Failure to use corollary discharge to remap visual target locations is associated with psychotic symptom severity in schizophrenia

Lara Rösler¹,⁴, Martin Rolfs², Stefan van der Stigchel³, Sebastiaan F.W. Neggers¹, Wiepke Cahn¹, René S. Kahn¹, Katharine N. Thakkar¹

¹ Department of Psychiatry, University Medical Center 3584 CX Utrecht, the Netherlands
² Bernstein Center for Computational Neuroscience & Department of Psychology, Humboldt Universität, 10099 Berlin, Germany
³ Department of Experimental Psychology, Helmholtz Institute, Utrecht University, 3584 CX Utrecht, The Netherlands
⁴ Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Goethe University, 60528 Frankfurt am Main, Germany

Abbreviated title: Corollary discharge for saccades in schizophrenia patients

Corresponding author
Katharine Thakkar, Ph.D.
Department of Psychiatry
University Medical Center Utrecht
Heidelberglaan 100
3584 CX Utrecht
The Netherlands
k.n.thakkar@umcutrecht.nl

Author contributions: All authors developed the study concept and M.R. designed the paradigm. Data collection was performed by L.R. Data analysis was performed by L.R. and K.N.T. L.R. and K.N.T. drafted the paper and all other co-authors provided critical revisions. All authors contributed to and approved the final version of the submitted manuscript.
Corollary discharge (CD) refers to "copies" of motor signals sent to sensory areas, allowing prediction of future sensory states. They enable the putative mechanisms supporting the distinction between self- versus externally-generated sensations. Accordingly, many authors have suggested that disturbed CD engenders psychotic symptoms of schizophrenia, which are characterized by agency distortions. CD also supports perceived visual stability across saccadic eye movements and is used to predict the post-saccadic retinal coordinates of visual stimuli—a process called remapping. We tested whether schizophrenia patients (SZP) show remapping disturbances as evidenced by systematic transsaccadic mislocalizations of visual targets. SZP and healthy controls (HC) performed a task in which a saccadic target disappeared upon saccade initiation and—after a brief delay—reappeared at a horizontally-displaced position. HC judged the direction of this displacement accurately, despite spatial errors in saccade landing site, indicating that their comparison of the actual to predicted post-saccadic target location relied on accurate CD. SZP performed worse, and relied more on saccade landing site as a proxy for the pre-saccadic target, consistent with disturbed CD. This remapping failure was strongest in patients with more severe psychotic symptoms, consistent with the theoretical link between disturbed CD and phenomenological experiences in schizophrenia.

Keywords: corollary discharge, efference copy, schizophrenia, saccadic eye movements, remapping
Introduction

To successfully distinguish between self-generated versus externally-generated experiences, sensory brain regions must be updated about motor commands in order to predict future sensory states. A match between predicted and actual sensations is theorized to engender a sense of agency over action (Feinberg, 1978; Frith, 1992). These predictions can be accomplished via corollary discharge (CD) — correlates of motor commands that are sent to sensory areas (Crapse and Sommer, 2008). CD signals attenuate sensations that match predictions, rendering unpredicted, externally-generated sensations more salient. Accordingly, disturbed CD might cause those psychotic symptoms of schizophrenia that are characterized by agency abnormalities (e.g. delusions of being controlled by aliens; Feinberg, 1978).

The most rigorous investigations of CD have been performed in the saccadic eye movement system. Saccadic CD signals convey spatial information about the impending eye movement to visual neurons, allowing these neurons to update activity in their retinotopic maps to compensate for the displacement of the retinal image that results from the impending saccade (Wurtz, 2008; Hall and Colby, 2011). While saccadic eye movements can provide valuable insight into the integrity of CD, few studies have investigated saccade-related CD in the oculomotor system of schizophrenia patients (Richard et al., 2014; Thakkar et al., in press).

Previous studies indicate that saccadic CD signals contain information about spatial error in the saccade vector (Collins et al., 2009; Ostendorf et al., 2010; Joiner et al., 2013). Support for this claim comes from a task in which a saccadic target disappeared upon saccade initiation and reappeared after a brief delay to the right or left of its pre-saccadic location, after which observers had to indicate their perceived direction of the shift. Results showed that these perceptual judgments were independent of the distance between saccade landing site and pre-saccadic target, henceforth referred to as landing site error, suggesting that observers did not use post-saccadic eye position as a proxy for the pre-saccadic target location. Rather, they appeared to use a CD signal associated with the actual (rather than intended) saccade vector to correctly remap the pre-saccadic target location and accurately localize the post-saccadic target. Accurate performance on this task, therefore, requires an intact CD signal (see Figure 1A).
Here we used this same paradigm to investigate oculomotor CD signals in schizophrenia. We hypothesized that CD dysfunction would result in a failure to accurately remap the pre-saccadic target location. Consequently, patients would rely more on saccadic landing site to estimate the direction of the target displacement (Figure 1B, top). As saccadic landing site is generally an unreliable proxy of the pre-saccadic target location, we expect patients to be less precise in judging the direction of the target displacement (Figure 1B, bottom). Moreover, as CD dysfunction has been purported to give rise to the failure to distinguish internally versus externally generated sensory experiences, and psychotic symptoms are characterized by such agency disturbances, we further hypothesized that both of these effects—increased reliance on saccade landing site and reduced precision of perceptual judgments—would correlate with psychotic symptom severity.

