Research Paper

Altered use of extraretinal information during sequential saccadic eye movements among people with schizophrenia and bipolar disorder with psychotic features

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Background: Impaired corollary discharge (CD) signalling disrupts the ability to predict the sensory consequences of one's own actions; impaired CD signalling may be specific to schizophrenia or it may also be a transdiagnostic mechanism of psychosis. We sought to assess whether disruptions in oculomotor CD signalling are equally present in schizophrenia and bipolar disorder (BD) with psychotic features, and whether these putative CD disruptions relate to anomalous self-experiences. **Methods:** We recruited patients with schizophrenia and patients with BD with psychotic features, as well as healthy controls, to complete a double-step saccade task. On each trial, 2 visual targets (T1 and T2) flashed in rapid succession. For half of the trials, participants could use visual information to look at T2. For the other half, looking correctly at T2 required CD. **Results:** We included 66 patients with schizophrenia, 43 patients with BD with psychotic features, and 37 healthy controls. On trials requiring CD, patient groups were significantly less accurate than controls in localizing T2 ($F_{2,131}$ = 8.40, p < 0.001). This reduced accuracy was related to difficulty in compensating for variability in the first saccade ($F_{2,131}$ = 9.11, p < 0.001). Among controls, anomalous self-experiences predicted worse performance ($F_{1, 57}$ = 14.23, p < 0.001). **Limitations:** Our sample comprised stable outpatients with relatively low symptom scores, which may limit the generalizability of our results. **Conclusion:** These results suggest CD impairments may be a marker of predisposition for psychosis. However, observed inconsistencies suggest that this relationship is nuanced.

Introduction

Anomalous self-experiences are a core feature of schizophrenia spectrum disorders, and they engender positive symptoms. Central to these altered self-experiences are distortions in the subjective sense of agency — the feeling of controlling one's thoughts and actions.[1–3] For example, difficulty in distinguishing between oneself and the external environment could lead to the feeling that one's thoughts or actions are being externally controlled; such feelings contribute to the experience of delusions of control that are a characteristic of schizophrenia.[4–6] Notably, the severity of self-disturbances among people at high risk for psychosis predicts later onset of positive psychotic symptoms[7] and eventual transition to schizophrenia.[8]

A compelling biological explanation for agency disturbances centres on corollary discharge (CD) signalling.[4,9,10] Corollary discharge signals are copies of motor signals that are sent to sensory areas of the brain and allow agents to predict the sensory consequences of impending actions. A match between predicted and actual sensory information may engender a sense of agency (e.g., the sense that if an agent accurately predicted the experience, they must have caused it) whereas mismatches leave agents to infer external causes for sensory experiences. Evidence suggests that CD signalling has reduced influence across multiple sensory systems among people with schizophrenia[9,11,12] and that this reduced influence is frequently correlated with the severity of positive symptoms.[13] Psychotic features characterize several other psychiatric conditions, but whether disturbed CD signalling is a transdiagnostic mechanism of psychosis remains unknown. Establishing the extent to which CD alterations are present transdiagnostically would inform our ability to predict and treat symptoms across the psychosis spectrum.

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Psychotic symptoms are frequently observed among patients with bipolar disorder (BD) with psychotic features (BDP).[14] Therefore, these patients may be a valuable clinical control group to test whether disruptions in CD signalling form a common mechanism across psychosis. Research exploring CD in BDP is scarce; current findings suggest that people with BDP have disruptions in auditory and oculomotor CD signalling similar to those with schizophrenia.[15,16]

The visuomotor system is ideal for exploring CD signalling. Studies involving human and nonhuman primates have revealed the critical role of the mediodorsal thalamus in relaying CD signals associated with saccadic eye movements.[17,18] This work can be leveraged to probe neurophysiological circuits involved in self and agency disturbances in people with psychosis. The double-step saccade task is an oculomotor task that has been shown to precisely measure the influence of CD signalling on successive movement execution. In this task, participants must look at 2 targets presented in rapid succession. Because the task is performed in total darkness and the targets are flashed only briefly, no visual information is available to inform the participant about the location of the second target. Moreover, sequential saccades are prepared in parallel (i.e., the second saccade is being prepared before the participant looks at the first target). Thus, accurate localization of the second target depends on an accurate prediction of gaze location when executing the second saccade. That is, when preparing the second saccade, participants must use CD signals to predict the upcoming gaze location following the first saccade. Previously, we found that patients with schizophrenia showed mislocalization of the second target, consistent with a reduced influence of CD.[19]

We sought to replicate and extend our previous findings in several ways. We aimed to replicate findings of impaired performance on the double-step task in a larger group of patients with schizophrenia using a modified version of the task that allowed us to better dissociate performance impairments related to a reduced influence of CD versus more general visuomotor impairments. We sought to determine whether disruptions in CD signalling are a transdiagnostic marker of psychosis by including a group of patients with BDP. By using a more sophisticated analytic method, we sought to explore trial-by-trial variations in performance, thereby allowing us to differentiate between individual- and group-level effects on performance. We hypothesized that, compared with controls, patients with schizophrenia and those with BDP would be impaired at localizing the second target on trials where localization would rely on accurate CD. We also sought to test whether altered CD signalling contributed to psychosis and self-disturbances by examining associations between double-step task performance and both clinical symptoms and anomalous self-experiences. We predicted that more severe anomalous self-experiences, general positive symptoms, and passivity symptoms would be associated with reduced influence of CD on saccade planning across groups.

Methods

We recruited patients with schizophrenia or schizoaffective disorder, patients with BDP, and healthy controls to complete the double-step task. Diagnoses were determined using an electronic version of the Structured Clinical Interview for DSM-5 (SCID-5),[20] which was supplemented with information from medical records and collateral informants when possible. We calculated chlorpromazine equivalent dosages for any participant taking antipsychotic medication.[21–23] Details regarding recruitment procedures and exclusion criteria can be found in Appendix 1, Methods, available at www.jpn.ca/lookup/doi/10.1503/jpn.240060/tab-related-content.

