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Trans-saccadic perception deficits in schizophrenia reflect the improper internal monitoring of eye movement rather than abnormal sensory processing

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Abstract

Background—Symptoms of psychosis in schizophrenia (SZ) reflect disturbances in sense of agency (SoA)—difficulty distinguishing internally from externally generated sensory and perceptual experiences. One theory attributes these anomalies to a disruption in corollary discharge (CD), an internal copy of generated motor commands used to distinguish self-movement generated sensations from externally-generated stimulation.

Methods—We used a trans-saccadic shift detection paradigm to examine possible deficits in CD and SoA based on the ability to perceive visual changes in 31 SZ patients (SZP) and 31 healthy controls (HC). We derived perceptual measures based on manual responses indicating the trans-saccadic target shift direction. We also developed a distance-from-unity-line measure to quantify use of CD versus purely sensory (visual) information in evaluating visual changes in the environment following an eye movement.

Results—SZP had higher perceptual thresholds in detecting shift of target location than HC, regardless of movement direction or amplitude. Despite producing similar hypometric saccades, HC overestimated target location, whereas SZP relied more on the experienced visual error and consequently underestimated the target position. We show that in SZP the post-saccadic judgment

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of the initial target location was largely aligned with the measure based only on visual error, suggesting a deficit in utilization of CD. This CD deficit also correlated with positive SZ symptoms and disturbances in SoA.

Conclusions—These results provide a novel approach in quantifying abnormal utilization of CD in SZP and provide a framework to distinguish deficits in sensory processing versus defects in the internal CD-based monitoring of movement.

Keywords

Schizophrenia; saccade; corollary discharge; positive symptoms; visual perception; sense of agency

INTRODUCTION

Schizophrenia (SZ) is associated with positive psychotic symptoms, negative symptoms and cognitive impairments. Psychotic symptoms (e.g. hallucinations and delusions) are marked by sensory perception disturbances and difficulty distinguishing between origins of endogenous and exogenous stimuli. Patients with schizophrenia (SZP) may sense that their actions and thoughts are controlled by external forces or may ascribe ownership to external events. Reports have often described inaccurate agency judgments in SZP (1–6) but neurobiological mechanisms underlying these debilitating symptoms remain unclear.

It is suggested that predictive coding mechanisms (e.g. action-based corollary discharge, CD) mediating sensory cortex modulation may be compromised in SZ. A purported copy of issued motor commands prepares the sensory cortex for inputs resulting from self-generated motor acts, and distinguishes sensations resulting from endogenous actions from those externally generated by comparing the actual and predicted sensory consequences of motion (7–10). This comparator mechanism is thought to support evaluation of action awareness—directly guiding subjective sense of agency (SoA, i.e., recognition of action ownership, 3,11). Based on this framework, delusions of influence, hallucinations and misattribution of agency may ensue from inadequacies in CD (12–17).

Although CD deficits in SZP have been studied within the auditory (18,19,21,22,23) and somatosensory systems (4–6,24–26), the saccadic eye-movement system is advantageous in probing SoA defects due to a comprehensive understanding of movement generation (27). Specifically, the saccadic CD signal can be used to update knowledge about eye position and allow for distinction between endogenous and exogenous visual scene changes (28–34,38). Thus, the saccadic system provides a tractable approach to study SoA.

Eye movement CD impairment in SZP has been previously demonstrated in various paradigms (saccade-based tasks: 39,40,41,42,43; smooth pursuit based tasks: 44–49). We build off this previous work by examining CD dysfunction within the comparator model framework, directly quantifying a measure that specifically distinguishes perception based on sensory feedback from that based on CD-derived predicted feedback, and demonstrating a strong link of this deficit to positive symptoms and SoA. We used a task in which subjects make a saccade to an initial target location and then evaluate the direction of target location changes that occurred during the movement (trans-saccadic shifts). To study localization, we remove the target while the saccade is in flight and after a blank period it reappears at a shifted location. In this task, proprioception from the eye muscles is not likely to play a significant role as it has been shown that these signals are likely to be too slow to be effective, and performance is not affected when these signals are eliminated (50–52). Due to lack of visual references and imprecise proprioceptive information, subjects must make a perceptual judgment based on the CD vector of the initial movement. Thus, this task serves as a sensitive assay of CD utilization in visual perception. We assess the role of CD by quantifying where subjects perceptually estimate initial target location. An ideal eye movement would land on the initial target location and shifts would be judged relative to this eye position. However, eye movements typically undershoot the target resulting in a discrepancy between saccade landing point and target. If the CD of the saccade is impaired and the discrepancy is not accounted for, estimation of initial target location would rely on experienced visual error rather than the CD-based predicted error resulting from the inaccurate saccade. This task allows separation of visual error processing disturbances from internal monitoring deficits by comparing target location estimation based on visual error (VE only, 53) versus location estimation derived from the perceptual reports (VE+CD, 53,54). Since we hypothesize that CD is impaired in SZP, we expect that patients will base location estimation on post-movement sensory information (visual error) and display a perceptual bias closely aligned to that derived from the visual error. In order to quantify this alliance and utilization of CD, we formulated a 'distance-from-unity-line' measure - the difference between the VE-only and VE+CD based bias. Our aim is to examine CD disruption and dissociate components of the comparator mechanism that are intact from those that are impaired in SZ. Our data demonstrate that reliance on visual error feedback and a corresponding decrease in CD-based estimation is correlated with impaired SoA and psychotic symptoms, collectively providing compelling support for the hypothesis that CD and comparator model deficits underlie perceptual abnormalities in SZ.