Methods

Participants
We recruited 21 antipsychotic-medicated schizophrenia patients (SZP) from a longitudinal study (Genetic Risk and Outcome in Psychosis Investigators, 2011) and an outpatient psychiatric facility in the Netherlands. Schizophrenia or schizoaffective disorder diagnoses were based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and verified with the Comprehensive Assessment of Symptoms and History interview (Andreasen et al., 1992) or Schedules for Clinical Assessment for Neuropsychiatry, version 2.1 (Wing et al., 1990). Chlorpromazine (CPZ) equivalent antipsychotic dosages were calculated for each patient (Woods, 2003). Clinical symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). 20 healthy controls (HC) without a personal or family history of DSM-IV Axis I diagnosis were recruited via community advertisements. Criteria for participant exclusion were: history of head trauma or neurological illness, and recent substance abuse or dependence. One SZP was excluded based on performance (see Data Analysis). The remaining SZP and HC were matched for gender, age and handedness (Table 1). Although groups were not IQ-matched, there was no significant relationship between IQ and any CD measures in either group. All subjects gave written informed consent and were reimbursed for participation.
Apparatus and stimuli

Participants were seated in a dimly lit room, their head stabilized 68 cm away from a computer screen. Stimuli were black and red 0.2°-diameter dots on a grey background presented on a 24'' monitor (spatial resolution: 1920x1080 pixels, vertical refresh rate: 100 Hz). Eye position was recorded using an Eyelink 1000 (SR Research, Canada). Manual responses were recorded with a button box. Stimulus presentation and response collection were controlled with MATLAB (MathWorks, Natick, Massachusetts, USA), using the Psychophysics (Brainard, 1997) and EyeLink toolboxes (Cornelissen et al., 2002).

Design and procedure

Each trial (Figure 1C) began with participants fixating a red circle appearing at one of six equiprobable locations presented at an x-location of either 1° or -1° relative to center and at a y-location of either 0°, 1°, or -1° relative to center. This was done to reduce anticipation and stereotypical behavior (cf. Collins et al., 2009). Once fixation had been maintained for 200 ms, the target turned black and after a random delay of 500-1000 ms, jumped to a new location 10° to the left or right of fixation. Participants were instructed to look at the target as quickly as possible. Saccade initiation caused the target to be extinguished for 250 ms and then reappear at one of 13 equiprobable locations from -3° to 3°, in increments of 0.5°, to the left or right of the pre-saccadic location. Negative displacements indicate backward jumps (towards the initial fixation position), and positive displacements indicate forward jumps (further away from the initial fixation position). Upon target displacement, participants reported whether the post-saccadic target appeared to the right or left of the pre-saccadic target. Each combination of fixation position and post-saccadic target location was tested twice, one for each saccade direction, resulting in 156 total trials. The experiment duration varied across participants, and typically ranged from 15 to 30 minutes.

Online saccade detection was performed using a boundary technique. Saccade initiation was defined by the eyes leaving a 2° window around fixation. Saccades detected before target presentation triggered a warning on the screen and the trial was restarted.
Data analysis

Offline, saccades were detected using the automated EyeLink procedure (velocity>30°/sec, acceleration>8000°/sec², motion>0.1°). Response saccades were defined as the first saccade following pre-saccadic target presentation that were larger than 1° and brought gaze within 8° of the pre-saccadic target. If observers made a saccade before pre-saccadic target presentation or a key press before post-saccadic target presentation, the trial was excluded. There was no difference between the number of excluded trials between HC and SZP (HC: mean=2.4%, s.d.=2.4%; SZP: mean=2.8%, s.d.=3.6%; t(38)=0.53, p=0.60). Although observers reported target jumps as left or right, we recoded responses as forward and backward when subjects perceived the post-saccadic target as jumping away from and towards the initial fixation point, respectively.

We used signal detection theory (Green and Swets, 1966) to evaluate overall response accuracy in order to exclude subjects on the basis of performance. We defined hit rate as the proportion of forward responses for forward jumps and false alarm rate as the proportion of forward responses for backward jumps (due to the lack of a correct response alternative, the zero displacement condition was excluded for this analysis). The sensitivity index (d') was calculated as the z-score of the hit rate minus the z-score of the false alarm rate. Subjects were excluded from analysis if d' was smaller than 1, resulting in the exclusion of one SZP.