Assessments

We assessed clinical symptoms in patient groups using the Scale for the Assessment of Positive Symptoms (SAPS)[24], the Scale for the Assessment of Negative Symptoms (SANS)[25], the Brief Psychiatric Rating Scale,[26] the Young Mania Rating Scale,[27] and the Hamilton Depression Rating Scale.[28] We used the Scale for the Assessment of Passivity Phenomena (SAPP)[29] and the Inventory of Psychotic-like Anomalous Self-Experiences (IPASE)[30] to assess symptoms and experiences more directly linked to agency and putative CD disturbances. The SAPP is an interview-based measure of current and lifetime passivity experiences. The IPASE is a self-report questionnaire of subjective self-disturbances. We collected SAPP scores for patients only and IPASE for all participants. Details about missing data can be found in Appendix 1, Methods.

Double-step task

Participants completed a double-step task, which required them to make 2 saccades in sequence (Figure 1 and Appendix 1, Methods). Participants were first required to fixate on a central stimulus (white square subtending 0.5°), which remained on the screen for a random duration (2–3 s). Upon fixation offset, 2 targets (T1 and T2) were flashed in succession to which participants were required to make 2 saccades (S1 and S2, respectively). This task comprised randomly interleaved retinal and extraretinal trials, which differed in stimulus timings. On retinal trials, T1 was displayed on screen for 1000 ms and, after a 20 ms delay, T2 appeared for 50 ms. The average reaction time for S1 is around 240 ms; thus participants' gaze was at T1 when T2 was presented, allowing participants to use the retinal position of T2 to guide S2. Extraretinal trials were identical to retinal trials with the exception that T1 remained on the screen for only 120 ms. The average S1 reaction time for extraretinal trials is around 229 ms, thus, T2 is extinguished around 50 ms before S1 is completed. Therefore, participants have no visual information to direct S2 and must rely on extraretinal information to make an accurate saccade; an accurate CD signal would allow the participant to anticipate future eye position, thereby allowing them to remap the location of T2 relative to gaze location after looking at T1. Participants had a maximum of 2 s to complete saccades to T2 before the next trial began. Most participants performed 4 experimental blocks of 96 trials each.[1]

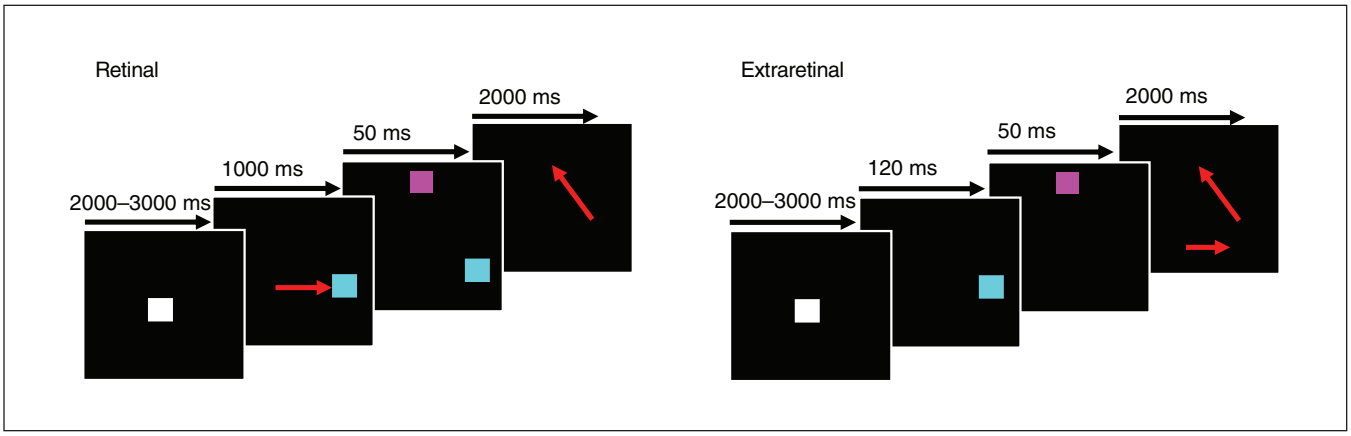

Figure 1: Double-step task. On this task, participants were required to make 2 saccades in sequence from a fixation point (white square). On retinal trials, the first target (T1, cyan target) remained on the screen for 1000 ms then, after a 20 ms delay, a second target (T2, magenta target) appeared for 50 ms. During these trials, the participant had made a saccade to T1 when T2 appeared; thus, participants could use the retinal position of T2 to guide their saccades. Extraretinal trials were identical to retinal trials, with the exception that T1 duration was 120 ms; therefore, T2 was typically extinguished before the saccade to T1 was initiated. Thus, on these trials, participants had to rely on corollary discharge signals to inform them of the future position of their gaze when the second saccade was initiated. Red arrows depict saccade vectors.

Statistical analysis

In the double-step task, the influence of CD is measured by S2 kinematics (saccade angle and amplitude) and accuracy in targeting T2. We had 3 predictions about how impaired CD would manifest in task performance. First, we expected that impaired CD signalling would lead to greater inaccuracies in S2, but only on trials where participants had to rely on extraretinal information to guide their movement to T2 (T2 error analysis). We also predicted that S2 would not simply be more inaccurate, but that it would be biased in a direction that indicated failure to use CD to compensate either for moving the eyes from fixation or for variability in the S1 endpoint (Figure 2). On trials where a participant's S1 fell short of T1 (hypometric trials), we computed the angle between the actual and expected S2 vector. These trials were then classified as CD loss amplitude (i.e., difficulty in compensating for hypometricity in S1) or CD loss direction (i.e., difficulty in compensating for having moved the eyes from fixation) based on the direction of deviation from the expected S2 vector (Appendix 1, Methods). Both CD loss variables were continuous variables, with larger values reflecting impairments in compensating for aspects of the first eye movement when planning the second movement. In our third analysis, we further probed the extent to which participants compensated for variability in the S1 endpoint. In 2 separate models, we predicted the amplitude and angle of S2 from the expected angle or amplitude (i.e., from the angle or amplitude that would bring the participant's gaze directly to T2). We expected that reduced influence of CD signals on motor planning would manifest as an attenuated effect of expected S2 kinematics on actual S2 kinematics, particularly on extraretinal trials.