METHODS AND MATERIALS

Subjects

Demographic information is presented in Table 1. Sixty-two veterans between 24–70 years of age were recruited from the Washington DC Veterans Affairs Medical Center (DCVAMC). Thirty-one subjects met DSM-IV criteria for schizophrenia (N=19) or schizoaffective disorder (N = 12) confirmed using the Structured Clinical Interview for DSM IV and chart review. They were outpatients receiving stable doses of either typical (N=1) or atypical (N=29) antipsychotic medication, or an antidepressant (N=1) for at least three months prior to testing. Thirty-one age, gender and education-matched subjects with no history of psychiatric or substance abuse disorder and no first-degree relative with mental illness were enrolled in the control group (HC). Subjects were naïve to the purpose of the study and were compensated for participation. Exclusion criteria were: significant medical/neurological disorder, history of loss of consciousness for > five minutes, substance use disorder within the three months prior to the study, and history of eye surgery or impaired vision. The DCVAMC Institutional Review Board approved the study and informed consent was obtained from subjects.

Clinical Measures

The Positive and Negative Syndrome Scale (PANSS) (55) was used to assess severity of positive, negative and general symptoms in SZP. To assess abnormal experiences of agency in both groups, we used the Sense of Agency Scale (SOAS) (56–58, Supplement) having three subscales: 1) Mental SoA-sense of agency involving thoughts, mental activity or perception, 2) Physical SoA-sense of agency involving somatic experiences, and 3) Social SoA-sense of agency involving social activities. Subjects reported how often the items applied to their daily life. High scores indicated unstable sense of agency.

Apparatus

Data were collected using a SMI eye tracker (Sampling rate 240 Hz, iView v2.2.4, SensoMotoric Instruments GmbH). E-Primev2 software (Psychology Software Tools, Inc.) was used to present stimuli onto an Acer AL1715 monitor with a 75 Hz refresh rate. The eye tracker system had a spatial resolution of 0.01° and proces sing latency of < 0.5 ms. Subjects were seated 56 cm from the computer screen in a headrest containing the camera. A chin and forehead rest stabilized the participant's head with a Plexiglas molded notch holding the nose in place. To eliminate effects of visual cues on localization, the task was performed in a dimly lit room. The fixation cross and circular targets were white with a luminance of 56 cd/m^2 viewed against a black background of luminance of < 0.1 cd/m^2. At the start of each session, a 9-point gaze calibration was performed.

Design and Procedure

We modified a task previously used in our studies on trans-saccadic perception (53,54,59–62 Figure 1A). Trials began with a variable fixation period, after which an initial saccade target appeared at one of two amplitudes (4º or 8º) and two directions (leftward or rightward) from the fixation cross. When eye position was detected beyond a virtual square window around the fixation cross, the target was extinguished, followed by a 250 ms blank period. The target reappeared at a shifted position (± 0.5º collinear increments) between ± 3.5º. Target shifts were randomly drawn from a Gaussian distribution centered at 0º, with smaller shifts sampled with greater frequency than larger, more detectable shifts. Subjects judged the direction of target shift with a manual response. Each subject completed 384 trials in one session that included a break. On each trial the initial target amplitude and direction were randomly selected.

Eye movement recording and analysis

Eye movements were analyzed offline using MATLABv8.1.0 (Mathworks,MA,USA). During the task, saccade initiation was detected when the saccade left a 3.2° square fixation window. Due to system limitations, this online detection may have occurred with some minimal lag. Details on saccade durations and offset are provided in Figure S4. For offline analysis, saccades were identified as follows: (1) occurring ≥ 75 ms after the initial target appeared, (2) velocity ≥ 75°/s and acceleration ≥ $2000°/s^2$. Primary saccades included in the analyses were required to be initiated within the fixation window, with a distance exceeding 1/3 of initial target amplitude, and endpoint within the average eye position ± 2 SD (79.4 ± 3.2% of trials for SZP and 83.4 ± 2.2% for HC were included).

Analysis

Saccade Measures—We analyzed saccade characteristics (amplitude, latency, variability (SD)) and manual response reaction times to assess any group differences, or asymmetry based on target amplitude or direction. Endpoints of the primary saccade were determined per target amplitude and direction. To assess whether the primary saccade endpoint influenced shift detection, percent gain of initial saccade amplitude was also quantified as the ratio between the mean saccade endpoint and initial target position.