To evaluate the task performance of each individual, we collapsed trials across initial fixation positions and saccade directions and calculated the percentage of forward responses as a function of target displacement. A 4-parameter logistic function of the following form was fit to this data:

\[ f(x) = a + (d - a)/(1 + 10^{b(x-c)}) \]

where a and d are minimum and maximum values, respectively; b is the slope; and c is the point midway between a and d. Furthermore, we determined the perceptual null location (PNL) for each individual. The PNL is the displacement at which subjects did not perceive a difference between the pre- and post-saccadic target location, i.e., the post-saccadic target location for which observers reported an equal proportion of forward and backward jumps (50% point on the logistic function).

Moreover, we derived the just-noticeable difference (JND) from each participant’s logistic function to measure the extent to which participants relied on target displacement to make perceptual judgments.
JND was calculated as the difference in target displacements between the points at which the function reached 50% versus 75% of its full growth. Smaller JNDs indicate greater precision and, accordingly, greater sensitivity to target displacements.

To investigate whether landing site error was associated with perceptual judgments, we collapsed trials across target displacements for each participant and divided landing site errors into the same bins for each observer. These bins ranged from -8° to 8° from the pre-saccadic target, in increments of 0.5°. For each individual, we then calculated the slope of the relationship between the mean saccade landing site of each bin and the corresponding proportion of forward responses. Since the number of included trials varied per bin, we used a weighted linear regression to derive the slope parameters, weighting perceptual judgments according to the number of observations in each bin.

**Statistical analysis**

To test for group effects and asymmetries in response kinematics, we assessed RTs (saccade and perceptual judgment), saccade amplitude, saccade peak velocity, and saccade peak acceleration using separate mixed-design ANOVAs, including group as a between-subjects factor and response direction as a within-subjects factor in the model. For simple group comparisons, we first assessed normality of the dependent measures within diagnostic groups using Shapiro-Wilk tests. If the dependent measure was normally distributed in both groups, we evaluated group performance differences using two-tailed independent-sample t-tests and computed Pearson’s product-moment correlation coefficients (r) to evaluate relationships between continuous measures. For non-normally distributed measures, we used independent-samples Mann Whitney U tests to evaluate group differences, and Spearman’s rho (rs) to evaluate relationships between continuous measures.

With respect to correlations between clinical measures and performance measures, our only two *a priori* correlations of interest were between PANSS positive scores and both JNDs of the psychometric function and the slope of the function plotting perceptual judgments against landing site error. Thus, we evaluated these correlations at an uncorrected alpha level of 0.05. Six additional exploratory analyses were performed. Correlations between both JND and the slope of the forward response-landing site error function and both negative symptom severity and standardized medication dose were computed. In
addition, mean saccade amplitude was correlated with both positive and negative symptom severity. These exploratory correlation analyses were assessed at a Bonferroni-corrected alpha level of 0.008 (0.05/6), although uncorrected p-values are still reported. All other statistical tests were evaluated at an alpha level of 0.05.

**Results**

**Saccade and manual response metrics**

As a first step, we report response kinematics separated by group and saccade direction (Table 2). Saccade RTs did not differ by saccade direction (F(1,38)=2.79, p=0.10) or group (F(1,38)=0.23, p=0.64), and there was no group-by-direction interaction effect (F(1,38)=0.001, p=0.97). On the other hand, there was an effect of both group (F(1,38)=8.28, p=0.007) and direction (F(1,38)=14.80, p=0.0004) on saccade amplitude. Rightward saccades were larger than leftward saccades, and SZP made shorter saccades than HC. There was no significant group-by-direction interaction (F(1,38)=0.07, p=0.79).

Consistent with directional effects on amplitude, there was also a significant effect of direction on saccade peak velocity (F(1,38)=7.24, p=0.01). Rightward saccades were faster than leftward saccades. However, there was no significant effect of group (F(1,38)=0.08, p=0.78) on peak velocity, nor a group-by-direction interaction effect (F(1,38)=0.64, p=0.43). Saccade peak acceleration did not differ as a function of either group (F(1,38)=0.10, p=0.76) or direction (F(1,38)=0.002, p=0.96), and there was no group-by-direction interaction effect (F(1,38)=0.48, p=0.49). Finally, although saccade RTs did not differ between groups, RTs of perceptual judgments were significantly longer in SZP than HC (F(1,38)=11.2, p=0.002). There was, however, no effect of response direction on RTs (F(1,38)=0.60, p=0.44) and no group-by-direction interaction effect (F(1,38)=0.03, p=0.87).

Thus, although there were some effects of saccade direction on movement kinematics, these parameters were not differentially affected by saccade direction in controls and patients. That is, we did not observe any significant group-by-saccade direction interaction effects. Moreover, we had no *a priori* hypotheses regarding saccade direction. Therefore, unless otherwise specified, we collapsed across saccade directions for subsequent analyses.
Perceptual judgments as a function of target displacement

Figure 2A shows the fit of the 4-parameter logistic function plotting the percentage of forward reports as a function of target displacement for each participant (group-averaged psychometric functions are shown in Figure 2B). These functions provided very good fits to the data, as measured by $R^2$ values, in both healthy controls (mean=0.98, s.d.=0.02) and schizophrenia patients (mean=0.94, s.d.=0.07).

