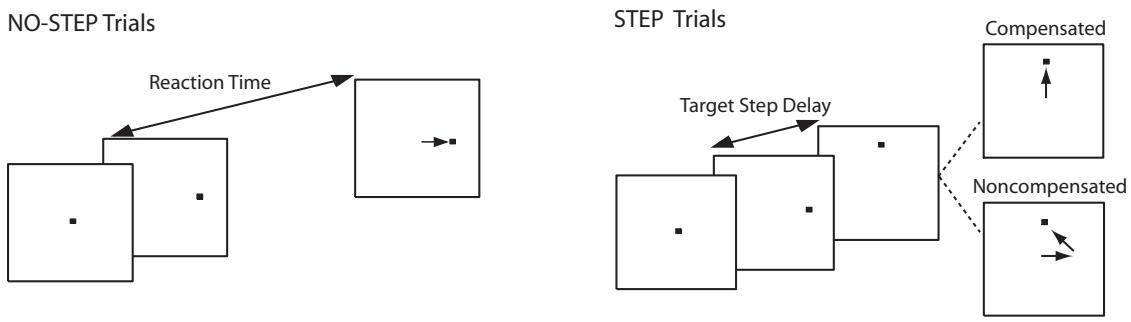

Figure 7. Double-step task. Arrows indicate the direction of the saccade. Trials begin with the presentation of a central fixation spot. After the fixation spot disappears, a target appears simultaneously at a non-central location. On step trials, an alternate target appears simultaneously with the offset of the initial target after a delay (target step delay; TSD). A target step is cue for the subject to withhold a saccade to the first target and instead redirect towards the second target. Trials in which the subject is successful in redirecting gaze shift are referred to as compensated trials, and trials in which the subject makes a saccade to the first target are referred to as noncompensated trials. On most noncompensated trials, a corrective saccade is made to the second target location. For the remaining majority of trials (no-step trials), the target did not step, and the subject was instructed to make a saccade to the initial target.

task permits more specific hypotheses to be drawn about the nature of putative deficits in response inhibition and monitoring in schizophrenia.

A double-step modification of the traditional saccadic countermanding paradigm has also been developed (*Figure 7*; Camalier, et al., 2007). In this task, the majority of trials are *no-step* trials, in which the subject is instructed to direct gaze towards a suddenly-appearing visual target. *Step* trials are initially identical to no-stop trials and begin with the onset of a visual target. However, at some delay following initial target onset, referred to as the *target step delay* (TSD), another target appears at an alternate location. On these trials, the subject is instructed to inhibit the initial saccade to the first target, and instead redirect gaze towards the second target. Like with the traditional countermanding task, as TSD increases, subjects become less able to inhibit their saccades to the first target. Step trials in which the initial saccade is accurately

redirected to the second target are referred to as *compensated*. Likewise, step trials in which the subject directs their first saccade toward the initial target are labeled *noncompensated*. The compensation function plots the proportion of noncancelled trials at each stop signal delay. Like in the traditional countermanding task, double-step performance can also be a accounted for by a race model (Camalier, et al., 2007)—in the case of the double-step task, the race is between processes producing the saccade to the initial target and processes involved in interrupting that saccade and executing a saccade to the final location. The model architecture that assumed an initial GO process that is interrupted by a STOP process and simultaneous second GO process to the final target location was found to provide the best fit to empirical data on this task (Camalier, et al., 2007). Again, the time needed to cancel a movement, the *target step reaction time* (TSRT), can be estimated from the distribution of RTs on no-step trials and the probability of making a saccade to the initial target location given a step occurred.

Along with measures of inhibition, the double-step task also allows for the investigation of subtle aspects of error-based adjustments. On noncompensated trials, both monkeys and humans make corrective responses to the second target. As such, we can measure the incidence, spatial accuracy, and latency of these corrective movements. The latency between the noncompensated saccade and the corrective saccade is referred to as the intersaccadic interval (ISI), and the latency between the onset of the second target and noncompensated saccade initiation is referred to as the reprocessing time (RPT). See *Figure 8*. The RPT is the time available to the subject to process the visual information of the second target before initiating a saccade to the first

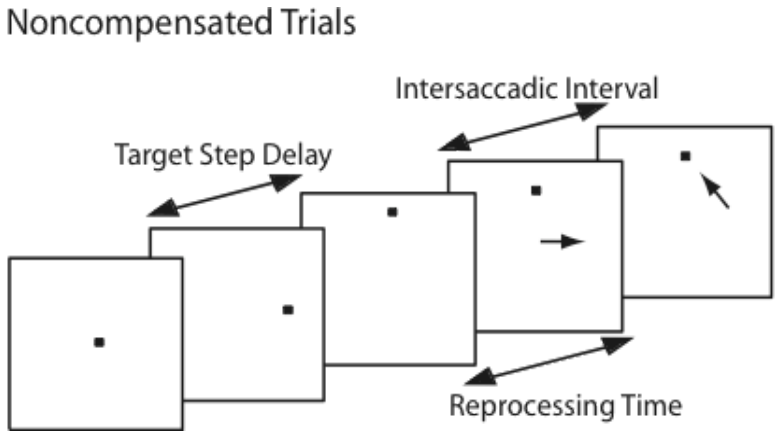

Figure 8. Noncompensated trials. Reprocessing time (RPT) refers to the time between the onset of the second target and the initial noncompensated saccade. The intersaccadic interval (ISI) refers to the time between the onset of the noncompensated saccade and corrective saccade.

target. The slope of the relationship between these two measures can provide an index of the degree to which noncompensated and corrective saccades are being programmed in parallel. A flat slope of the relationship between ISI and RPT would indicate that corrective saccades were not being programmed in parallel with the error noncompensated saccade. See *Figure 9* for illustration. That is, it would indicate that the corrective saccade was initiated at some relatively constant time following the noncompensated saccade. However, a negative relationship between the ISI and RPT has been observed, such that a longer period of time between the onset of the second target location and the initiation of the first saccade allows for faster error corrections (Becker & Jurgens, 1979; Camalier, et al., 2007). That is, the more time the subject has to process the visual information of the final target, the faster he or she could make the corrective movement. It has been shown that movement neurons in FEF become active before the erroneous saccade can be detected by visual input, and the latency of

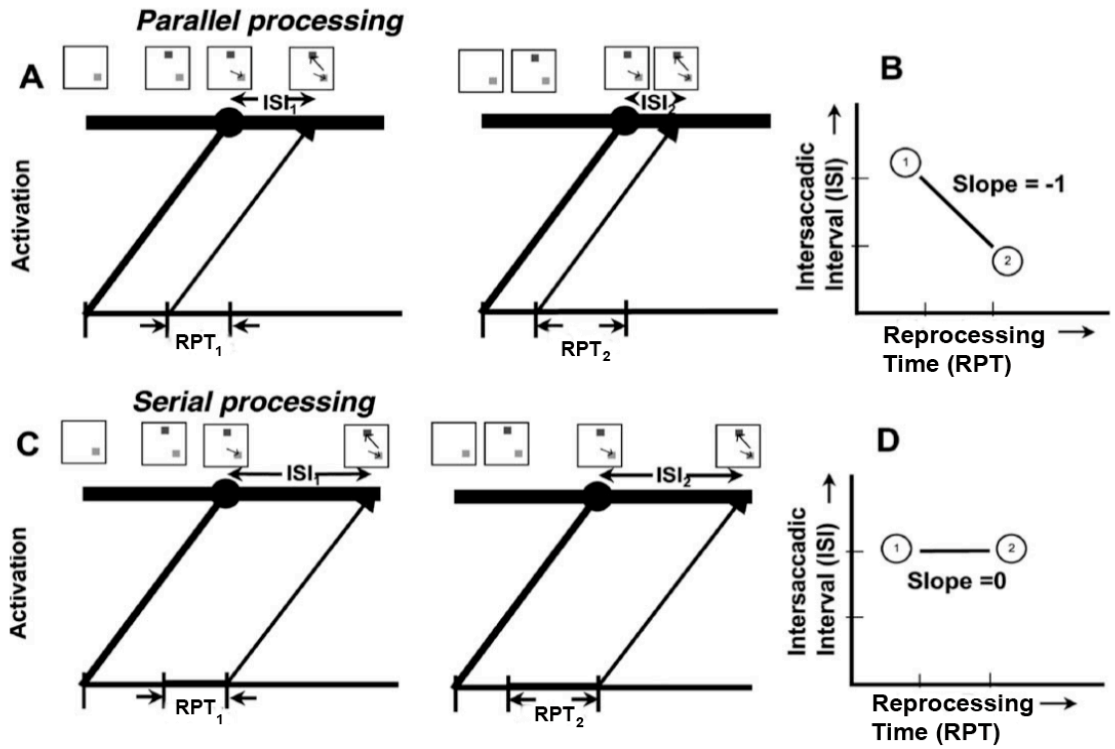

Figure 9. (A) Temporal sequence of events assuming parallel processing of two saccades. Longer reprocessing time (RPT) should produce shorter intersaccadic intervals (ISI). (B) Ideal relation between ISI and RPT during parallel programming of two saccades. The slope of the line should be negative one. (C) If two saccades are produced serially the length of the RPT should not affect the ISI and (D) there should be no relation between ISI and RPT (slope = 0). The dark black line represents the threshold for which neural activity must rise for saccade initiation. Adapted from Murthy, et al. (2007)

corrective saccades can be predicted by the timing of activity of these cells (Murthy, et al., 2007).

This combination of work in humans and non-human primates provides leverage on these crucial questions of the nature of response inhibition and response monitoring in schizophrenia through the application of sophisticated models of behavior, as well as spatially and temporally precise measures of brain activity, to understanding the processes and their underlying mechanisms that are impaired and preserved in the disease.

CHAPTER II

EXPERIMENT 1: INHIBITION AND MONITORING OF SACCADES IN A COUNTERMANDING TASK

Experiment 1A: Inhibition and Monitoring of Saccades in a Countermanding Task in Schizophrenia

Aims

1) To investigate the speed of response inhibition in patients with schizophrenia.
2) To investigate changes in speed of response as a function of trial history.
3) To investigate whether putative abnormalities in speed of response inhibition and performance-related RT adjustments are related to symptoms and social and occupational functioning in patients with schizophrenia.
4) To examine whether putative abnormalities in speed of response inhibition and performance-related RT adjustments are related to generalized failures in maintaining goals and task instructions by correlating countermanding measures with working memory performance.

Methods

Participants. Individuals who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia were recruited from outpatient psychiatric facilities in Nashville, TN. Diagnoses were confirmed using structured clinical interviews (SCID-IV; First, Spitzer, Gibbon, & Williams, 1995). All

patients were taking atypical antipsychotic medications, with the exception of one patient taking Depakote. The chlorpromazine (CPZ) equivalent dose (mg/day) was calculated for each subject. Patients taking antipsychotics for which published CPZ equivalent doses were not available (i.e. Paliperidone) were not included in this analysis. Healthy, unmedicated control subjects 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; Overall & Gorham, 1962), the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). Social and occupational functioning was assessed by the 79-item Social Functioning Scale (SFS; Birchwood, Smith, Cochrane, Wetton, & Copestake, 1990), validated in schizophrenia, that assesses seven areas: social engagement, interpersonal communication, frequency of daily living activities, competence of daily living activities, recreational activities, social activities, and occupational activity. The Adult North American Reading Test (ANART; Blair & Spreen, 1989; O'Carroll et al., 1992) or Wechsler Abbreviated Scale of Intelligence (WASI) was used to assess IQ. Although mean IQ and education were lower in patients compared to controls, their mean IQ was in the normal range, and the average patient had achieved a high school education. Moreover, IQ has not been found to be related to response inhibition ability (Friedman et al., 2006; Logan, 1994) or to the RT cost of task-switching (Friedman, et

al., 2006). Handedness was assessed using the Modified Edinburgh Handedness Inventory (Oldfield, 1971).

All participants were screened to exclude substance use within the past 6 months, neurological disorders, history of head injury, inability to fixate, and excessive sleepiness. All subjects had normal or corrected-to-normal vision. Two schizophrenia patients were excluded based on countermanding task performance, as outlined in the *Statistical Methods* section. Analyses were conducted on the remaining 17 patients and 16 controls. Groups were matched for age, sex, and handedness (*Table 1*).

All subjects gave written informed consent approved by the Vanderbilt Institutional Review Board and were paid.

Table 1.	**SZ Patients** Mean (s.d.)	**Controls** Mean (s.d.)	**statistic**	**p**
Age	36.0 (7.7)	34.9 (7.9)	t = 0.4	0.70
Sex	6F / 11M	7F / 9M	Phi = 0.2	0.73
Edinburgh handedness	51.5 (54.9)	56.7 (67.7)	t = 0.4	0.70
Years of Education	13.4 (1.9)	16.2 (2.1)	t = 4.0	0.0003
IQ	102.6 (10.8)	110.5 (4.6)	t = 2.7	0.01
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)	t = 3.4	0.002
SFS Employment Score	5.2 (3.8)	9.7 (0.7)	t = 4.6	<0.0001

Apparatus and stimuli. Eye position was monitored using the EyeLink II eyetracker (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 57cm from the computer monitor with their head in a chinrest. The fixation and targets subtended 1° and were light gray (34 cd/m^2) on a darker gray (18 cd/m^2) background.

Design and procedure. ***Countermanding Task.*** Subjects performed a saccadic countermanding task (*Figure 5*). Seventy percent of the trials were *no-stop signal* trials. These trials required subjects to fixate on the central fixation spot until it disappeared (after a random delay between 500-1000 ms) 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 re-illuminated after a variable delay (*stop signal delay*; SSD) following target presentation, cuing subjects to inhibit a saccade to the target. Stop signal trials were labeled *cancelled* or *noncancelled* based on whether subjects inhibited or failed to inhibit the saccade, respectively. Response inhibition becomes more difficult with increasing SSDs. SSDs were dynamically adjusted using a 1-up/1-down tracking procedure, thereby ensuring successful inhibition on 50% of the stop signal trials (Osman, Kornblum, & Meyer, 1986). The initial SSD was set at 225 ms and increased or decreased by 47 ms when the subject succeeded or failed to inhibit,

respectively. The testing session consisted of a practice block of 60 trials, and 4 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, the proportion of trials in which a participant successfully inhibited a saccade was quantified. 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 process) and inhibit (STOP process) the movement (Logan & Cowan, 1984). The response is executed if the GO process finishes before the STOP process, 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 *stop signal reaction time* (SSRT). According to the race model, on each trial, the RT of the STOP and GO process are random variables. If, on a particular stop signal trial, the GO RT is less than the sum of the STOP RT and SSD, the GO process 'wins', and the response is executed. Likewise, if GO RT is greater than the sum of STOP RT and SSD, the STOP process 'wins', and the response is inhibited. The trials that escape inhibition are from the fastest portion of the no-stop signal RT distribution (Figure 6). Thus, the race model accounts for the finding that the proportion of noncancelled trials increases with increasing SSD and that noncancelled RTs are shorter than no-stop signal RTs.

We estimated SSRT using data from the tracking procedure, which adjusted SSD so that subjects would fail to inhibit eye movements on approximately half of the stop signal trials (Osman, et al., 1986). Under these conditions, the race between STOP and GO is tied (i.e., SSD + SSRT = GO RT), so SSRT can be estimated simply by subtracting mean SSD from mean no-stop signal RT (Logan, et al., 1997). A series of simulations (Band, et al., 2003) showed that this tracking procedure provided more accurate estimates of SSRT than other methods.

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. Since variability in GO RT does not reflect inhibition ability, the slope can be corrected for variability in GO RT by applying a Z-transformation to the SSDs (Logan & Cowan, 1984). This transformation expresses the SSDs in terms of the latency relative to finishing times of GO and STOP processes standardized with respect to variability in GO RT using the equation:

$$ZRFT = \frac{\mu_{RT} - SSD - SSRT}{\sigma_{RT}}$$

where ZRFT is the Z-transformed SSD, μ_{RT} is the mean no-step RT, and σ_{RT} is the standard deviation of the no-step RTs.

To index response monitoring, RT was examined as a function of trial history. Mean RT was computed separately for no-stop signal trials preceding and following no-stop signal trials, correctly cancelled stop signal trials, and noncancelled stop signal trials (i.e. stop-task errors). RTs on no-stop signal trials preceding and following two consecutive stop signal trials were included in this analysis only if the response on the

two stop signal trials was the same (i.e. if both trials were cancelled or noncancelled). 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 an erroneously noncancelled (error) trial.

Verbal and spatial working memory tasks. Verbal working memory was measured using the Letter Number Sequencing task (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997) in which subjects were verbally presented a series of letters and numbers and asked to report back the numbers in numerical order, followed by the letters in alphabetical order. Verbal working memory scores were unavailable for one patient and one control.

Spatial working memory was assessed using a delayed-response task with an intervening task that does not interfere with the visuospatial sketchpad of working memory (Park, et al., 1995). Subjects fixated at the center. Then a target, a black circle subtending 2°, was presented for 300ms at one of eight locations 12° from the central fixation spot, followed by a delay of 8s. During the delay, numbers were presented at the center, in descending order in steps of four and subjects were instructed to note any subtraction errors. The purpose of the intervening subtraction task was to prevent verbal rehearsal and to maintain central fixation. After the delay, subjects were asked to indicate location of the target using the keypad. After responding, subjects indicated if they noticed a subtraction error using a keypress corresponding to yes and no. There

were 48 trials. Spatial working memory scores were unavailable for two patients and one control.

Statistical methods. Fisher's exact tests, independent t-tests, and repeated measures ANOVAs were used where appropriate. Non-parametric correlations were calculated between symptoms and countermanding performance. Since occupational functioning was bimodally distributed in the patient group, a median split was performed on these scores, and countermanding performance was compared between employment groups. All tests were two-tailed except where otherwise specified. Subjects were excluded from analyses if the adaptive tracking procedure in the countermanding task was ineffective, defined by a proportion of successfully inhibited responses lying outside a 95% binomial confidence interval around p=0.5.

Results

Table 2.	**Controls** Mean (s.d.)	**SZ patients** Mean (s.d.)	**t-statistic**	***p***
Probability of Inhibition (%)	50.7 (4.2)	48.0 (4.6)	1.7	0.09
No-stop signal RT (ms)	273 (55)	283 (59)	0.5	0.60
Noncancelled RT (ms)	222 (40)	232 (44)	0.7	0.50
SSRT (ms)	124 (24)	147 (31)	2.5	0.02
Post-error slowing (ms)	40 (22)	48 (38)	0.7	0.50
Post-cancelled slowing (ms)	24 (22)	51 (42)	2.3	0.03

Table 2 shows stop signal performance and RT adjustments for patients and controls.

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 calculated (*Figure 10*). There was no group difference in the slope of the Z-transformed inhibition function ($t(31) = 1.3$, $p = 0.20$), 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 ANOVA with group as a between-subjects variable and trial type as a within-subjects variable. There was a

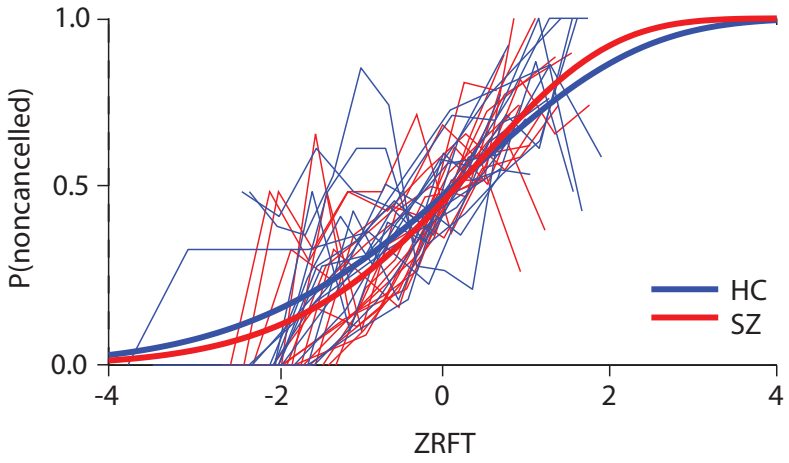

Figure 10. Individual normalized inhibition functions for healthy controls (blue) and schizophrenia patients (red). Probability of inhibition is plotted as a function of a Z score that measures time relative to the finish time of the GO and STOP processes in standard deviation units using the formula: ZRFT = (mean no-stop signal RT – SSD – SSRT)/standard deviation of no-stop signal RT. Separate cumulative Weibull functions are fit to the normalized inhibition functions for patients and controls.