Perceptual Performance Data

CD and Sensory-Information Based—Consistent with our previous work (28,53,54), we derived post-saccadic estimates of initial target location and quantified the difficulty in detecting target shifts. These measures were based on psychometric curves (inferential models that relate subject performance to a physical quantity of a stimulus). These curves were fitted to the proportion of manual responses and specified the relationship between the probability of forward responses and the magnitude of the target shift. Psychometric functions from manual responses are assumed to be based on visual error + extraretinal information (VE+CD), because post-saccadic visual error as well as extraretinal information, such as the CD signal, are available to make perceptual judgments (32,53,54). Perceptual bias, inferred as the post-saccadic estimation of the location of the pre-saccadic (initial) target, was quantified as shift from 0 at the point where the percentage of forward responses was 50% (28,53,54). Since CD (see CD vector, Figure 1C) provides information about saccade metrics (hypo or hyper), this is purportedly used to make a perceptual estimation about presaccadic target location with respect to eye movement, and this estimation is quantified by the bias measure. A positive bias indicated that the initial target location was perceived to be ahead of its actual position; a negative bias indicated that initial target location was perceived to be behind the actual position. (Note that when there is a lack of CD utilization, saccade end-point errors could be used for this perceptual decision; the postsaccadic errors resulting from hypometric saccades would appear forward of the saccade endpoint more frequently. Thus, more frequent forward reports would shift the psychometric function to the left, resulting in a negative bias.) As done previously (53,54), we quantified the difference between the perceptual estimate (the bias) and actual target location as a percent error of the target location: bias divided by the initial target amplitude scaled by 100. This was done to compare over or underestimaton of initial target amplitude to the percent gain of initial saccade amplitude (Figure 2). Perceptual threshold, calculated as difference in shift size between the 50% and 75% points on the psychometric curve, quantified perceptual sensitivity in detecting target shifts; larger thresholds represent increased difficulty in perceiving trans-saccadic shifts (Figure 1B).

Solely Sensory-Information Based—We derived hypothetical psychometric functions if the perceptual decision was driven by only the visual error (VE) (53). We assume that VE represents shifted target direction, and that the CD-based estimate of eye position is not utilized. On every trial we determined the difference between the eye position at time of target reappearance and the shifted target location (VE) (Figure 1C) and direction of the resultant error vector was used as the basis for the simulated target shift judgment. Percentage of these VE-based forward judgments was plotted as a function of target shift to obtain a hypothetical psychometric function. Our assumption in the “VE-based” condition is that subjects have no extraretinal/CD-based information about the saccade metrics; only post-saccadic VE information is available for the perceptual judgment. This is a simplification, but provides a baseline under experimental conditions to determine how actual perceptual performance (utilizing extraretinal information, specifically CD) is superior to the limited VE-based situation.

Statistical Analyses

We assessed group differences in saccade metrics using separate mixed-design ANOVAs, and a Group by Direction by Amplitude ANOVA was performed on psychophysical measures; Group (SZP vs HC) being a between-subject factor, and Direction (right or left) and Target Amplitude (4° or 8°) within-subject factors. Since we observe d group differences in Wide Range Achievement Test scores, we conducted ANCOVA using these scores as a covariate. We report ANOVA results, as covariate analyses yielded the same results. We performed correlation tests between perceptual performance and clinical measures. Statistical analyses were performed using MATLAB and SPSS software (IBM SPSS Statistics, Version 20.0. Armonk, NY: IBM Corp). Significance level was set at 0.05.

RESULTS

Saccade and Response Measures

Table 2 shows the saccade metrics that we compared between groups. Although SZP made shorter saccades than HC, this was not significant [F(1,60)=1.13,P=0.293]. SZP had more variable saccadic endpoints, but there were no significant effects of group or direction for saccade variability (SD). The variability was higher for saccades to 8° targets [F(1,60)=9.61, P=0.004]. Sac cadic latencies did not differ by direction [F(1,60)=0.42, P=0.53], or group [F(1,60)=1.78, P=0.175], but were longer for 8 degree saccades [F(1,60)=21.74,P<0.001]. Also, the frequency of corrective saccades was larger for 8° targets [F(1,60)=12.65,P<0.001], with no direction [F(1,60)=1.38, P=0.32] or group effect [F(1,60)=0.56, P=0.27]. Manual response reaction time (RT) did not differ by direction, [F(1,60)=0.04, P=0.84], but RT was shorter for 4° t han for 8° targets [F(1,60)=7.226, P=0.01] and SZP took longer to respond [F(1,60)=10.01, P=0.003]. As reported in the Supplement, due to hardware/software system limitations, online detection may have occurred with some system lag, and on a small portion of trials saccades may have landed prior to target offset. We compared the percentage of correct responses on trials in which the target was still illuminated to the accuracy when the saccade was still in flight. The percent correct was not significantly different between the two groups (SZP and HC) or saccade amplitudes (all $P > 0.23$ in all cases) and there was no interaction effects ($P > 0.44$ in all cases).

