Schizophrenia Research 159 (2014) 101–106

Contents lists available at ScienceDirect

Schizophrenia Research

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

Disease and drug effects on internally-generated and externally-elicited responses in first episode schizophrenia and psychotic bipolar disorder

Sarah K. Keedy [a,*], Jeffrey R. Bishop [b], Peter J. Weiden [c], John A. Sweeney [d], Cherise Rosen [c], Robert Marvin [c], James L. Reilly [e]

[a] Department of Psychiatry and Behavioral Neuroscience, 5841 S. Maryland Ave., MC3077, University of Chicago, IL 60637, United States
[b] Department of Pharmacy Practice, University of Illinois at Chicago, IL, United States
[c] Department of Psychiatry, University of Illinois at Chicago, IL, United States
[d] Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, United States
[e] Department of Psychiatry and Behavioral Sciences, Northwestern University, Chicago, IL, United States

ARTICLE INFO

Article history:
Received 3 June 2014
Received in revised form 18 July 2014
Accepted 21 July 2014
Available online 8 August 2014

Keywords:
Psychosis
Saccades
Dorsolateral prefrontal cortex
Striatum
Risperidone

ABSTRACT

Neurocognitive deficits are associated with most psychotic disorders, but may differ across diagnosis and by treatment status. This ambiguity is partly addressed in longitudinal pre/post treatment studies with first episode patients. Antipsychotic-naïve first-episode schizophrenia patients have shown intact performance on a predictive saccade task that assesses simple motor learning, spatial abilities, and response planning. After antipsychotic treatment, however, schizophrenia patients performing this task show a selective impairment in the accuracy of anticipatory responses, generated from learned internal representations of the task stimulus. This finding is in line with other observations of antipsychotic medication effects on frontostriatal systems, particularly dorsolateral prefrontal cortex. We sought to replicate this provocative finding with an independent sample of antipsychotic-naïve first-episode schizophrenia patients and extend it by including a group of patients with first episode bipolar disorder with psychosis (BDP). Matched healthy controls were also studied in parallel. Schizophrenia patients demonstrated intact performance pretreatment followed by impairment post-treatment for accuracy of anticipatory responses, and worse accuracy was associated with higher antipsychotic dose. BDP patients displayed saccade accuracy deficits before and after treatment and had no correlation of performance and antipsychotic dose. The findings suggest different neural alterations early in the course of each psychotic disorder, and different vulnerabilities to antipsychotic treatment effects between schizophrenia and BDP.

1. Introduction

Longitudinal assessment of cognitive abilities in antipsychotic-naïve first-episode schizophrenia patients before and after initial antipsychotic treatment is a method to disentangle impairments caused by illness and by antipsychotic medication. However, such work has been limited by the difficulty in identifying measures that are sensitive to these factors. One approach that has been successful in this regard has been the use of eye movement tasks assessing cognitive and sensorimotor functions, as these have been shown to be sensitive to changes pre-to-post treatment in first-episode schizophrenia (Reilly et al., 2005; Keedy et al., 2006; Reilly et al., 2006; Harris et al., 2009) and are further advantaged by the neural system physiology being well characterized in animal and human literature (Stahl, 2004; Schiller and Tehovnik, 2005; Sweeney et al., 2007; Hutton, 2008).

A key observation of change pre-to-post treatment has been reported for the predictive saccade task, a motor learning paradigm requiring shifts of gaze (saccades) to track a visual target as it alternates between two locations at a constant interval. As the target continues in this predictable pattern, rapid learning ensues as evidenced by saccades becoming faster than could occur in response to the stimulus appearance. Such anticipatory saccades are therefore generated on the basis of internalized representations of the visual target. These internally-generated anticipatory responses rely on spatial learning and response planning, functions supported by premotor and dorsolateral prefrontal cortex, hippocampus, and striatum (Simo et al., 2005; McDowell et al., 2008). Prior to antipsychotic treatment, schizophrenia patients display intact predictive saccade performance (Harris et al., 2009), a rare finding among studies of cognition in schizophrenia (Gold et al., 2009; Mesholam-Gately et al., 2009). After antipsychotic treatment, however, anticipatory response accuracy is decreased, while accuracy of longer latency, stimulus-driven responses does not change (Harris et al., 2009). This is consistent with studies showing chronically-treated