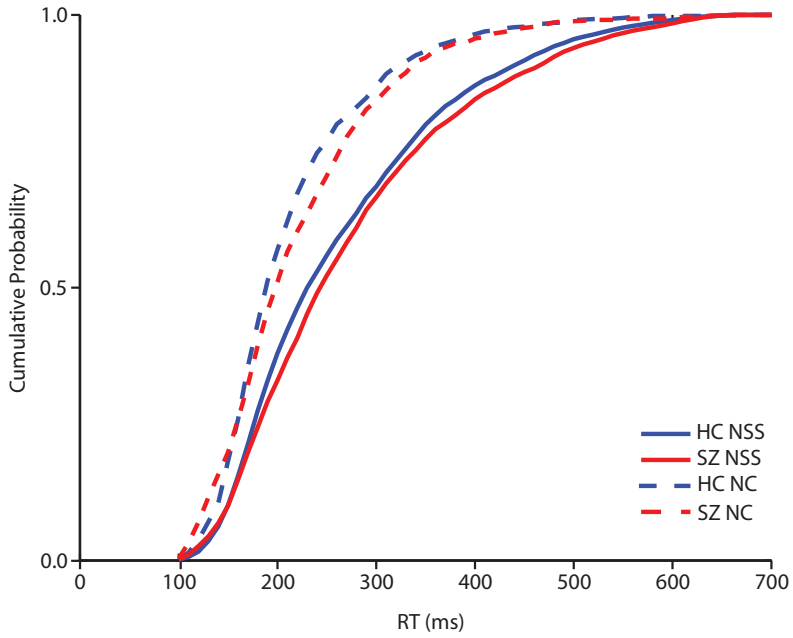

Figure 11. Cumulative distributions of saccade latencies in no-stop signal (NSS; solid lines) and noncancelled (NC; dotted lines) trials for healthy controls (blue) and schizophrenia (red) groups.

significant effect of trial type ($F(1,31) = 106.7$, $p < 0.0001$), with no-stop signal trials being slower than error noncancelled trials. There was no main effect of group ($F(1,31) = 0.38$, $p = 0.54$) or group-by-trial type interaction effect ($F(1,31) = 0.0003$, $p = 0.99$). Cumulative distributions of RTs are presented in *Figure 11*.

SSRT. SSRT was significantly longer in schizophrenia patients ($t(31)=2.5$, $p=0.02$), who required more time to inhibit a saccade than healthy controls.

RT adjustments across three trials in sequence. RT adjustment effects are presented in *Figure 12*. To assess effects of trial history on current no-stop signal trial, a repeated-measures ANOVA 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

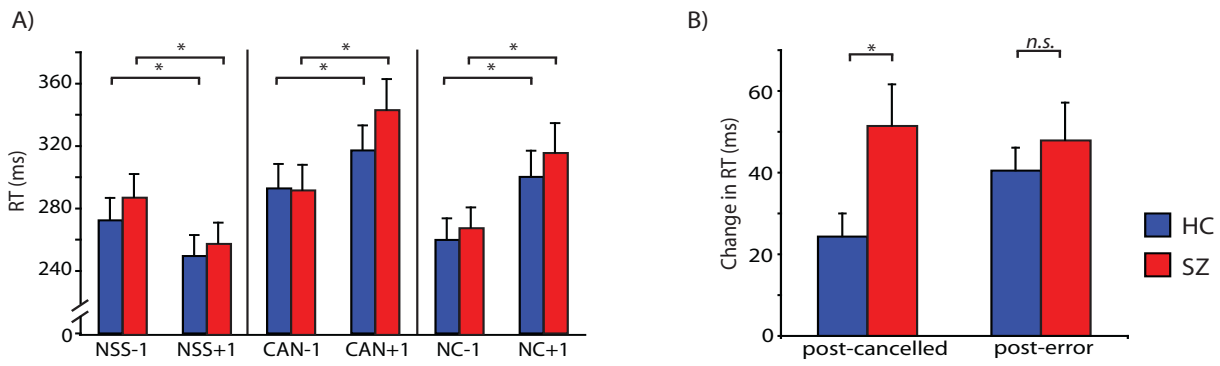

Figure 12. *A)* Mean no-stop signal RT (with standard error) for trials following (+1) and preceding (-1) no-stop signal (NSS), cancelled (CAN) and noncancelled (NC) trials for healthy controls (blue bars) and schizophrenia patients (red bars). ***B)*** Mean post-cancelled and post-error slowing.

variables. There was a significant effect of history ($F(1, 31) = 68.2$, $p < 0.0001$), and critical trial ($F(2,62) = 61.5$, $p < 0.0001$). Notably, there was a significant history-by-critical trial interaction ($F(2,62) = 57.3$, $p < 0.0001$).

Planned contrasts revealed that RTs for no-stop signal trials were slower when they followed cancelled ($F(1,62) = 54.4$, $p < 0.0001$) and noncancelled ($F(1,62) = 74.0$, $p < 0.0001$) 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 ($F(1,62)=25.8$, $p<0.0001$). 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 ($F(1, 62)=30.7$, $p<0.0001$) and no-stop signal trials ($F(1,62)=5.9$, $p=0.02$). This suggests 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 ($F(1,62)=9.7$, $p=0.003$). Likewise, this suggests that faster saccadic RT may result in subsequent failure to cancel a saccade.

There was no main effect of group ($F(1,31)=0.32$, $p=0.58$), but there was a significant group-by-history effect ($F(1, 31) = 4.23$, $p=0.05$). Planned contrasts revealed slower performance in patients compared to controls, and this difference was more pronounced after the critical trial ($F(1,31)=26.0$, $p < 0.0001$) than before the critical trial ($F(1,31)=4.8$, $p=0.04$). There was a trend towards a group-by-history-by-critical trial effect ($F(2, 62) = 2.7$, $p = 0.07$). Independent t-tests were conducted to assess group differences in post-cancelled and post-error slowing and speeding following no-stop signal trials. Patients slowed down significantly more following cancelled trials than controls ($t(31)=2.3$, $p=0.03$). There were no group differences in post-error slowing ($t(31)=0.7$, $p=0.50$) or speeding following no-stop signal trials ($t(31)=1.7$. $p=0.10$).

Symptoms and social functioning. Spearman rank-correlation coefficients were used to evaluate the association between the severity of psychiatric symptoms and behavioral measures in schizophrenia patients. SANS score was positively correlated with SSRT ($r_s = 0.61$, $p = 0.009$); those with increased negative symptoms needed more time to inhibit saccades (*Figure 13*).

Since SFS employment scores were bimodally distributed in the patient group, a median split was performed on the scores, and independent t-tests were conducted to compare behavioral measures in those scoring high and low on occupational functioning. SSRT was significantly longer in the low compared to high employment group, ($t(14) = 2.8$, $p = 0.02$) (*Figure 14*). That is, in patients with schizophrenia, better

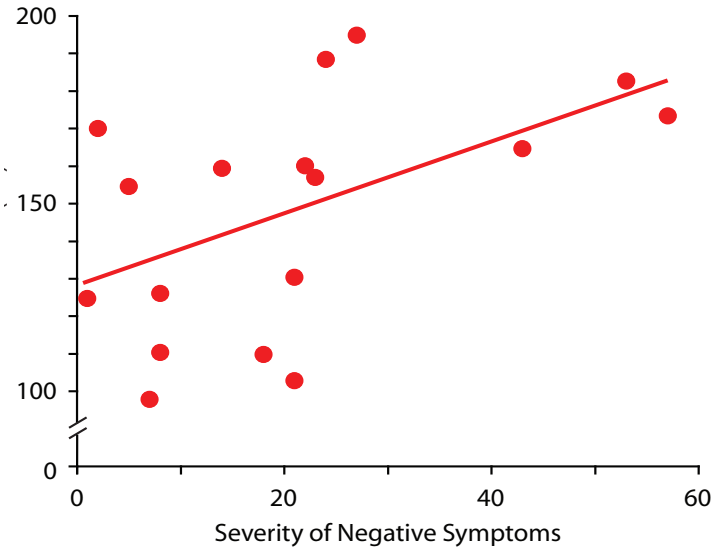

Figure 13. Relationship between SSRT and severity of negative symptoms, indexed by SANS score, in schizophrenia patients. Greater SANS scores represent more severe negative symptomology.

occupational functioning was associated with less time needed to inhibit a planned movement. 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 schizophrenia patients who were excluded from analyses based on performance indices would have fallen into the low employment group and SANS scores were above the group mean.

Working Memory. Since we had an a priori hypothesis of poorer working memory performance in schizophrenia (Lee & Park, 2005), one-tailed independent t-tests were conducted to compare working memory between groups. Patients had significantly fewer correct sequences (M = 13.6, s.d. = 3.5) on the verbal working

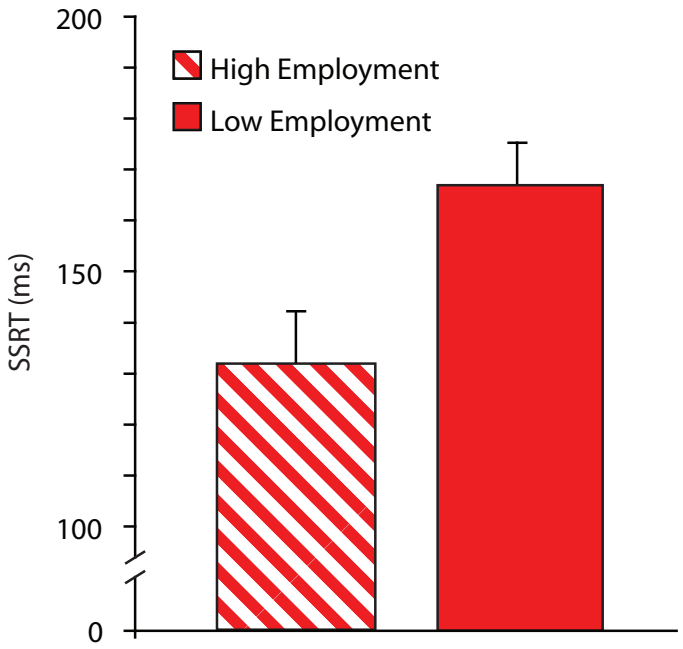

Figure 14. SSRT (plus standard error) for schizophrenia patients scoring high (striped) and low (solid) on SFS employment subscale, defined by median split within patient group.

memory task (t(28)=1.9, p=0.03, 1-tailed) than controls (M = 15.7, s.d. = 2.4). Since variances were unequal, a Welch's t-test was used to compare accuracy on the spatial working memory task. Patients (M=89.0%, s.d. = 10.9%) were less accurate than controls (M=96.8%, s.d.=4.9%) (t(19.4)=2.5, p=0.01,1-tailed).

Pearson product-moment correlation coefficients were used to evaluate the association between working memory performance and SSRT, post-error slowing, and post-cancelled slowing. One-tailed tests of significance were conducted to examine the strength of the correlation between working memory performance and SSRT, given their purported relationship (Goldman-Rakic, 1987). In patients, the relationship between SSRT and verbal working memory performance was significant (r_s=-0.45, p=0.05, 1-tailed). That is, better verbal working memory was associated with less time needed to

cancel a planned saccade. There were no other significant correlations between working memory performance and countermanding measures.

Effects of antipsychotic medication. To examine the effect of medication on countermanding performance, we calculated chlorpromazine (CPZ) equivalent dosages for each subject taking antipsychotic medication (Woods, 2003) and correlated it with no-stop signal and noncancelled RTs, SSRT, slope of the inhibition function, post-error slowing, and post-cancelled slowing. CPZ equivalent dose was not significantly related to any of the countermanding measures (*r* range: [-0.22, 0.22], *p* range: [0.42, 0.94]).

Experiment 1B: Specificity of Impaired Saccade Inhibition and Idiosyncratic Saccade Monitoring to Schizophrenia

Aims

1) To investigate whether slower response inhibition is also present in patients with bipolar disorder.
2) To investigate whether exaggerated slowing following correctly inhibited saccades is also present in bipolar disorder.
3) To examine linear relationships between psychosis-proneness, as indexed by diagnostic group, and inhibition efficiency and exaggerated trial history effects, given evidence suggesting that psychosis is represented on a continuum ranging from unipolar depression to schizophrenia (Crow, 1986).

Methods

Participants. Eighteen individuals who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for bipolar disorder were recruited from outpatient psychiatric facilities in Nashville, TN. Diagnoses were confirmed using

Table 3.

Subject 1	Valproic Acid
Subject 2	Aripiprazole
Subject 3	Fluoxetine, Quetiapine
Subject 4	Trazodone
Subject 5	Aripiprazole, Citalopram
Subject 6	Valproic Acid, Paliperidone
Subject 7	Lamotrigine, Lithium, Aripiprazole, Trazodone
Subject 8	Venlafaxine, Oxcarbazepine, Diazepam, Ziprasidone
Subject 9	Olanzapine
Subject 10	Aripiprazole
Subject 11	Risperidone, Valproic Acid, Buproprion
Subject 12	Lamotrigine
Subject 13	unmedicated
Subject 14	Buprioprion, Amitriptyline, Diazepam
Subject 15	Valproic Acid
Subject 16	Valproic Acid, Lamotrigine
Subject 17	unmedicated
Subject 18	Olanzapine

Table 4.	HC (n=16)	BP (n=18)	SZ (n=17)	HC v SZ		HC v BP		SZ v BP	
				t	*p*	*t*	*p*	*t*	*p*
Age	34.9 (7.9)	32.0 (8.4)	36.0 (7.7)	0.4	0.7	1.0	0.3	1.5	0.15
Sex	7F / 9M	10F / 8M	6 F / 11 M	ϕ=0.2	0.7	ϕ=0.7	0.5	ϕ=1.45	0.31
IQ	110.5 (4.6)	105.8 (10.2)	102.6 (10.8)	2.7	0.01	1.7	0.1	0.90	0.37
Years of Education	16.2 (2.1)	13.4 (2.3)	13.4 (1.9)	4.0	<0.001	3.6	0.001	0.13	0.9
Handedness	59.7 (67.7)	69.4 (31.3)	51.5 (55.0)	0.4	0.7	0.5	0.6	1.2	0.24
SFS Total	156.8 (14.6)	132.3 (18.4)	132.3 (17.9)	3.4	0.002	4.3	<0.001	0.007	0.99
SFS Employment	9.7 (0.7)	6.6 (3.3)	5.2 (3.8)	4.6	<0.001	3.6	0.001	1.16	0.26
Years of Illness	*n/a*	10.6 (7.8)	15.7 (8.3)					1.9	0.07
CPZ Equivalent	*n/a*	160.7 (275.8)	383.7 (354.3)					2.02	0.05
BPRS	*n/a*	12.8 (7.6)	11.8 (7.1)					0.4	0.7
YMARS	*n/a*	8.5 (7.9)	*n/a*						
HRSD	*n/a*	10.1 (6.7)	*n/a*						
SAPS	*n/a*	*n/a*	13.8 (19.1)						
SANS	*n/a*	*n/a*	20.8 (16.7)						

the SCID-IV (First, et al., 1995). All but three bipolar patients were medicated with mood stabilizers, antidepressants, atypical antipsychotics, or a combination (*Table 3*). Antipsychotic dose was normalized by calculating CPZ equivalent dose for each subject. Patients taking antipsychotics for which published CPZ equivalent doses were not available (i.e. Paliperidone) were not included in this analysis. The healthy control and schizophrenia samples were identical to those described in *Experiment 1A*. All groups were matched on age, sex, and handedness.

Clinical symptoms in bipolar patients were assessed with the BPRS, Hamilton Rating Scale for Depression (HRSD; Hamilton, 1980) and Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978). Social and occupational functioning, IQ, and handedness were assessed as outlined in *Experiment 1A*. Exclusion criteria are outlined in Experiment 1A. The three groups were matched for age, sex, and handedness (*Table 4*). Schizophrenia and bipolar patients were also matched on IQ, years of education, social and occupational functioning, and general psychiatric symptom severity as indexed by BPRS score. However, schizophrenia patients were taking a significantly higher antipsychotic dose and showed a non-significant trend towards longer illness length. Bipolar patients and healthy controls were also matched on estimated IQ, but bipolar patients had significantly fewer years of education and poorer social and occupational functioning. All subjects gave written informed consent approved by the Vanderbilt Institutional Review Board and were paid.

Apparatus and Stimuli. Described in *Experiment 1A*.

Design and procedure. ***Countermanding task.*** Described in *Experiment 1A*.

Statistical Methods. Described in *Experiment 1A*. In addition, we performed a linear contrast to measure whether post-cancelled slowing and SSRT varies as a function of psychosis-proneness. Healthy controls were assigned a value of -1, bipolar patients were assigned a value of 0, and schizophrenia patients were assigned a value of +1.

Table 5.	**HC (n=16)**	**BP (n=18)**	**SZ (n=17)**	**HC v SZ**		**HC v BP**		**SZ v BP**	
				t	*p*	*t*	*p*	*t*	*p*
Probability of Inhibition (%)	50.7 (4.2)	47.9 (4.4)	48.0 (4.6)	1.7	0.09	1.9	0.06	0.1	0.94
No-stop signal RT (ms)	273 (55)	275 (42)	283 (59)	0.5	0.60	0.1	0.91	0.5	0.63
Noncancelled RT	222 (40)	225 (37)	232 (44)	0.7	0.50	0.3	0.78	0.5	0.64
SSRT (ms)	124 (24)	136 (24)	147 (31)	2.5	0.02	1.6	0.13	1.2	0.25
Post-error slowing (ms)	40 (22)	36 (32)	48 (38)	0.7	0.50	0.5	0.65	1.7	0.10
Post-cancelled slowing (ms)	24 (22)	32 (26)	51 (42)	2.3	0.03	0.9	0.4	1.0	0.33

Results

Table 5 shows stop signal performance and RT adjustments for the three groups.

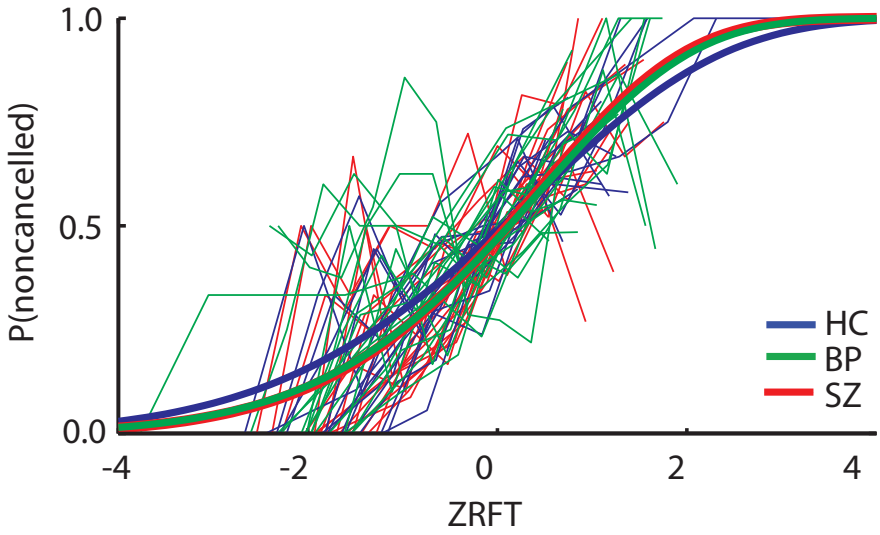

Figure 15. Individual normalized inhibition functions for healthy controls (blue), schizophrenia patients (red), and bipolar patients (green). Probability of inhibition is plotted as a function of a Z score that measures time relative to the finish time of the GO and STOP processes in standard deviation units using the formula: ZRFT = (mean no-stop signal RT – SSD – SSRT)/standard deviation of no-stop signal RT. Separate cumulative Weibull functions are fit to the normalized inhibition functions for the three groups.

Probability of inhibition. The dynamic tracking procedure was successful, and the mean proportion of noncancelled trials was 49%. The three groups did not differ in the proportion of noncancelled trials ($F(2,48)=2.16$, $p=0.13$). For each subject, the estimated slope of the inhibition function plotted against ZRFT was calculated (*Figure 15*). There was no group difference in the slope of the Z-transformed inhibition function ($F(2,48) = 1.2$, $p = 0.31$), providing evidence for equal variability in the inhibitory process across 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 ANOVA with group as a between-subjects variable and trial type as a within-subjects variable. There was a significant effect of trial type ($F(1,48) = 188.9$, $p < 0.0001$), with no-stop signal trials

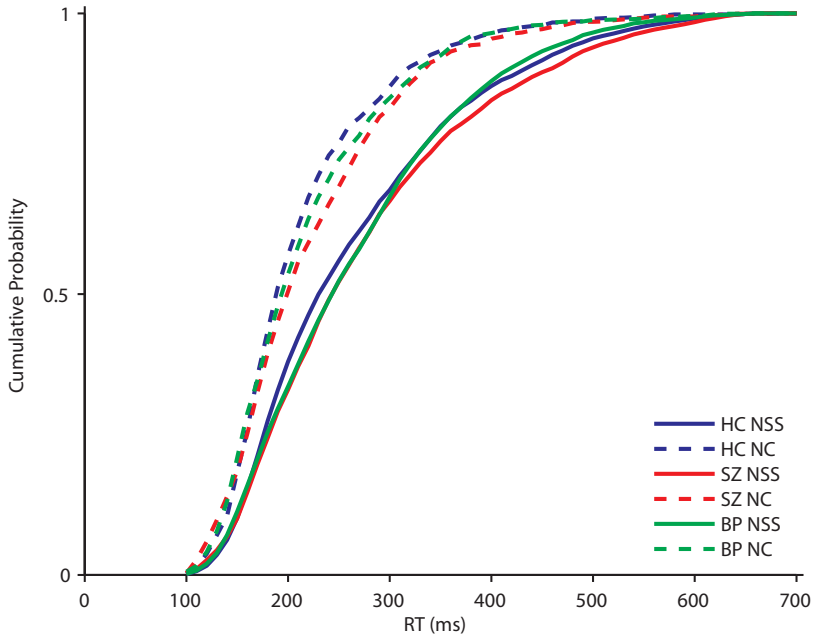

Figure 16. Cumulative distributions of saccade latencies in no-stop signal (NSS; solid lines) and noncancelled (NC; dotted lines) trials for healthy controls (blue), schizophrenia patients (red), and bipolar patients (green).

being slower than error noncancelled trials. There was no main effect of group ($F(2,48) = 0.24$, $p = 0.79$) or group-by-trial type interaction effect ($F(2,48) = 0.03$, $p = 0.97$). Cumulative distributions of RTs are presented in *Figure 16*.