Perceptual Performance

We investigated the detection of trans-saccadic shifts of visual targets and found that SZP, consistent with previous studies (40,41), had greater difficulty in detecting trans-saccadic shifts than HC (higher perceptual thresholds) [F(1,60)=21.71, P<0.001]. Thresholds increased with target amplitude for both groups [F(1,60)=13.29,P<0.001].

For the purpose of this report, we focus our analyses on perceptual bias as it provides a direct assay of perceptual estimation as related to eye movements. Detailed perceptual threshold results (and associated correlations) are provided in Table S1. For perceptual bias, there was a significant direction by group interaction, [F(1,60)=12.23,P=0.001]. SZP displayed more negative biases (−0.18 ± 0.75) than HC (0.32 ± 0.46), [F(1,60)=29.69, P<0.001], indicating SZP mostly underestimated whereas HC overestimated the pre-saccadic target location. Note that the average bias value does not reveal the overall distribution of the negative and positive bias values within each group. In the supplementary materials we provide the median and spread of the bias values to give information on the collective perceptual accuracy (Figure S1).

CD Utilization for Perceptual Judgments

To assess group similarities in saccade metrics, but differences in perceptual judgments, we compared the percent gain in saccade amplitude and percent error in target location (Figure 2). For both groups, the majority of eye movements were hypometric (91% in SZP and 97% in HC). In HC, despite movement undershoot, subjects largely (in 72.6% of cases) overestimated target location, whereas SZP overestimated target location in only 38.7% of cases. In addition, to determine whether the saccadic end-point error influenced shift detection judgments, we plotted the percent of forward responses as a function of saccade error (Figure S3). For HC, we see that perception is independent of saccade error, whereas for SZP, the forward perceptual report is influenced by the magnitude of this end point error.

Figure 3 shows eye positions, VE-based and actual psychometric functions (VE+CD-based) for a sample SZP (Figure 3A) and HC (Figure 3B). For simplicity, we only show results for saccades to the leftward 4^{o} target, but the results are consistent for the other amplitude and direction. For the SZP, post-saccade estimation of the pre-saccade target based on actual manual responses (purple square) is closely aligned to the estimate based solely on experienced visual error (green square). Importantly, both measures underestimate the true initial target location. This is not the case for the HC; while the VE-based measure underestimates the target location, the VE+CD measure based on the actual manual responses overestimates the location.

With respect to bias, the focus of the analysis was to assess differential CD utilization between the groups. Figure 4A displays perceptual biases derived from actual psychometric functions (based on VE+CD) on the abscissa, with biases derived from hypothetical VE curves on the ordinate. We found a significant interaction effect of group by condition (VE vs. VE+CD) by direction [F(1,60)=8.7, P=0.005], as well as a main effect of condition [F(1,60)= 5.974, P=0.018], and a condition by group effect [F(1,60)=12.778, P=0.001]. For HC, we found significant differences between VE-based and VE+CD-based biases (P<0.05 for all conditions) whereas in SZP, paired t-tests did not show any significant difference between VE-based biases and those based on VE+CD (Figure S5A). We further probed this relationship by examining dispersion of biases. We obtained a ‘distance-from-unity-line’ measure as a sensitive quantification of CD deficits to assay how the two perceptual bias derivations (VE+CD and VE only) were associated. Figure 4A shows that for patients, there is less dispersion and the majority of points lie close to the unity line, whereas for controls, points are more dispersed (Main effect of Group on 'distance-from-unity-line' measure [F(1,60)=32.02, P<0.001], more so for 8^o saccades [F(1,60)=6.47, P=0.04]).

Clinical Correlates

Considering the postulated link between CD impairment and aberrant perception leading to symptoms of psychosis, we assessed the relationship between psychophysical perceptual measures and PANSS positive symptoms in SZP, and associations with SoA measures in both groups. We observed various associations as seen in Figures 4B and C.

Our primary variable of interest, the distance-from-unity-line measure is a novel quantification of CD deficit showing over-reliance on exogenous sensory feedback, rather than CD-generated internal monitoring in SZP. We observed robust associations (Figures 4B and C) between this measure and symptoms of psychosis (hallucinations and delusions) and PANSS Total Positive Symptoms in SZP and SoA measures in both SZP and HC. Subjects whose perceptual judgments were closely related to hypothetical judgments derived from the experienced visual error, having lower values for distance-from-unity-line, also demonstrated a disturbed subjective sense of mental agency. In HC, there were no correlations with Physical SoA (R=−0.14, P=0.45), nor with Social SoA (R=−0.013, P=0.95). For SZP, the distance-from-unity-line correlated with Physical SoA (R=−0.49, P=0.008), but not with Social SoA (R=0.20, P=0.28). Perceptual measures did not correlate with negative symptoms in SZP (R=0.12, P=0.42, Total PANSS Negative Symptoms).