* Corresponding author. Tel.: +1 773 834 7178; fax: +1 773 834 4536.
E-mail addresses: skeedy@uchicago.edu (S.K. Keedy), jbishop@uic.edu (J.R. Bishop), pweiden@psych.uic.edu (P.J. Weiden), John.Sweeney@utsouthwestern.edu (J.A. Sweeney), crosen@psych.uic.edu (C. Rosen), rmarvin@psych.uic.edu (R. Marvin), james.reilly@northwestern.edu (J.L. Reilly).

http://dx.doi.org/10.1016/j.schres.2014.07.028
0920-9964/

schizophrenia patients make inaccurate anticipatory saccades during predictive saccade tasks (McDowell et al., 1996; Thaker et al., 1996). Altogether, this suggests antipsychotic treatment is associated with alterations in schizophrenia patients' neural systems supporting the accuracy of responses based on internal representations.

To establish the reliability of this treatment-related deficit for accuracy of anticipatory responses in schizophrenia, replication is needed. A useful expansion of such an effort may be to assess how antipsychotic treatment affects performance among bipolar disorder with psychosis (BDP) patients. Schizophrenia and BDP, often similar clinically at initial presentation (Rosen et al., 2012), show comparable positive symptom reduction with antipsychotic treatment. However, much less is known about neural alterations impacting cognition early in bipolar disorder (Lewandowski et al., 2011). To our knowledge, the only longitudinal studies assessing neurocognitive outcomes of antipsychotic treatment in first-episode BDP are those from our group which reported no effects of antipsychotic treatment on smooth pursuit eye movement tasks in either BDP or schizophrenia (Lencer et al., 2010; Lencer et al., 2011). The aim of the present work, therefore, was to replicate the observations of selective post-treatment deficits in anticipatory saccade accuracy in first-episode schizophrenia patients performing a predictive saccade task, and to evaluate whether similar effects are seen in BDP.

2. Methods

2.1. Participants

Written informed consent was obtained from 47 antipsychotic naïve patients at the University of Illinois Medical Center. Twenty-nine participants met DSM-IV criteria for schizophrenia spectrum disorders (SCZ; schizophrenia = 23, schizophreniform = 1, schizoaffective = 5), and 18 met criteria for BDP (6 manic, 9 depressed, 3 mixed current episodes), established via consensus meetings based on Structured Clinical Interview for DSM-IV (First et al., 2002) and all available collateral information. Demographically-matched healthy controls (HC; n = 59) with no Axis I diagnosis history and no known first degree relative with psychotic or mood disorders were recruited via community advertisements (Table 1). All participants met the following criteria: no known systemic or neurologic disorders, no history of head trauma or loss of consciousness >5 min, no lifetime history of substance dependence or current abuse, and no caffeine or cigarettes within 1 h of testing. The study protocol was approved by the university institutional review board.

For patients, symptom ratings and eye movement studies were performed at pretreatment baseline and again at follow-up (SCZ = 18; BDP = 11 [5 manic, 5 depressed, 1 mixed episode at time of baseline]) as close as possible to the planned 4–6 weeks of treatment with antipsychotic medication. HC participants (n = 43) repeated eye movement testing at a retest interval similar to that of patients (Table 1).

Treatment of choice was risperidone, dosed per clinician judgment or switched to alternative antipsychotic medication per clinician judgment. All patients were taking risperidone at follow-up except three schizophrenia patients that were switched to aripiprazole due to intolerance for risperidone. Medication for mood symptoms or side effect management was also permitted. One BDP was taking antidepressant medication at baseline but not follow-up. Five SCZ patients taking risperidone were also taking antidepressant medications at follow-up, and two were taking benztropine (0.5 and 2 mg/day, respectively). One BDP patient was taking carbamazepine.