SSRT. There was a significant effect of group on SSRT ($F(2,48)=3.33$, $p=0.04$). SSRT was significantly longer in schizophrenia patients than controls ($t(31)=2.5$, $p=0.02$). In bipolar patients, although there was a pattern of longer SSRT compared to controls, this difference did not reach significance $t(32)=1.56$, $p=0.13$). Finally, there was no difference in SSRT between the two patient groups ($t(33)=1.18$, $p=0.25$). However, there was a significant increase in SSRT as diagnostic groups moved up the psychosis continuum towards schizophrenia ($F(1,49)=6.79$, $p=0.01$; Figure 17a).

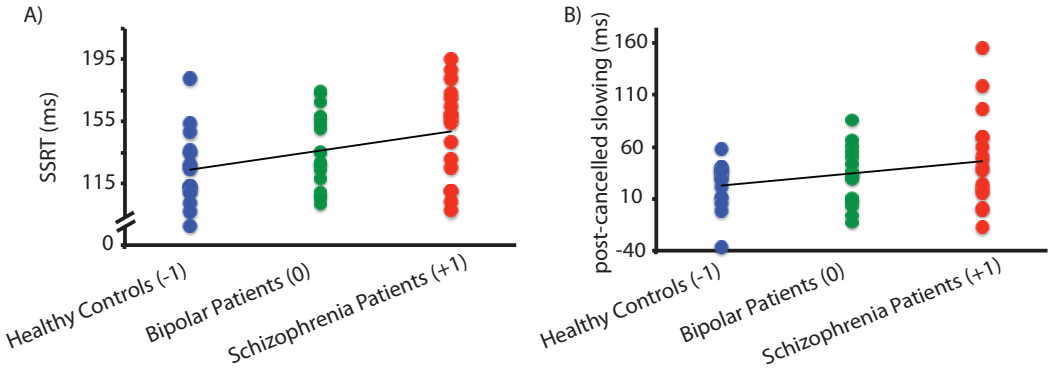

Figure 17. A) Linear relationship between severity of psychosis proneness (healthy=-1, bipolar=0, schizophrenia=1) and SSRT. B) Linear relationship between psychosis proneness and post-cancelled slowing.

RT adjustments across three trials in sequence. RT adjustment effects are presented in *Figure 18*. To assess effects of trial history on current no-stop signal trial, a repeated-measures ANOVA 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 ($F(1, 48) = 92.1$, $p < 0.0001$), and critical trial ($F(2,96) = 89.94$, $p < 0.0001$). Notably, there was a significant history-by-critical trial interaction ($F(2,96) = 87.52$, $p < 0.0001$).

RTs for no-stop signal trials were slower when they followed cancelled ($t(50)=7.9$, $p<0.0001$) and noncancelled ($t(50)=9.47$, $p<0.0001$) 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 ($t(50)=16.04$, $p<0.0001$). Additionally, pairwise comparisons revealed significant differences between RTs of the

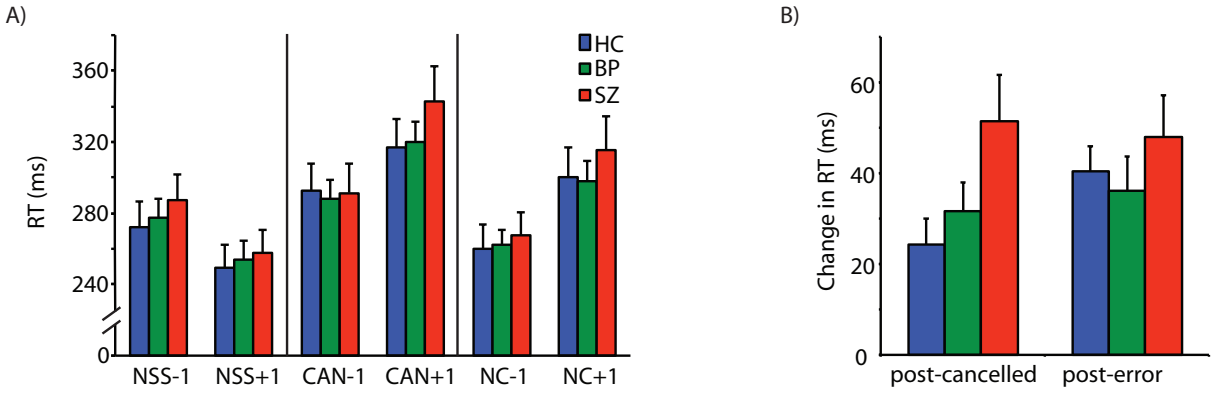

Figure 18. ***A)*** Mean no-stop signal RT (with standard error) for trials following (+1) and preceding (-1) no-stop signal (NSS), cancelled (CAN) and noncancelled (NC) trials for healthy controls (blue), schizophrenia patients (red), and bipolar patients (green). ***B)*** Mean post-cancelled and post-error slowing.

trials preceding each of the critical trial types. Trials preceding cancelled trials were slower than those preceding both noncancelled ($t(50)=6.72$, $p<0.0001$) and no-stop signal trials ($t(50)=3.17$, $p=0.003$). This suggests 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 ($t(50)=6.37$, $p<0.0001$). Likewise, this suggests that faster saccadic RT may result in subsequent failure to cancel a saccade.

There was no main effect of group ($F(2,48)=0.24$, $p=0.79$), but there was a statistical trend towards a group-by-history effect ($F(2, 48) = 2.71$, $p=0.08$). Planned contrasts revealed slower performance in schizophrenia patients compared to controls and this difference was more pronounced after the critical trial ($F(1,48)=26.3$, $p < 0.0001$) than before the critical trial ($F(1,48)=4.87$, $p=0.03$). However, there was no difference between controls and bipolar patients in RT before ($F(1,48)=0.09$, $p=0.76$) or

after ($F(1,48)=0.29$, $p=0.59$) the critical trial. Compared to bipolar patients, schizophrenia patients tended towards longer RTs prior to the critical trial ($F(1,48)=3.85$, $p=0.06$); this group difference did not meet significance. However, schizophrenia patients had significantly longer RTs compared to bipolar subjects following the trial of interest ($F(1,48)=22.40$, $p<0.0001$). Although the group-by-history-by-critical trial effect ($F(4, 96) = 1.73$, $p = 0.15$) did not reach significance, a one-way ANOVA was conducted to assess group differences in post-cancelled and post-error slowing and speeding following no-stop signal trials. There was a main effect of group on post-cancelled slowing ($F(2,48)=3.35$, $p=0.04$). Schizophrenia patients slowed down significantly more following cancelled trials than controls ($t(31)=2.3$, $p=0.03$), and tended to decelerate more than bipolar patients ($t(33)=1.69$, $p=0.10$). Additionally, there was a significant increase in post-cancelled slowing as diagnostic groups moved up the psychotic continuum ($F(1,49)=6.79$, $p=0.01$; *Figure 17b*). There were no effects of group on either post-error slowing ($F(2,48)=0.62$, $p=0.54$) or speeding following no-stop signal trials ($F(2,48)=1.79$, $p=0.18$).

Symptom and social functioning. Spearman rank-correlation coefficients were used to evaluate the association between the severity of psychiatric symptoms using the BPRS, YMRS, and HRSD and behavioral measures in bipolar patients. Along with total BPRS score, a positive and negative subscale score were calculated. None of the clinical symptom ratings correlated with any of the countermanding measures.

Since SFS employment scores were also bimodally distributed in bipolar patients, a median split was performed on the scores, and independent t-tests were conducted to

compare behavioral measures in those scoring high and low on occupational functioning. There was a trend for greater post-cancelled slowing in the low compared to high employment group, ($t(16) = 2.1$, $p = 0.056$). That is, better occupational functioning was associated with less slowing following correctly inhibited saccades. There was no significant difference in any other behavioral measure between employment groups, and no significant relationship between SFS total score and countermanding task performance was observed.

Experiment 1C: Impaired Saccade Inhibition and Idiosyncratic Saccade Monitoring as Potential Endophenotypic Markers in Healthy Relatives of Schizophrenic Patients

Aims

1) To investigate whether slower response inhibition and exaggerated slowing following correctly inhibited saccades is also present in healthy first-degree relatives of patients with schizophrenia.
2) To investigate whether slower response inhibition and exaggerated slowing following correctly inhibited saccades is associated with psychometric schizotypy in a healthy population.

Methods

Participants. 12 unaffected and unmedicated first-degree relatives were recruited from our database of schizophrenia patients and through a mental health

advocacy organization. Proband diagnosis was verified through a structured clinical interview (SCID-IV; First, et al., 1995) whenever possible (6 proband diagnoses were confirmed). 14 Healthy control subjects were recruited as outlined in *Experiment 1A,* and are largely a subset of that sample. Social and occupational functioning, IQ, and handedness were assessed as outlined in *Experiment 1A*. The Schizotypal Personality Questionnaire (SPQ; Raine, 1991) was also administered to examine the relationship between schizotypal traits and countermanding performance. Exclusion criteria were identical for healthy controls and unaffected relatives, and are outlined in *Experiment 1A.* Controls and healthy relatives were matched on age, sex, education, IQ, and handedness (*Table 6*). All subjects gave written informed consent approved by the Vanderbilt Institutional Review Board and were paid.

Table 6.	**Controls** Mean (s.d.)	**Relatives** Mean (s.d.)	**t**	**p**
Age	36.5 (8.6)	36.5 (11.0)	0	1.00
Sex	7F/7M	7F/7M	ϕ =0.2	0.67
Edinburgh handedness	61.78 (69.3)	72.91 (31.58)	0.51	0.61
IQ	108.2 (6.04)	102.4 (11.51)	1.6	0.12
Education (years)	15.8 (1.8)	15.2 (3.7)	0.8	0.76
SPQ-Total	9.5 (6.9)	20.1 (11.1)	2.96	0.007
SPQ-Positive	3.4 (3.7)	8.8 (6.5)	2.70	0.01
SPQ-Negative	4.1 (4.6)	10.4 (6.3)	2.93	0.007

Apparatus and stimuli. Described in *Experiment 1A*.

Design and procedure. The countermanding task was identical to that outlined in *Experiment 1A*.

Statistical methods. Statistical methods are described in *Experiment 1A*.

Table 7.	**Controls** Mean (s.d.)	**Relatives** Mean (s.d.)	**t-statistic**	***p***
Probability of Inhibition (%)	49.6 (3.7)	48.0 (4.3)	1.0	0.30
No-stop signal RT (ms)	269.4 (60.0)	316.8 (34.9)	2.76	0.01
Noncancelled RT (ms)	215.7 (36.9)	257.9 (39.2)	2.83	0.009
SSRT (ms)	128.6 (33.5)	173.2 (34.2)	3.36	0.002
Post-error slowing (ms)	43.8 (25.8)	37.3 (34.1)	0.55	0.59
Post-cancelled slowing (ms)	26.0 (31.2)	19.8 (35.0)	0.48	0.64

Results

Table 7 shows stop signal performance and RT adjustments for the two groups.

Probability of inhibition. The dynamic tracking procedure was successful, and the mean proportion of noncancelled trials was 49%, which did not differ between groups ($t(24)=1.05$, $p=0.31$). For each subject, the estimated slope of the inhibition function plotted against ZRFT was calculated (*Figure 19*). There was no group difference in the slope of the Z-transformed inhibition function ($t(24) = 1.2$, $p = 0.24$), providing evidence for equal variability in the inhibitory process across groups.

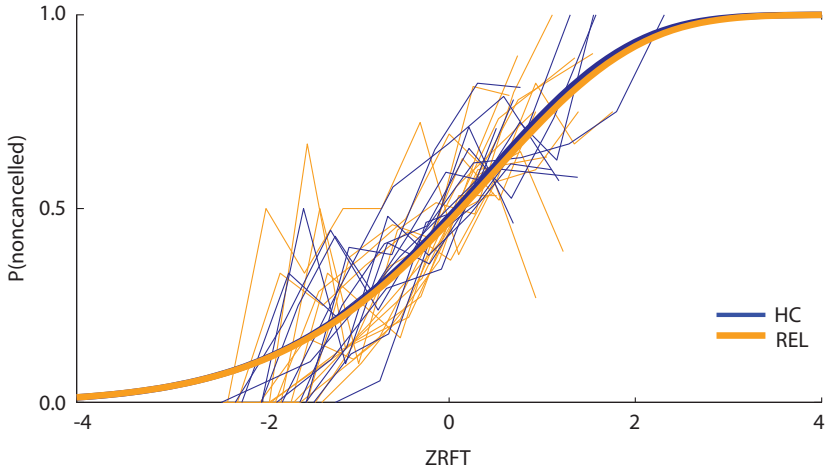

Figure 19. Individual normalized inhibition functions for healthy controls (blue) and relatives (orange). Probability of inhibition is plotted as a function of a Z score that measures time relative to the finish time of the GO and STOP processes in standard deviation units using the formula: ZRFT = (mean no-stop signal RT – SSD – SSRT)/standard deviation of no-stop signal RT. Separate cumulative Weibull functions are fit to the normalized inhibition functions for relatives and controls.

No-stop signal and noncancelled RT. The effect of trial type (no-stop signal or noncancelled) on RT was assessed with a repeated-measures ANOVA with group as a between-subjects variable and trial type as a within-subjects variable. There was a significant effect of trial type ($F(1,24) = 117.9$, $p < 0.0001$), with no-stop signal trials being slower than error noncancelled trials. There was also a main effect of group ($F(1,24) = 8.6$, $p = 0.007$), with healthy relatives being slower than controls. There was no group-by-trial type interaction effect ($F(1,24) = 0.25$, $p = 0.62$); relatives were slower than controls for both no-stop signal and noncancelled trials. Cumulative distributions of RTs are presented in *Figure 20*.

SSRT. There was a significant effect of group on SSRT ($t(24)=3.36$, $p=0.003$). SSRT was significantly longer in first-degree relatives than controls.

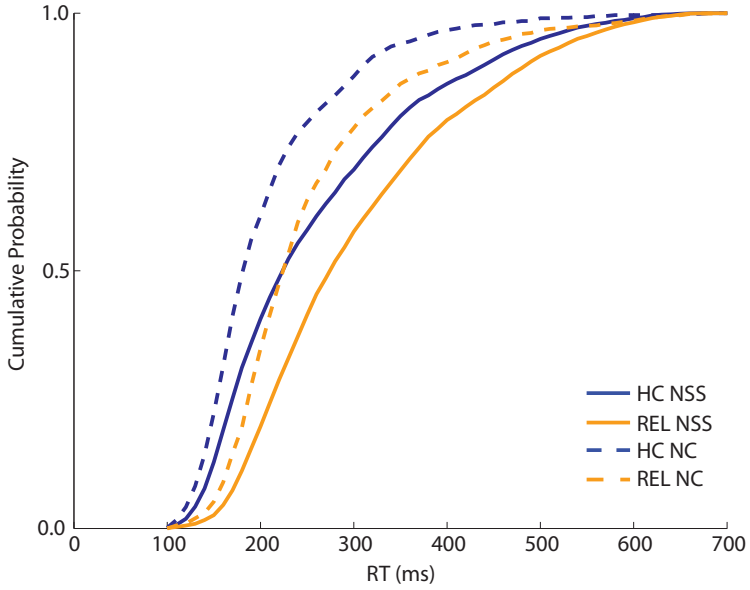

Figure 20. Cumulative distributions of saccade latencies in no-stop signal (NSS; solid lines) and noncancelled (NC; dotted lines) trials for healthy controls (blue) and relatives (orange).

RT adjustments across three trials in sequence. RT adjustment effects are presented in *Figure 21*. To assess effects of trial history on current no-stop signal trial, a repeated-measures ANOVA 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 ($F(1, 24) = 28.4$, $p < 0.0001$), and critical trial ($F(2,48) = 46.77$, $p < 0.0001$). Notably, there was a significant history-by-critical trial interaction ($F(2,48) = 33.80$, $p < 0.0001$).

RTs for no-stop signal trials were slower when they followed cancelled ($t(25)=3.6$, $p=0.001$) and noncancelled ($t(25)=7.06$, $p<0.0001$) trials than when they preceded them. This suggests that presenting a stop signal increases saccadic RT on the

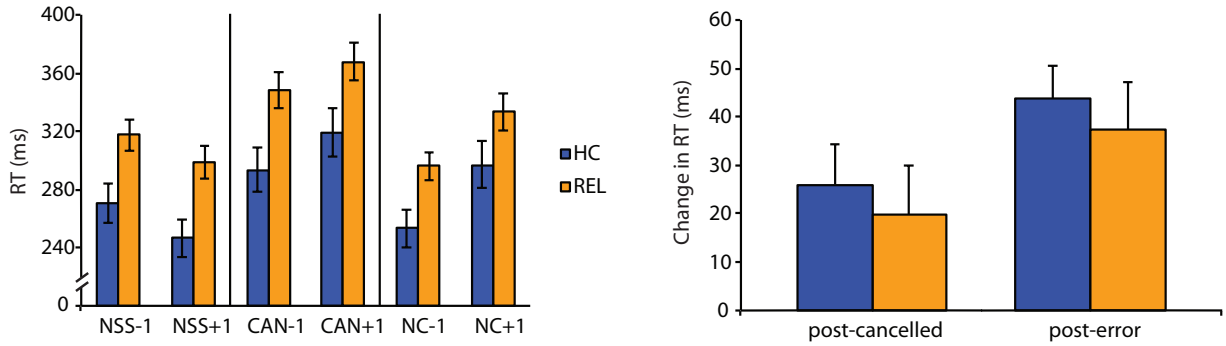

Figure 21. ***A)*** Mean no-stop signal RT (with standard error) for trials following (+1) and preceding (-1) no-stop signal (NSS), cancelled (CAN) and noncancelled (NC) trials for healthy controls (blue) and relatives (orange). ***B)*** Mean post-cancelled and post-error slowing.

subsequent trial, whether or not the saccade was cancelled. When three no-stop trials were presented in a row, participants got faster throughout ($t(25)=10.27$, $p<0.0001$). Additionally, pairwise comparisons 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 ($t(25)=6.02$, $p<0.0001$) and no-stop signal trials ($t(25)=3.78$, $p=0.0009$). This suggests 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 ($t(25)=4.45$, $p<0.0002$). Likewise, this suggests that faster saccadic RT may result in subsequent failure to cancel a saccade. There was a main effect of group ($F(1,24)=7.17$, $p=0.01$), again with relatives having slower saccadic RTs than healthy controls. However, there were no significant interaction effects with group.

Psychometric schizotypy. Spearman rank-correlation coefficients were used to evaluate the association between the syndromes of schizotypy and both SSRT and

post-cancelled slowing, since these measures were greater in patients than controls. Contrary to expectation, increased positive schizotypy was associated with decreased SSRT (r_s=-0.84, 0.0002). There were no significant correlations between negative symptoms and countermanding task performance in healthy controls, nor any significant correlations between positive or negative schizotypy and countermanding task performance in relatives.

Experiment 1: Discussion

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

Importantly, the performance of both patients and controls satisfied two criteria for the race model to hold. First, the probability of successfully inhibiting decreased with longer SSDs. After normalizing each individual's SSD with respect to their mean and variance of no-stop signal RT, the slopes of the two groups' inhibition functions were not statistically different, 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 (Gale & Holzman, 2000; Holzman, Proctor, & Hughes, 1973).

For the most part, our data conform to the existing cognitive control literature in schizophrenia. Increased SSRT in patients indicates that they needed more time to inhibit a saccade, consistent with mounting evidence for impaired response inhibition in schizophrenia (See *Introduction*). We also found that patients had working memory deficits, and poorer verbal working memory was related to longer SSRT. It has been argued that inhibitory deficits in schizophrenia are due, wholly or in part, to an inability to use working memory to guide behavior. Indeed, failure to trigger the inhibitory process inflates estimates of SSRT (Band, et al., 2003). We found no evidence for a group difference in triggering the stopping process, as indexed by equal slopes of the ZRFT transformed inhibition function. However, recent simulation data indicated that the slope of the ZRFT transformed inhibition function is not ideal for investigating trigger failures (Band, et al., 2003). We found that patients in this sample had working memory deficits, and poorer working memory was associated with longer SSRT. Thus, increased SSRT in schizophrenia may be partly due to inappropriate use of working memory to trigger the stopping process.

