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Disease and Drug Effects on Internally-Generated and Externally-Elicited Responses in First Episode Schizophrenia and Psychotic Bipolar Disorder

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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

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Conflict of interest

The other authors have nothing to disclose.

Contributors

All authors contributed to recruitment, evaluation, and management of participants in the study, and to manuscript preparation. Dr. Keedy conducted statistical analyses and primary interpretation of the data.

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.

Keywords

psychosis; saccades; dorsolateral prefrontal cortex; striatum; risperidone

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 difficulty 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 function, as these have been shown to be sensitive to changes pre-to-post treatment in first-episode schizophrenia (Harris et al., 2009; Keedy et al., 2006; Reilly et al., 2006; Reilly et al., 2005) and are further advantaged by the neural system physiology being well characterized in animal and human literature (Hutton, 2008; Schiller and Tehovnik, 2005; Stahl, 2004; Sweeney et al., 2007).

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 (McDowell et al., 2008; Simo et al., 2005). 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 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., 2011; Lencer et al., 2010). 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 >5min, no lifetime history of substance dependence or current abuse, and no caffeine or cigarettes within 1 hour 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 bupropion (0.5 and 2mg/day, respectively). One BDP patient was taking carbamazepine.

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 degrees of visual angle. A head-mounted

infrared eye tracker (ASL model 310; Bedford, MA) recorded eye movements, which were digitized at 500Hz 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 seconds, 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 750ms 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 msec) from target appearance to primary saccade initiation. Latencies were averaged into blocks to characterize learning, with smaller blocks towards 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 90ms were considered ambiguous ($\sim 10\%$ 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. (2011).

3. Results

3.1 Anticipatory response accuracy

Anticipatory saccade accuracy at baseline—For the larger pretreatment sample, there were significant group differences in anticipatory saccade accuracy ($F = 4.18$, $df = 2$, $p = .018$). Post-hoc comparisons indicated BDP patients, but not schizophrenia patients, had lower anticipatory saccade accuracy than HC (BDP vs HC $p = .017$; schizophrenia vs HC $p = 0.54$, Bonferroni corrected).

Anticipatory saccade accuracy over time—Group $\times$ time analyses indicated only a main effect of group ($F = 5.6$, $df = 2$, $p = .006$) and post-hoc analysis indicated that BDP participants had poorer anticipatory saccade accuracy than HC ($p = .008$, Bonferroni corrected). A subsequent, additional repeated measures ANOVA was conducted with only schizophrenia and HC to precisely replicate analyses in Harris et al. (2009), which had no

BDP group. This yielded a significant group x time interaction ($F = 4.68$, $df = 1$, $p = .035$). Contrasts indicated that SCZ had lower anticipatory saccade accuracy than HC at follow-up ($p = .002$) and relative to their own baseline before treatment ($p = .009$; Fig 1).

Correlations—For schizophrenia patients, lower anticipatory saccade accuracy post-treatment was associated with higher antipsychotic dose (Fig 2; Pearson $r = -0.61$, $p = 0.009$; risperidone only $r = -0.70$, $p = .006$). No significant correlation between dose and performance was found for BDP. Anticipatory saccade accuracy was not correlated significantly with any clinical ratings for either patient group at either time point.

3.2 Prosaccade response accuracy

Prosaccade accuracy at baseline—Analyses of the larger samples at baseline yielded no significant differences among groups for prosaccade accuracy.

Prosaccade accuracy over time—Group x time analyses indicated only a significant main effect of group ($F = 5.0$, $df = 2$, $p = .01$). Post hoc tests indicated that, as with anticipatory saccade accuracy, only BDP accuracy was significantly worse than that of HC ($p = .014$, Bonferroni corrected; Fig 1).

Correlations—No correlations with antipsychotic dose or clinical ratings were found for prosaccade accuracy.