DISCUSSION

We examined the ability of HC and SZP to detect trans-saccadic visual changes and show that for SZP, post-saccadic judgment of the initial target location was largely influenced by the experienced VE, suggesting a deficit in CD utilization. Consistent with previous studies (40,41), we provide evidence that SZP show impairments in the CD-based ability to remap visual targets following saccades and to make perceptual judgments of trans-saccadic target shifts. Similar to previous studies that related behavioral results to saccade metrics (38, 40), we obtained a sensitive measure to assess the type of information (retinal or extraretinal) subjects utilized to make perceptual judgments. We show that perceptual deficits in the task were selectively associated with positive symptoms in SZP, and demonstrate an association to SoA in both HC and SZP.

Behavior similarities between SZP and CD inactivation in nonhuman primates

Our results may relate to neural mechanisms involved in saccade CD. One of its transmission pathways (29,30,31,63,64) relays information pertaining to saccade metrics from the superior colliculus (SC) through the mediodorsal (MD) nucleus of the thalamus in order to update the receptive fields in frontal cortex (FEF). Recently, it has been shown that inactivating the MD relay alters perception in a similar trans-saccadic task (32). Additionally, thalamic lesion patients demonstrate deficits in making successive eye movements required for double-step saccades (34) and in perceptual performance in a trans-saccadic displacement task (38). These studies show that when the thalamic MD pathway is impaired, the ability to discriminate visual displacement becomes inaccurate. Cavanaugh and colleagues (32) showed that when the CD pathway was inactivated, there was a shift of the psychometric curve resulting in a perceptual bias that was more negative than the experimental control. This is the same difference we observe between our HC and SZP groups, suggesting that the inactivation resulted in an overreliance on the external sensory information, similar to the finding that SZP had more reliance on the VE in forming their perceptual decision. Trans-saccadic and similar tasks are an effective method for estimating properties of the CD signals that contribute to visual stability; however, our results do not necessarily insinuate visual instability in SZP, but rather an inefficient use of the CD in perception.

We can speculate that our findings in SZP are associated with disruptions to the SC-MD-FEF pathway, leading to imprecision of CD signal generation or relay. Additionally, there is evidence of neuroanatomical abnormalities in the MD of SZP. Young and colleagues (65) observed a post- reduced number of neurons and volume of MD in SZP. Reduction in glucose metabolism and size of MD in SZP (66–69) could disrupt the CD pathway (30,31,33,38), thus impeding the spatial updating required for visual stability. Studies have also shown compromised cortical-MD connectivity in SZP that is related to psychotic symptoms (70–72). Based on these neurobiological findings, it is possible that MD and associated pathway abnormalities underlie the CD impairments that contribute to symptoms of psychosis and disturbance of agency.

Sensory processing vs. impairments in internal monitoring of movement

Accurate anticipation of a self-generated action outcome (e.g., sensory consequences of a saccade) or perception of an environmental change (e.g., visual scene change) is based on internal motor predictions that guide SoA. It has been proposed that predictive or sensory feedback cues are weighted and integrated according to their relative efficiency, guiding the distinction between internally and externally generated stimuli (73,74). Such a context-dependent weighted integration of imprecise internal predictions and noisy external cues might explain misattributions of agency in SZP. Various visual perceptual (sensory processing) deficits have been found repeatedly in schizophrenia (for review see 75,76). Here, using quantitative, implicit measures we identify that the internal predictive information is likely responsible for these abnormalities, possibly ruling out impairment of sensory feedback processing. We deconstruct two elements of the comparator model that contribute to integration (internal prediction via CD signals, and sensory feedback via external, post-saccadic visual error), and demonstrate that SZP rely more on the sensory feedback (VE). This is corroborated by lack of significant group differences in saccade metrics. We observe that SZP are able to plan movement just as HC, but there is a possible breakdown in utilization of the CD for post-saccadic prediction of movement metrics. Whereas HC are able to implicitly make adjustments to perception, SZP appear to heavily rely on experienced post-saccadic VE, suggesting that sensory processing and saccade metrics of SZP are intact (within this paradigm), but a diminished internal prediction accompanying these movements drives the observed perceptual deficits.

