Schizophrenia Research 159 (2014) 491–498

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Behavioral response inhibition in psychotic disorders: Diagnostic specificity, familiality and relation to generalized cognitive deficit

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ARTICLE INFO

Article history:
Received 9 July 2014
Received in revised form 11 August 2014
Accepted 14 August 2014
Available online 26 September 2014

Keywords:
Response inhibition
Schizophrenia
Psychotic bipolar disorder
Family study
Stop signal

ABSTRACT

Difficulty inhibiting context-inappropriate behavior is a common deficit in psychotic disorders. The diagnostic specificity of this impairment, its familiality, and its degree of independence from the generalized cognitive deficit associated with psychotic disorders remain to be clarified. Schizophrenia, schizoaffective and bipolar patients with history of psychosis (n = 523), their available first-degree biological relatives (n = 656), and healthy participants (n = 223) from the multi-site B-SNIP study completed a manual Stop Signal task. A nonlinear mixed model was used to fit logistic curves to success rates on Stop trials as a function of parametrically varied Stop Signal Delay. While schizophrenia patients had greater generalized cognitive deficit than bipolar patients, their deficits were similar on the Stop Signal task. Further, only bipolar patients showed impaired inhibitory control relative to healthy individuals after controlling for generalized cognitive deficit. Deficits accounted for by the generalized deficit were seen in relatives of schizophrenia and schizoaffective patients, but not in relatives of bipolar patients. In clinically stable patients with psychotic bipolar disorder, impaired inhibitory behavioral control was a specific cognitive impairment, distinct from the generalized neuropsychological impairment associated with psychotic disorders. Thus, in bipolar disorder with psychosis, a deficit in inhibitory control may contribute to risk for impulsive behavior. Because the deficit was not familial in bipolar families and showed a lack of independence from the generalized cognitive deficit in schizophrenia spectrum disorders, it appears to be a trait related to illness processes rather than one tracking familial risk factors.

1. Introduction

Stop Signal paradigms examine the interplay between response activation, triggered by internal plans or orienting toward salient stimuli, and inhibition processes, triggered by top-down control from goal-maintenance networks to stop prepotent responses. They are widely used to assess inhibitory behavioral control (Logan et al., 1984; Logan, 1994; Bissett and Logan, 2011). Participants respond as quickly as possible to Go cues; however, some Go cues are followed after a brief delay (Stop Signal Delay, SSD) by a Stop cue instructing subjects to inhibit their response. Difficulty inhibiting cued Go responses increases with longer delays, putatively because increasing SSD has the effect of delaying initiation of inhibitory processes relative to onset of response activation processes (Logan et al., 1984). Inhibitory control impairments are of clinical interest because of potential relations to substance abuse, impulsive behavior and suicide, particularly in bipolar disorder where disinhibited behavior is a defining characteristic.

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http://dx.doi.org/10.1016/j.schres.2014.08.025
0920-9964/

Meta-analyses on inhibitory control deficits in schizophrenia (Sitskoorn et al., 2004) and bipolar disorder (Bora et al., 2009) and their first-degree relatives, mainly using the Stroop task (Stroop, 1935; Besnier et al., 2009; Kravariti et al., 2009; Levy and Weiss, 2010; Westerhausen et al., 2011), suggest that schizophrenia patients may show milder inhibitory deficits than bipolar patients. In contrast, in the antisaccade task of inhibitory control, greater deficits have been observed in schizophrenia than in bipolar disorder (Blackwood et al., 1996; Martin et al., 2007; Harris et al., 2009; Reilly et al., 2014). Relative to other tasks, the SST does not depend on semantic associations as in the Stroop paradigm, or require simultaneous response suppression and initiation demands as in the antisaccade task, so it is a potentially more direct approach for assessing inhibitory processes that has not yet been used in larger sample studies contrasting psychotic disorders.

Schizophrenia and bipolar patients, especially bipolar with psychosis, typically have generalized cognitive impairments as well as impaired inhibitory control (Bora et al., 2010; Harvey et al., 2010; Hill et al., 2013). Generalized neuropsychological deficits are typically greater in schizophrenia than bipolar disorder, with schizoaffective patients showing intermediate deficits (Woolard et al., 2010; Hill et al., 2013). It is unknown whether inhibitory deficits represent a specific cognitive deficit or one manifestation of generalized cognitive deficit across these disorders. Specific deficits can provide independent information for clinical evaluation, tracking treatment outcomes, and gene discovery. Moreover, there is interest in assessing inhibitory control deficits in relatives and whether they are familial endophenotypes (Ferrier et al., 2004; Allen et al., 2009; Giakoumaki et al., 2011; Christodoulou et al., 2012).

Stop Signal tasks can assess strategic adjustments made to enhance inhibitory control. Healthy individuals strategically delay reaction times to Go cues, allowing time for inhibitory processes if a Stop cue occurs (Verbruggen and Logan, 2008). Evidence supports reduced strategic latency adjustments in schizophrenia (Vink et al., 2006) but strategic slowing relative to a baseline control task has not been evaluated in psychotic patients (Verbruggen and Logan, 2008; Bissett and Logan, 2011).

