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Response inhibition and response monitoring in a saccadic double-step task in schizophrenia

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ABSTRACT

Background: Cognitive control impairments are linked to functional outcome in schizophrenia. The goal of the current study was to investigate precise abnormalities in two aspects of cognitive control: reactively changing a prepared response, and monitoring performance and adjusting behavior accordingly. We adapted an oculomotor task from neurophysiological studies of the cellular basis of cognitive control in nonhuman primates. *Methods*: 16 medicated outpatients with schizophrenia (SZ) and 18 demographically-matched healthy controls performed the modified double-step task. In this task, participants were required to make a saccade to a visual target. Infrequently, the target jumped to a new location and participants were instructed to rapidly inhibit and change their response. A race model provided an estimate of the time needed to cancel a planned movement. Response monitoring was assessed by measuring reaction time (RT) adjustments based on trial history. *Results*: SZ patients had normal visually-guided saccadic RTs but required more time to switch the response to the new target location. Additionally, the estimated latency of inhibition was longer in patients and related to employment. Finally, although both groups slowed down on trials that required inhibiting and changing a response, patients showed exaggerated performance-based adjustments in RTs, which was correlated with positive symptom severity. *Conclusions*: SZ patients have impairments in rapidly inhibiting eye movements and show idiosyncratic response monitoring. These results are consistent with functional abnormalities in a network involving cortical oculomotor regions, the superior colliculus, and basal ganglia, as described in neurophysiological studies of non-human primates using an identical paradigm, and provide a translational bridge for understanding cognitive symptoms of SZ.

1. Introduction

Cognitive impairments in schizophrenia are omnipresent across domains and are likely closer to disease pathophysiology than the surface manifestation of psychotic symptoms (Elvevag & Goldberg, 2000; Lencz et al., 2006; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004). Cognitive control, the ability to control thoughts and actions and respond flexibly to the environment, is particularly affected in schizophrenia and linked to functional outcome (Bilder et al., 2000; Green, Kern, Braff, & Mintz, 2000). Since cognitive control impairments are major treatment targets, understanding their biological underpinnings is of great clinical interest. In exploring these biological mechanisms, it is important to consider that cognitive control is a multifaceted construct (Bilder, 2012; Braver, 2012; Miyake et al., 2000). One pragmatic way of dissecting cognitive control is to separate *proactive* and *reactive* control. Proactive control refers to maintaining goal-relevant information in an anticipatory manner in order to *prepare* for having to override prepotent response tendencies. Reactive control, on the other hand, refers to later recruitment of control processes in response to some external event in order to meet the challenges of cognitively demanding circumstances. As reactive and proactive control are partly dissociable at the level of behavior and brain (Braver, 2012), we can further elucidate the nature and etiology of cognitive control impairments in schizophrenia. Moreover, adopting a translational approach and comparing behavior across species using identical paradigms provides a concrete framework for inferring the cellular basis of impairments in schizophrenia.

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One crucial aspect of cognitive control studied extensively in schizophrenia is response inhibition. Most of these studies have focused on proactive inhibition, preparing to inhibit prior to stimulus onset (Clementz, 1998; Gooding & Basso, 2008; Hutton & Ettinger, 2006; Westerhausen, Kompus, & Hugdahl, 2011). Fewer studies have investigated reactive inhibition, the stimulus-driven process of inhibiting during motor preparation. From the perspective of pharmacological interventions in particular, characterizing reactive in addition to proactive inhibition is important as different pharmacological manipulations in rodents have differing effects on these two functions (Eagle, Bari, & Robbins, 2008; Eagle, Tufft, Goodchild, & Robbins, 2007). The countermanding, or stop-signal, task is widely used for investigating reactive inhibition (Lappin & Eriksen, 1966; Verbruggen & Logan, 2008). Participants are instructed to respond quickly to a stimulus (GO stimulus). On some trials, a second signal is presented (STOP stimulus), and subjects are instructed to inhibit the prepared response. Performance is described as a race between competing GO and STOP units, and based on this model, the time needed to inhibit a response, the stop-signal reaction time (SSRT), can be estimated (Logan & Cowan, 1984). We recently showed that patients with schizophrenia have longer SSRT in a saccadic countermanding task, which was related to negative symptom severity and unemployment (Thakkar, Schall, Boucher, Logan, & Park, 2011; Thakkar, Schall, Logan, & Park, 2015). Based on neurophysiology studies of non-human primates performing the saccadic countermanding task, these findings suggest specific and clinically relevant abnormalities within a network involving frontal eye fields (FEF), superior colliculus (SC), and basal ganglia (BG; Hikosaka, Takikawa, & Kawagoe, 2000; Schall & Boucher, 2007; Schall & Godlove, 2012).