For analyses of double-step performance, we constructed multilevel models using restricted maximum likelihood. More details regarding our statistical analyses can be found in Appendix 1, Methods. In all models, we included diagnostic group, condition, S1 laterality, and all interactions as fixed effects. Our random effects structure included variances for the intercepts and variances of the slopes for condition, S1 laterality, and target configuration.

We evaluated S1 latency (latency from T1 to S1 onset), error (Euclidian distance of saccade endpoint to target), and amplitude (Euclidian distance of saccade start to endpoint). Next, we evaluated S2 error, CD loss amplitude, and CD loss direction. Finally, we predicted, in 2 separate models, S2 amplitude and angle from the predictors and from expected S2 amplitude and angle, respectively. In these models, we wanted to explore which variables influenced the relationship between expected and actual S2 amplitude or angle. To account for individual differences in performance, we preserved the random effects structure of our basic model but also included main and interaction effects of expected S2 angle or amplitude, as applicable.

In subsequent models, we assessed the potential moderating effects of anomalous self-related experiences (IPASE scores) and clinical symptoms (SAPS, SANS, and SAPP scores) on double-step task performance. Our random effects structure was identical to our basic models. Given large group differences in total IPASE scores, we tested clinical and control groups in separate models for this predictor. To account for multiple testing (4 symptom predictors), we used a Bonferonni corrected α value of 0.0125.

Results

Overall, 66 patients with schizophrenia or schizoaffective disorder, 37 patients with BDP, and 42 controls completed the double-step task. After exclusion for task performance (Appendix 1, Methods), we had a final sample of 62 patients with schizophrenia, 34 patients with BDP, and 42 controls (Table 1). Age, sex, and maternal education did not differ between groups. Patient groups did not differ in illness duration

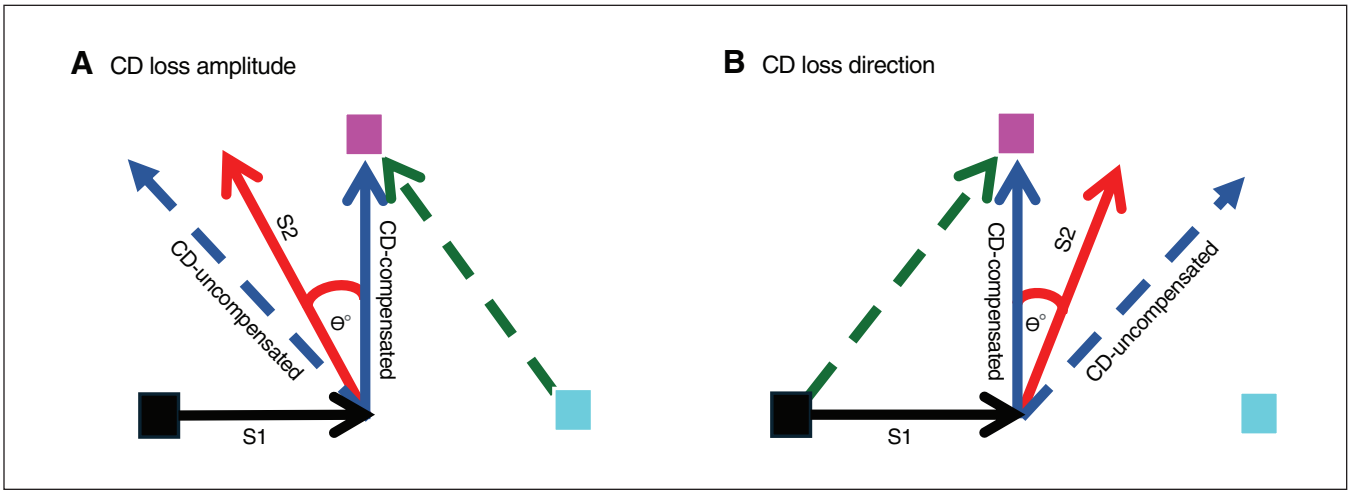

Figure 2: Schematic outlining computation of corollary discharge (CD) loss on trials when saccade 1 (S1) is hypometric. Impaired use of CD signals may manifest in saccades to target 2 (T2) that are biased in a direction that reflects a failure in using CD to compensate for either (A) variability in the S1 endpoint or (B) moving the eyes from fixation. For trials in which S1 (black line) was hypometric, we computed the angle (θ) between the actual saccade 2 (S2) vector (red line) and expected S2 vector (CD-compensated, blue solid line). We also computed the vector between target 1 (T1) and T2 (i.e., the saccade vector that would have been produced had the participant failed to compensate for S1 hypometricity, indicated by dashed green line in panel A) and the vector between fixation and T2 (i.e., the vector that would have been produced had the participant failed to compensate for having moved the eyes from fixation, indicated by dashed green line in panel B). We classified trials based on the direction of the deviation of the S2 vector (red line) from the expected vector (i.e., the saccade that would accurately move gaze to T2; solid blue line). Trials in which the S2 vector was closer to the saccade vector between T1 and T2 (dashed blue line in panel A) were labelled CD loss amplitude, and trials in which the S2 vector was closer to the vector between fixation and T2 (dashed blue line in panel B) were labelled CD loss direction. On CD loss amplitude trials, we calculated the angular deviation between the actual S2 vector (red line) and the expected saccade (CD-compensated, solid blue line) and indexed the degree to which S2 was biased in the direction predicted by a failure to compensate for S1 variability. (B) On CD loss direction trials, we calculated the angular deviation between the actual S2 vector (red line) and the expected saccade (CD-compensated, solid blue line) and indexed the degree to which S2 was biased in the direction predicted by a failure to use CD to compensate for moving the eyes from fixation.

or proportion using antipsychotics; however, chlorpromazine equivalent doses were higher among patients with schizophrenia. This group also had higher IPASE total scores than patients with BDP, who in turn had higher scores than controls (Table 1). Patients with schizophrenia had more severe clinical symptoms than patients with BDP. There were no group differences in S1 latency; however, both patient groups were significantly less accurate than controls at targeting T1, but only on extraretinal trials (Appendix 1, Results).