Finally, we acknowledge that CD may not fully account for conscious experience about one's actions. Previous studies (77,78) have shown, in certain patient groups, intact compensation for conflict between predicted sensory signals and outcomes. This may indicate that the CD, within the comparator/forward model has more of a role in awareness of the discrepancy between movement and its consequences, versus automatic compensation for conflict. Nonetheless, the current perceptual paradigm is an effective method for examining the role of movement-related CD signals in complex self-monitoring systems from which a sense of agency is derived.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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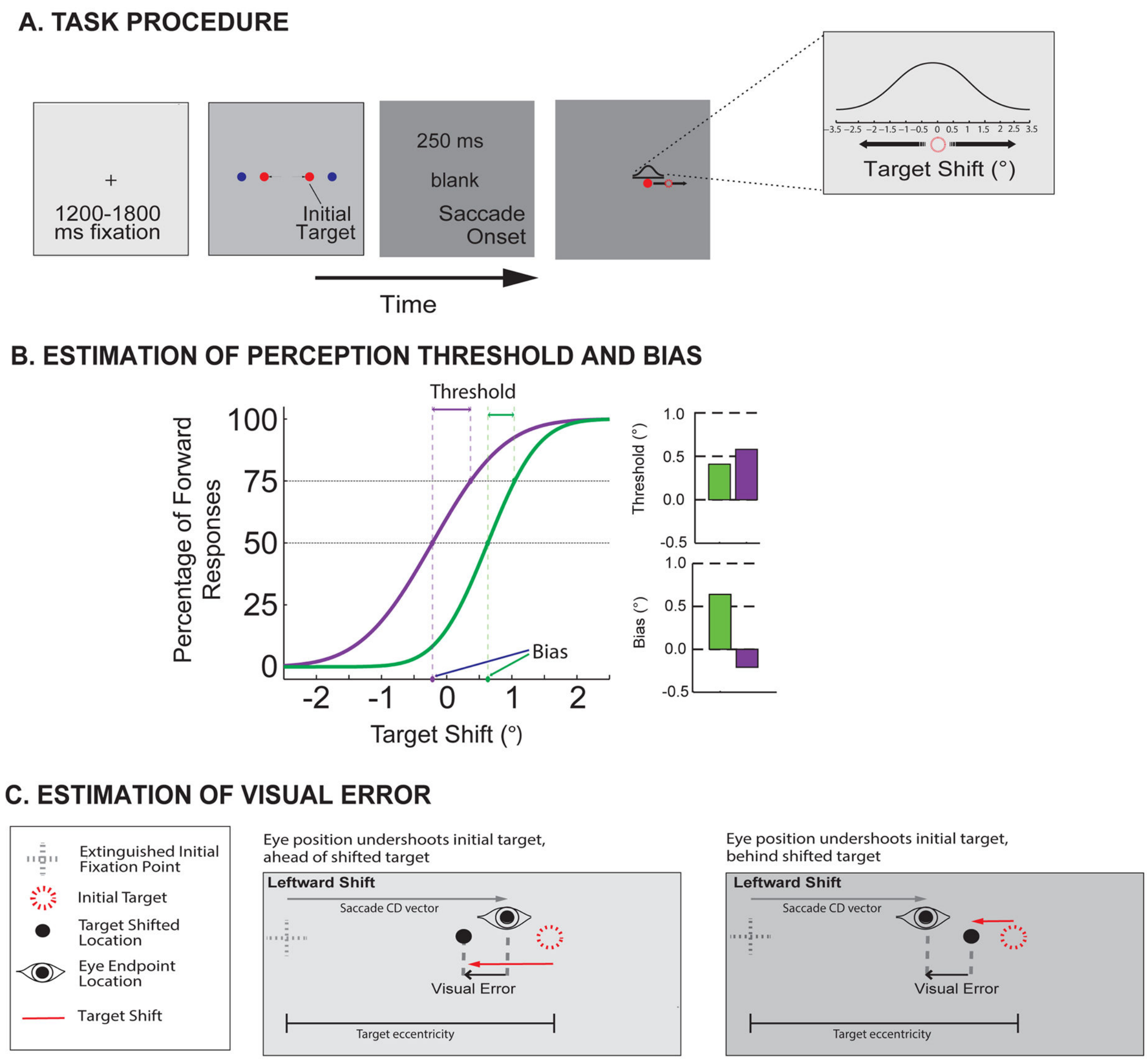

Figure 1. Trans-saccadic shift-detection task

(A) Task procedure. Each trial began with a central fixation cross (0.3º in extent) appearing for a variable period (random duration between 1200 and 1800 ms), followed by the appearance of an initial target that could appear randomly at any one of the two amplitudes (4° or 8°) and two directions (leftward or rightward). Subjects were required to make a saccadic eye movement toward this initial target, and upon online detection (when eye position exceeded a virtual window, 3.2° in extent) the target was displaced during the saccade, reappearing at a new location after a 250 ms blank period. This blank period was used to measure properties of the saccade CD rather than the effect of saccadic suppression on perception—an effect studied when the target immediately reappears at the shifted location. Previous results suggest that differences in perception due to CD are observable during this blank target condition (32,57). The displaced target, T2, appeared randomly at shifted positions according the illustrated Gaussian distribution ranging from -3.5° to 3.5° shifts. After the reappearance of the target a t the shifted location, subjects were required to indicate the direction of the displacement (backward or forward) using the left or right mouse buttons. A successful trial required a response to occur within 3000 ms of the shifted target's reappearance, but no instructions or feedback were given regarding reaction time and accuracy. **(B)** The percentage of forward responses on the y-axis is plotted as a function of target displacement on the abscissa. The manual response data were fitted with a cumulative Gaussian distribution to determine the psychometric function and measures of perceptual bias and threshold. Two example psychometric curves are shown with different slopes. Two perceptual measures are derived: perceptual threshold and bias. The threshold, top right, is computed as the difference in target displacement between the 50% and the 75% points of the sample psychometric curves. The perceptual bias, bottom right, was taken as the displacement from 0 (x-axis) at the point where the forward and backward responses were equal to 50% (y-axis). Each example curve yields a different threshold and bias. **(C)**The visual error was quantified by taking the vector magnitude, in visual angle degrees, between the eye position at the time when the shifted target appeared and the location of the shifted target. The examples show rightward saccades that undershoot the target, and leftward target shifts. Upon presaccadic target appearance the corollary discharge (CD) vector is used to predict the saccadic landing position. In this example, the saccade falls short of the target and the postsaccadic target is to the left of the presaccadic target, efficient CD-driven remapping would predict that subjects will perceive the shift as backward. In the left panel the large target shift and visual error are aligned, resulting in the correct 'backward' response. In the right panel the small target shift is in the opposite direction of the resulting visual error since the landing site is 'behind' the shifted target, with no CD vector information, it would result in an incorrect 'forward' response. These visual errors were used to derive hypothetical responses for target localization and psychometric curves based solely on the experienced sensory information.