In our analysis of RT adjustments based on trial history, we found that both groups were slower on no-stop signal trials when they were preceded by cancelled and noncancelled trials than no-stop signal trials. Post-cancelled slowing has been observed in both humans and nonhuman primates performing this task (Cabel, et al., 2000; Emeric, et al., 2007; Kornylo, et al., 2003; Rieger & Gauggel, 1999; but see Verbruggen,

et al., 2008). Post-error slowing is commonly observed in choice manual response tasks (Rabbitt, 1966b), including the manual countermanding task (Rieger & Gauggel, 1999; Verbruggen, et al., 2008), but it has not been consistently observed in the saccade countermanding task (Emeric, et al., 2007; Li, et al., 2008). One potential explanation for our finding of significant post-error slowing lies in our analysis method. In previous studies, only no-stop signal RTs immediately *following* the trial of interest were averaged without taking into account latency of the trial immediately *preceding* the trial of interest. However, according to race model logic, when subjects are going faster overall, they are more likely to fail to inhibit on stop signal trials, and non-independence of RTs across trials is commonly observed (Gilden, 2001; Welford, 1980). Following Nelson, et al (2010), we compared no-stop signal RTs on trials following no-stop signal, cancelled and noncancelled trials with those immediately preceding no-stop signal trial in order to circumvent confounds created by local fluctuations in RT. There was no group difference in post-error slowing, consistent with prior reports (Mathalon et al., 2003; Polli, et al., 2006). These data suggest that the ability to evaluate performance and make appropriate short-term changes to repsonse strategy is spared in schizophrenia. Further, we found no group difference in speeding following no-stop signal trials. However, patients slowed down significantly more than controls following inhibited saccades. This finding is in line with recent evidence of prolonged effects of prior antisaccades on saccadic latency in schizophrenia (Barton, et al., 2005; Franke, et al., 2009; Franke, et al., 2007), which are interpreted as abnormal perseveration in the saccadic response system (Barton, et al., 2005). Compromised working memory might

result in abnormal updating of information about trial sequence (Barton, Kuzin, Polli, & Manoach, 2006), leading to idiosyncratic changes in RTs as a function of trial history in schizophrenia. However, correlations between working memory and the degree of post-cancelled slowing did not reach significance in either group; further research is needed to fully address this issue.

Although our findings partially replicate existing response inhibition and response monitoring data in schizophrenia 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, the current findings in schizophrenia are related to the extensive neurophysiology literature on this task.

Potential Neural Mechanisms Underlying Abnormal Saccade Countermanding in Schizophrenia

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 on to saccade- and fixation-related neurons, respectively (see *Introduction*). On no-stop signal and noncancelled trials, activity in saccade-related neurons reaches a threshold and the saccade is executed (Bruce & Goldberg, 1985; Munoz & Wurtz, 1995). On correctly cancelled trials, activity in saccade-related neurons begins to decay following the stop signal but before SSRT, while activity in fixation neurons begins to grow (Hanes, et al., 1998; Paré & Hanes, 2003). Thus, activity in gaze-shifting and gaze-holding neurons in FEF and SC appear to play a crucial role in the control of saccades.

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 (Hikosaka, Takikawa, & Kawagoe, 2000; Isoda & Hikosaka, 2008) and human functional imaging studies (Aron & Poldrack, 2006) point to the role of subthalamic nucleus (STN) in response inhibition. Additionally, deep brain stimulation of STN in patients with Parkinson's disease improved inhibitory control and resulted in shorter manual SSRT (van den Wildenberg, et al., 2006). A role of the right inferior frontal gyrus in countermanding movements has also been described (Aron, et al., 2004). Although there have not been any neuroimaging studies of the countermanding task in schizophrenia, fMRI studies that have examined neural activity during the antisaccade task suggest abnormalities in fronto-striatal-thalamo-cortical circuits (Raemaekers, et al., 2002; Tu, et al., 2006).

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 SEF neurons following correctly inhibited saccades is thought to reflect conflict between incompatible gaze-shifting and gaze-holding signals in FEF. SEF can bias saccadic latency via connections to cortical and subcortical oculomotor regions (Schall & Boucher, 2007) and

appears to be the basis of slowing following cancelled saccades (Stuphorn & Schall, 2006).

Based on these findings, a few potential hypotheses emerge regarding the mechanism of enhanced slowing following cancelled saccades in schizophrenia. Because the inhibitory process might take longer to complete in schizophrenia, as indexed by longer SSRT, the saccade could be cancelled at a longer delay following the rise of movement-related activity in FEF and SC, leading to more co-activation and subsequent conflict between gaze-holding and gaze-shifting neurons on correctly cancelled saccades. Alternatively, gaze-holding and gaze-shifting related neurons might be co-activated longer in patients with schizophrenia, 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 schizophrenia 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 (Hong et al., 2005) and volitional saccade tasks (Camchong, Dyckman, Austin, Clementz, & McDowell, 2008; Camchong, Dyckman, Chapman, Yanasak, & McDowell, 2006) in schizophrenia, findings of abnormal SEF activity are not consistent (Keedy, Ebens, Keshavan, & Sweeney, 2006; McDowell et al., 2002; Raemaekers, et al., 2002; Tu, et al., 2006).

Interpretation of Behavioral Differences in Schizophrenia in the Context of Computational Models of Countermanding Performance

In the context of the independent horse race model of countermanding performance (Logan & Cowan, 1984), which is described in the *Methods* section, our findings of longer SSRT and equal slopes of the inhibition function would suggest that the latency of the stop process is longer in schizophrenia. A variation of the independent race model, the interactive race model, accounts for both behavioral data and interactions between neurons associated with the STOP and GO processes, namely gaze-holding and gaze-shifting neurons in the FEF (Boucher, et al., 2007). In this model, on cancelled trials, the STOP process inhibits the GO process and keeps it from reaching the threshold for response execution. The best fitting model accounted for the behavioral data by having a STOP process that became active only slightly before SSRT and exerted potent inhibition on the GO process. In the framework of this model, a longer delay for the STOP process to become active in schizophrenia, rather than weakened inhibition of the STOP process on the GO process, would be consistent with equal slopes of the inhibition functions and relations between no-stop and noncancelled RTs between groups.

Recently, Lo et al. (2009) proposed a neural network model that considers the role of top-down control of pre-stop signal activity in gaze-holding neurons in countermanding saccades and described impaired inhibitory control when reducing input to neurons in the top-down control module of their network. Further explorations of neurobiologically plausible models to replicate countermanding performance in

schizophrenia have the potential to contribute to the understanding neural origins of inhibitory deficits.

Specificity of Abnormal Response Inhibition and Response Monitoring in Schizophrenia

To examine the specificity of inefficient response inhibition and exaggerated adjustments following correctly inhibited saccades, we investigated the performance of patients diagnosed with bipolar disorder. Mean SSRT in bipolar patients fell between that of controls and schizophrenia patients. Although SSRT in bipolar patients was approximately 12 ms slower than controls and 12 ms faster than schizophrenic patients, these differences did not reach the level of significance, suggesting that slowed inhibition is not specific to schizophrenia. Additionally, patients showed a statistical trend towards slowing down more than bipolar patients following cancelled trials, but there was no difference in trial history-based adjustments between bipolar patients and healthy controls. Interestingly, greater post-cancelled slowing was associated with poorer occupational functioning in bipolar patients. That is, those bipolar patients whose trial history effects more closely resembled those of the schizophrenia patients had poorer work outcomes. Finally, although differences in SSRT and post-cancelled slowing between bipolar and schizophrenia patients did not reach the level of significance, they did vary significantly as a function of psychosis-proneness. That is, both SSRT and post-cancelled slowing increased from controls to bipolar patients and from bipolar patients to schizophrenia patients in a linear manner. These results are in line with data supporting a psychosis continuum, rather than a categorical distinction

between affective disorders and schizophrenia spectrum disorders, and suggest that this continuum might also be represented at the level of cognition.

Importantly, patients with bipolar disorder and schizophrenia were matched on overall psychiatric symptom severity, as indexed by BPRS scores, and overall social and occupational functioning; thus, differences between the two patient groups cannot be attributed to differences in general level of psychopathology nor the psychosocial consequences of having a mental illness. Additionally, the majority of bipolar patients were also taking antipsychotic medications. Finally, performance of bipolar patients also satisfied the criteria for the race model to hold, there was no difference across groups in the sensitivity to the stop signal as indexed by equivalent slopes of the normalized inhibition function, and there were no group differences in basic visually-guided saccade latency.

Liability for Schizophrenia and Stop Signal Performance in Healthy Individuals

We examined whether longer SSRT and greater post-cancelled slowing were also present in healthy individuals with a genetic liability towards the disorder (healthy first-degree relatives) or varied as a function of liability for the illness as measured by psychometric schizotypy, which refers to the personality traits that are related to symptoms of schizophrenia. First-degree relatives had longer SSRT than healthy controls, consistent with prior studies reporting poorer antisaccade performance in these individuals (see *Introduction*). Although reports of impaired antisaccade performance in first-degree relatives have been brought into question due to imbalanced selection

criteria (Levy, O'Driscoll, et al., 2004; e.g. allowing Axis I disorders in relatives but not controls), this cannot account for longer SSRT in relatives in the current study since exclusion criteria were equivalent across groups.

Along with slowed response inhibition, first-degree relatives also had slower visually-guided saccades compared to healthy controls; this finding was not observed in patients with schizophrenia. One possible explanation is that first-degree relatives simply have slower reflexive saccades; however, a recent meta-analysis showed that relatives are typically found to have both normal amplitude and latency of visually-guided saccades (Calkins, Iacono, & Ones, 2008). Another possibility is that longer RT reflects a shift in speed-accuracy trade-off towards a more cautions response style. It has been shown that subjects performing the stop-signal task adjust their response bias as the probability of a stop signal increases; when the probably of a stop signal is high, subjects slow down and no-stop RTs are longer (Logan & Burkell, 1986; Verbruggen & Logan, 2009b). Thus, longer saccadic RT during this task in healthy relatives could represent proactive control of response style as an effort to compensate for slower inhibition. It is impossible to test this hypothesis in the current study as we used a tracking procedure to ensure equal accuracy across participants; that is, subjects were not able to adjust their overall error rate by applying a more cautious strategy. We are not aware of any studies that have explicitly examined speed-accuracy trade-offs or response bias in speeded RT tasks in first-degree relatives.

Consistent with prior reports, healthy first-degree relatives had higher total SPQ scores than healthy non-relatives (Relatives: mean=20.1, s.d.=11.1; Non-relatives:

mean=9.5, s.d.=6.9; t(24)=2.96, p=0.007). In healthy non-relatives, increased positive schizotypy, the dimension particularly associated with vulnerability towards full manifestation of the disease (Vollema, Sitskoorn, Appels, & Kahn, 2002), was associated with faster response inhibition. Given slower SSRT in patients with schizophrenia, the opposite relationship was expected. However, it should be noted that the mean SPQ score in the non-relatives sample was markedly lower than the average SPQ score found in a random sample of college students (mean score≈26; Raine, 1991). One possible explanation of these findings is that there is a U-shaped relationship between schizotypy and SSRT, such that both very low and very high schizotypy are associated with poorer inhibition, and that this sample captures the descending portion of the curve. This argument is bolstered by evidence of a non-linear relationship between latent inhibition and schizotypy (Wuthrich & Bates, 2000).

Limitations

Results of the present study should be considered in light of several limitations. One clear 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 (Harris, et al., 2006). If deficits in countermanding and antisaccade tasks reflect inhibition impairments, longer SSRT in schizophrenia is unlikely to be a result of neuroleptics. Further, administration of haloperidol (a first-generation antipsychotic) had no significant effect on post-error slowing in healthy individuals (de Bruijn, Sabbe, Hulstijn, Ruigt, & Verkes, 2006;

Zirnheld et al., 2004). Finally, in *Experiment 1A*, normalized antipsychotic dose was not related to any countermanding measures. A second limitation is the small sample sizes in the current study. Finally, in our healthy relatives sample, proband diagnosis from several participants could not be confirmed independently because of difficulties involved in contacting the proband (e.g., distance, death).

Conclusions and Implications

Results from *Experiment 1* suggested that patients with schizophrenia needed more time to inhibit a planned saccade, which was related to negative symptom severity and occupational functioning. Further, patients exhibited more pronounced RT effects after saccade inhibition. These findings were observed to a lesser degree in bipolar subjects, and both slower inhibition and exaggerated trial history-based slowing were related to psychosis-proneness in a linear fashion. Finally, there was evidence for heritability of these deficits. Longer SSRT was also observed in healthy first-degree relatives of patients with schizophrenia, suggesting that it might function as a candidate endophenotype. Inefficient response inhibition and idiosyncratic trial history effects are consistent with functional abnormalities in FEF, SC, and SEF. Further, 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 schizophrenia (McGurk, Mueser, Feldman, Wolfe, & Pascaris, 2007; McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007).

CHAPTER III

EXPERIMENT 2: INHIBITION AND MONITORING OF SACCADES IN A DOUBLE-STEP TASK IN SCHIZOPHRENIA

Aims

1) To replicate findings of longer time needed to inhibit a saccade in schizophrenia, as indexed by longer target step reaction time (see *Experiment 1A*).
2) To replicate findings of exaggerated slowing following cancelled saccades in schizophrenia (see *Experiment 1A*).
3) To investigate the incidence and latency of corrective saccades in schizophrenia.
4) To investigate the degree to which corrective saccades are programmed in parallel with erroneous noncompensated saccades by measuring the slope and goodness of fit of the function plotting intersaccadic interval (ISI) as a function of reprocessing time (RPT).
5) To investigate integrity of corollary discharge signals in schizophrenia by examining the spatial accuracy of corrective saccades.
6) To assess the clinical relevance of the present study by examining the relationship between current positive symptoms and both current and lifetime passivity symptoms and indices of response monitoring.

Methods

Participants. Individuals with schizophrenia and healthy controls were recruited for this study using the recruitment methods and inclusion criteria as specified in *Experiment 1A.* Subject characteristics, including clinical symptoms, demographics, and social functioning were assessed as in *Experiment 1A*. Additionally, the Scale for Passivity Phenomena (Spence et al., 1997) was administered to assess current and lifetime passivity symptoms. Three schizophrenia patients were excluded based on double-step task performance, as outlined in the *Statistical Methods* section, and one subject aborted the experiment early due to discomfort with the darkness. Analyses were conducted on the remaining 16 patients and 18 controls. Groups were matched for age, sex, and handedness (Table 8). All subjects gave written informed consent approved by the Vanderbilt Institutional Review Board and were paid.

Apparatus and stimuli. Eye position was monitored using the EyeLink II eyetracker (SR Research, Canada) at a sampling rate of 250 Hz with average gaze position error $<0.5^{o}$, noise limited to $<0.01°$ RMS. Saccades were detected on-line using a velocity criterion (35°/sec). Subjects were seated 57cm from the computer monitor with their head in a chinrest. One of the aims of this experiment was to examine the integrity of corollary discharge signals by measuring the spatial accuracy of the corrective saccade to the final target on step trials (*see Figure 2*). To eliminate the effect of visual reference cues on saccade localization, the task was performed in darkness by reducing the stimulus presentation computer monitor brightness to the minimum value and using a 3-stop neutral density gel filter to block stray monitor light. This technique

Table 8.	Controls (n=18)	SZ Patients (n=16)	Statistic	p
Age	37.6 (8.3)	39.9 (9.4)	t = 0.8	0.5
Sex	7F / 11M	7F / 9 M	ϕ = 0.08	0.8
IQ	107.7 (2.2)	101.1 (2.3)	t = 2.0	0.05
Years of Education	16.1 (2.1)	12.9 (1.9)	t = 2.4	0.0002
Handedness	67.8 (62.5)	54.4 (49.0)	t = 0.7	0.5
SFS Total	156.6 (14.8)	130.7 (17.9)	t = 4.6	<0.0001
SFS Employment	9.9 (0.2)	4.7 (3.7)	t = 6.0	<0.0001
Years of Illness	*n/a*	19.9 (8.3)		
CPZ Equivalent	*n/a*	486.6 (531.6)		
BPRS	*n/a*	17.2 (7.0)		
SAPS	*n/a*	17.0 (7.8)		
SANS	*n/a*	24.8 (14.4)		

has been used in prior studies (e.g. Park, Schlag-Rey, & Schlag, 2003). Subjects were instructed to notify the experimenter, who was seated outside the testing room, if they saw any stray monitor light that revealed the monitor outline as they began to dark-adapt. However, no subjects reported seeing any visual reference cues.

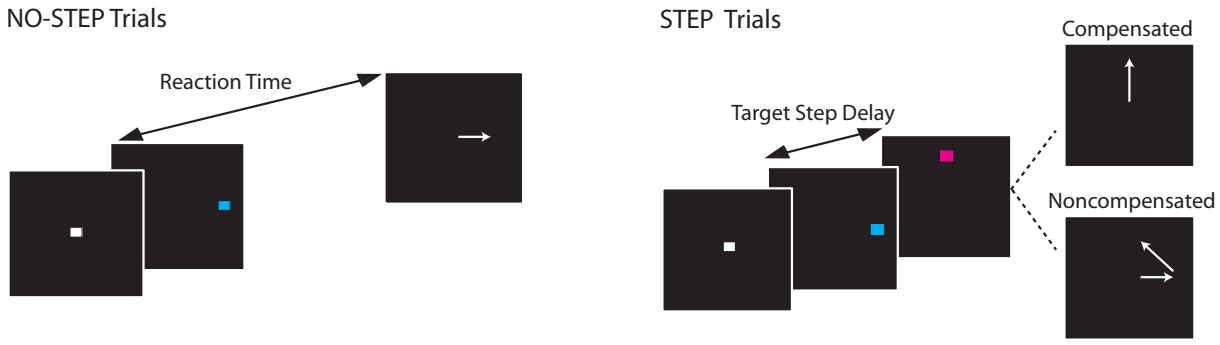

Figure 22. Double-step task. Arrows indicate the direction of the saccade. Trials began with the presentation of a central fixation spot. After the fixation spot disappeared a target flashed at a non-central location. On step trials, a second target flashed at some delay following onset of the first target (target step delay; TSD). A target step was the cue for the subject to withhold a saccade to the target and instead redirect gaze towards the second target. Trials in which the subject was successful in redirecting gaze shift were referred to as compensated trials, and trials in which the subject made a saccade to the first target were referred to as noncompensated trials. On most noncompensated trials, a corrective saccade was made to the second target location. For the remaining trials (no-step trials), the target did not step, and the subject was instructed to make a saccade to the location of the flashed target.

Design and procedure. Subjects performed the saccadic double-step task (*Figure 22*). Sixty percent of the trials were *no-step* trials. These trials required subjects to fixate on the central fixation spot (white square subtending 0.5°) until it disappeared (after a random delay between 500-1000 ms) and a peripheral target (T1), subtending 1°, flashed for 94 ms at an alternate location. The first target could be presented at one of eight positions 12° equidistant from fixation. Subjects were instructed to look directly at the target as quickly as possible. The remaining 40% of trials were *step* trials. These trials were initially identical to the no-step trials, but after a variable delay (*target step delay*; TSD) following initial target presentation, a second target (T2) flashed for 94 ms

at an alternate location[1]. T1 and T2 location were constrained such that the angle between the two targets was at least 90°, to minimize the number of saccades that land between T1 and T2 (Ottes, Van Gisbergen, & Eggermont, 1984; Walker, Deubel, Schneider, & Findlay, 1997), and could not be separated by 180° (directly opposite to each other). Thus, targets could be separated by either 90° or 135°. The target step instructed subjects to inhibit a saccade to the initial target and instead look towards the second target as quickly as possible. Step trials were labeled *compensated* or *noncompensated* based on whether subjects redirected or failed to redirect their first saccade towards the final target, respectively. The first and second targets were different isoluminant colors (cyan and magenta, 2.06 cd/m^2), making it easier to distinguish target order at short TSDs. Color mapping was counterbalanced across subjects. As with the standard countermanding task, response inhibition and redirection become more difficult with increasing TSDs. TSDs were dynamically adjusted using two independent, interleaved tracking procedures, 2-up/1-down (converging near 71% successful inhibition) and 1-up/2-down (converging near 29% successful inhibition). This procedure ensures successful inhibition on approximately 50% of the step trials, but also makes the TSD on any given trial less contingent on the previous trial than a 1-up/1-down procedure. The initial TSD was set at 94 ms. If the particular step trial was part of the 2-up/1-down staircase, the TSD was increased by 47 ms if the previous two trials that were part of that staircase were compensated and decreased by 47 ms if the

[1] If the TSD was less than 94ms, T1 was only presented for the length of the TSD. At TSDs of 47 or 94 ms, T1 offset and T2 onset were simultaneous.

[2] In Experiment 1, SSRT was calculated for each block for each subject, and a repeated measures ANOVA was run on SSRT with group entered as a between subjects variable and block entered as a within-subject variable. Although we observed a significant effect of group ($F(1, 31)=5.99$, $p=0.02$), with patients having longer SSRT than controls, there was no significant effect of block ($F(3,93)=0.87$, $p=0.46$)

previous step trial in that staircase was noncompensated. Otherwise, the TSD was held constant. Likewise, for trials that were part of the 1-up/2-down staircase, the TSD was increased by 47 ms if the previous trial was compensated, decreased by 47 ms if the previous two step trials were noncompensated, and was otherwise held constant. The testing session consisted of a practice block of 60 trials, and 4 experimental blocks of 120 trials each.