T2 error

In tests of T2 error, we observed a significant main effect of group ($F_{2,131}$ = 8.40, p < 0.001) and condition ($F_{1,136}$ = 556.15, p < 0.001) on participants' ability to accurately look at T2 (Figure 3). Consistent with our hypothesis, when holding all other factors constant, T2 error was higher in the schizophrenia group (mean 2.98°, standard error of the mean [SEM] 0.09°) than the control group (mean 2.45°, SEM 0.11°). The BDP group was intermediate between the other groups but did not significantly differ from them (mean 2.74°, SEM 0.12°). Similarly, we found that participants made significantly more T2 errors on extraretinal trials (mean 3.79°, SEM 0.14°) than on retinal trials (mean 1.99°, SEM 0.14°). We found a significant 2-way interaction between condition and group ($F_{2,136}$ = 4.14, p = 0.018). Simple slope analyses revealed that the group effect was only significant on extraretinal trials. On these trials, T2 error was higher among patients with schizophrenia (mean 4.11°, SEM 0.11°) and those with BDP (mean 3.79°, SEM 0.14°) than controls (mean 3.30°, SEM 0.13°). These results suggest that people with a history of psychosis made less accurate saccades when they had to rely on extraretinal information, suggesting impaired CD. Given group differences in targeting T1, we repeated this model including S1 error as a factor. The group by condition effect remained significant (Appendix 1, Results).

We evaluated whether severity of psychotic symptoms moderated T2 error. Contrary to our hypothesis, we found no significant effect of positive (SAPS), negative (SANS), or passivity (SAPP) symptoms on T2 error.

In our models exploring whether task performance varied as a function of anomalous self-experiences, we found a significant interaction between condition and IPASE scores for controls ($F_{1,31}$ = 7.62, p = 0.009). Simple slope analyses indicated that controls with higher levels of anomalous self-experiences made significantly less accurate saccades, but only on extraretinal trials ($F_{1,48}$ = 6.72, p = 0.01) (Figure 4). We also found a significant 3-way interaction between S1 laterality, S1 error, and IPASE in the control group ($F_{1,31}$ = 9.70, p = 0.005). To explore this interaction, we first examined the S1

Table 1: Demographic and clinical characteristics of the study sample

Characteristic	Mean ± SD*			$F/t/\chi^2$	p value	Pairwise comparisons
	Patients with SCZ $n = 62$	Patients with BDP $n = 34$	Controls $n = 42$			
Age, yr	35.7 ± 10.9	35.9 ± 10.5	35.9 ± 9.8	0.005	1.0	
Sex, no (%) of participants				0.62	0.7	
Female	26 (41.9)	17 (50.0)	18 (42.9)			
Male	36 (58.1)	17 (50.0)	24 (57.1)			
Race or ethnicity, no (%) of participants				31.38	0.002	
Asian or Indian	0 (0.0)	0 (0.0)	4 (9.5)			SCZ > BDP = HC
Black	22 (35.5)	3 (8.8)	5 (11.9)			
Native American	1 (1.6)	0 (0.0)	0 (0.0)			
White	33 (53.2)	26 (76.5)	29 (69.0)			
Multiracial	4 (6.4)	0 (0.0)	2 (4.8)			
Other	2 (3.2)	5 (14.7)	2 (4.8)			
WTAR, IQ	94.7 ± 27.4	106.2 ± 9.7	104.8 ± 24.4	3.62	0.03	SCZ < BDP = HC
Education, yr	13.5 ± 2.4	14.8 ± 1.9	17.0 ± 2.5	29.4	< 0.001	SCZ < BDP < HC
Maternal education, yr	13.9 ± 3.9	15.2 ± 2.8	14.0 ± 4.3	1.47	0.2	
IPASE	138.9 ± 44.8	114.1 ± 43.4	76.0 ± 20.0	26.92	< 0.001	SCZ > BDP > HC
Illness duration, yr	9.2 ± 9.7	12.8 ± 9.7	–	1.72	0.09	
Antipsychotic use, no (%) of participants				2.35	0.1	
Yes	52 (83.9)	24 (70.6)	–			
No	10 (16.1)	10 (29.4)	–			
CPZ equivalent dose†, mg	314.5 ± 374.2	127.7 ± 144.8	–	2.79	0.006	
BPRS	44.9 ± 13.3	35.2 ± 9.4	–	3.99	< 0.001	
YMRS	10.1 ± 7.3	6.0 ± 8.2	–	2.39	0.02	
HAMD	10.8 ± 7.7	8.8 ± 6.8	–	1.17	0.2	
SAPS total score	21.8 ± 16.7	9.3 ± 12.4	–	3.68	< 0.001	
SANS total score	26.2 ± 20.4	13.7 ± 14.3	–	3.44	0.002	
CGI severity label‡	Moderately ill	Normal	–	–	–	
SAPP						
Lifetime	2.5 ± 2.6	1.8 ± 2.5	–	1.22	0.3	
Current	0.8 ± 1.7	0.2 ± 0.5	–	2.58	0.01	

BDP = bipolar disorder with psychotic features; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; CPZ = chlorpromazine; HAMD = Hamilton Depression Rating Scale; HC = healthy control; IPASE = Inventory of Psychotic-like Anomalous Self-Experiences; SANS = Scale for the Assessment of Negative Symptoms; SAPP = Scale for the Assessment of Passivity Phenomena; SAPS = Scale for the Assessment of Positive Symptoms; SCZ = schizophrenia or schizoaffective disorder; SD = standard deviation; WTAR = Wechsler Test for Adult Reading; YMRS = Young Mania Rating Scale.
*Unless indicated otherwise.
†CPZ equivalent doses were calculated in accordance with published guidelines.[21–23]
‡Clinical Global Impressions severity labels derived by converting SAPS and SANS scores into Positive and Negative Syndrome Scale equivalents.[31,32]

error by IPASE effect in left- and right-presented trials separately and found the interaction was significant only on right-presented trials. We then calculated estimates based on high and low S1 error for right-presented trials and found no significant effect of IPASE for either the high- or low-error group.