One-sample t-tests revealed that the PNL was significantly greater than zero in both HC (mean=0.32°, s.d.=0.48°, $t(19)=2.9$, $p=0.008$) and SZP (mean=0.25°, s.d.=0.53°, $t(19)=2.1$, $p=0.048$), indicating that when there was no displacement, the post-saccadic target was perceived as moving slightly towards fixation. There were no group differences in PNL ($t(38)=0.4$, $p=0.69$).

We also examined the correlation between mean saccade amplitude and PNL across subjects. We expected that if saccade landing site was being used as a proxy for the pre-saccadic target location due to failed remapping, then participants with smaller saccade amplitudes would have reduced PNLs (Figure 1B; lower panel inset). That is, if a subject’s saccades were more hypometric, the post-saccadic target would appear forward of the saccade landing site more frequently. This would manifest in a psychometric function that was shifted to the left and, accordingly, a smaller PNL. Consistent with disturbed CD-based remapping, mean saccade amplitude was correlated with PNL in SZP ($r=0.50$, $p=0.03$), but not in HC ($r=-0.04$, $p=0.86$; Figure 2D). We used a Fisher r-to-z transformation to test our a priori hypothesis that this correlation was greater in SZP, and evaluated the significance using a one-tailed test. Indeed, we found that the correlation between mean saccade amplitude and PNL was significantly greater in SZP than HC ($Z=1.7$, $p=0.04$). Despite this correlation between mean saccade amplitude and PNL in SZP and group differences in mean saccade amplitude, there was still no group difference in PNL when conducting an ANCOVA and controlling for mean saccade amplitude ($F(1,37)=0.13$, $p=0.73$).

To investigate the extent to which participants relied on target displacement for their perceptual reports, we compared JNDs of the observer’s logistic functions. SZP had significantly larger JNDs than HC ($U=298$, $p=0.007$; inset in Figure 2B), indicating reduced precision of perceptual reports in SZP. There was no correlation between mean saccade amplitude and precision in either HC ($r_s=0.19$, $p=0.44$) or SZP ($r_s=-0.01$, $p=0.97$). Further, we observed a positive relationship between PNL and JND in HC.
(r_s=0.60, p=0.006), indicating that HC who perceived the target displacement more accurately were also more precise in their perceptual judgments. In SZP, we did not see a correlation between JND and PNL (r_s=0.08, p=0.75), suggesting either a dissociation of the precision (JND) and accuracy (PNL) of the response in SZP, or a reduced reliability of these measures in SZP.

We found no correlation between symptom severity and either PNL or JND (all r_s<0.34, p >0.14). At an uncorrected significance level, there was a trend towards a relationship between CPZ dose and the JND (r_s=-0.40, p=0.10). SZP with higher antipsychotic dosages tended to respond with higher precision, suggesting that medication may partially normalize performance.

Finally, we examined potential asymmetries in performance by testing whether PNL and JND were differentially affected by saccade direction in controls and patients. To this end, we fit separate logistic functions for leftward and rightward saccades in each participant and derived the JND and PNL for each saccade direction (Figure 2C). We submitted PNLs and JNDs to separate mixed-design ANOVAs, including diagnostic group as a between-subjects factor and saccade direction as a within-subjects factor. For the JND, there was a trend effect of group (F(1,38)=3.0, p=0.09), with SZP having a larger JND than HC. Note that when we fitted psychometric functions based on all trials (i.e., collapsed across leftward and rightward saccades), the group difference in JND was much more robust. We attribute this to more reliable curve fits when more trials were used for the estimation. There was no significant effect of saccade direction on JND (F(1,38)=0.03, p=0.85) and no group-by-saccade direction interaction effect. For the PNL, there was no significant effect of group (F(1,38)=0.03, p=0.87), which we also observed when we collapsed data across leftward and rightward saccades. However, there was a trend-level main effect of saccade direction (F(1,38)=3.1, p=0.09) and a trend-level group-by-saccade direction interaction effect (F(1,38)=4.0, p=0.054). Post-hoc paired t-tests indicated that the PNL was smaller for leftward saccades than rightward saccades in SZP (t(19)=2.3, p=0.04) but not HC (t(19)=0.2, p=0.84). Nevertheless, the PNL did not differ significantly between HC and SZP for either leftward (t(38)=1.4, p=0.18) or rightward (t(38)=0.84, p=0.40) saccades.

Given asymmetries in the PNL, we calculated the correlation between PNL and mean saccade amplitude separately for leftward and rightward saccades within each group and used Raghunathan, Rosenthal, and Rubin’s (1996) test to evaluate the difference between two dependent correlations from a
single sample. The correlation between PNL and mean saccade amplitude was not different for leftward versus rightward saccades in either HC (Z=0.11, p=0.91) or SZP (Z=0.38, p=0.68), thus justifying our decision to collapse across saccade directions for this analysis.

