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Cognitive control of gaze in bipolar disorder and schizophrenia

Katharine N. Thakkar [a,e,*], Jeffrey D. Schall [a,b,c], Gordon D. Logan [a,b,c], Sohee Park [a,b,d]

[a] Department of Psychology, Vanderbilt University, Nashville, TN, USA
[b] Center for Integrative Cognitive Neuroscience, Vanderbilt University, Nashville, TN, USA
[c] Vanderbilt Vision Research Center, Vanderbilt University, Nashville, TN, USA
[d] Department of Psychiatry, Vanderbilt University, Nashville, TN, USA
[e] Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands

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ABSTRACT

The objective of the present study was to compare two components of executive functioning, response monitoring and inhibition, in bipolar disorder (BP) and schizophrenia (SZ). The saccadic countermanding task is a translational paradigm optimized for detecting subtle abnormalities in response monitoring and response inhibition. We have previously reported countermanding performance abnormalities in SZ, but the degree to which these impairments are shared by other psychotic disorders is unknown. 18 BP, 17 SZ, and 16 demographically matched healthy controls (HC) participated in a saccadic countermanding task. Performance on the countermanding task is approximated as a race between movement generation and inhibition processes; this model provides an estimate of the time needed to cancel a planned movement. Response monitoring was assessed by the reaction time (RT) adjustments based on trial history. Like SZ patients, BP patients needed more time to cancel a planned movement. The two patient groups had equivalent inhibition efficiency. On trial history-based RT adjustments, however, we found a trend towards exaggerated trial history-based slowing in SZ compared to BP. Findings have implications for understanding the neurobiology of cognitive control, for defining the etiological overlap between schizophrenia and bipolar disorder, and for developing pharmacological treatments of cognitive impairments.

1. Introduction

Executive functioning refers to cognitive abilities involved in the control of thought and action. Despite strong empirical support for executive functioning impairments in schizophrenia that predict functional outcome (Bilder et al., 2000; Hutton et al., 1998), evidence for stable impairments in executive functioning in bipolar disorder, as measured by standard neuropsychological tests, is equivocal. Although current diagnostic classification considers schizophrenia and bipolar disorder to be distinct disorders, there is ample evidence for neurobiological overlap (e.g. Lichtenstein et al., 2009; Maier et al., 2006; Moskvina et al., 2009). Mapping the overlapping and unique cognitive markers in these two clinical populations can contribute to our understanding of shared etiology and pathophysiology of bipolar disorder and schizophrenia.

Although a recent meta-analysis reported executive function impairments of medium to large effect sizes in euthymic bipolar patients, particularly response inhibition (Bora et al., 2009), a subsequent large-scale study found that impairments in response inhibition were largely symptom-dependent (Langenecker et al., 2010). Along with differences in clinical status of participants across studies, heterogeneity of tasks used to assess executive function likely also gives rise to discrepant findings across studies, as different tasks place different demands on various subdivisions of executive functioning. As an alternative to these standard neuropsychological tests, a translational approach that applies simple experimental tasks that have been performed by humans and non-human primates under similar conditions is valuable in outlining precise cognitive phenotypes and making specific hypotheses about the etiology of putative deficits.

One such translational paradigm that has been used to explore the cellular basis of executive functioning in non-human primate studies is the saccadic countermanding task (Hanes and Schall, 1995). In this task, participants must make a speeded eye movement to a target unless a stop-signal is presented at some delay following the initial target. On these trials, participants must inhibit the prepared eye movement. The time needed to cancel a movement, the *stop signal reaction time* (SSRT), can be estimated from the distribution of RTs on no-stop signal trials and the probability of making a saccade given that a stop signal occurred,

* Correspondence to: Brain Center Rudolf Magnus, University Medical Center Utrecht, Huispost A.01.126, Postbus 85500, 3508 GA Utrecht, The Netherlands.
E-mail address: k.n.thakkar@umcutrecht.nl (K.N. Thakkar).

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assuming a race between STOP and GO processes (Logan and Cowan, 1984). Along with response inhibition, trial-by-trial adjustments in response speed have been used to measure response monitoring (e.g. Emeric et al., 2007). Neural activity necessary to accomplish the preparation and inhibition of saccades has been identified in the frontal eye fields (FEF; Brown et al., 2008; Hanes et al., 1998) and the superior colliculus (SC; Paré and Hanes, 2003). In contrast, neurons in the medial frontal cortex display performance monitoring signals such as those associated with errors, reward and conflict (Ito et al., 2003; Stuphorn et al., 2000). These performance-monitoring signals may contribute to specific behavioral adjustments based on trial history.

In a previous study, we found that, compared with controls, patients with schizophrenia had longer SSRT, which was associated with occupational functioning (Thakkar et al., 2011). To our knowledge, performance on the saccadic countermanding task has not been investigated in individuals with bipolar disorder. Although there are data from the manual (keypress) version of this task, the results are mixed. Generally, impairments in adult bipolar patients on the manual countermanding task appear to be state-related. Strakowski et al. (2009) reported that BP in a manic/mixed episode had longer SSRT; however, SSRT in these same patients had normalized after converting to depression or euthymia (Strakowski et al., 2010).