Angular deviance

We tested whether the angle of S2 was biased in a direction predicted by failing to compensate for variability in S1 endpoint on trials where S1 was hypometric (CD loss amplitude). We found significant main effects of group ($F_{2,132} = 9.11$, $p < 0.001$) and condition ($F_{1,134} = 155.55$, $p < 0.001$), as well as a significant interaction of group by condition ($F_{2,134} = 3.46$, $p = 0.03$). Consistent with predictions, participants had greater CD loss amplitude on extraretinal trials (mean 12.85°, SEM 0.84°) than on retinal trials (mean 6.73°, SEM 0.81°). The main effect of group is best explained in the context of the group by condition interaction. The angle of S2 was more biased in the direction predicted by a failure to fully compensate for S1 hypometricity in the schizophrenia (mean 15.21°, SEM 0.63°) and BDP groups (mean 12.85°, SEM 0.84°) compared with the control group (mean 10.55°, SEM 0.74°), consistent with compromised CD signalling.

We next tested whether symptom severity and anomalous self-experiences influenced how well participants were able to compensate for hypometricity in their saccades to T1. There was a significant main effect of IPASE ($F_{1,33} = 8.18$,

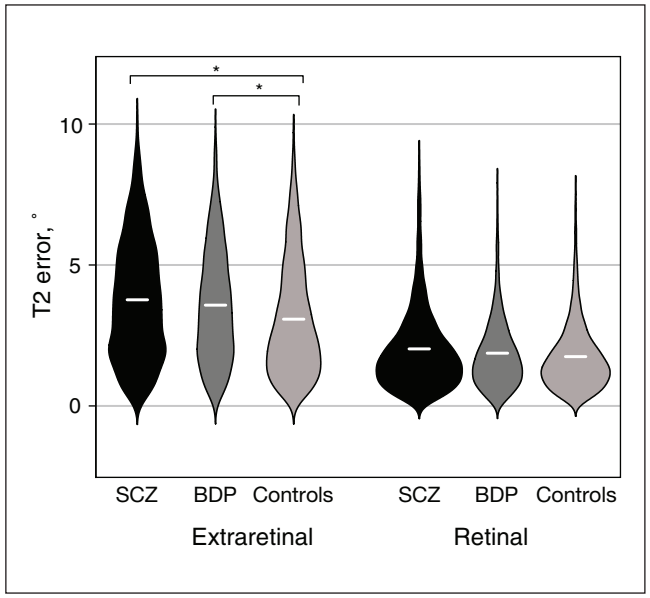

Figure 3: Target 2 (T2) error on extraretinal and retinal trials. White bar represents the mean. Supporting data are presented in Appendix 1, Results. BDP = bipolar disorder with psychotic features; SCZ = schizophrenia. *$p < 0.05$.

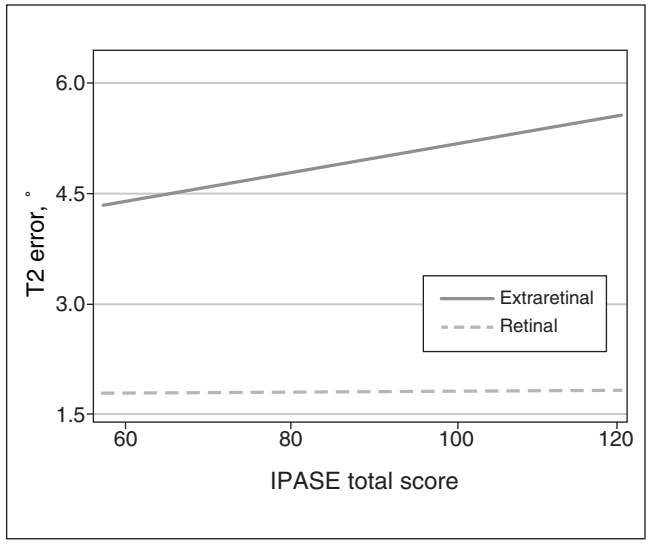

Figure 4: Target 2 (T2) error and scores on the Inventory of Psychotic-like Anomalous Self-Experiences (IPASE) among controls. Higher IPASE scores predicted greater T2 inaccuracy among controls, but only on extraretinal trials.

$p = 0.007$) and interaction effect of IPASE by condition ($F_{1,33} = 8.03$, $p = 0.008$) among controls. This main effect is best understood in the context of the interaction; higher IPASE scores predicted higher values of CD loss amplitude, but only on extraretinal trials ($F_{1,57} = 14.23$, $p < 0.001$) (Figure 5). In comparison, IPASE scores were not a significant predictor of CD loss amplitude among patients with schizophrenia or BDP. In addition, we found no effect of positive, negative, or passivity symptoms on CD loss amplitude.

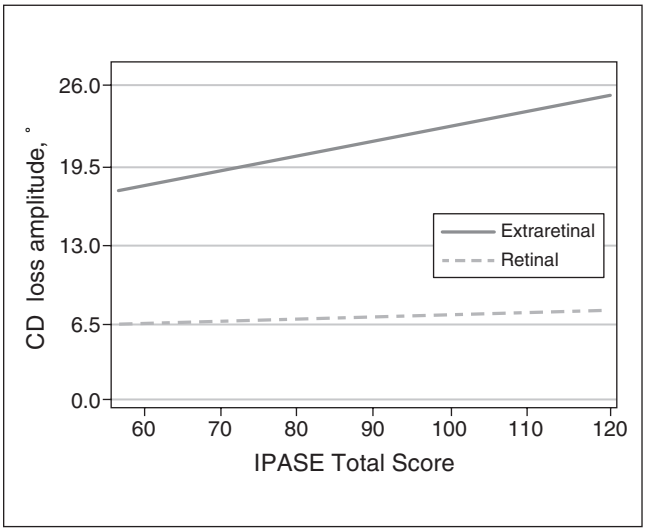

Figure 5: Corollary discharge (CD) and scores on the Inventory of Psychotic-like Anomalous Self-Experiences (IPASE) among controls. Higher IPASE scores predicted higher CD loss amplitude among controls, but only on trials requiring CD.