To measure basic response times, saccadic RT on no-step and noncompensated trials was calculated as the time between initial target onset and saccade initiation. Saccadic RT on compensated trials was calculated as the time between second target onset and saccade initiation. Inhibitory performance was examined using analogous methods to those in the countermanding task outlined in *Experiment 1*. At each TSD, the proportion of trials in which a participant successfully inhibited a saccade was quantified. The proportion of compensated trials at each delay is referred to as the *compensation function*. Race model logic also applies to the double-step task, and TSRT was calculated in the same way that SSRT was calculated in the countermanding task (outlined in *Experiment 1A*). That is, TSRT equals the mean no-step trial RT minus the mean TSD. As described in *Experiment 1*, a Z-transformation was applied to the TSDs, which expressed them in terms of the latency relative to finishing times of GO and STOP processes standardized with respect to variability in GO RT using the equation:

$$ZRFT = \frac{\mu_{RT} - TSD - TSRT}{\sigma_{RT}}$$

where ZRFT is the Z-transformed TSD, μ_{RT} is the mean no-step RT, and σ_{RT} is the standard deviation of the no-step RTs. The slope of the compensation function was interpreted as a measure of the ability to trigger the stop process or variability in TSRT.

This task also affords the opportunity to examine several aspects of response monitoring since noncompensated saccades on step trials are nearly always followed by corrective saccades to the final target. To distinguish corrective saccades from saccades that return the eyes to the central fixation point, the following criteria were used to define corrective saccades: 1) the saccade brings the eye closer to T2; 2) the saccade brings the eye closer to T2 than to the fixation point; 3) the direction of the saccade is closer to the direction necessary for the eyes to land on T2 than the direction necessary for the eyes to land on the central fixation. Corrective saccade latency was measured as the interval between the initiation of the erroneous noncompensated saccade and corrective saccade.

Additionally, the spatial accuracy of corrective saccades was examined in two ways. First, the degree to which subjects took into account the anticipated change in eye position following a saccade to T1 was indexed by measuring the angle of deviation between the endpoint of the corrective saccade and the final target location. Angular deviations in the direction that would be expected if the subject were making a saccade to T2 from fixation (i.e. not compensating for the change in eye position) were assigned a positive value (*see Figure 23a*).

Integrity of the corollary discharge mechanisms that support accurate saccades can be measured in a second way on noncompensated step trials. Saccades to T1 are

often slightly hypometric or hypermetric. As discussed in the *Introduction*, healthy primates can adjust for these inaccuracies in the saccade to T1 when making their saccade to T2. We calculated these adjustments to correct for variations in amplitude of the first saccade in two ways. In the first method, we measured the angle of deviation between the endpoint of the corrective saccade and the final target location. Angular deviations in the direction that would be expected if the subject were making a saccade to T2 from T1 (i.e. not compensating for spatial inaccuracy in the saccade to T1) were assigned a positive value (*see Figure 23b*). We also used a second method, following Joiner, et al. (2010). For each corrected noncompensated trial, the angle of the second

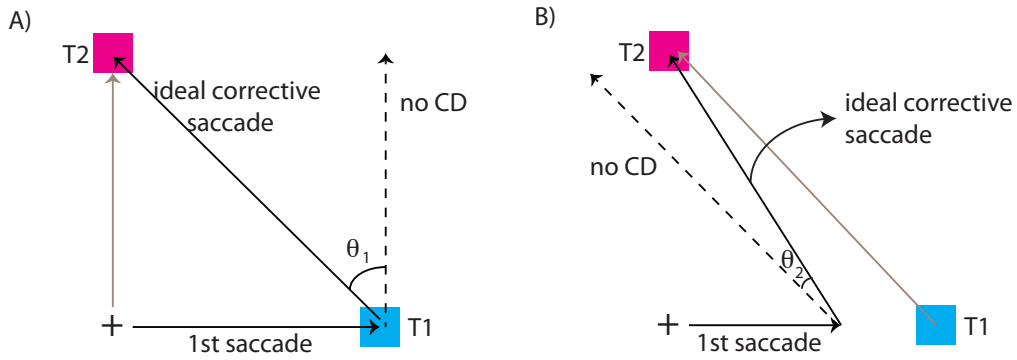

Figure 23. Calculations of corollary discharge. ***A)*** Schematic of not compensating for the change in eye position brought about by the first saccade. The grey arrow is the saccade vector from fixation to T2. The dotted arrow represents the saccade that would be made from T1 if the subject had not adjusted for change in position brought about by the first saccade. Angle θ_1 represents the bias in the second saccade vector if the subject had not compensated at all for the first eye movement. Any saccade that fell in the direction between the ideal saccade and saccade indicating no corollary discharged was assigned a positive bias. ***B)*** Schematic of not compensating for variability in amplitude of the first saccade. The grey arrow is the saccade vector from T1 to T2. The dotted arrow represents the saccade that would be made from the endpoint of the first saccade if the subject had not adjusted for error in the endpoint of the first saccade. Angle θ_2 represents the bias in the second saccade vector if the subject had not compensated at all for error in the first saccade endpoint. Any saccade that fell in the direction between the ideal saccade and saccade indicating no corollary discharged was assigned a positive bias.

saccade vector whose origin was at the end of the first saccade was determined and plotted against the ideal angle required for the subject to reach the target. For each subject, the slope and R^2 values of the regression analysis between the two angles were calculated; the slope was interpreted as the proportion of compensation for variation in amplitude of the first saccade, and the R^2 value was interpreted as an indicator of how well the linear model fit the data. Slope and R^2 values were compared across groups.

As discussed in the *Introduction*, in double-step tasks, an inverse relationship is observed between the intersaccadic interval (ISI; interval between first and second saccade) and reprocessing time (RPT; interval between second target onset and initiation of the first saccade). That is, as the subject has more time to process the visual information of the second target prior to the first saccade, the saccade to that target from the first target location becomes faster because programming of the noncompensated saccade and corrective saccade overlap. Thus, we can investigate the strength of the relationship between ISI and RPT as a measure of parallel processing of the corrective movement with the initial erroneous movement. Previous studies have found that these ISIs are comprised of two distributions: shorter ISIs that decrease with RPT and long ISIs that do not change with RPT (Murthy, et al., 2007; *Figure 24*). At these very long ISIs, parallel processing is assumed not to have taken place. To quantify whether ISI varies with RPT, only ISIs with latencies less than the 95th percentile latency of saccades produced on no-step trials were analyzed. This procedure removed ISIs that were greater than typical visually-guided saccade latencies. As Murthy, et al. (2007) explain, this procedure removes trials in which the

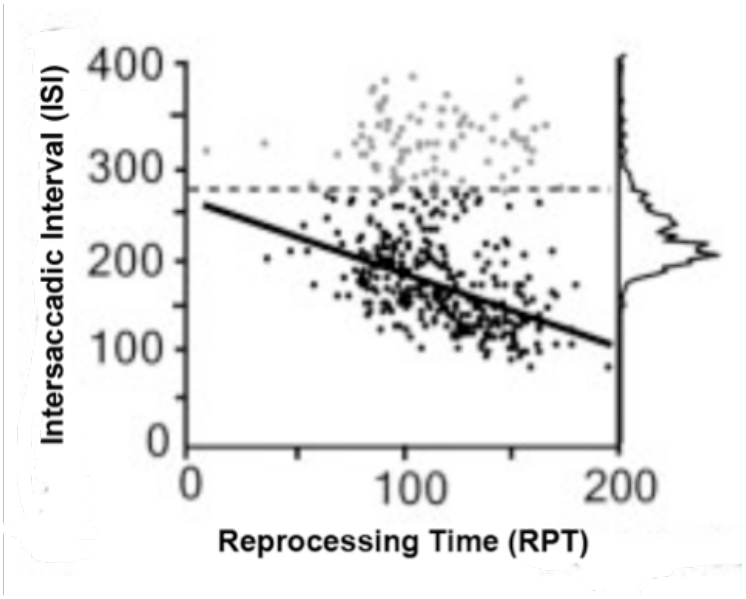

Figure 24. ISI plotted against RPT. Dashed lines indicate 95th percentile of no-step latencies. Adapted from Murthy, et al. (2007)

noncompensated and corrective saccade are clearly achieved through serial processing since the corrective saccade was programmed after complete visual processing of the second target.

Finally, to examine RT adjustments based on trial history, mean RT was computed separately for no-step trials preceding and following no-step trials, correctly compensated step trials, and noncompensated step trials (i.e. step errors). RTs on no-step trials preceding and following two consecutive step trials were included in the analysis only if the response on the two step trials was the same (i.e. if both trials were compensated or noncompensated). Post-compensated slowing was calculated as the difference between mean RT for no-step trials preceding and following a compensated trial. Likewise, post-error slowing was calculated as the difference between mean RT for step trials preceding and following an erroneously noncompensated trial.

Statistical methods. Fisher's exact tests, independent t-tests, and repeated measures ANOVAs were used where appropriate. Spearman rank-correlation coefficients were calculated between symptoms and double-step performance. All tests were two-tailed except otherwise specified. Subjects were excluded from analyses if the adaptive tracking procedure in the double-step task was ineffective, defined by a proportion of successfully compensated responses lying outside a 95% binomial confidence interval around p=0.5.

Results

Probability of inhibition. The dynamic tracking procedure was successful, and the mean proportion of noncancelled trials was 48%. The two groups did not differ in the

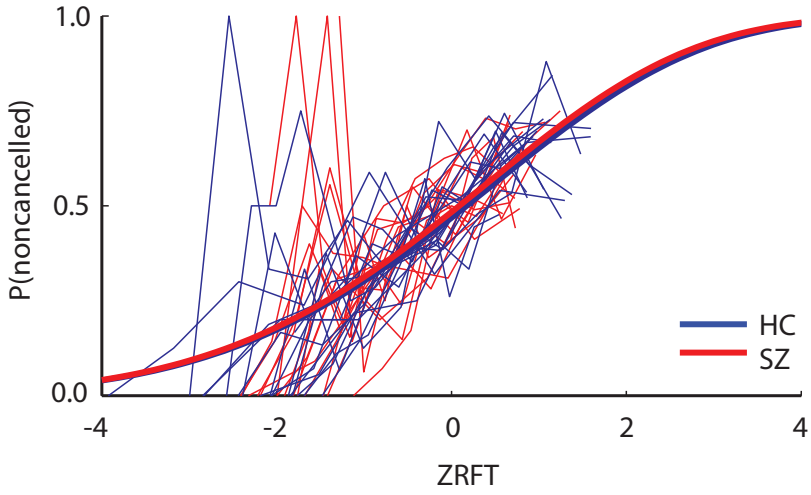

Figure 25. Individual normalized compensation functions for healthy controls (blue) and schizophrenia patients (red). Probability of inhibition is plotted as a function of a Z score that measures time relative to the finish time of the GO and STOP processes in standard deviation units using the formula: ZRFT = (mean no-stop signal RT – SSD – SSRT)/standard deviation of no-stop signal RT. Separate cumulative Weibull functions are fit to the normalized compensation functions for patients and controls.

proportion of noncancelled trials (t(32)=0.01, p=0.99). For each subject, the estimated slope of the inhibition function plotted against ZRFT was calculated (*Figure 25*). There was no group difference in the slope of the Z-transformed inhibition function (t(32) = 0.18 p =0.86), providing evidence for equal variability in the inhibitory process across groups.

No-step, noncompensated, and compensated RT. The effect of trial type (no-step, noncompensated, or compensated) on RT of the first saccade was assessed using a repeated measures ANOVA with group as a between-subjects variable and trial type as a within-subjects variable (*Figure 26*). There was a significant effect of trial type ($F(2,64) = 11.67$, $p < 0.0001$). Noncompensated trials were significantly faster than both no-step trials ($t(33)=5.85$, $p<0.0001$) and compensated trials ($t(33)=3.77$, $p=0.0006$). There was no difference between compensated and no-step trial latency ($t(33)=0.45$, $p=0.66$). There was a trend towards both a main effect of group ($F(1,32)=3.56$, $p=0.06$) and a group-by-trial type interaction ($F(2,64)=2.70$, $p=0.07$). Planned comparisons indicated longer compensated RTs in patients ($t(32)=2.34$, $p=0.03$) but no significant differences between no-step ($t(32)=1.36$, $p=0.18$) or noncompensated ($t(32)=1.48$, $p=0.15$) RTs. That is, saccadic RT in schizophrenia was only longer when they were required to first inhibit a saccade and then redirect gaze towards a second target, providing evidence for impaired inhibition.

TSRT. TSRT was significantly longer in patients than controls ($t(32)=2.76$, $p=0.009$), suggesting poorer inhibitory efficiency in schizophrenia. Further, TSRT was highly correlated with mean RT on successfully compensated trials (controls: $r=0.71$,

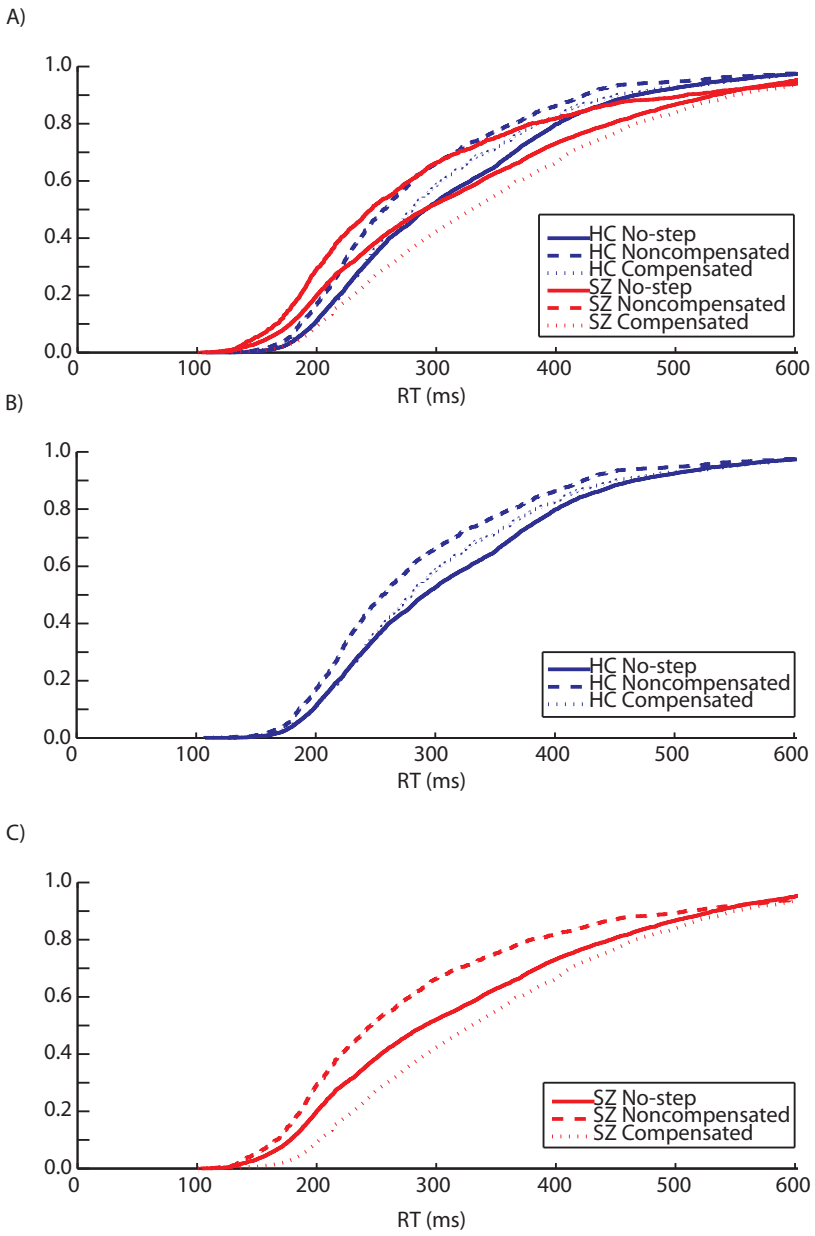

Figure 26. ***A)*** Cumulative distributions of saccade latencies in no-step (solid lines), noncompensated (thick dotted lines) and compensated (thin dotted line) for healthy controls (blue) and schizophrenia patients (red). For ease of visualization, data is also presented for groups separately: ***B)*** Healthy controls, ***C)*** Schizophrenia patients.

p=0.001; schizophrenia: r=0.67, p=0.005), suggesting that longer compensated saccades are related to patients' slowed inhibitory processing.

RT adjustments across three trials in sequence. To assess effects of trial history on current no-step trial, a repeated measures ANOVA was conducted on no-step RTs with diagnostic group as a between-subjects variable and critical trial (no-step, compensated, noncompensated) and history (before or after critical trial) entered as within-subjects variables. There was a significant effect of history ($F(1, 32) = 8.38$, $p=0.007$) and critical trial ($F(2,64) = 29.29$, $p < 0.0001$). Notably, there was a significant history-by-critical trial interaction ($F(2,64) = 30.92$, $p < 0.0001$).

RTs for no-stop signal trials were slower when they followed compensated ($t(33)=2.62$, $p=0.01$) and noncompensated ($t(33)=6.52$, $p<0.0001$) trials than when they preceded them. This suggests that presenting a target step increases saccadic RT on the subsequent trial, whether or not the trial was compensated. When three no-step trials were presented in a row, participants got faster throughout ($t(33)=9.31$, $p<0.0001$). Additionally, pairwise comparisons revealed significant differences between RTs of the trials preceding each of the critical trial types. Trials preceding compensated trials were

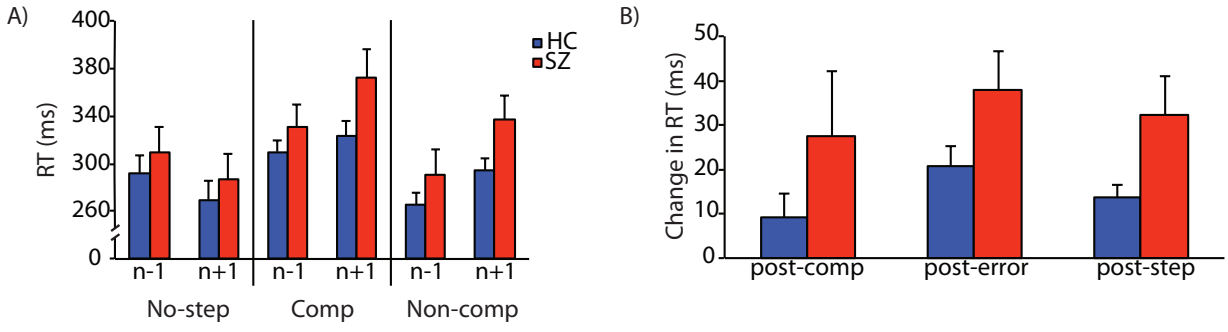

Figure 27. Mean no-stop signal RT (plus standard error) as a function of trial history. ***A)*** Mean no-stop signal RT for trials following (n+1) and preceding (n-1) no-step, compensated (Comp) and noncompensated (Non-comp) trials for healthy controls (blue bars) and schizophrenia patients (red bars). ***B)*** Mean post-compensated, post-error, and post-step trial slowing.

slower than those preceding both noncompensated (t(33)=5.94, p=<0.0001) and no-step trials (t(33)=2.40, p=0.02). This suggests that when subjects are responding slower, they are more able to redirect a saccade on the subsequent trial. Trials preceding no-step trials were slower than those preceding noncompensated trials (t(33)=4.14, p<0.0002). Likewise, this suggests that faster saccadic RT may result in subsequent failure to redirect a saccade.

There was no main effect of group (F(1,32)=2.56, p=0.12), nor any group interactions on mean no-step RTs, contrary to prior findings on the countermanding task. Along with mean no-step RTs, we also investigated median no-step RTs as a function of trial history (*Figure 27*). As with mean RTs, there was a significant effect of trial history, such that participants slowed down following compensated and noncompensated step trials and sped up following successive no-step trials. There was also a trend towards a group-by-history effect (F(1,32)=3.37, p=0.08). Planned contrasts revealed slower performance in patients compared to controls and this difference was more pronounced after the critical trial (F(1,32)=37.53, p < 0.0001) than before the critical trial (F(1,32)=12.47, p=0.001). Although the group-by-history-by-critical trial effect (F(2, 64) = 0.97, p = 0.38) did not reach significance, independent t-tests were conducted to assess group differences in median post-compensated, post-noncompensated, and post-step (collapsed across compensated and noncompensated) slowing and median speeding following no-step trials. Patients did not differ significantly from controls in either post-compensated slowing (t(32)=1.26, p=0.22), post-noncompensated slowing (t(32)=1.79, p=0.08), or speeding following no-step trials

(t(32)=0.46, p=0.65); however, collapsed across noncompensated and compensated trials, patients slowed down significantly more following step trials (t(32)=2.15, p=0.04).