Relationship between saccade landing site and perceptual judgments

To examine whether subjects used saccade landing sites to make perceptual judgments about post-saccadic target locations, we evaluated the relationship between landing site error and the proportion of forward responses. If participants had impaired CD and were relying on saccade landing site, rather than the remapped pre-saccadic target location, they would show an increased proportion of forward judgments as the saccade fell increasingly short of the target. **Figure 3A** shows the mean percentage of forward responses as a function of landing site error. In neither HC (W=66, p=0.15), nor SZP (W=85, p=0.46), did the slope of this function differ from zero. On an individual level, however, saccade landing site was a significant predictor (alpha-level: 0.05) of perceptual judgments in one HC and three SZP, such that more hypometric saccades were associated with a greater proportion of forward responses. In a fourth SZP, this relationship was significant in the opposite direction.

Since, in SZP, but not HC, mean saccade amplitude was significantly correlated with slopes of the linear function plotting forward responses against landing site error (SZP: $r_s=-0.49$, $p=0.03$, HC: $r_s=-0.31$, $p=0.18$), we performed group comparisons of the slopes using ANCOVAs, including mean saccade amplitude as a covariate. Even when controlling for average saccade amplitude, we found no significant difference in the slope between SZP and HC ($F(1,37)=0.33$, $p=0.56$).

Finally, given the hypothesized link between disturbed CD and positive symptoms of schizophrenia (e.g. delusions, hallucinations), we tested if patients who had more severe positive symptoms (greater PANSS positive subscale scores) relied less on the remapped location of the pre-saccadic target and more on landing site error when making their perceptual judgment. Indeed, positive symptom severity related to a more negative slope of the function plotting the proportion of forward responses against landing site error (**Figure 3B**; $r_s=-0.51$, $p=0.02$). This relationship became even more robust after one bivariate outlier was removed ($r_s=-0.56$, $p=0.01$). There was no significant relationship between these slopes and the PANSS negative subscale ($r_s=-0.17$, $p=0.47$). Importantly, as there was no
relationship between saccade amplitude and either positive ($r_s=0.31$, $p=0.18$) or negative ($r_s=0.35$, $p=0.13$) symptom severity, saccade metrics cannot explain the relationship between clinical symptoms and greater reliance on eye position on perceptual judgments in SZP. No correlation between the slope and CPZ equivalent dose was observed ($r_s=0.31$, $p=0.22$), suggesting that medication cannot account for the greater reliance on saccade landing site in SZP with more severe symptoms.

Discussion

In the present study, we provide evidence that SZP have symptom-related disturbances in the ability to remap visual targets following saccades—a function that crucially relies on intact CD. SZP judged the direction of a post-saccadic target displacement less accurately than HC, potentially relying more on saccade landing site rather than a remapped representation of the pre-saccadic target. Across SZP, we found that those individuals that made shorter saccades were more likely to report the post-saccadic target as jumping forward. This relationship was not observed in HC and suggests that SZP are more likely to judge the post-saccadic target location relative to saccade landing site, consistent with disturbed CD-based remapping.

In line with previous studies investigating target localization across saccadic eye movements (Collins et al., 2009; Ostendorf et al., 2010; Joiner et al., 2013), we did not observe a relationship between saccade landing site and perceptual judgments at the single trial level in HC. However, contrary to our expectations, we also did not observe evidence for such a dependency across the entire sample of SZP, and the trial-by-trial relationship between landing site error and perceptual judgments did not differ between groups. Despite the absence of a group difference in this dependency, its strength correlated with symptom severity within SZP. SZP with more severe positive, but not negative, symptoms showed a greater influence of saccade landing site on perceptual judgments across single trials.

As a CD vector allows healthy individuals to generate a correct spatial representation of the pre-saccadic target following the saccade (Collins et al., 2009), CD disturbances could potentially cause the reduced sensitivity to target displacement observed in SZP and increased reliance of perceptual judgments on saccade landing site. Thus, these findings support mechanistic theories positing a link between psychotic experiences and disturbed CD (Feinberg, 1978; Frith, 1992).
The current results are consistent with emerging evidence for disturbed oculomotor CD in SZP and extend these findings in important ways. Recent studies have suggested that failures in continuous CD might underlie the robust smooth pursuit impairments (Thaker et al., 1996; Hong et al., 2003; Hong et al., 2005; Lindner et al., 2005; Nkam et al., 2010; Spering et al., 2013) and larger shifts in peri-saccadic localization of visual stimuli in SZP (Richard et al., 2014). Our findings suggest that SZP are also impaired in generating and/or using the transient CD signals that accompany saccadic eye movements (Sommer and Wurtz, 2004). These findings are consistent with Thakkar et al. (in press) in which participants executed two saccades in rapid succession. SZP showed evidence for failing to appropriately use CD to anticipate the change in eye position brought about by the first saccade when executing the second saccade. In the current study, we now show evidence for putatively disturbed CD having a systematic effect on visual perception, particularly in SZP with more severe psychotic symptoms.