Inhibition of eye movements has been measured in bipolar disorder using the antisaccade task. Similar to the saccadic countermanding task, participants are required to inhibit a saccade to a visual target; however, in the antisaccade task, participants are instructed to saccade to the mirror location in the opposite hemifield. There is robust evidence for higher antisaccade error rates and longer antisaccade latency in patients with schizophrenia (see Clementz (1998), Gooding and Basso (2008), and Hutton and Ettinger (2006) for reviews). Compared to controls, elevated antisaccade error rates have also been reported in bipolar disorder (Gooding and Tallent, 2001; Harris et al., 2009; Katsanis et al., 1997; Martin et al., 2007; McDowell and Clementz, 1997; Tien et al., 1996; but see Crawford et al. (1995)) and mixed affective groups comprising mainly bipolar patients (Sereno and Holzman, 1995). With regard to diagnostic specificity of antisaccade performance, results are mixed. Some studies report greater anitisaccade errors in schizophrenia patients compared to bipolar patients (Crawford et al., 1995; Gooding and Tallent, 2001; McDowell and Clementz, 1997), and others report no difference between the two groups (Harris et al., 2009; Katsanis et al., 1997; Martin et al., 2007). Given evidence for temporal instability of antisaccade deficits in bipolar disorder (Gooding et al., 2004), differences across studies could be attributed to differences in clinical status of study samples. It is important to note, however, that the antisaccade and saccadic countermanding tasks provide different information about two dissociable aspects of response inhibition: proactive inhibition and reactive inhibition. Proactive inhibition, also referred to as action restraint, refers to the ability to prepare to inhibit based on advance information. Reactive inhibition, or action cancellation, refers to the ability to rapidly interrupt an ongoing action plan. Although the antisaccade and countermanding task tax both aspects of inhibition, the countermanding task provides much more information about reactive inhibition ability.

In a previous study, we also observed idiosyncratic response monitoring in schizophrenia patients. Although both groups slowed down following both canceled and non-canceled trials, schizophrenia patients slowed down nearly twice as much following correctly inhibited trials. That is, they were *more* influenced by the prior trial than controls. In contrast to response inhibition, response monitoring has not been investigated in bipolar disorder to our knowledge. Despite evidence for general executive dysfunction (Bora et al., 2009), there are no published studies that have examined history-based adjustments in response speed in bipolar disorder.

To summarize, we previously observed slower response inhibition and exaggerated trial history effects in schizophrenia during the saccadic countermanding task. The aim of the current study was to investigate the diagnostic specificity of these findings by investigating cognitive control of gaze during the same task in bipolar disorder.

2. Methods and materials

2.1. Participants

Individuals who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for bipolar disorder (BP) or schizophrenia (SZ) were recruited from outpatient psychiatric facilities in Nashville, TN. Diagnoses were confirmed using structured clinical interviews (SCID-IV; First et al., 1995). All but two BP were medicated with mood stabilizers, antidepressants, atypical antipsychotics, or a combination. All SZ were medicated with a combination of atypical antipsychotic medications, mood stabilizers, and antidepressants. Detailed information about medication is presented in Supplementary data 1. Healthy, unmedicated control subjects (HC) without a personal and self-reported family history of DSM-IV Axis I disorders were recruited from the same community by advertisements. Personal history of Axis I disorders was also assessed using the SCID-IV in HC. The SZ and HC samples are identical to those published in Thakkar et al. (2011).

Clinical symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962; BP and SZ), Hamilton Rating Scale for Depression (HRSD; Hamilton, 1980; BP only), Young Mania Rating Scale (YMRS; Young et al., 1978; BP only), the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984; SZ only), and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983; SZ only). Subscale scores of the BPRS were calculated based on Ventura et al. (2000): Positive, Negative, Depression-Anxiety, and Manic-Excitement. Social and occupational functioning was assessed by the 79-item Social Functioning Scale (SFS; Birchwood et al., 1990), which 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 North American Adult Reading Test (NAART; Blair and Spreen, 1989) or Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) were used to assess IQ.

All participants were screened to exclude self-reported substance use, neurological disorders, history of head injury, inability to fixate, and excessive sleepiness. All subjects had normal or corrected-to-normal vision. Two SZ were excluded based on countermanding task performance, as outlined in the *Statistical Methods* section. Analyses were conducted on the remaining 18 BP, 17 SZ, and 16 HC; demographic data are presented in Table 1. The three groups were matched for age, sex, and handedness. Years of education were significantly higher in HC than SZ and BP. Estimated IQ was higher in HC than SZ, but not BP. BP and SZ were matched on all demographic variables, including social and occupational functioning and general psychiatric symptoms as indexed by BPRS score. However, SZ were taking a significantly higher antipsychotic dose and showed a non-significant trend towards longer length of illness. Ten out of the 18 bipolar patients had a lifetime history of psychosis. All participants gave written informed consent approved by the Vanderbilt Institutional Review Board, and the study was carried out in accordance with the