Finally, we tested whether the angle of S2 was related to difficulty in compensating for moving the eyes away from fixation (CD loss direction). We found significant main effects of group ($F_{2,132} = 5.27$, $p = 0.006$) and condition ($F_{1,131} = 446.29$, $p < 0.001$) but no significant interaction effect for group by condition. Across our sample, participants showed a reduced ability to compensate for moving the eyes toward T1 on extraretinal trials compared with retinal trials. Furthermore, patients with schizophrenia (mean 11.11°, SEM 0.38°) were less able to compensate for moving their eyes toward T1 than controls (mean 9.13°, SEM 0.44°), whereas patients with BDP (mean 10.31°, SEM 0.50°) did not differ significantly from either group.

Testing the influence of psychotic symptom severity on CD loss direction revealed no effect of SAPS, SAPP, or SANS on CD loss direction values (all $p > 0.01$). Furthermore, there was no significant effect of IPASE scores on CD loss direction in any group.

Compensating for S1 endpoint variability

In our final set of analyses, we examined the extent to which participants compensated for variability in the endpoint of the saccade to T1. Full model results are reported in Appendix 1, Results.

First, we tested the ability of participants to adjust the amplitude of their second saccade (Figure 6). We found a significant main effect of expected amplitude ($F_{1,134} = 926.60$, $p < 0.001$). Holding all other factors constant, a 1° increase in expected S2 amplitude predicted a 0.64° increase in actual amplitude, consistent with our expectations of a close relationship between actual and expected S2 amplitude. We also found a significant 2-way interaction between condition and expected amplitude ($F_{1,133} = 5.21$, $p = 0.02$). Expected amplitude

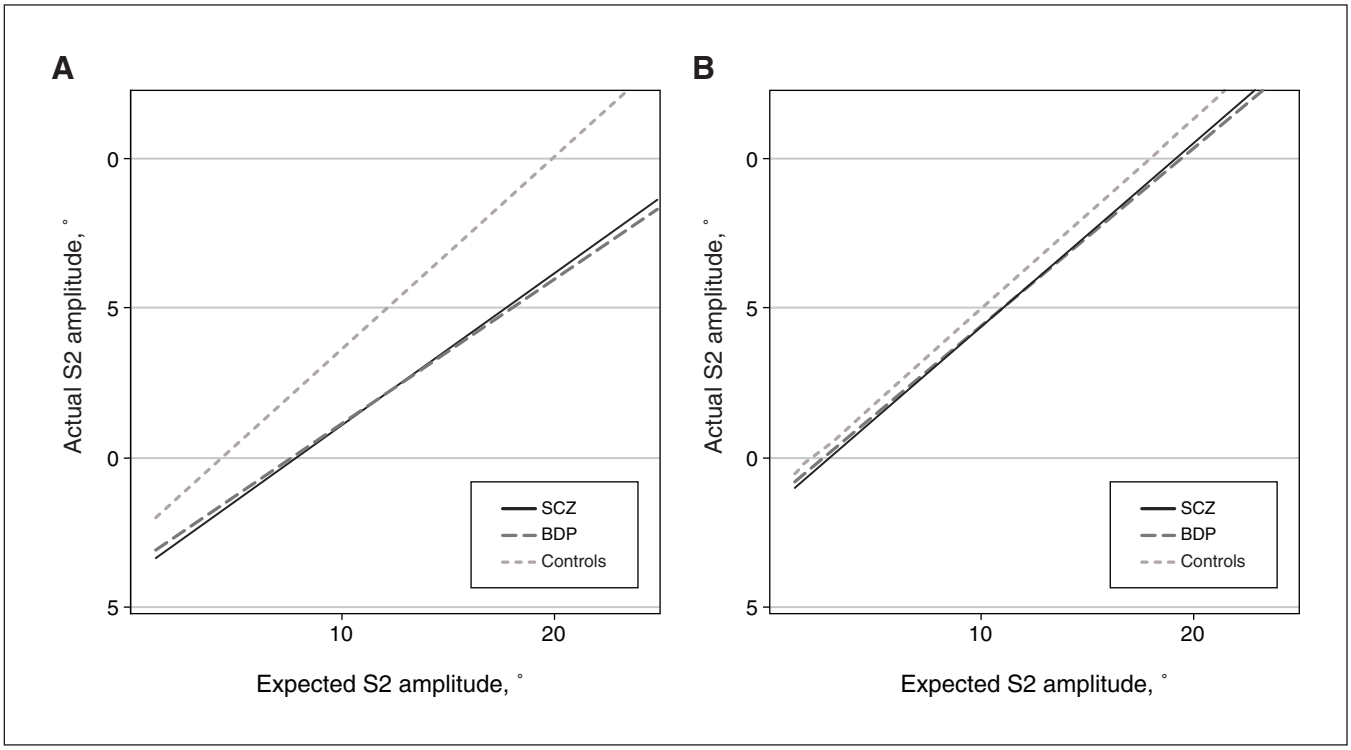

Figure 6: The ability of participants to adjust the amplitude of their second saccade (S2) in (A) extraretinal and (B) retinal trials among patients with schizophrenia (SCZ), patients with bipolar disorder with psychotic features (BDP), and controls. Some participants were unable to tolerate a full block of 96 trials. In these cases, participants completed more than 4 blocks with a reduced number of trials each such that the total number of trials did not exceed 384. Supporting data are presented in Appendix 1, Results.

was a better predictor of actual amplitude on retinal trials than extraretinal trials. This finding is consistent with predictions as participants had access to visual information to compensate for variability in S1 endpoint and correctly localize T2 on retinal trials. There were no other significant main or interaction effects involving expected amplitude.