Corrective saccades. ***Incidence and latency.*** Patients with schizophrenia corrected a smaller proportion of errors than healthy controls (controls: mean=88.1%, s.d.=12.4%, patients: mean=78.1%, s.d.=13.4%; t(32)=2.15, p=0.04). To examine corrective saccade latency compared to primary saccade latencies as well as putative group differences in corrective saccade latency, a repeated measures ANOVA was conducted on mean RT, with saccade type (corrective, noncompensated, compensated, no-step) as a within-subjects variable and diagnostic group as a between-subjects variable. There was a significant effect of trial type ($F(3,96)=11.98$, $p<0.0001$). Differences between noncompensated, compensated, and no-step RTs are outlined in an earlier section. Collapsed across groups, corrective saccades were shorter latency than no-step (t(33)=3.88, p=0.0005) and compensated saccades (t(33)=4.77, p<0.0001), but not erroneous noncompensated saccades (t(33)=1.36, p=0.18). There was a main effect of group (F(1,32)=8.27, p=0.04). Although the group-by-trial type interaction was non-significant, independent and matched pairs t-tests were conducted to examine differences in corrective saccade latencies between groups and differences between saccade latencies within diagnostic groups, respectively. In healthy controls, corrective saccades were faster than no-step (t(17)=4.69, p=0.0002), compensated (t(17)=3.31, p=0.004) and non-compensated (t(17)=2.54, p=0.02) trials. In contrast, corrective saccade latency in schizophrenia was only longer than compensated saccade latency; there was no difference in latency between corrective and either no-step

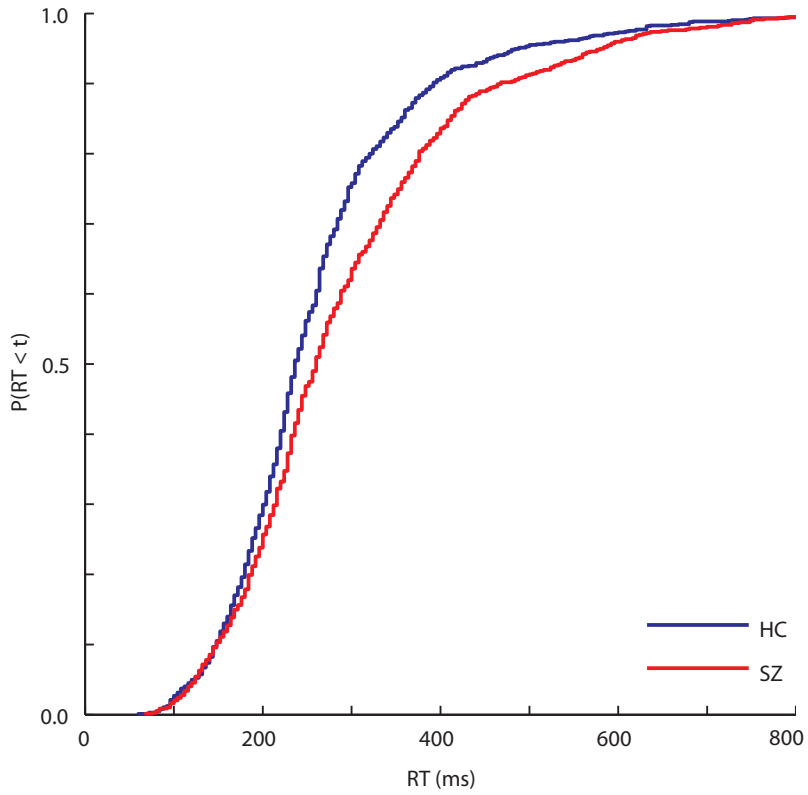

Figure 28. Cumulative distributions of corrective saccade latencies for healthy controls (blue) and schizophrenia patients (red).

(t(15)=1.67, p=0.11) or noncompensated (t(15)=0.44, p=0.67) saccades. Direct comparison of groups revealed longer corrective saccade latency in schizophrenia (controls: mean=257 ms, s.d.=52 ms, patients: mean=302 ms, s.d.=62 ms; t(32)=2.26, p=0.03; *Figure 28*).

Spatial accuracy. First, the degree to which corrective saccades were biased in the direction predicted by a failure to use corollary discharge signals to adjust to the change in eye position brought about by a saccade to T1 was examined. A repeated measures ANOVA was conducted on mean angular bias in the corrective saccade, with diagnostic group as a between-subjects variable and angular separation between T1 and T2 as a within-subjects variable (*Figure 29, left panel*). There was a significant

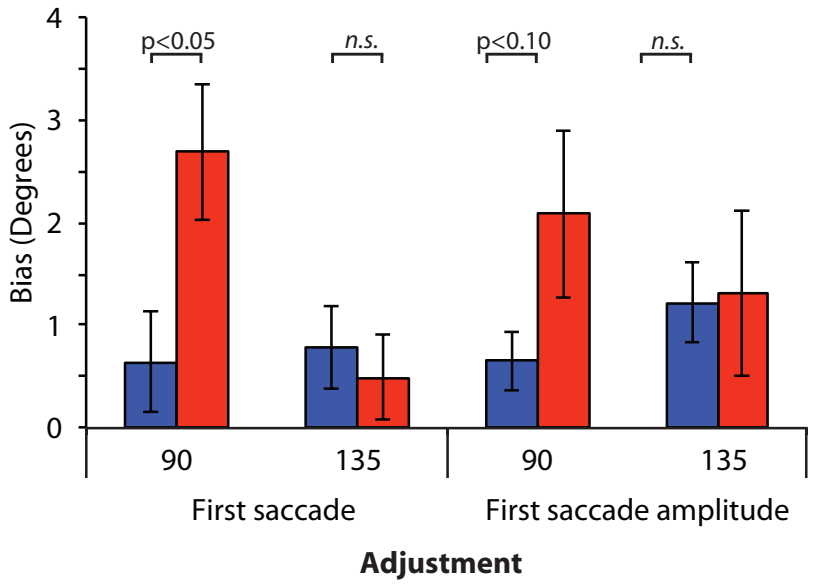

Figure 29. Mean bias (plus standard error) of the second saccade vector in the direction predicted by not compensating for change in eye position resulting from first saccade (left panel) and not compensating for variability in first saccade endpoint (right panel) for controls (blue bars) and schizophrenia patients (red bars).

effect of target separation, with angular bias being greater when targets were 90° apart ($F(1,32)=5.66$, $p=0.02$). Although the main effect of group did not reach significance ($F(1,32)=2.43$, $p=0.13$), there was a significant group-by-separation interaction effect ($F(1,32)=7.36$, $p=0.01$). Patients had greater angular bias in the direction predicted by not compensating for the first saccade than healthy controls when targets were separated by 90° ($t(32)=2.51$, $p=0.02$) but not 135° ($t(32)=0.50$, $p=0.62$).

The degree to which subjects compensated for variation in the amplitude of the first saccade when making their corrective saccades was examined first by investigating the bias in the corrective saccade in the direction predicted by not compensating for hypo- or hypermetricity of the saccade to T1 using a repeated measures ANOVA with diagnostic group as a between-subjects variable and target separation as a within-

subjects variable (*Figure 29, right panel*). There was no significant main effect of group ($F(1,32)=2.54$, $p=0.12$), target separation ($F(1,32)=0.02$, $p=0.88$), or group-by-target separation interaction ($F(1,32)=0.92$, $p=0.34$). Although the interaction was not significant, we examined this angular bias across groups for each target separation angle. There was a trend for patients to have greater bias in the direction predicted by not compensating for variability in the first saccade when targets were separated by 90° ($t(32)=1.72$, $p=0.09$), but not 135° ($t(32)=0.10$, $p=0.92$).

Compensation for variability in amplitude to T1 was also examined by comparing the slope and R^2 of regression analysis comparing actual to ideal angle of the corrective

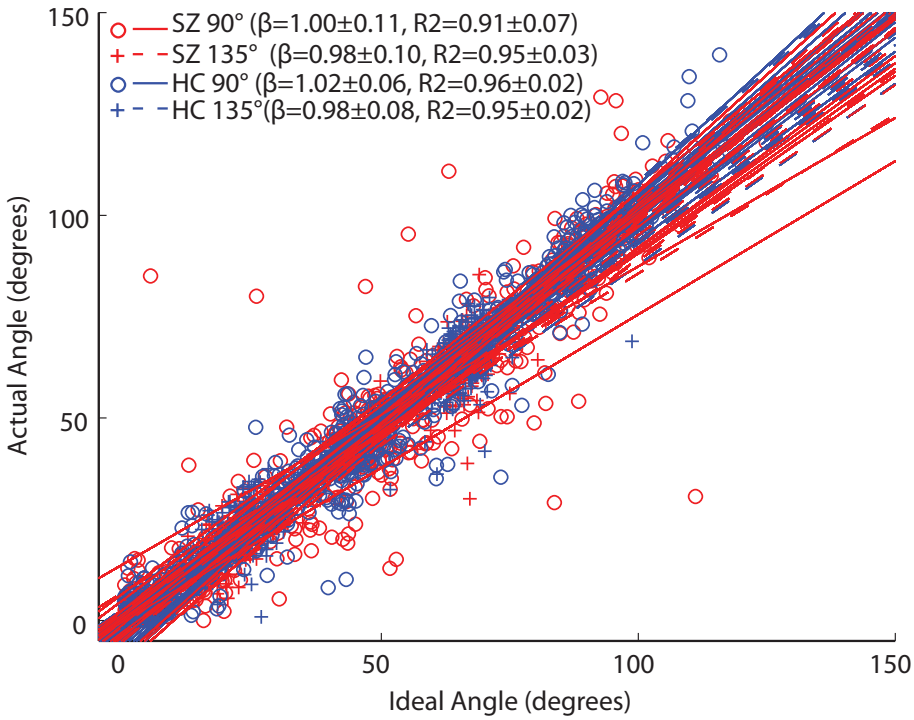

Figure 30. Actual corrective saccade vector angle plotted as a function of ideal saccade vector when targets were separated by 90° (circles and solid line) and 135° (crosses and dotted line) for controls (blue) and schizophrenia patients (red).

saccade vector (*Figure 30*). Consistent with previous report, both the mean goodness-of-fit (mean R^2= 0.94) and slope (mean=1.00) were close to 1. Repeated measures ANOVAs were conducted on both slope and R^2 values with diagnostic group as a between-subjects variable and target separation as a within-subjects variable. There was no significant main effect of group ($F(1, 32)=0.28$, $p=0.60$) or target separation ($F(1,32)=2.9$, $p=0.10$), nor a significant group-by-target separation interaction ($F(1,32)=0.51$, $p=0.48$) on slope of the relationship. However, for goodness-of-fit, there was a significant main effect of group ($F(1,32)=4.35$, $p=0.05$) and group-by-target separation interaction ($F(1,32)=8.70$, $p=0.006$). There was a trend towards a main effect of target separation ($F(1,32)=3.26$, $p=0.08$), with better model fits when targets were separated by 135°. Planned comparisons revealed poorer fits in patients compared to controls when targets were separated by 90° ($t(32)=2.67$, $p=0.01$), but not 135° ($t(32)=0.29$, $p=0.78$), suggesting that patients were not compensating as accurately as controls for variability in the first saccade endpoint. That is, because patients were not as accurately or as frequently taking into account that the eyes landed just short or long of the first target, the fit of actual versus ideal second saccade direction was poorer in patients.

To rule out the possibility that decreased spatial accuracy to T2 in the direction of not compensating for the change in eye position brought about by the first saccade or variability in the amplitude of the first saccade was due to group differences in spatial accuracy to T1, we also examined amplitude of the first, noncompensated saccade and it's angular deviation from T1 (*Figure 31*). Repeated measures ANOVAs were

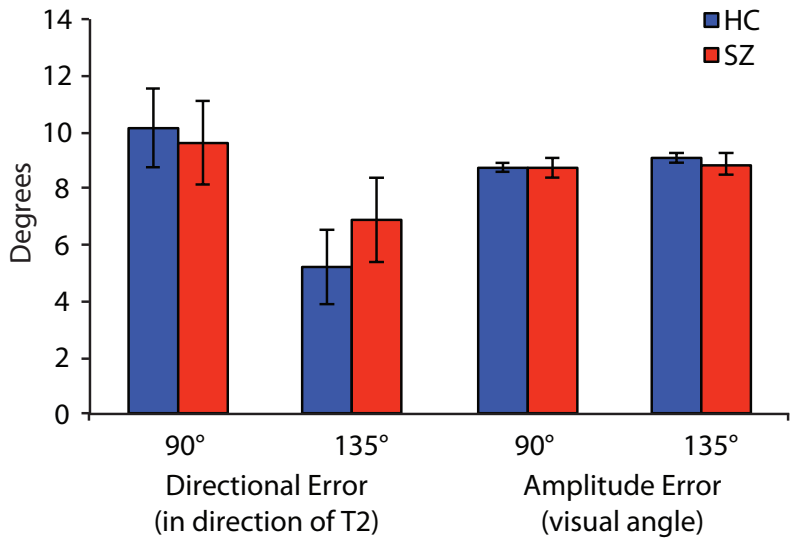

Figure 31. Mean bias (plus standard error) in the first saccade vector angle in the direction of T2 (left panel) and amplitude of the first saccade (in degrees of visual angle; right panel) for controls (blue bars) and schizophrenia patients (red bars)

conducted on amplitude and angular deviation (in the direction of T2), with angular separation of T1 and T2 (90° or 135°) entered as a within-subject variable and diagnostic group as a between-subjects variable. For saccadic amplitude, there was a main effect of angular separation ($F(1,32)=5.75$, $p=0.02$), with saccades being slightly more hypometric when targets were separated by 90° (mean=8.73° visual angle, s.d.=1.04°) than 135° (mean=8.97° visual angle, s.d.=1.12°). Importantly, there was no significant effect of either group ($F(1,32)=0.14$, $p=0.71$) or group-by-target separation interaction ($F(1,32)=0.88$, $p=0.36$). For saccade direction, there was also a significant main effect of target separation ($F(1,32)=26.33$, $p<0.0001$). Saccade averaging (Becker & Jurgens, 1979) was observed, and saccades to T1 were biased more in the direction of T2 when targets were separated by 90° (mean: 9.89°, s.d.=5.83°), than 135°

(mean=5.99°, s.d.=5.83). Again, there was no significant effect of either group (F(1,32)=0.10, p=0.76) or group-by-target separation interaction (F(1,32)=2.20, p=0.15).

Parallel programming. Parallel programming of saccades was indexed by the relationship between ISIs and RPTs on noncompensated trials in which a corrective saccade was made. Consistent with prior studies, we observed a subset of trials in which ISIs were substantially longer than average visually-guided saccade latency (slower than the 95th percentile of no-step trial latency). These trials were excluded from analysis. Upon visual inspection of the data, we also observed trials in which RPTs were longer than would be expected. Again, RPT is the latency between the onset of T2 and the onset of the erroneous saccade to T1. We would not expect RPT to be substantially longer than TSRT, the time needed to inhibit the saccade to T1 and

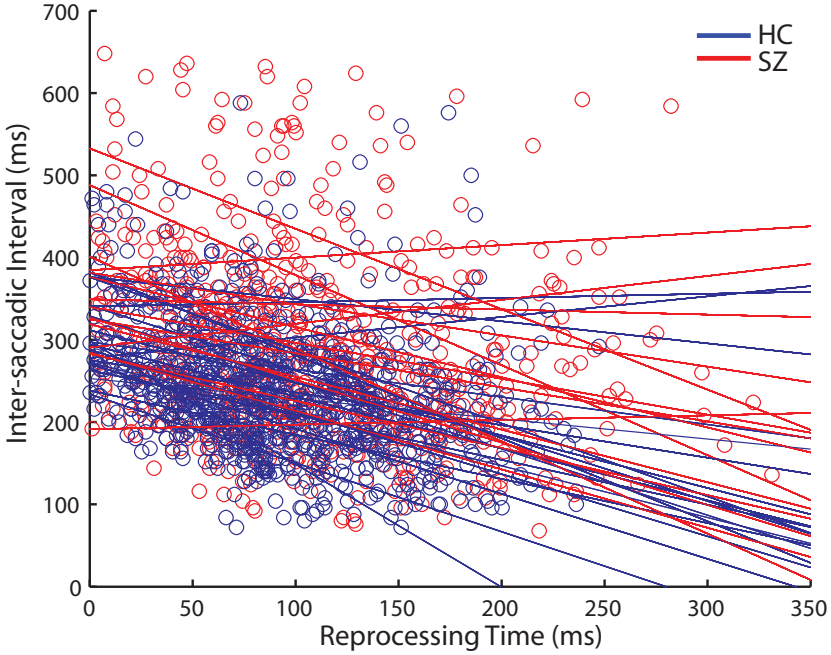

Figure 32. Intersaccadic interval (ISI) between first saccade and corrective saccade plotted as a function of reprocessing time (RPT) for controls (blue) and patients (red), with regression lines for each subject.

redirect the movement towards T2. That is, the more time the subject has to process the second target, the more they would be expected to make an accurately compensated saccade to T2. Specifically, if the time available to process the second target were greater than TSRT on that particular trial, we would not expect a noncompensated saccade to be produced. Visual inspection indicated that for these long RPTs, a relationship with ISI was not observed. One possible explanation for these long RPTs is degraded perceptual processing of the second target. Specifically, in our paradigm the targets stayed on the screen only briefly, and this may have caused observers to confuse T1 and T2 on some trials. In prior studies, the second target remains on the screen, which perhaps accounts for the absence of these long RPTs. Since we cannot calculate variability in TSRT across trials, a cutoff of TSRT+50ms was used to exclude trials from this analysis for each subject. Qualitative inspection of the data indicated that this criterion was adequate in removing those trials with long RPTs in which a linear relationship between RPT and ISI was not observed. After exclusion of long ISIs and RPTs, the relationship between RPT and ISI was calculated using linear regression (*Figure 32*). Across subjects, the slope of this relationship was significantly different from 0, (mean slope=0.55, $p<0.0001$). An inverse relationship reached significance in 13/18 healthy controls and 8/16 patients; this proportion did not differ between groups as indicated by Fisher's Exact Test ($\chi^2=1.78, p=0.29$). Independent t-tests were conducted to compare slope and goodness of fit (R^2 values) between groups. There was no significant difference in the slope (controls: mean=-0.63, s.d.=0.36, patients: mean=-0.45, s.d.=0.44; t=1.28, p=0.21) or fit (controls: mean=0.23, s.d.=0.17, patients:

mean=0.15, s.d.=0.16; t=1.55, p=0.13), indicating comparable parallel processing of saccades in controls and patients. Importantly, there was no difference in the number of trials excluded based on RPT cut-off values (controls: mean=8.83, s.d.=6.17, patients: mean=9.21, s.d.=5.38; t=0.19, p=0.85), ISI cut-off values (controls: mean=3.67, s.d.=4.68, patients: mean=2.84, s.d.=5.35; t=0.48, p=0.63), or both (controls: mean=0.76, s.d.=1.06, patients: mean=0.40, s.d.=0.92; t=1.04, p=0.30).

Clinical symptoms and social functioning. We examined correlations between clinical symptoms and the following measures in patients: TSRT, median post-compensated slowing, median post-error slowing, median post-step slowing, proportion of corrected errors, corrective saccade latency, slope and fit (R^2 value) of the RPT-ISI regression line, biases in the corrective saccade vector in the direction predicted by not compensating for both the first saccade and variability in amplitude of the first saccade, slope and fit (R^2 value) of the regression line fitting the angle of the second saccade vector needed to reach T2 and the actual saccade vector angle. These performance measures were correlated with SAPS, SANS, BPRS, and SFS scores. Given the specific interest in the relationship between monitoring-related double-step performance

Figure 33. Histogram of SFS Employment scores in schizophrenia

measures and hallucinations and delusions, SAPS items related to these two symptoms were summed for each participant and correlated with performance measures. Because of the constricted range scores on the Scale for the Assessment of Passivity Phenomena scores in this sample, participants were divided into those with and without a current or lifetime history of passivity symptoms, and performance measures were compared across these two groups. Visual inspection again revealed bimodality in SFS Employment scores (*Figure 33*), which essentially characterized subjects as employed or unemployed, and performance measures were compared across these two employment groups.

There was a robust correlation between trial history effects and positive symptoms such that post-compensated, post-error, and more generally, post-step slowing were significantly correlated with greater SAPS score. Specifically, post-step

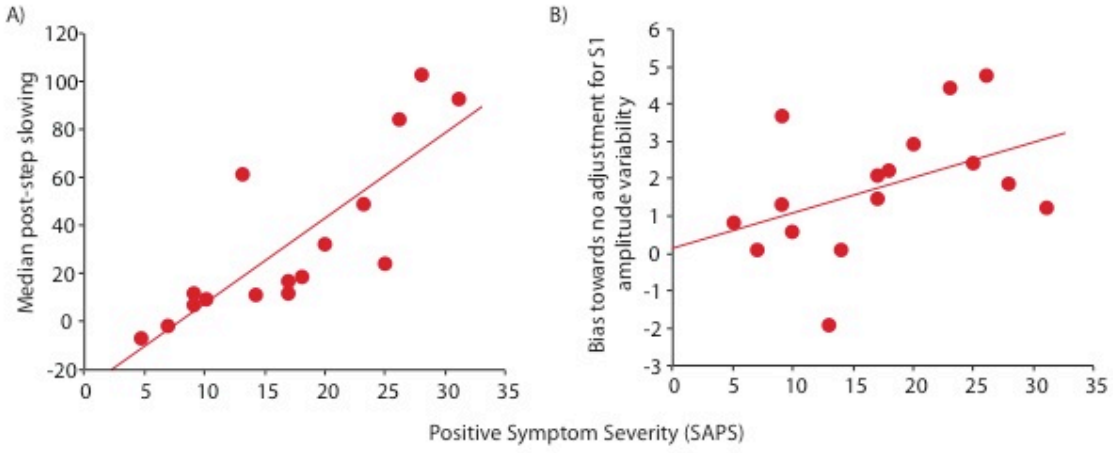

Figure 34. ***A)*** Relationship between post-step trial slowing and severity of positive symptoms, indexed by SAPS score , in schizophrenia patients. ***B)*** Relationship between bias in second saccade angle in the direction predicted by not compensating for variability in the initial saccade. Greater SAPS scores represent more severe positive symptomology.