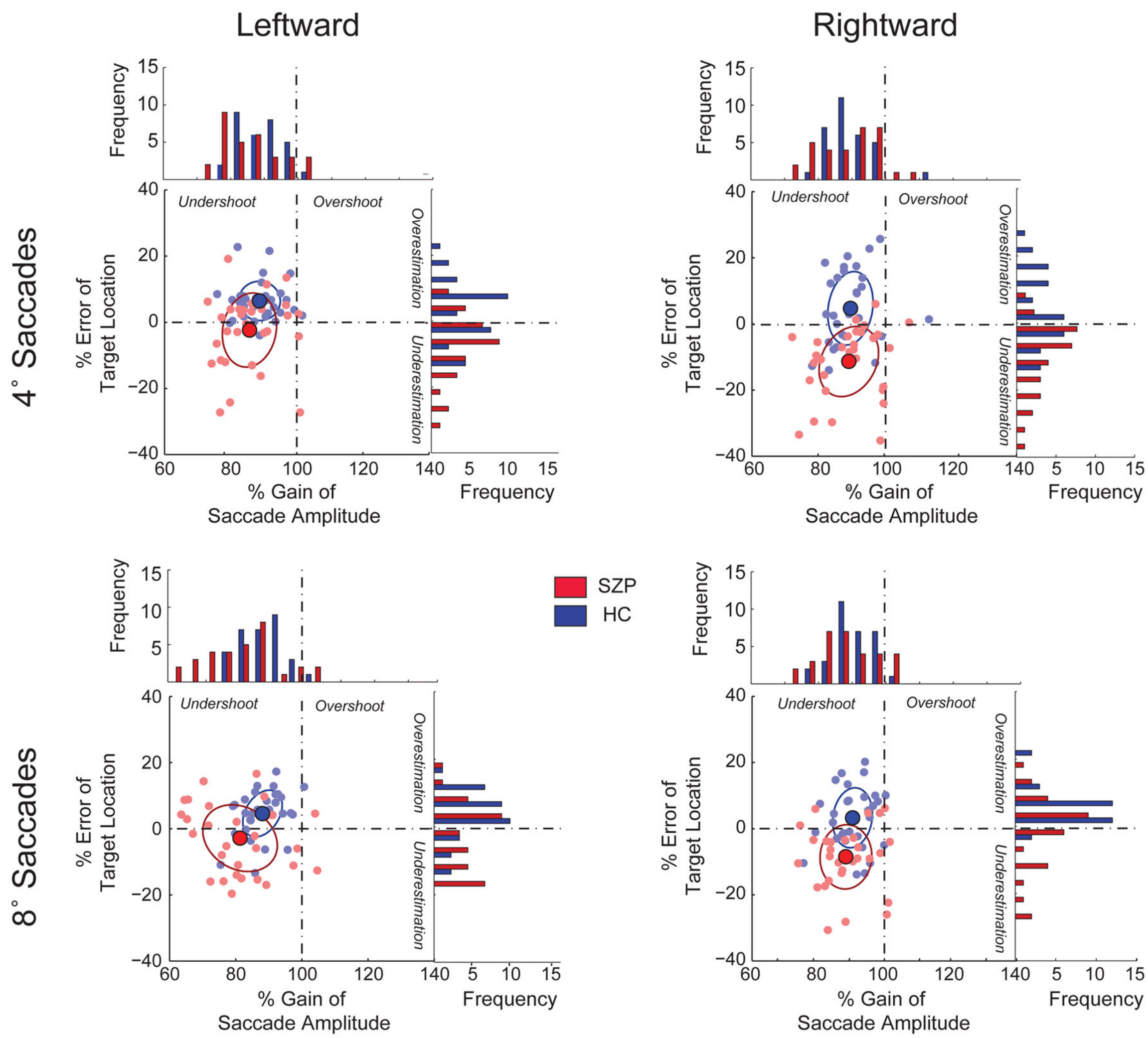

Figure 2. Percent gain of saccade amplitude and percent error estimation of target location