We must consider, however, why we did not see group differences in the dependency between saccade landing site and perceptual judgments at the single-trial level. One potential explanation is that there is more noise in the response and/or visual system in SZP (Loh et al., 2007). SZP might also fail to appropriately encode or maintain the pre-saccadic target location during the 250 ms blanking period, consistent with spatial working memory deficits (Lee and Park, 2005). Increased noise and spatial working memory failures would likely result in an imprecise representation of the pre-saccadic target and/or motor errors during perceptual reports. We argue that both of these factors would attenuate a relationship between saccade landing site and perceptual judgments. Accordingly, such a dependency between saccade landing site and perceptual judgments may only be observable at the group level, which is indeed what we found. Further, consistent with the observed correlation with positive symptoms, it is possible that as SZP become increasingly psychotic, CD-based remapping disturbances become more severe. Only for these patients, relationships between saccade landing site and perceptual judgments seem to emerge above visual and response system noise. On a related note, SZP in this study were only very mildly ill at the time of testing, based on symptom ratings (Leucht et al., 2005). A sample of more symptomatic patients would potentially result in a significant group difference in the relationship between saccade landing site and perceptual judgments. Alternatively, the relationship between clinical symptoms and the dependency between landing site and perceptual judgments could cause greater
variability of this dependency in SZP versus HC and, accordingly, result in a non-significant overall group
difference between these slopes. Finally, we must acknowledge that our study comprises a relatively
small number of trials. While a larger number of trials would have certainly rendered our statistical
analyses more powerful, increasing the experiment duration would also lead to a decline of subject
motivation, particularly in patients. Nevertheless, a significant group difference in the relationship between
saccade landing site and perceptual judgments at the single-trial level might have been discernible had
we collected more data per subject.

Despite the above limitations, our findings provide support for CD dysfunction in schizophrenia
that is related to psychosis. Since for most patients saccade landing site error was not a significant
predictor of perceptual judgments (although in three patients it was), the current results are limited in
terms of their diagnostic utility. Still, the negative relationship between positive symptom severity and the
reliance on saccadic landing site to inform perceptual judgments supports an association between
psychotic symptoms and disrupted CD signals. That is, the main clinical implication of these findings is
that they inform mechanisms of psychosis.

Neurophysiological studies can guide mechanistic interpretations of the current findings.

Remapping properties have been observed in cortical and subcortical visual neurons in non-human
primates (reviewed in Hall and Colby, 2011). Remapping, at least in frontal eye fields, is accomplished via
CD signals sent from superior colliculus (SC) via the medial dorsal nucleus of the thalamus (MD; Sommer
and Wurtz, 2002, 2004, 2008). Additionally, lesions to MD in humans results in a dependency between
landing site error and perceptual judgment in this task (Ostendorf et al., 2010). We can thus speculate
that the current findings in SZP are related to disturbances in this SC-MD-FEF pathway, resulting in
abnormalities in the generation, timing, or precision of CD signals. Indeed, recent studies have shown
altered MD-cortical connectivity in SZP that is related to psychotic symptoms (Woodward et al., 2012;
Shinn et al., 2013; Anticevic et al., 2014). Interestingly, it has recently been suggested that receptive field
shifts in FEF neurons during saccade planning do not reflect the prediction of retinal changes following
the saccade (Zirnsak et al., 2014), but rather a convergence towards the saccade target. This new
interpretation of RF shifts, however, remains compatible with our hypotheses and findings. CD likely
contributes to the acquisition of information about the location of the target space during saccade
planning and impaired CD might accordingly result in flawed compression of visual space, not focused on
the actual saccade endpoint.
To conclude, we observed evidence for impairments in remapping of visual targets following
saccadic eye movements in schizophrenia, suggesting disturbances in CD. Remapping disturbances
were greater in patients with more severe psychotic symptoms, supporting a link between CD
disturbances and those symptoms of the disease that manifest in profound agency distortions.
Acknowledgements: The authors would like to thank Ilse Thompson and Helene Hopman for their contributions to subject recruitment and clinical interviews.