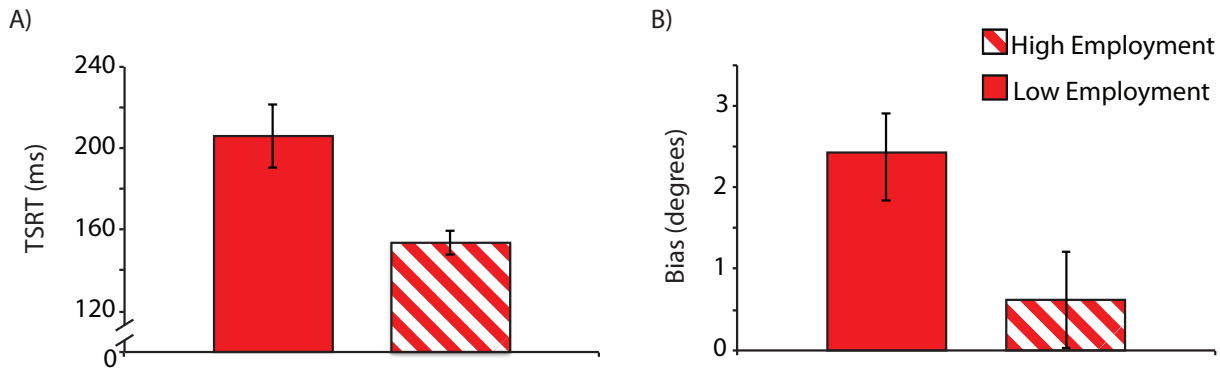

Figure 35. ***A)*** TSRT (plus standard error) for schizophrenia patients scoring high (striped) and low (solid) on SFS employment subscale. ***B)*** Bias towards not compensating for variability in first saccade endpoint for patients scoring high and low on SFS employment scale.

slowing was related to overall SAPS (r_s=0.87, p<0.0001; *Figure 34a*) and BPRS scores (r_s=0.60, p=0.01), as well the SAPS Hallucinations and Delusions subscale score (r_s=0.85, p<0.0001). Additionally, bias in the second saccade in the direction predicted by not compensating for variability in amplitude of the initial saccade was related to greater overall SAPS score (r_s=0.50, p=0.05; *Figure 34b*) as well as SAPS Hallucinations and Delusions subscale score (r_s=0.50, p=0.05). Comparing unemployed to employed patients, those with better occupational functioning had shorter TSRT (*Figure 35a;* Employed: mean=154 ms, s.d.=15; Unemployed: mean=206 ms, s.d.=49; t(14)=2.34, p=0.03) and less bias in the direction predicted by not using corollary discharge signals to adjust for variability in amplitude of the first saccade (*Figure 35b;* employed: mean=0.62°, s.d.=1.44, unemployed: mean=2.43°, s.d.=1.53; t(14)=2.51, p=0.02).

Discussion

The results of *Experiment 2* largely replicated results from *Experiment 1A*, and also revealed more subtle response monitoring abnormalities in schizophrenia. First, patients with schizophrenia showed more inefficient response inhibition and redirection, as indexed by longer TSRT and compensated saccade RT, despite equal sensitivity to the target step and similar latencies to initiate saccades on no-step and error noncompensated trials. Further, longer TSRT was related to occupational functioning, which again suggests clinical relevance for these findings. Second, patients showed exaggerated trial history effects and slowed down more than healthy controls following step trials, which showed a robust relationship to positive symptom severity. Third, patients with schizophrenia had fewer and slower corrective saccades on noncompensated trials. Finally, patients showed evidence for an impairment in using corollary discharge signals to accurately execute two saccades in rapid succession, which was also related to positive symptom severity. These findings will be discussed in turn.

Response inhibition. The pattern of double-step task performance across controls and patients was consistent with previous studies in healthy samples. Importantly, both groups satisfied two important criteria for the race model to hold. First, the probability of successfully compensating for a target step decreased with longer TSDs. After normalizing each individual's TSD with respect to the mean and variance of their no-step RTs, the slopes of the two group's inhibition functions were not statistically different, suggesting equal sensitivity to the target step. Second, error noncompensated

saccades were faster than both no-stop and compensated saccades, 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 on no-step and noncompensated trials, in line with prior findings in basic saccade tasks (Gale & Holzman, 2000; Holzman, et al., 1973) and the saccadic countermanding task (Thakkar, Schall, Boucher, Logan, & Park, 2011). However, consistent with findings of poorer inhibitory ability in schizophrenia, saccadic RT on successfully compensated trials was longer in patients and significantly related to longer TSRT. Combined with the results of Experiment 1A, findings of longer TSRT, which was related to occupational functioning, and slower compensated saccades suggest replicable and clinically relevant impairments in the efficiency of response inhibition in schizophrenia.

Possible mechanistic accounts of slower response inhibition in the double-step task in schizophrenia are similar to those outlined in the *Discussion* section of *Experiment 1*. Specifically, a crucial role of the FEF in the ability to change an oculomotor plan has been highlighted. Ramakrishnan, Sureshbabu, and Murthy (2012) used microstimulation techniques to show that the saccade vector produced following stimulation to the FEF during step trials in macaques performing the modified double-step task was dependent on when the pulse was applied relative to the onset of T2. When the stimulation was delivered early, the resulting saccade was biased in the direction of T1; however, when stimulation was delivered later in time relative to T2 onset, the saccade was biased in the direction of T2. These results are consistent with an initial GO process, represented by movement neurons in FEF and SC (Hanes, et al.,

1998; Paré & Hanes, 2003), that is interrupted by an inhibitory process, represented by fixation neurons in the same regions, and a second GO process that directs the eyes to T2.

Computational models that account for both behavioral and neurophysiological aspects of performance in the modified double-step task have shed further light on the mechanisms that give rise to a change in motor plan. Two major models of performance have been put forth. In the first model, performance is modeled as a race between two GO processes—one that directs the eyes to T1 (GO1) and the other that directs the eyes towards T2 (GO2). In the second model, an explicit STOP process that interrupts GO1 is included. The latter model has been found to fit both behavioral and neuropsychological data better than a model that does not include a separate STOP process that inhibits GO1 (Camalier, et al., 2007; Ramakrishnan, et al., 2012), and suggests that TSRT measures the latency of the STOP process (Camalier, et al., 2007). Thus, consistent with the results of *Experiment 1A*, longer TSRT in schizophrenia likely reflects a longer latency of inhibitory processes.

Response Monitoring

Trial History effects. Consistent with the findings of *Experiment 1* and previous studies (see *Introduction*), both controls and patients slowed down following both correctly compensated and erroneous noncompensated step trials. Additionally, results of the present experiment are generally consistent with the findings from *Experiment 1A* that patients show exaggerated slowing following correctly inhibited trials in the

countermanding task (Thakkar, et al., 2011). However, in the present study, although patients showed a pattern of greater slowing following both error and compensated step trials, neither of these differences reached significance. Collapsed across step trials, on the other hand, patients showed significantly greater slowing than controls. Previous studies have described greater slowing following correct antisaccade trials in schizophrenia and have argued for perseverative effects of inhibition in the saccadic system in schizophrenia. This argument could explain greater slowing following both correct and incorrect step trials in schizophrenia, since, provided a STOP process is initiated even on error trials, there is some degree of inhibitory activity and conflict between GO and STOP related neural activity present during noncompensated trials.

Alternatively, given that step trials comprised a minority of trials, greater post-step slowing in schizophrenia could be related to greater attention to novel or infrequent stimuli. As discussed in the *Introduction*, one recent theory of post-error slowing supposes that the mechanism is not specific to errors, but extends to rare events. That is, slowing arises due to attention being oriented away from current task demands by novel, infrequent events (Notebaert, et al., 2009). This theory was supported by the findings that post-error slowing was present when errors were unlikely, and post-correct slowing was observed when the majority of trials were errors. A recent report found evidence for greater post-error slowing in schizophrenia, but only when errors were infrequent and the inter-trial interval was short (Nunez Castellar et al., 2012). That greater post-step slowing in schizophrenia is due to increased attentional orienting towards infrequent trial types fits neatly with a highly regarded theory that psychosis

arises from aberrant novelty detection and salience attribution, which was first formally outlined by Gray and colleagues (Gray, Feldon, Rawlings, Hemsley, & Smith, 1991) and has been a key element of several subsequent biological and phenomenological accounts of psychotic symptoms (e.g. Christensen & Bilder, 2000; Kapur, 2003). This explanation for the trial history findings of *Experiment 2* is further bolstered by the strikingly high correlation between positive symptom severity and post-step slowing. Arguing against the theory that post-error adjustments arise from novelty detection, however, are recent findings of *increased* post-stop slowing in the countermanding task with both increases in the probability of a stop signal and increases in the probability of error commission (Bissett & Logan, 2011).

Another possibility is that greater post-step slowing in schizophrenia arises due to aberrant probability estimation. An impairment in probabilistic reasoning has been reported in schizophrenia, particularly those patients with delusional beliefs (Bell, Halligan, & Ellis, 2006). Patients are more likely to 'jump to conclusions' and make probabilistic judgments based on less evidence than healthy individuals (Garety, 1991; Garety, Hemsley, & Wessely, 1991; Huq, Garety, & Hemsley, 1988). Further, and more relevant to the current findings, schizophrenia patients tend to over-adjust based on disconfirmatory evidence (Garety, et al., 1991; Langdon, Ward, & Coltheart, 2010; Moritz & Woodward, 2005). That is, they rely on the most recent events to make probabilistic decisions. Preliminary results from a partially overlapping sample indicated that patients with schizophrenia were less sensitive to the overall probability of events over a series of trials and made more probabilistic judgment errors (see *Appendix A*). In

relating aberrant probabilistic reasoning in schizophrenia to exaggerated trial history effects, it is possible that a step/stop signal occurring in the prior trial leads to a reactive shift in the estimated proportion of step/stop trials. Since RT scales with the proportion of stop trials in the countermanding task (Logan & Burkell, 1986; Verbruggen & Logan, 2009b), this change in estimate could result in a transient increase in RT. Again, given the theorized relationship between probabilistic reasoning and the development of delusional beliefs, this explanation for exaggerated trial history effects would be consistent with the correlation between post-step slowing and positive symptom severity.

Corrective saccades. Patients with schizophrenia made fewer and slower corrective saccades. This finding is consistent with a theory of impaired internal monitoring in schizophrenia; however, it is largely inconsistent with previous studies of error monitoring that have typically found intact incidence and latency of error corrections in patients (Brownstein, et al., 2003; Kopp & Rist, 1994, 1999; Morris, et al., 2006; Polli, et al., 2008; Polli, et al., 2006; Reuter, et al., 2006). A handful of studies have observed impaired online adjustment of errors in schizophrenia, but generally these studies have used tasks with high working memory demands such that impaired behavioral adjustments could be explained by a poor representation of the correct response (Malenka, et al., 1982; Malenka, et al., 1986; Turken, et al., 2003). It is unlikely that the current findings of impaired error correction in patients are due to patients having a less clear representation of the correct response for two main reasons. First, the dynamic tracking procedure to adjust task difficulty on the basis of

performance was effective, and both groups had equal likelihood of error commission. Second, there was no group difference in the degree to which the likelihood of error commission was affected by trial difficulty, as measured by equal slopes of the compensation function.

There is also some evidence, albeit inconsistent, that error-correcting deficits are only found in those patients experiencing delusions of passivity or in a more acute stage of illness (Frith & Done, 1989; Waters, et al., 2009). Thus, discrepancy between the current results and those studies that reported no difference in error corrections could be related to differences in patients' clinical status. That explanation is also unlikely, however, since this is a sample of fairly clinically stable outpatients.

One potentially critical difference between the current study and studies that have reported no difference in error correction incidence or latency in schizophrenia is the amount of external feedback available to the subject. In *Experiment 2*, targets were flashed only briefly and were typically extinguished from the screen before the onset of the erroneous saccade. Also, subjects were performing the task in total darkness. Thus, there was no visual information available to indicate an error. Participants were forced to rely on internal models of the motor plan or proprioceptive signals indicating the position of the eye in order to recognize that an error had been committed. It is possible that when patients have access to external visual cues regarding, for example, the position of the eyes, error correction is intact; however, error correction is disrupted in patients only when there is no external information to signal that an error has been committed. In fact, this explanation is precisely what impaired monitoring theories of psychosis would

predict. Further, this interpretation is consistent with findings that patients performing smooth pursuit tasks rely more on external retinal motion cues than predictive extra-retinal mechanisms to support accurate tracking; in fact, they have been found to follow the target *better* than controls following unexpected changes in target velocity (Hong, Avila, & Thaker, 2005). Along with disruptions in predictive mechanisms in the motor system, patients with schizophrenia have been found to have disruptions in proprioception (Rado, 1953). In this task, if forward models of action are not available or distorted, proprioception is the only other mechanism to support error recognition. Although proprioception appears to provide little extraretinal information in making sequential saccades (Lewis, et al., 2001; Steinbach, 1987), there are proprioceptive signals of eye position (Wang, Zhang, Cohen, & Goldberg, 2007) that can assist in sequential saccade preparation, albeit slowly. Thus, lower incidence and slower latency of corrective saccades in schizophrenia in the absence of any visual information could arise from a combination of impaired use of predictive mechanisms in the motor system and/or impaired proprioceptive mechanisms signalling eye position.

Importantly, the current data would suggest that the described impairments in corrective saccade latency and incidence in schizophrenia are not solely due to impairments in programming sequential eye movements. Parallel programming of saccades was investigated by quantifying the relationship between the time available for the subject to process the second target before initiating the first saccadic eye movement (reprocessing time) and corrective saccade latency. The inverse slope of this relationship is taken as a measure of the degree to which participants are programming

the first erroneous and second corrective saccade in parallel. That is, if saccades are programmed in parallel, corrective saccade latency should decrease when the participant has more time to process the second target. On the other hand, a flat slope of this function would inidcate that the corrective saccade could not be programmed until termination of the initial saccade. Consistent with previous studies (Camalier, et al., 2007; Murthy, et al., 2007), a significant inverse relationship was observed between reprocessing time and corrective saccade latency, and no significant difference in the slope or fit of these linear models was observed between groups. The absense of a group difference in this relationship suggests that there is no significant difference in the degree of parallel programming in the saccadic eye movement system in schizophrenia. Thus, it would indicate that impaired error correction cannot be accounted for by impairments in simply programming two sequential movements, but rather suggests that impaired error correction in schizophrenia arises due to an impairment in the monitoring and processing of erroneous responses.

Along with impairments in the incidence and latency of corrective responses, we also found systematic errors in the spatial accuracy of the corrective saccade in patients with schizophrenia. Specifically, patients, more so than controls, failed to fully take into account eye position brought about by the first saccade when making their corrective saccade. This impairment was manifested in two ways in the current dataset. First, patients with schizophrenia did not fully take into account that the eye had moved from the central fixation when preparing the corrective saccade; thus, corrective saccades were biased in the direction that would be expected if they were moving their

eyes from fixation to the second target. Second, patients with schizophrenia showed a statistical trend towards not taking into account variability in the amplitude of the first saccade when preparing the corrective saccade, and this was significantly related to greater positive symptom severity and poorer occupational functioning. Thus, corrective saccade direction was biased in the direction that would be expected if they were moving their eyes directly from the first to the second target, even when the actual first saccade overshot or undershot the target.

Combined, these findings suggest an impairment in the use of corollary discharge signals to anticipate the future position of the eye when making rapid, sequential saccadic eye movements, and that this impairment might be related to positive symptomology. Importantly, there was no group difference in the spatial accuracy of the first saccade. Of note, the described impairments in using corollary discharge signals to make sequential saccades were evident when targets were separated by 90°, but not 135°; that is, patients were impaired only when the required saccade amplitude was shorter. One potential explanation for this effect of target distance is that when patients had more distance, and therefore time, to adjust their saccade vector, performance was normalized. This explanation is consistent with findings from studies showing that the degree of compensation for the first saccade increases with saccade amplitude (Munuera, Morel, Duhamel, & Deneve, 2009).

These findings are particularly exciting as they arguably provide the most direct current evidence for an impairment in corollary discharge in patients with schizophrenia that is not confounded with other processes known to be impaired in the disease,

notably, working memory. Further, based on findings from the neurophysiology literature of monkeys performing the double-step the work of Sommer and Wurtz (2002, 2008), the current findings generate specific hypotheses about the underlying neural substrates of impaired corollary discharge. The way in which the current findings fit with current conceptualizations of corollary discharge disruption in schizophrenia and the potential brain pathology underlying these impairments will be discussed in turn.

Corollary Discharge in Schizophrenia

The current findings, which suggest abnormal corollary discharge signals in schizophrenia, are certainly not without precedent. Ford, Mathalon, and colleagues were among the first to test how abnormal corollary discharge could contribute to symptomology. Specifically, they explored evidence for corollary discharge in the auditory system, exploring the idea that corollary discharge signals from motor speech areas prepared the auditory cortex for self-generated speech and that these signals were disrupted in schizophrenia such that self-generated covert speech was misinterpreted as externally generated. In an elegant series of experiments, they observed electrophysiological evidence for altered communication between frontal and temporal areas in patients with schizophrenia (Ford, et al., 2004; Ford & Mathalon, 2004; Ford, Mathalon, Heinks, et al., 2001; Ford, Mathalon, et al., 2001a, 2001b). Auditory potentials were dampened during both overt and covert speech in healthy controls but not in schizophrenia patients; oversimplified, patients were talking and listening at the same time. Additionally, it has been observed that patients with

schizophrenia, particularly those with hallucinations and passitivity delusions, can tickle themselves—the argument being that, due to impaired corollary discharge, patients do not anticipate the sensory consequences of their actions and the resultant sensations are not dampened (Blakemore, Wolpert, & Frith, 2000). Evidence from the rubber hand illusion in schizophrenia indirectly supports this hypothesis. In this illusion, the participants hand, which is hidden from view, is stroked synchronously with a visible rubber hand. A large number of heatlhy individuals report a distinct feeling of ownership over the fake hand (Botvinick & Cohen, 1998), and this illusion is even greater in patients with schizophrenia. They report a greater subjective sense of ownership over the rubber hand (Peled, Pressman, Geva, & Modai, 2003; Thakkar, Nichols, McIntosh, & Park, 2011) and show a greater perceived drift of their real hand towards the rubber hand (Thakkar, et al., 2011). One potential interpretation of these findings is that because of disordered corollary discharge, patients rely less on an internal model of the bodily state and more on external (e.g. visual) feedback, resulting in greater suceptibility to the illusion.

I would argue that the major addition of the current findings to the literature in schizophrenia is the degree to which they can be related to the role of single neurons in the primate brain, and hence they offer a direct translational link between neurophysiological and behavioral data . To date, most of the precise psychophysiological and neurophsysiology data supporting corollary discharge have been shown in the oculomotor system. Specifically, inactivating neurons in the medial dorsal nucleus of the thalamus that relay between SC and FEF during double-step task

performance was found to have similar effects to those we currently observed in patients with schizophrenia, albeit to a greater degree. Despite making equally accurate saccades to the first target, saccades to the second target were perturbed in the direction predicted by both not compensating for the change in eye position brought about by the first saccade as well as not compensating for variability in amplitude of the first saccade. Providing further support for the role of the thalamus in processing corollary discharge are findings of impaired performance in the classic double-step task, with second saccade vectors not fully accounting for the first saccade, in thalamic lesion patients . Thus, altered functioning in the medial dorsal nucleus of the thalamus could play a role in the abnormality of the incidence, latency, or precision of corollary discharge signals in schizophrenia. This hypothesis would be consistent with findings of reduced thalamic volume in schizophrenia (see Adriano, Spoletini, Caltagirone, & Spalletta, 2010; Konick & Friedman, 2001 for meta-analyses), although these findings are modest and inconsistent, and altered dopamine transmission in the thalamus (Clinton et al., 2005). Interestingly, there is also evidence from case studies that damage to the thalamus can cause schizophrenia-like symptomology (Carrera & Bogousslavsky, 2006; Crail-Melendez, Atriano-Mendieta, Carrillo-Meza, & Ramirez-Bermudez, 2012; McGilchrist, Goldstein, Jadresic, & Fenwick, 1993), and Sim et al. (2009) reported reduced microstructural integrity of the thalamus using diffusion tensor imaging in patients with passivity symptoms compared to those without. Futher, given the role of the thalamus in sending and receiving information from multiple cortical and subcortical regions, altered thalamic structure and function is consistent with multiple

theories of schizophrenia, which argue that dysconnection lies at the heart of the illness (Andreasen, Paradiso, & O'Leary, 1998; Stephan, Baldeweg, & Friston, 2006). Another hypothesis to consider is that corollary discharge signals are being generated appropriately in schizophrenia, but that there is a problem with their transmission to sensory areas. In a recent theory paper, Whitford et al. (2012) argue that abnormalities in frontal myelination result in delayed corollary discharge signals, which result in sensory predictions that arrive too late.