Next, we evaluated whether symptom severity moderated the relationship between expected and actual amplitude. We followed up only on interaction terms that involved symptom severity scores and expected amplitude. Our models revealed a significant 3-way interaction between S1 laterality, SANS, and expected amplitude ($F_{1,74} = 8.92$, $p = 0.004$). To investigate how negative symptom severity moderated the relationship between expected and actual amplitude, we tested the interaction effect of expected amplitude by SANS on left- and right-presented stimuli separately. We found no significant effect of expected amplitude by SANS for either left- ($F_{1,134} = 3.62$, $p = 0.06$) or right-presented ($F_{1,138} = 0.83$, $p = 0.4$) stimuli. We found no significant effect of SAPS, SAPP, or IPASE scores on participants' ability to adjust the amplitude of their second saccade.

In our model exploring the degree to which expected S2 angle explained variability in actual S2 angle, we found interactions between expected angle and both condition ($F_{1,129} = 8.26$, $p = 0.005$) and laterality ($F_{1,129} = 5.13$, $p = 0.02$), such that expected angle was a better predictor of actual angle on extraretinal conditions and of when T1 was presented to the right of fixation. These findings contrast with a significant interaction of condition by S1 laterality by expected angle ($F_{1,137} = 8.33$, $p = 0.005$), which revealed that the effect of condition by expected angle was significant only for left-presented trials. Finally, we found a significant effect of group by S1 laterality by expected angle ($F_{2,128} = 8.33$, $p = 0.02$). To break down this interaction, we first evaluated whether there was a significant effect of group by expected angle in left- and right-presented trials separately. We found a significant effect for left-presented trials only ($F_{2,195} = 4.27$, $p = 0.02$). Expected angle was a better predictor of actual angle for the schizophrenia group relative to the control group, whereas the BDP group did not differ significantly from either group. This finding was surprising, given our previous observation that people with psychosis had significantly greater difficulty with compensating for variability in S1 endpoint. To test whether this contradiction was related to differences in trials that were used in these 2 different analytic samples (Appendix 1, Results), we repeated the analyses including only trials where S1 was hypometric and the trial was categorized as CD loss amplitude. When restricting our analysis to only this subset of trials, we found no significant group differences in the predictive ability of expected S2 angle on actual S2 angle.

In our models investigating the potential moderating effects of symptom severity on the ability to adjust the angle of the second saccade to compensate for variability in the first saccade, we found no significant interactions that included symptom severity and expected S2 angle.

Discussion

In this study, patients with schizophrenia, patients with BDP, and healthy controls performed a double-step task designed to isolate and measure the influence of extraretinal information (i.e., CD signalling) on motor preparation. Participants looked at 2 visual targets flashed in rapid succession. Trials varied in their stimulus timings, yielding 2 conditions whereby participants were or were not required to rely on extraretinal information to make an accurate saccade to the second target. Our findings were partly in line with the reduced influence of CD on motor preparation in schizophrenia and BDP in a way that was relevant to clinical status. These findings replicate previous reports of impaired double-step task performance in schizophrenia[19] and align with a broader literature documenting the reduced influence of oculomotor CD in schizophrenia[12,33] and recent findings suggesting altered trans-saccadic perception related to psychotic symptoms in schizophrenia and BDP.[16,34] Our results add to a small but growing literature indicating that impaired CD signalling may be a transdiagnostic marker of psychosis.[15,16]

Consistent with the notion of impaired CD signalling, we found patients with schizophrenia or BDP were less accurate in localizing the second target but only in the extraretinal condition. These effects could not be explained by problems localizing the first target. To probe the influence of CD more specifically, we performed additional analyses aimed at understanding the nature of less accurate second saccades, given that a failure to appropriately send or use CD in this task may manifest in (at least) 2 ways, namely that participants may fail to compensate either for having moved the eyes at all or for their gaze not landing on the second target.[35]

To distinguish between these 2 types of CD loss, we divided trials into those whose second saccade angle was more biased in the direction predicted by not moving the eyes at all versus those where participants were not compensating for the first saccade. In our previous study, we found that the second saccades' angles were more biased in the direction predicted by failing to compensate for moving the eyes at all.[19] In the current study, we observed such an effect in both schizophrenia and BDP; however, this bias was evident regardless of whether extraretinal information was required. Thus, this bias in the direction of failing to compensate for moving the eyes away from fixation may reflect a more general visuomotor weakness, rather than a specific CD impairment. We did, however, find that the bias in the angle of second saccades in schizophrenia and BDP were consistent with a failure to compensate for variability in S1, but only on trials requiring CD. Although this bias could indicate an impairment in CD signalling, we observed no such bias in schizophrenia in our previous study.[19] Discrepant findings between studies may reflect greater power to detect effects in the current study, paradigm differences, analytical differences, or differences in sample composition.

In our final set of analyses, we evaluated the extent to which participants adjusted the angle or amplitude of their second saccade to compensate for variability in their first saccade. This was accomplished by analyzing the relationship of the actual second saccade angle or amplitude as a function of the expected saccade angle or amplitude. We found essentially no group differences in these relationships. This finding appears to directly contradict our observation that patients with schizophrenia or BDP were less accurate than controls at adjusting the angle of their second saccade to compensate for variability in the first saccade. However, there are notable differences in those 2 analyses. Our measure of angular deviation included only trials in which the first saccade was hypometric and that were further characterized as a loss of information related to the planned saccade kinematics; however, the analysis of actual and expected saccade angle included all trials. To address this difference, we repeated our analysis of actual and expected saccade angle using only trials we classified as CD loss amplitude. We found no group differences in the relationship between the actual and expected angle. Our findings were nonsignificant, but this new analysis produced a tighter relationship between actual and expected angle. Thus, the inclusion of all trials may have contributed some noise to our models but cannot account for our discrepant findings.