3.3 Latency of responses across trial blocks

Pretreatment, groups did not differ on mean saccade latency in any trial block. There was a main effect of block ($F = 32.3$, $df = 4$, $p < 0.001$). Contrasts indicated block 1 latencies were longer than all others, and block 2 latencies were longer than blocks 3, 4, and 5. There was also a significant quadratic effect for block ($F = 23.8$; $p \leq 0.001$) reflecting the fast initial rate of learning to anticipate target appearance and respond more quickly, as well as sustained faster responding after the rapid learning over the first two blocks. No differential changes in learning rates were found after treatment. There was no correlation of saccade latency with saccade accuracy for any group (e.g., no speed-accuracy trade off), nor any correlation of saccade latencies with antipsychotic dose or clinical measures.

3.4 Symptom ratings

There was significant improvement pre-to-post-treatment for all psychosis and mood symptoms except for negative symptoms in BDP. Motor control, assessed by the Simpson Angus Scale, was not significantly altered pre-to-post treatment, nor did groups differ (Table 2).

3.5 Attrition bias check

There were no differences between patients who were followed longitudinally vs not followed in terms of age, education, symptom severity, or pretreatment saccade task performance.

Discussion

Antipsychotic-naïve first-episode schizophrenia patients had intact performance on a predictive saccade task prior to treatment, but after antipsychotic treatment, had a selective deficit in the accuracy of anticipatory responses. These findings replicate those of Harris et al. (2009), and we additionally demonstrate in the current study that the adverse antipsychotic treatment effect on predictive saccade accuracy is dose dependent, such that higher doses of second generation antipsychotic medication were associated with poorer anticipatory saccade accuracy. These findings suggest an adverse treatment-related effect on motor planning and/or spatial memory in a dose-dependent manner among individuals with schizophrenia. BDP patients, on the other hand, had deficits in saccade accuracy prior to initiation of antipsychotic treatment. Further, the BDP group had no changes after treatment, or dose correlations, a markedly different pattern from the observations in the schizophrenia sample. These findings suggest differential effects of illness on neural systems supporting the accuracy of saccades guided by internal representations, and differential effects of antipsychotic treatment on these neural systems in the two psychotic disorders.

In schizophrenia patients, the specificity of the post-treatment deficit for saccades guided by learned, internal representations of a predictable target's appearance in time and space, and no deficit in accuracy of saccades made in response to sensory input, is a replication of findings in a prior study with an independent sample of antipsychotic-naïve first-episode schizophrenia (Harris et al., 2009). The dose-dependent decline in anticipatory saccade accuracy after treatment suggests that antipsychotic medication may directly alter the integrity of neural systems supporting operations such as spatial learning and memory, response planning or procedural learning. Frontostriatal circuitry provides key support for such functions, including dorsolateral prefrontal cortex (DLPFC), premotor cortex, anterior cingulate and striatum (Simo et al., 2005). Of these cortical regions, DLPFC has shown reduced activation after 4–6 weeks of second generation antipsychotic treatment in first-episode schizophrenia patients performing a prosaccade task (Keedy et al., 2009) and a predictive saccade task (Keedy et al., in press). Such observations are also in line with reports of reduced accuracy of internally-generated saccades needed to perform an oculomotor delayed response task after initiation of antipsychotic treatment in first-episode schizophrenia patients (Reilly et al., 2006; Reilly et al., 2007), an effect also seen in non-human primates exposed to antipsychotics (Castner et al., 2000). While it is not clear how antipsychotic medication may alter prefrontal function, non-human primate studies show that antipsychotic medication exposure is associated with reduced D1 receptor expression (Lidow et al., 1997). Altered function in DLPFC could also impact striatal function via its role in corticostriatal loops.