Limitations

The results of *Experiment 2* should be considered in light of several limitations. First, all patients were taking antipsychotic medication. As outlined in the *Limitations* section of *Experiment 1*, it is unlikely that medication effects can account for longer latency of inhibitory processes or exaggerated trial history effects. Previous studies suggest that atypical neuroleptics improve, but do not normalize, antisaccade performance (Harris, et al., 2006). If deficits in double-step performance and antisaccade tasks reflect inhibition impairments, longer TSRT in schizophrenia is unlikely to be a result of neuroleptics. Further, administration of haloperidol had no significant effect on post-error slowing in healthy individuals (de Bruijn, et al., 2006; Zirnheld, et al., 2004). To my knowledge, there is no data to speak to neuroleptic effects on corollary discharge signals; however, degree of impairments on tasks putatively relying on forward models of motor control have been found to correlate with psychometric schizotypy in unmedicated, healthy samples (Asai, Sugimori, & Tanno,

2008; Lenzenweger & Maher, 2002), which argues against medication effects accounting for impaired use of corollary discharge in schizophrenia. Finally, in our study, CPZ equivalent dose was not related to any double-step measures.

Another potential limitation of the current study is that poorer performance of the schizophrenia patients on the double-step task (i.e. slower inhibition, slower and fewer corrective saccades, mislocalization of the second target following corrective saccades) might be due to group differences in perceptual processes. Specifically, patients with schizophrenia have been found to have a coarser window of temporal integration of visual stimuli—that is, they are more likely to perceive the onset of two visual stimuli as simultaneous (Foucher, Lacambre, Pham, Giersch, & Elliott, 2007; Lalanne, van Assche, & Giersch, 2012). Since targets were flashed briefly and the time between T1 and T2 was short, it is possible that schizophrenia patients were more likely to perceive T1 and T2 as simultaneous. However, there are several reasons why we do not believe differences in the frequency of perceived simultaneity of T1 and T2 can account for the current results. First, data from previous studies indicate that even in schizophrenia, the threshold for perceiving the onset of two visual stimuli as synchronous (~37 ms) is shorter than even our shortest TSD (47ms). Secondly, there is evidence that perceived simultaneity differences between controls and patients are smaller when targets are presented in opposite hemifields (Lalanne, et al., 2012), which was typically the case in the current study. Further, if it was the case that schizophrenia patents were more often confusing the temporal order of T1 and T2, we would expect to see marked differences in the compensation functions, with lower accuracy at the shortest TSDs; in fact, the

slope of the compensation function was similar across groups and the dynamic tracking algorithm was equally effective.

Conclusions and implications

We replicated findings of *Experiment 1* and found that patients with schizophrenia required more time to inhibit a planned saccade, which was related to occupational functioning. Further, patients exhibited more pronounced RT effects after both correctly compensated and incorrectly noncompensated step trials, which correlated highly with positive symptom severity. Additionally, patients with schizophrenia showed impairments in the fast, online monitoring of behavior. Patients had decreased incidence and latency of corrective responses, which cannot be totally accounted for by an impairment in programming two motor responses. Further, these corrective saccades were mislocalized in the direction predicted by not using corollary discharge signals to compensate for the change in eye position brought about by the first saccade, nor variability in the first saccade endpoint, which was correlated with positive symptom severity. Replicable impairments in response inhibition and their relationship to employment again suggest the utility of this task to measure functional improvements in cognition. Further, these findings provide evidence for abnormal rapid monitoring of motor responses in the absence of external feedback, specifically using corollary discharge signals to predict the sensory consequences of behavior and exaggerated adjustments of responses based on immediate trial history, that might contribute to the bizarre and pathognomonic symptoms of schizophrenia.

CHAPTER IV

GENERAL DISCUSSION

The current series of experiments demonstrated abnormalities in the control of action in patients with schizophrenia. Patients demonstrated replicable impairments in the efficiency of response inhibition. In addition, abnormal response monitoring was observed in two ways. First, across two studies, patients showed an exaggerated response to an unexpected cue requiring them to inhibit; their reaction times were more influenced by the immediately preceding trial. Second, patients showed evidence for fauly response monitoring in their difficulties with rapid, online adjustments of behavior. Compared to controls, they had fewer and slower error corrections and they failed to appropriately use feed-forward signals to predict the future position of the eye, putativley reflecting altered corollary discharge signals. Finally, there was evidence for heritability of response inhibition impairments, as longer SSRT was observed in healthy relatives. Further, both exaggerated trial history effects and slower response inhibition varyed as a function of psychosis-spectrum, with the performance of bipolar patients falling between that of schizophrenia patients and controls. In this section, I will discuss the potential clinical relevance of these findings, outstanding questions, and future directions.

Clinical Relevance

Two major questions that emerge from these experiments are: 1) whether findings of altered inhibition and monitoring of saccadic eye movements are clinically relevant, and 2) whether these findings potentially have implications for treatment or treatment studies. With regard to the first question, *Experiment 1* revealed a relationship between poorer inhibition efficieny and negative symptoms, but that finding was not replicated in *Experiment 2*. Interestingly, across two studies, efficiency of inhibition was related to a functional outcome measures, namely employment. Although future studies with larger and more clinically heterogenous samples are needed to further explore the relationship between symptoms, functional outcome, and response inhibition, these correlations provide compelling evidence that SSRT/TSRT could serve as a valuable quantitative cognitive marker to assess medication-related changes in cognition in schizophrenia. Double-step and countermanding paradigms could be particularly valuable in treatment studies because of the rich neurophysiological data showing how individual neurons in FEF and SC support performance in this task. That is, because of the work with both human and non-human primates performing these task under similar experimental conditions, medication-related changes in performance in these tasks can provide neurobiologically-constrained hypotheses that could help towards developing medications that are more effective at managing the debilitating cognitive symptoms. Further, given the relationship between SSRT/TSRT and functional outcome, medications that putatively improve inhibition efficiency might also result in an improvement in functional status.

The feasibility of using these tasks outside of the laboratory settings, in clinics and clinical trials, is unclear. In the current tasks, the proportion of individuals that were unable to complete the study was not negligible. Reasons that patients could not perform the eye tracking study were mostly related to daytime somnolence, difficulties with gaze fixation, and an inability to perform the task (e.g. they were not able to inhibit at any delay). Further complaints included discomfort with the eye tracking headpiece and fatigue due to length of testing. Since the current sample was an older group of chronic patients, some of the reasons for failing to complete the study might be less problematic in a younger group of first-episode patients. Future studies might investigate the fewest number of trials needed to obtain a valid estimate of SSRT, which is likely to be less that what was used in the current study as SSRT did not vary significantly over the course of four 120-trial blocks[2] in *Experiment 1A*. Additionally, newer eye trackers are available that are not head-mounted and allow the head to move freely. Reducing the testing burden and alleviating some of the physical discomfort of eye tracking is likely to increase the practicality of using these measures outside of the laboratory. Further, the antisaccade task has been used in treatment studies (Harris, et al., 2006), attesting to the feasibility of using eye movement tasks to track cognitive changes.

Abberant response monitoring also holds potential clinical relevance as it features prominently in several cognitive neuropsychiatric accounts of positive

[2] In Experiment 1, SSRT was calculated for each block for each subject, and a repeated measures ANOVA was run on SSRT with group entered as a between subjects variable and block entered as a within-subject variable. Although we observed a significant effect of group ($F(1, 31)=5.99$, $p=0.02$), with patients having longer SSRT than controls, there was no significant effect of block ($F(3,93)=0.87$, $p=0.46$) nor any group-by-block interaction ($F(3,93)=0.46$, $p=0.71$).

symptomatology, most notably delusions of passivity. Findings of *Experiment 2* suggesting impaired corollary discharge signals in schizophrenia are particularly relevant to and supportive of these theories. Since corollary discharge signals are argued to be the mechanism by which one distinguishes the sensory consequences of willed actions from those that are externally driven, these findings are relevant to longstanding theories that conceptualize the disorder as a fundamental disturbance in the sense of self (Bleuler, 1911; Pollack, 1989; Sass & Parnas, 2003). Further, they offer strong hypotheses for investigating the neural underpinnings of these disturbances. Still, an obvious concern lingers: can prediction failures due to disrupted corollary discharge in the sensorimotor system be related to the profound impairments in thought that characterize the most pathognomic symptoms of schizophrenia? Although this question might currently be of a more philosophical nature rather than amenable to scientific inquiry, several prominent theories of brain organization are based on the idea, for which John Hughlings Jackson was amongst the first to fully articulate, that "energising of lower, more organised, nervous arrangements, although unattended by any sort of conscious state, is essential for, and leads to, particular energisings of the highest and least organised—the now-organising—nervous arrangements, which last mentioned organising is attended by consciousness (Hughlings Jackson, 1878)" – essentially, that nuanced human functions like thought and language are rooted in complex combinations of basic sensorimotor processes (see Franz & Gillett, 2011 for review). In this sense, the current findings of may have true

implications for understanding the nature of some of the more bizarre symptoms of schizophrenia.

Correlations between positive symptomology and aberrant use of corollary discharge signals were observed in *Experiment 2*, but only modestly, and no relationship was observed with current or lifetime incidence of passivity delusions. Again, future studies with larger and more clinically heterogeneous samples will be useful in exploring subtle aspects of the relationship of these cognitive/sensorimotor measures with clinical symptoms. Further, if disturbances in agency and sense of self are at least partly rooted in disturbed sensorimotor processes, could behavioral treatments aimed at improving the bodily sense of self or a putative sensory training emphasizing the link between action and resulting sensory consequence be effective, when combined with medication, in attenuating positive symptoms? Of course, this notion is speculative, but represents a potential novel and non-invasive avenue for treatment. Indeed, yoga, which emphasizes the awareness of the bodily self in space, has found to have beneficial effects on clinical symptoms in schizophrenia over and above the effects of aerobic exercise (Behere et al., 2010; Duraiswamy, Thirthalli, Nagendra, & Gangadhar, 2007).

Remaining Questions and Future Directions

Several questions and avenues for future research emerge from the findings of the current series of experiments. Given the focused hypotheses they generate about potential neural mechanisms underlying disrupted response inhibition and response

monitoring in the countermanding and double-step task in schizophrenia, a natural next step would be to explore structural and functional brain correlates of performance in these tasks. In particular, these findings generate specific hypotheses about disrupted function in a network involving FEF, SC, SEF, and ACC. Further, findings that suggest a particular role of the medial dorsal thalamus in corollary discharge signals would predict disrupted functional and/or structural connections between this region and SC and FEF during the execution of two sequential saccades in this task.

Another important future direction is to investigate whether findings of impaired response inhibition and response monitoring are effector specific. That is, will similar findings be observed when responding with the hands as with the eyes? Findings from previous countermanding studies indicate response inhibition impairments even with manual responding (Enticott, et al., 2008; Huddy, et al., 2009; Hughes, Fulham, Johnston, & Michie, 2012; Nolan, D'Angelo, & Hoptman, 2011). Although some studies have reported no difference or mixed (i.e. only in one hand) SSRT between groups (Badcock, et al., 2002; Bellgrove et al., 2006; Zandbelt, van Buuren, Kahn, & Vink, 2011), mixed findings across studies are likely related to the complexity of the GO task or sample-specific factors (e.g. early-onset patient group). However, for response monitoring impairments, the role of the response system is unclear. Previous studies have largely found equivalent rate of error correction using manual responses in patients with schizophrenia and healthy controls (see *Introduction*), but other aspects of the experimental design differ in important ways from the current study; namely, visual feedback is available. An interesting future study would be to investigate whether

similarly impaired corrective movement dynamics resulting from impaired corollary discharge signals would be observed in schizophrenia using, for example, a joystick version of the task in which the participant's hand is hidden from view.

A question that is particularly important for understanding the clinical relevance of the current findings is whether abnormal response inhibition and monitoring on the countermanding and double-step tasks are more enduring aspects of the disease. That is, are they independent of symptomatology? Correlations between performance on these tasks and both positive and negative symptom severity does not preclude them being state-related disease traits. Previous studies have shown than neurocognitive deficits tend to be more stable aspects of the disease (Park, Puschel, Sauter, Rentsch, & Hell, 1999; Rund, 1998), and there is a suggestion from the current results that impaired and idiosyncratic performance on these tasks could be a stable marker of illness. Namely, inhibition and monitoring impairments were present even in a fairly high-functioning group of outpatients who were, for the most part, living independently. Further, longer SSRT was also observed in non-psychotic relatives of schizophrenia patients. Full investigation of this question, however, requires a longitudinal design in which performance is measured during both during an acute episode and again after symptoms have at least partially remitted.

A key question that emerges, which is relevant to all studies of cognition in schizophrenia, is whether impairments and idiosyncrasies in response inhibition and response monitoring represent domain-specific deficits, or whether they are secondary to one unified impairment. Indeed, a central argument of several influential theories of

schizophrenia posits a core deficit in failing to form or maintain internal representations (e.g. failure in using working memory or context to guide behavior, failure to use 'stored regularities' for current perception; Goldman-Rakic, 1994; Hemsley, 1987; Park, et al., 1995; Servan-Schreiber, Cohen, & Steingard, 1996). To what extent are impairments in the control of action in the current study related to the maintenance and control of internal representations? In *Experiment 1A*, poorer verbal working memory accuracy was related to longer time needed to inhibit a saccadic eye movement, but only weakly; a similar study using a keypress version of the task reported no significant correlation between SSRT and spatial working memory (Huddy, et al., 2009). Zandbelt and colleagues reported a significant relationship between a working memory task and proactive inhibitory ability (the ability to prepare to inhibit), but not reactive inhibition (the ability to stop a planned response) in schizophrenia (Zandbelt, et al., 2011). A more robust relationship between working memory and SSRT has been observed in children with ADHD (Clark et al., 2007) and results of a meta-analysis of countermanding performance in ADHD reported that group differences in SSRT were amplified with putative working memory demands as indexed by complexity (stimulus-response incompatibility) of the GO task (Huizenga, van Bers, Plat, van den Wildenberg, & van der Molen, 2009). Although no relationship was observed between response monitoring indices and working memory, it certainly seems viable that the failure to use 'stored regularities' could result in an exaggerated effect of the most immediate trial on current trial performance. To more fully address the issue of the degree to which working memory deficits can account for impaired response inhibition and response monitoring

in patients, a within-subjects design should be implemented in which working memory demands, perhaps in the form of an intervening task to "tie up" resources, are manipulated to investigate whether patients might be differentially affected by the added demands. Another enigmatic avenue to explore will be the control of action as it relates to the control of mental representations of actions. Interestingly, despite failing to accurately maintain representations, recent data from Park and colleagues have provided evidence for *enhanced* control and manipulation of mental representations, in the form of faster and more accurate mental image generation and mental rotation (Benson & Park, 2012; Collins, Matthews, Thakkar, & Park, 2009; Thakkar & Park, 2010). This split between the control of action and control of mental representations of action provides a compelling distinction to be addressed in future studies.

Concluding Remarks

This series of studies revealed impaired response inhibition and response monitoring in two tasks that have been used in neurophysiological studies with awake primates under similar experimental conditions. The findings of longer latency of response inhibition, exaggerated effects of a cue to inhibit a saccade on the following trial, fewer and slower error corrections, and an impairment in the use of corollary discharge signals to predict the sensory consequences of a motor command shed further light on the cognitive profile of schizophrenia and lead to neurobiologically constrained hypotheses about the etiology of cognitive dysfunction. Further, these data

contribute significantly to cognitive neuropsychiatric theories of some of the bizarre and pathognomonic symptoms of the disease.

APPENDIX A

PROBABILITY ESTIMATION IN SCHIZOPHRENIA

Aims

The aim of the current study was to investigate probabilistic judgments in patients with schizophrenia. We hypothesized that over the course of a series of events with two possible outcomes, patients with schizophrenia would be less sensitive to the overall probability distribution of the two events.

Methods

Participants. Five healthy controls and 13 schizophrenia patients were recruited as described in *Experiment 1A* using the same exclusion criteria and were administered the same clinical rating scales.

Design and procedure. Subjects were told to imagine a deck of 20 cards, on which one of two shapes would be printed (e.g. circle and square), and that they would be dealt one card from this deck at a time. They were instructed that there would be no specific pattern to how the cards were organized (e.g. circle-square-circle-square), but that the deck might contain more of one card than the other. Shapes were presented for 1 second in sequence on the monitor, each representing one card. After each shape presentation, the subject was presented with the two shapes in the deck and asked to guess which shape appeared more frequently in the deck, using a left or right keypress.

They were then asked to rate on a scale from 0 to 4 how confident they were in that decision.

Subjects were administered 10 blocks of trials, each representing a different deck of cards. The frequency distribution of the two shapes in each block was either 50-50, 60-40, 70-30, 80-20 or 90-10, and there were two blocks of each frequency distribution. Each shape pair consisted of one shape with rounded edges and one angular shape, of different colors, to minimize confusion between shapes. Each block consisted of unique shape pairs, to avoid interference from previous shape-frequency contingencies. Subjects were first administered the task using a real deck of cards, and then had one practice block of trials on the computer.

Statistical analyses. Proportion of correct choices and mean confidence ratings were analyzed using separate repeated measures ANOVAs with diagnostic group entered as a between-subjects variable and probability distribution of events entered as a within-subjects variable. Since there was no correct answer when events were distributed evenly (in the 50-50 condition), one event was arbitrarily coded as the "correct" event.

Results

Accuracy. Results are presented in *Figure 36*. Consistent with expectation, there was a significant effect of frequency distribution ($F(4,64)=30.7$, $p<0.0001$), such that subjects were more accurate at determining the most likely event as the overall probability of one event over the other increased. Although there was no significant

effect of group (F(1,16)=3.1, p=0.09), there was a significant group-by-probability distribution interaction effect (F(4,64)=2.5, p=0.05). Pairwise comparisons indicated that there was no difference in accuracy between groups when events were distributed equally in the 50-50 condition (t(16)=0.87, p=0.4). However, for the other conditions, patients were generally less accurate than controls (60-40: t(16)=2.7, p=0.02; 70-30: t(16)=1.7, p=0.12; 80-20: t(16)= 1.8, p=0.09; 90-10: t(16)=1.5 0.15).

Confidence. Results are presented in *Figure 37*. Similar to accuracy findings, there was a significant effect of probability distribution (F(4,64)=37.1, p<0.0001), such that subjects were more confident in their decisions as the overall probability of one event over the other increased. Although there was no significant effect of group (F(1,16)=1.1, p=0.32), there was a significant group-by-probability distribution interaction effect (F(4,64)=14.5, p<0.001). Pairwise comparisons indicated that for the conditions when the distribution of events was equal or close to equal, patients were more confident in their decisions than healthy controls. However, when inequality in the

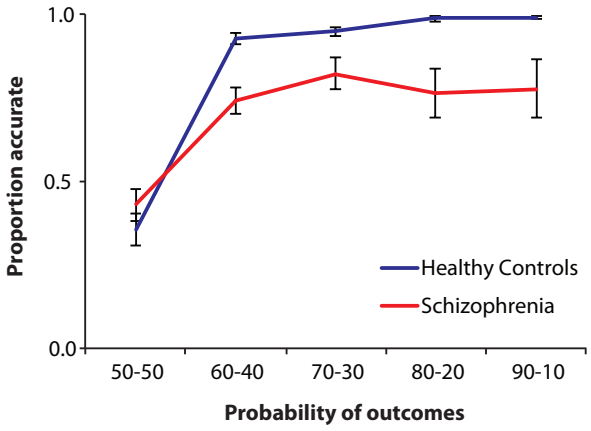

Figure 36. Accuracy as a function of probability distributions for healthy controls (blue) and schizophrenia patients (red).

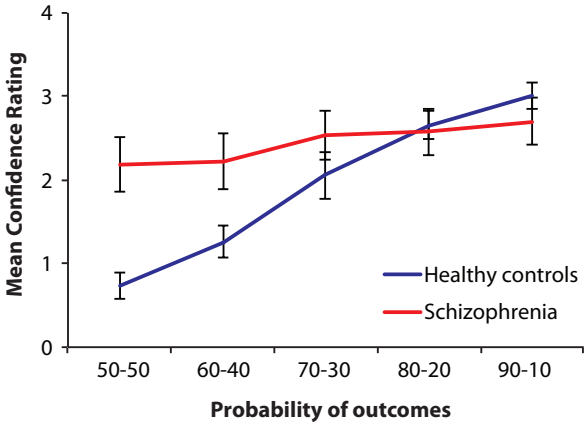

Figure 37. Confidence ratings as a function of probability distributions for healthy controls (blue) and schizophrenia patients (red).

probability of the two events became more obvious, this difference in confidence across groups disappeared. Essentially, patients with schizophrenia were less sensitive of the overall probability of events in their confidence of probabilistic decisions.

Conclusion

Preliminary data from this study indicated that patients with schizophrenia were less sensitive to the overall probability of outcomes across a series of events. Further, their confidence in their probabilistic judgments was less influenced by the overall probability of outcomes. Given small sample sizes, results should be interpreted with caution.

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