Funding: This work was supported by a Netherlands Organisation for Scientific Research Rubicon grant (KNT), DFG Emmy Noether grant RO 3579/2–1 (MR). The infrastructure for the GROUP study was funded through the Geestkracht programme of the Dutch Health Research Council (ZON-MW, grant number 10-000-1001), and matching funds from participating pharmaceutical companies (Lundbeck, AstraZeneca, Eli Lilly, Janssen Cilag) and universities and mental health care organizations (Amsterdam: Academic Psychiatric Centre of the Academic Medical Center and the mental health institutions: GGZ Ingeest, Arkin, Dijk en Duin, GGZ Rivierduinen, Erasmus Medical Centre, GGZ Noord Holland Noord. Maastricht: Maastricht University Medical Centre and the mental health institutions: GGZ Eindhoven en de kempen, GGZ Breburg, GGZ Oost-Brabant, Vincent van Gogh voor Geestelijke Gezondheid, Mondriaan Zorggroep, Prins Clauscentrum Sittard, RIAGG Roermond, Universitair Centrum Sint-Jozef Kortenberg, CAPRI University of Antwerp, PC Ziekeren Sint-Truiden, PZ Sancta Maria Sint-Truiden, GGZ Overpelt, OPZ Rekem. Groningen: University Medical Center Groningen and the mental health institutions: Lentis, GGZ Friesland, GGZ Drenthe, Dimence, Mediant, GGNet Warnsveld, Yulius Dordrecht and Parnassia psycho-medical center (The Hague). Utrecht: University Medical Center Utrecht and the mental health institutions Altrecht, GGZ Centraal, Riagg Amersfoort and Delta.)
Footnotes

1Note that the PNL equates the parameter $c$ of the above function only if the function is centered on 50% forward reports, that is, if $d = 1-a$. 

Footnotes
References


Genetic Risk Outcome in Psychosis Investigators. Evidence that familial liability for psychosis is expressed as differential sensitivity to cannabis: an analysis of patient-sibling and sibling-control pairs. *Arch Gen Psychiatry* 68:138-147, 2011.


Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, Jablenski A, Regier D, Sartorius N. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. *Arch Gen Psychiatry* 47:589-593, 1990.


Figure Legends

Figure 1. (A) Stimulus configuration and basis of perceptual judgment. Upon pre-saccadic target presentation (upper panel), the corollary discharge (CD) vector can be used to predict the saccadic landing site (gray cross). In this example, the planned saccade will fall short of the pre-saccadic target. After saccade initiation (lower panel), the pre-saccadic target is extinguished and reappears displaced to the left or right. If the pre-saccadic target has been appropriately remapped, then the vector $a$ between this remapped location and the post-saccadic target should roughly match the actual target displacement. As, in this example, the post-saccadic target appears to the left of the pre-saccadic target, proper remapping would predict that participants judge the displacement as backwards. Alternatively, saccade landing site could serve as a proxy of the pre-saccadic target location, predicting that the location of the post-saccadic target relative to the saccadic landing site (vector $b$) drives the judgment (forwards in this example). (B) Predictions in schizophrenia patients (SZP) and healthy controls (HC). If CD is disturbed in schizophrenia, we expect SZP to use the actual landing site as a proxy for the pre-saccadic target, rather than its remapped location. Consequently, we expect that SZP rely less on the target displacement predicted from remapping (vector $a$ in panel A) and thus make more perceptual judgment errors. Due to impaired remapping in SZP, we expect that they will show an increased relationship between the percentage of forward responses and the saccadic landing site error (upper panel)—the more hypometric a saccade, the more likely SZP should be to report “forward”. In the relationship between the percentage of forward responses and target displacement (lower panel), less reliance on the actual target displacement in SZP should manifest in a larger just-noticeable difference (JND). The perceptual null location (PNL) denotes the post-saccadic target location at which participants report an equal proportion of forward and backwards jumps. As we expect patients to rely more on saccade landing site when making a judgment, we expect that SZP with shorter average saccade amplitudes should perceive the post-saccadic target as jumping forward more frequently (as it will more often fall forward of saccade landing site). This increase in forward judgments will result in a smaller PNL. Thus, we expect a positive relationship between mean saccade amplitude and PNL in SZP but not HC (see inset). (C) Trial procedure. Dotted circles denote eye position. See Methods section for details.
Figure 2. (A) Individual fits of the mean percentage of forward responses as a function of target displacement. On the x-axis, negative and positive values indicate post-saccadic targets that are presented towards or away from the fixation point, respectively, relative to the pre-saccadic target location. (B) Functions shown here were fitted to group-averaged responses for visualization purposes only, and thus differ from the analyses of individual observer’s data described in the Results section. Insets show median JNDs and mean PNLs from the individually-fitted psychometric functions. (C) Mean percentage of forward responses as a function of target displacement fitted to group-averaged responses, separated by saccadic directions. (D) Relationship between PNL and mean saccade amplitude. Each dot corresponds to one participant.

Figure 3. (A) Relationship between landing site error and perceptual judgments. Mean percentage of forward responses in each group is shown as a function of landing site error (distance between saccadic landing site and pre-saccadic target). For each observer, we divided the distribution of landing site errors into the same bins, ranging from -8° to 8° of the pre-saccadic target in increments of 0.5°, and calculated the percentage of forward reports for each bin. We subsequently fitted a weighted linear regression model to these data for each subject, weighting data points by the number of observations in each bin. Bins in which fewer than two participants per group contributed are not shown. For visualization purposes, we averaged the proportion of forward responses in each bin per group. Bins in which less than two participants per group contributed are not depicted. Error bars are SEM. (B) Correlation between positive symptom severity and individual slopes of the function in panel A. Each dot corresponds to one SZP.
Table 1. Participant demographics.