As noted, CD signalling is believed to be a key mechanism that engenders a sense of agency, and we therefore predicted that reduced influence of CD would be associated with greater levels of psychotic and passivity symptoms and anomalous self-experiences in schizophrenia and BDP. We did not observe any significant relationships between these symptoms and measures of CD loss. The lack of compelling symptom relationships is surprising as previous literature supported a relationship between positive symptoms and oculomotor CD signalling.[13,16] However, relationships between symptoms and behavioural measures are infrequently observed because symptom presentation can be confounded by various factors such as medication effects and willingness to divulge them to a rater.[36] Moreover, because studies reporting significant relationships relied on different paradigms — more specifically, the influence of CD on visual perception rather than motor planning — it is possible that inconsistencies in these symptom relationships are related to task differences. Supporting this idea, other studies that used a double-step paradigm also found no significant relationship between positive symptoms and performance.[19] Thus, our lack of significant symptom relationships may suggest that current symptom severity is related to the influence of CD on perception rather than motor planning.

Alternatively, sample characteristics may have influenced our ability to detect significant relationships between symptoms and CD measures. Our clinical groups were composed of stable outpatients who reported relatively low levels of symptoms. Thus, the null relationships between psychotic symptoms and measures of CD may have been confounded by the limited range of symptoms. Arguing against null effects being related to clinical stability, however, are findings of significant relationships between symptoms and oculomotor CD signalling in stable outpatient samples.[13,16]

Relationships between CD signalling and anomalous self-experiences were more compelling but largely restricted to controls, consistent with a recent study investigating the influence of oculomotor CD signals on trans-saccadic visual localization[16] and literature reporting a significant influence of anomalous self-experiences on auditory speech perception in schizophrenia.[36] As we predicted, controls with high levels of anomalous self-experiences had significantly lower accuracy on trials requiring CD; this lower accuracy was related to greater difficulty with compensating for variability in the S1 endpoint and for moving the eyes away from fixation, suggesting that dysfunctional CD signalling could give rise to these self-experiences. Convincing relationships between performance and anomalous self-experiences were not observed in schizophrenia or BDP. High IPASE scores may relate more specifically to psychotic-like symptoms in community samples,[37] while capturing a wider range of psychopathology in clinical samples.[38] Thus, our IPASE findings among controls may reflect a relationship between self-disturbance and CD signalling that was obscured by other factors in schizophrenia and BDP, such as medication effects.

Explanations other than altered CD signalling could account for our findings. Poor localization of the second target, particularly on extraretinal trials, could reflect the influence of general visual impairments on task performance in schizophrenia and BDP; this was supported by the significantly lower accuracy in patient groups when looking toward T1 and the increased prevalence of visual impairments among people with psychosis.[39] Furthermore, noisy localization of T1 may be expected to relate to noisy localization of T2, but not to systematic biases in a direction predicted by a loss of CD. Combined, these findings suggest that our pattern of results cannot be solely explained by general visual impairments. Alternatively, our findings could be explained by group differences in task-solving strategies. Although the double-step task is well validated as a measure of CD signalling, it has been suggested that people can solve the task by storing the T1–T2 vector in working memory, thereby eliminating the need to rely on CD signalling to accurately localize T2.[18] In this case, our observed group differences would reflect differences in cognitive function rather than CD dysfunction. However, it is unclear how differences in working memory could explain the significant relationship between performance on these extraretinal trials and self-disturbance symptoms among controls. Furthermore, the rapid stimulus presentation on extraretinal trials would have made preparation of a saccade vector based on visual representation in working memory more challenging.

Limitations

Our clinical group comprised stable outpatients, many of whom were taking antipsychotic medication. This sample selection likely affected our study in several meaningful ways. For example, the stable status of our clinical group and relatively low psychotic and passivity symptoms may have muted true relationships between CD measures and specific psychotic symptoms. Future studies should test symptom–performance relationships in an inpatient sample. In addition, group differences between clinical and non-clinical groups could reflect medication effects rather than disruptions in CD signalling. However, this explanation is unlikely as no evidence suggests antipsychotic medication influences CD signalling. In addition, if the poorer performance in schizophrenia and BDP was a consequence of medication use, we would expect to see significant differences in the performance between patients with BDP and those with schizophrenia because patients in the schizophrenia group were taking much higher doses of antipsychotic medication. Yet, in our analysis, the performance of the BDP group was similar to that of the schizophrenia group.

Finally, the variability in T2 accuracy in the extraretinal condition suggests our task may have been too challenging for our clinical sample, thereby adding noise to estimates of CD that relied on accuracy of gazing at T2. Poorer T1 localization on extraretinal trials in clinical groups should also be noted as a limitation as it suggests a more general visuomotor impairment, at least using the current task parameters. Although group differences in task performance remained after controlling for error in localizing T1, difficulty in localizing T1 may have contributed substantial noise to our estimates of the influence of CD, which could explain some of the inconsistencies in our results. As such, future studies would benefit from adapting the current paradigm to ensure participants are able to accurately localize T1. Based on these limitations and others, we must also consider that, although the double-step task is one of the most widely used measures to behaviourally assess CD transmission, it may not be an ideal task to use in clinical populations. Reasons for this include variability in visuomotor task performance, the large number of trials that must be performed in dark or near-dark conditions, and findings regarding CD not being unequivocally clear.

Conclusion

Our findings provide additional, albeit modest, support that CD alterations may be a transdiagnostic mechanism of psychosis and offer the opportunity to understand this mechanism at the level of neural circuits. The pathway between the superior colliculus and frontal eye fields via the mediodorsal thalamus is critical for relaying CD related to eye movements, and temporary inactivation of the mediodorsal thalamus in nonhuman primates impairs double-step performance in a similar way to what we observed in schizophrenia and BDP. Thus, the reduced ability of patients with schizophrenia or BDP to use CD to accurately perform the double-step task may reflect disruptions in fronto–thalamocortical activity. Future studies may wish to build on our findings by evaluating the extent to which disruptions in CD predict or precede the onset of psychosis. Given our findings of altered CD among controls endorsing anomalous self-experiences, longitudinal studies examining CD signals in people at risk for psychosis may be especially valuable for understanding the mechanisms through which psychotic symptoms may arise.

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