The saccadic countermanding task allows us to examine another aspect of cognitive control—response monitoring, the ability to track ongoing performance and adjust future behavior. In this task, humans and non-human primates slow down following trials in which they must inhibit a response (Bissett & Logan, 2011; Emeric et al., 2007; Nelson, Boucher, Logan, Palmeri, & Schall, 2010). Medial frontal cortex neurons are sensitive to performance history and can implement adjustments in response speed to optimize behavior (Emeric et al., 2008; Emeric, Leslie, Pouget, & Schall, 2010; Godlove et al., 2011; Ito, Stuphorn, Brown, & Schall, 2003; Stuphorn & Schall, 2006; Stuphorn, Taylor, & Schall, 2000). In our previous countermanding study, we observed idiosyncratic response monitoring in schizophrenia. Patients slowed down more than controls following trials in which inhibition was successful.

The major aim of the current study was to investigate another aspect of reactive cognitive control in schizophrenia and its relationship to functional outcome. In the current study, we probed the ability to rapidly *change* a prepared response with an oculomotor task used in neurophysiological studies—the modified double-step task (Bissett & Logan, 2013; Camalier et al., 2007; Murthy et al., 2007; Murthy, Ray, Shorter, Schall, & Thompson, 2009). In this task, participants are instructed to look at a visual target. On a minority of trials, the target jumps to a new location, and participants are instructed to inhibit the prepared saccade and look instead at the new target. This task differs from the countermanding task in that participants are instructed not just to inhibit an inappropriate response outright, but also to replace the old response with a new response rapidly—to change one's mind, as Ramakrishnan, Sureshbabu, and Murthy (2012) describe it. Although experiments with double-step tasks for movements of eyes (Becker & Jürgens 1979) and limbs (Georgopoulos, Kalaska, & Massey 1981) have a long history, the mechanisms whereby individuals change plan have gained renewed interest (e.g., Resulaj, Kiani, Wolpert, & Shadlen 2009). The race model can also be applied to double-step task performance (Camalier et al., 2007). Reactive inhibition can be computed from two variables: the estimated speed of inhibition, and reaction time (RT) to the final target location when the first saccade plan was successfully inhibited. Thus, the double-step task allows us to both estimate the speed of inhibition and directly measure the time it takes for subjects to redirect their movement to the new target location.

In addition, we explored trial-by-trial adjustments in behavior. Based on our previous findings, we expected to find clinically-relevant slowing of inhibition in schizophrenia and slower RTs to change the partially planned movement, providing further evidence for poorer reactive control. We also expected exaggerated trial history-based slowing in patients with schizophrenia. These findings may illuminate our understanding of very specific aspects of cognitive control in schizophrenia, resulting in more hypothesis-driven treatment development for cognitive deficits. Because this task has been used in humans and non-human primates under similar experimental conditions, the results provide a translational bridge for understanding the mechanisms of cognitive control impairments.

2. Methods and materials

2.1. Participants

Diagnostic information is presented in Table 1. Individuals who met DSM-IV criteria for schizophrenia (SZ) 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 antipsychotic medication, and half of the patient sample were also medicated with antidepressants, anxiolytics, mood stabilizers, or a combination thereof. Detailed medication status of patients is provided in Supplementary Table 1. Healthy, unmedicated control subjects (HC) without a personal and family history of DSM-IV Axis-I disorders were recruited from the same community by advertisements.

Clinical symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), and Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). Social and occupational functioning was assessed with the Social Functioning Scale (SFS; Birchwood, Smith, Cochrane, Wetton, & Copestake, 1990). IQ was measured with the North American Adult Reading Test (NAART; Blair & Spreen, 1989). Handedness was assessed using the Modified Edinburgh Handedness Inventory (Oldfield, 1971).

Exclusion criteria included substance use, neurological disorders, history of head injury, inability to fixate, and excessive sleepiness. All participants were native English speakers and had normal or corrected-to-normal vision. Three patients were excluded based on task performance, as outlined in Section 2.3.3, and one patient chose to abort the experiment. Analyses were conducted on the remaining 16 SZ and 18 HC. Nine SZ patients and 9 HC in this sample participated in the previous countermanding study (Thakkar et al., 2011). Groups were matched for age, sex, and handedness. All subjects gave written informed consent approved by the Vanderbilt Institutional Review Board and were paid.

2.2. Apparatus and stimuli

Eye position was monitored using the EyeLink II eyetracker (SR Research, Canada) at a sampling rate of 500 Hz with average gaze position error <0.5°, noise limited to <0.01° RMS. Saccades were detected on-line using a velocity criterion (35°/s) and minimum amplitude criterion (2° visual angle). Subjects were seated 57 cm from the monitor with their head in a chinrest.