The striatum itself is key for motor learning and control (Debas et al., 2010; Hikosaka and Isoda, 2010; Puttemans et al., 2005) and so the direct antagonistic effects of antipsychotic medication on D2 dopaminergic receptors there may also be involved in the changes observed in schizophrenia patients' anticipatory response accuracy. A similar selective impairment for anticipatory saccade accuracy is observed in unmedicated Parkinson's disease patients (Crawford et al., 1989; O'Sullivan et al., 1997), supporting an interpretation of striatal dopamine reduction contributing to the impairment. Overall, frontostriatal motor

learning systems in schizophrenia appear to have high sensitivity to antipsychotic effects, and as such may be useful markers of motor system alteration induced by antipsychotic medication exposure. As these neural system effects were not directly evaluated in the present study, further neuroimaging studies are needed.

A novel finding in this study was impaired anticipatory and prosaccade accuracy (the latter seen in the longitudinal analysis) in antipsychotic naïve BDP patients before treatment, and no change with antipsychotic treatment. Prior saccade studies in chronically ill bipolar patients reported intact performance of prosaccades (Gooding and Basso, 2008), including studies restricted to psychotic bipolar patients (Crawford et al., 1995; McDowell and Clementz, 1997; Reilly et al., 2013). The present study is unique in its sample of antipsychotic-naïve first episode BDP, with practically no mood stabilizer exposure as well (only one bipolar participant reported about 20 weeks of divalproex exposure, discontinued one year prior to the study). Mood stabilizers may be protective for brain structure and function (Benedetti et al., 2011; Emsell and McDonald, 2009), but whether saccade accuracy is restored with mood stabilizer treatment requires further investigation.

Higher rates of extrapyramidal effects of antipsychotic medication have been noted in bipolar disorder compared with schizophrenia (Gao et al., 2008). Our data may be consistent with this in that prior to treatment, BDP patients showed a motor system disturbance that schizophrenia patients did not. Yet, treatment did not more adversely impact BDP patients. One reason for this discrepancy may be that well-controlled studies showing risperidone is associated with worse motor system effects in BDP than in schizophrenia administer higher doses (4–6mg; [Chouinard et al., 1993; Hirschfeld et al., 2004; Smulevich et al., 2005]) than those in the present study (1–3mg/day). Furthermore, our patients had lower cumulative exposure to antipsychotic medications than those prior studies, as our patients started on lower doses for the first week or so, consistent with clinical practice in treating first episode patients.

The poorer anticipatory and prosaccade accuracy seen in our BDP sample suggests deficiencies in neural systems supporting precision of eye movement motor plans or of the execution of such plans. This implicates a range of potential neural systems as possibly dysfunctional in BDP, from frontal eye fields to cerebellum. The lack of impact of antipsychotic treatment on task performance in BDP may point to a stronger role for deficient cerebellar tuning of motor action execution, as this brain region is less impacted by antipsychotic treatment due to relatively low dopamine receptor expression there. Reduced volume in posterior (oculomotor) vermis has been reported in medication-naïve bipolar patients (Kim et al., 2013). When posterior vermis is compromised in nonhuman primates, hypometria of both externally and internally generated saccades is observed (Takagi et al., 1998). Also, compromised caudal dentate gyrus could disrupt spatial planning of saccades (Ashmore and Sommer, 2013). However, no model exists which clearly explains reduced accuracy for both externally- and internally-generated saccades without additional deficits in saccade metrics (Kheradmand and Zee, 2011) or in learning behavior (Lu et al., 1998). Additional investigation into cerebellar integrity in BDP is needed.

A performance deficit in BDP but not in schizophrenia on our predictive saccade task, as seen pretreatment, is another novel aspect of the present study, compared with other first episode studies showing BDP patients perform better than schizophrenia patients on general cognitive tests (Hill et al., 2009; Zanelli et al., 2010), and are not impaired relative to HC for several domains including attention and processing speed (Hill et al., 2009). One area in brain research where first episode BDP patients are more abnormal than schizophrenia patients is in white matter abnormalities (De Peri et al., 2012; Lu et al., 2011). This suggests that early BDP may be characterized by greater loss of integrity of connections supporting key pathways for saccade accuracy in frontostriatal and/or corticocerebellar circuitry relative to schizophrenia. Work assessing the relation of white matter integrity and eye movement control may elucidate this possibility.