<table>
<thead>
<tr>
<th></th>
<th>HC (n=20)</th>
<th>SZ (n=20)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong></td>
<td><strong>Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>13/7</td>
<td>15/5</td>
<td>1.378</td>
<td>.176</td>
</tr>
<tr>
<td>Age</td>
<td>35.05(9.14)</td>
<td>36.40(7.78)</td>
<td>-.503</td>
<td>.618</td>
</tr>
<tr>
<td>IQ(^1)</td>
<td>105.33(11.28)</td>
<td>94.6(12.63)</td>
<td>2.602</td>
<td>.014</td>
</tr>
<tr>
<td>Education(^2)</td>
<td>7.32(1.10)</td>
<td>4.65(1.84)</td>
<td>5.437</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Handedness(^3)</td>
<td>0.84(0.47)</td>
<td>0.94(0.19)</td>
<td>-.917</td>
<td>.365</td>
</tr>
<tr>
<td>PANSS positive</td>
<td></td>
<td>11.35(5.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS negative</td>
<td></td>
<td>12.45(5.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS general</td>
<td></td>
<td>24.65(7.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS total</td>
<td></td>
<td>48.55(16.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illness duration (years)</td>
<td></td>
<td>14.42(5.35)</td>
<td></td>
<td></td>
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<tr>
<td>CPZ equivalent dose (mg)</td>
<td></td>
<td>274.4(242.26)</td>
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</tbody>
</table>

\(^1\) Based on the Nederlandse Leestest voor Volwassenen (NLV)

\(^2\) Education: 0 – less than six years of primary education; 1 – finished six years of primary education; 2 – six years of primary education and low level secondary education; 3 – four years of low level secondary education; 4 – four years of average level secondary education; 5 – five years of average level secondary education; 6 – four years of average level secondary education; 7 – four years of high level of secondary education; 8 - university degree.

\(^3\) Based on the Edinburgh Handedness Inventory; scores range from 0.00 indicating complete left-handedness to 1.00 indicating complete right handedness.
Table 2. Response kinematics separated by group and saccade direction.

<table>
<thead>
<tr>
<th></th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saccade RT (ms)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean s.d.</td>
<td>mean s.d.</td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>207 42</td>
<td>219 56</td>
</tr>
<tr>
<td>SZP</td>
<td>201 42</td>
<td>212 47</td>
</tr>
<tr>
<td><strong>Saccade Amplitude (degrees)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>right</td>
<td></td>
</tr>
<tr>
<td>mean s.d.</td>
<td>mean s.d.</td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>9.4 0.7</td>
<td>9.8 0.8</td>
</tr>
<tr>
<td>SZP</td>
<td>8.7 0.7</td>
<td>9.2 1.0</td>
</tr>
<tr>
<td><strong>Saccade Peak Velocity (degrees/sec)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>right</td>
<td></td>
</tr>
<tr>
<td>mean s.d.</td>
<td>mean s.d.</td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>393.3 64.0</td>
<td>408.9 71.5</td>
</tr>
<tr>
<td>SZP</td>
<td>381.1 68.2</td>
<td>409.9 73.0</td>
</tr>
<tr>
<td><strong>Saccade Peak Acceleration (degrees/sec/sec x10^-4)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>right</td>
<td></td>
</tr>
<tr>
<td>mean s.d.</td>
<td>mean s.d.</td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>6.27 2.29</td>
<td>6.04 1.53</td>
</tr>
<tr>
<td>SZP</td>
<td>6.20 1.38</td>
<td>6.40 1.68</td>
</tr>
<tr>
<td><strong>Perceptual Decision RT (ms)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>right</td>
<td></td>
</tr>
<tr>
<td>mean s.d.</td>
<td>mean s.d.</td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>532 112</td>
<td>558 169</td>
</tr>
<tr>
<td>SZP</td>
<td>739 239</td>
<td>756 281</td>
</tr>
</tbody>
</table>
200 ms

500 - 1000 ms

until saccade initiation

250 ms

100

50

hyper-metric hypo-metric

Landing site error

Forward Responses (%)

Hypothesized data

CD vector (9°)

Target vector (10°)

Screen Position (degrees)

Fixation point

Before Saccade

Predicted landing site

Pre-saccadic target

CB

A

After Saccade

Actual landing site

Post-saccadic target

Remapped target location

Response period

0

Mean amplitude

Hypothesized data

PNL

Hypo-metric

Hyper-metric

Landing site error

AB C
Landing site error (deg) vs. forward responses:

- Positive symptom severity (PANSS positive subscale)

Forward responses (%)

**Slope (%/deg)**

- Landing site error vs. forward responses

rs = -0.51, p = 0.02

Outlier included:

- Outlier excluded:

**A**

**B**

HC

SZP

Outlier included:

$ r_s = -0.51, p = 0.02$

Outlier excluded:

$ r_s = -0.56, p = 0.01$