We used a SST to evaluate behavioral response inhibition in a large sample of psychotic patients and their first-degree relatives. Familiality and degree of deficit not accounted for by general neuropsychological deficit were examined. We hypothesized that inhibitory control deficits would be distinct from generalized cognitive deficit and familial in psychotic bipolar patients.

2. Method

2.1. Participants

As part of the Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP), participants were recruited at six sites: University of Chicago/University of Illinois-Chicago (Chicago, Illinois), Yale University/Institute of Living (Hartford, Connecticut), University of Texas Southwestern (Dallas, Texas), University of Maryland (Baltimore, Maryland), Wayne State University (Detroit, Michigan) and Beth Israel Deaconness Medical Center, Harvard University (Boston, Massachusetts). Primary groups were 214 schizophrenia patients (SZ) and 173 bipolar patients with history of psychosis (BPP), their available first-degree relatives (schizophrenia relatives n = 224, SZrel; bipolar psychosis relatives n = 194, BPrel), and healthy participants (n = 223; HP). Patients with schizoaffective disorder depressed-type (n = 45; SZA-D) and their first-degree relatives (n = 44; SZA-Drel), and patients with schizoaffective disorder bipolar-type (n = 91; SZA-BP) and their first-degree relatives (n = 105; SZA-BPrel) were also examined (Tamminga et al., 2013 for full cohort description). All participants provided written informed consent. This study was approved by Institutional Review Boards at each site.

All subjects were administered the Structured Clinical Interview for DSM-IV diagnosis (First et al., 1997) and the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004) to index generalized neuropsychological deficit. BACS subtest deficit patterns were similar across patient groups in the B-SNIP sample (Hill et al., 2013), so total score was used in the analyses. Exclusion criteria included: significant neurological or systemic medical illness, head trauma with >10 min unconsciousness, positive urine drug screen on testing day, and substance abuse within 3 months or dependence within 6 months.

2.1.1. Patients

Because acute illness may disrupt inhibitory control in bipolar disorder (Strakowski et al., 2010) and schizophrenia (Harris et al., 2006; Hill et al., 2009), patients were clinically stable and on consistent psychopharmacological treatment for at least one month. Symptom severity and functioning were rated using the Positive and Negative Symptom Scale (Lancon et al., 2000), Young Mania Rating Scale (Young et al., 2000), Montgomery–Asberg Depression Rating Scale (Montgomery and Asberg, 1979), Birchwood Social Functioning Scale (Birchwood et al., 1990), Schizo-bipolar Scale (Keshavan et al., 2011) and Barratt Impulsiveness Scale 11 (Patton et al., 1995). All but 37 patients were taking psychotropic medications (Table 1). Dosing of antipsychotic medication was standardized across drugs following Andreasen et al. (2010).

2.1.2. Relatives

Personality traits in first-degree relatives were assessed using the Structured Interview for DSM-IV Personality (Pfohl et al., 1997). Individuals within one criterion of diagnostic threshold for a Cluster A (psychosis spectrum) or a Cluster B (emotional lability) DSM-IV Axis II disorder were identified as in our prior studies (Hill et al., 2013; Reilly et al., 2014). Relatives were not excluded for Axis I diagnoses, although for group comparisons, relatives with lifetime history of psychosis (N = 64) were excluded from statistical modeling to characterize risk without confounding illness-related factors. All relatives were included in familiality estimates and clinical correlations to maintain representation of all population variations.

2.1.3. Healthy comparison sample

Healthy participants were excluded for lifetime psychotic or bipolar disorder or recurrent depression, or family history of psychotic or bipolar disorder in first-degree relatives.

2.2. Procedure

All trials began with presentation of a white central-fixation crosshair (1.5° in size) for a random interval between 750 and 1500 ms. On Go trials, a green circle (Go cue, 1.75° in size) appeared 12° right or left of center for 650 ms. On Stop trials, a Stop Signal (red stop sign; 1.75° in size) was presented at central-fixation (Fig. 1) at variable delays (SSDs) after the Go stimulus appeared. Participants responded as quickly and accurately as possible by pressing a left or a right button for stimuli appearing on the left or the right side of the screen, respectively. Responses were recorded using a button box sampling at 125 Hz. Equipment and procedures were identical across testing sites.

Participants first performed practice trials to verify comprehension of task instructions. Then, a baseline task of 50 consecutive Go trials was given, followed by the SST with four blocks of pseudorandomly interleaved Go and Stop trials (40% Stop). SSDs were blocked into fourteen 16.6 ms intervals (reflecting 60 Hz monitor refresh rate) between 50 and 282 ms to model group performance differences across a range of SSDs from relatively easy to very difficult to stop responses. To maintain a prepotent Go response tendency, lack of response within 650 ms on Go trials resulted in trial termination with a red 'X' and the word "faster". For every third Go trial without a timely response, a Go trial