Limitations of the present work include the smaller groups assessed post-treatment, particularly for BDP, limiting statistical power to find effects of smaller magnitude. Also, post-treatment changes cannot be definitely ascribed to direct pharmacological effects of medication vs. changes attributable to clinical stabilization, although associations were found within schizophrenia patients between dose and performance decline.

In summary, the findings from the current study suggest that accuracy on the predictive saccade task may be both a sensitive measure differentiating disease effects within the psychosis spectrum and a marker of effects of antipsychotic medication on frontostriatal neural systems underlying spatial learning and memory, response planning or procedural learning in schizophrenia.

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Figure 1.

Mean saccade accuracy values (bars = 1 std error) for each group and each saccade type at baseline (pre-treatment for patients) and follow-up (post-treatment). Data depicted is from longitudinal analyses (n=18 SCZ, 11 BDP, 43 HC). a) Schizophrenia patients (SCZ) had reduced anticipatory saccade accuracy post-treatment relative to pretreatment. b) Schizophrenia patients had reduced accuracy post-treatment relative to healthy controls' (HC) re-test performance. c) BDP patients had reduced accuracy relative to controls for both anticipatory and prosaccades (main effects).

Figure 2.

Antipsychotic dose calculated per Andreasen et al. (2010) and post-treatment accuracy for anticipatory saccades were significantly correlated only for schizophrenia patients ($r = -0.61$). SCZ=schizophrenia BDP=bipolar disorder with psychosis

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 11 Af Am 3 Asian 5 Hisp 2 Other	3 Cauc 10 Af Am 3 Asian 2 Hisp	17 Cauc 29 Af Am 1 Asian 9 Hisp 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).

Table 2

Mean (SDx) clinical characteristics of patients.

	Schizophrenia	BDP	Group Comparison
Daily risperidone dose (mg) (n=15 schizophrenia, n=11 BDP) at follow-up	2.6 (1.5)	2.2 (1.1)	ns
Chlorpromazine equivalent dose ^a	230 (125)	173 (95)	ns
PANSS Positive Baseline	24.3 (4.8)	23.3 (4.7)	ns
PANSS Positive Follow-up	18.3 (5.3) *	17.3 (5.9) *	ns
PANSS Negative Baseline	20.3 (7.1)	12.7 (4.2)	SCZ>BDP
PANSS Negative Follow-up	16.2 (5.9) *	11.5 (2.3)	SCZ>BDP
PANSS General Baseline	43.4 (8.4)	36.9 (6.2)	SCZ>BDP
PANSS General Follow-up	34.9 (6.5) *	28.6 (4.0) *	SCZ>BDP
YMRS Baseline	16.1 (6.3)	27.4 (9.8)	SCZ<BDP
YMRS Follow-up	9.3 (4.6) *	10.9 (4.7) *	ns
Ham-D Baseline	28.4 (9.8)	30.8 (7.9)	ns
Ham-D Follow-up	14.9 (6.3) *	14.5 (5.4) *	ns
Simpson-Angus Baseline	0.76 (2.0)	0 (0)	ns
Simpson-Angus Follow-up	1.4 (3.0)	.36 (0.8)	ns

Baseline means are for the entire baseline sample. Significant differences were assessed longitudinally. There were no significant differences in baseline means for those studied at post-treatment vs. those not studied.

* Within-group pre/post treatment comparison significantly different at $p < 0.05$. ns: not significant

^a Calculated per Andreasen et al. (2010). PANSS: Positive and Negative Symptom Scale (Kay et al., 1987). YMRS: Young Mania Rating Scale (Young et al., 1978). Ham-D: 21-item Hamilton Depression Scale (Hamilton, 1960). Simpson-Angus Scale (Simpson and Angus, 1970).