Table 1
Mean (SD) sample characteristics.

	Schizophrenia	BDP	Healthy
N baseline/follow-up	29/18	18/11	59/43
Males/females (baseline)	18/11	10/8	32/27
Age	24.2 (7.1)	25.2 (9.1)	25.6 (6.3)
Race	8 Cauc	3 Cauc	17 Cauc
	11 Af Am	10 Af Am	29 Af Am
	3 Asian	3 Asian	1 Asian
	5 Hisp	2 Hisp	9 Hisp
	2 other		3 other
Premorbid IQ[a]	97.6 (11.5)	96.3 (15.2)	99.9 (8.4)
Years of education	12.8 (3.0)	13.1 (3.7)	13.7 (1.9)
SES[b] participant	35.2 (15.5)	32.4 (13.4)	36.1 (9.7)
SES[b] parent	38.1 (13.6)	38.0 (12.4)	40.1 (10.5)
Days between baseline and follow-up	50 (45)	43 (25)	57 (33)

Differences assessed with ANOVA, except race and sex assessed with chi-square. There were no significant differences among groups. Cauc = Caucasian; Af Am = African American; Hisp = Hispanic.

[a] Estimated with the Wide Range Achievement Test IV, Reading standard scores (Wilkinson, 1993).

[b] SES: Socioeconomic status score (Hollingshead, 1975).

2.2. Procedures

For eye movement tasks, participants sat in a blackened room at a table with a chin and forehead rest for comfort and stability while they viewed the stimuli, which appeared along the horizontal meridian of the screen at ±6° of visual angle. A head-mounted infrared eye tracker (ASL model 310; Bedford, MA) recorded eye movements, which were digitized at 500 Hz with a 12-bit A/D converter (DATAQ Instruments, DI-720 series; Akron, OH). Electrodes were placed above and below the left eye to identify blinks. Participants were instructed to simply track the target (0.5-degree diameter white dot presented against a black background) as it changed location. After fixating a central target for 5 s, subjects tracked the target as it alternated between the ±6-degree positions from center, resulting in 12 degree target displacements. The target shifted between these two positions every 750 ms for 40 trials. Target onset and offset were simultaneous. Fixation of static targets before the task was used to calibrate eye movement recordings.

2.3. Analysis

Eye movements were scored using custom software operated by technicians blind to subject characteristics. Measures of interest were saccade accuracy (gain), measured as the proportion of distance the primary saccade covered toward the new target location, and latency, the time (in ms) from target appearance to primary saccade initiation. Latencies were averaged into blocks to characterize learning, with smaller blocks toward the beginning of the task where the most rapid learning occurs (Harris et al., 2009). Blocks were as follows: block 1 = trials 2–7 (totally unpredictable trial 1 excluded), block 2 = trials 8–13, block 3 = trials 14–20, block 4 = trials 21–30, and block 5 = trials 31–40. In accordance with Harris et al., each saccade was classified as either a stimulus-guided prosaccade (>129 ms latency) or an anticipatory saccade (≤90 ms latency). Saccades between 130 and 90 ms were considered ambiguous (~10% of responses for all groups), and their accuracy was not analyzed.

To assess pretreatment group differences, separate ANOVAs were run for each saccade measure in the larger pretreatment samples. To assess treatment effects, longitudinal analyses were conducted via repeated measures ANOVAs for each saccade measure for subjects with baseline and follow-up data. Pearson correlation coefficients were examined to assess associations among performance, clinical measures, and, separately, antipsychotic dose equivalents, per Andreasen et al. (2010).

3. Results

3.1. Anticipatory response accuracy

3.1.1. Anticipatory saccade accuracy at baseline

For the larger pretreatment sample, there were significant group differences in anticipatory saccade accuracy ($F = 4.18$, $df = 2$, $p = 0.018$).