We plot the percent error of the estimated target location per amplitude and direction as a function of percent gain in the mean saccade amplitude. Percent gain is the saccade amplitude as a percentage of the required movement amplitude. A percentage above 100 signifies that the mean saccade amplitude exceeded the target amplitude (overshoot); a percentage below 100 signifies that the mean saccade amplitude fell short of the target amplitude (undershoot). Percent error was perceptual bias as a percentage of the target amplitude. A percentage above 0 signified that the perceptual estimate exceeded the target amplitude (overestimation); a negative percentage signified that the perceptual estimate was lower than the target amplitude (underestimation). Each filled circle represents the mean values for each subject (Red: SZP, Blue:HC). Each panel shows the result for the respective saccade amplitude and direction. The larger solid circles represent the respective mean percent gains in saccade amplitude and mean percent errors in target location estimation, with the corresponding ellipses representing the 95% confidence interval. The histograms to the right and above each panel are the respective distributions of the percent error and the percent gain.

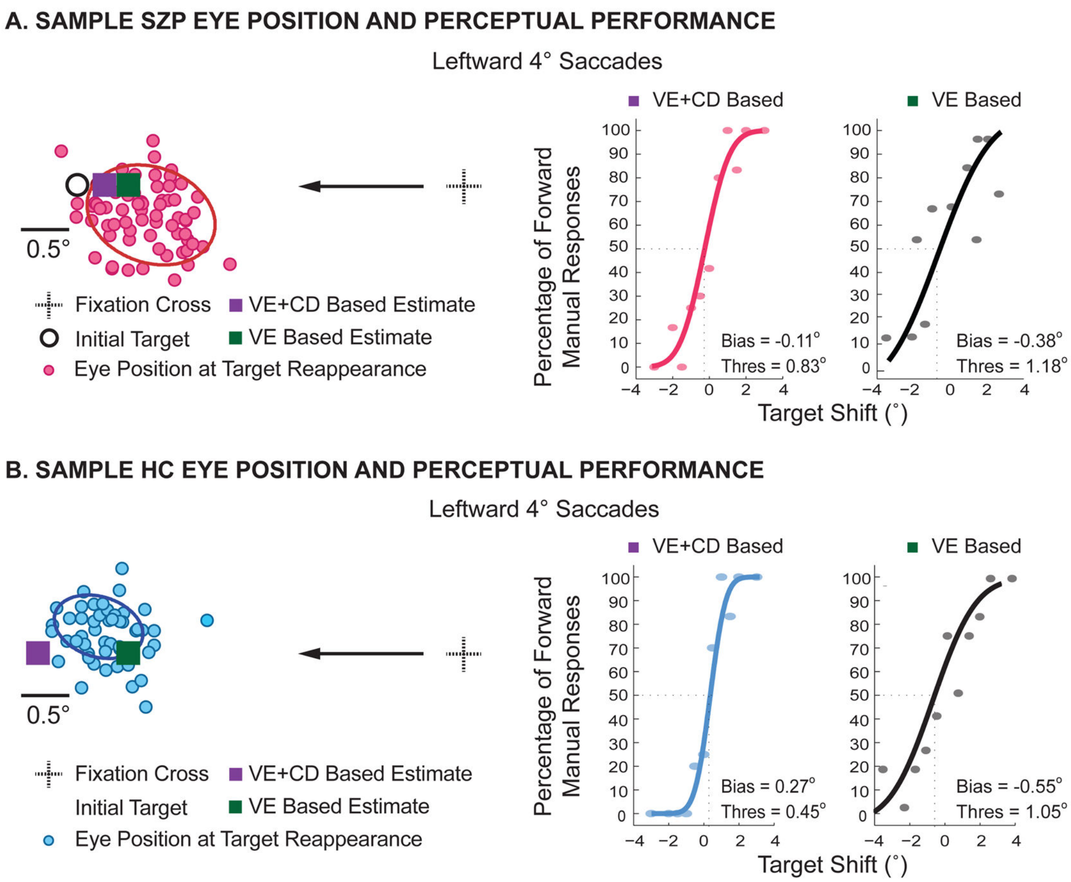

Figure 3. Example psychometric curves for leftward 4° saccades

Eye positions of an example subject from each group for saccades to a leftward target at 4°. Eye position at the time the target reappeared are displayed as filled red (A, SZP) and blue (B, HC) circles, respectively. The initial target is marked by a white circle with a black outline, and the solid ellipses represent the spatial extent of the 1 SD confidence interval of eye position variability. (Note that we could not depict the shifted target because this displacement varied on each trial.) Purple and green squares represent the perceptual (Visual Error + CD-based) and hyopothetical Visual Error-based estimates of the target location, respectively. Visual Error-based and Visual Error + CD-based psychometric functions of perceived target shift are shown next to the corresponding eye movements. The corresponding values for bias and threshold are given in each plot.

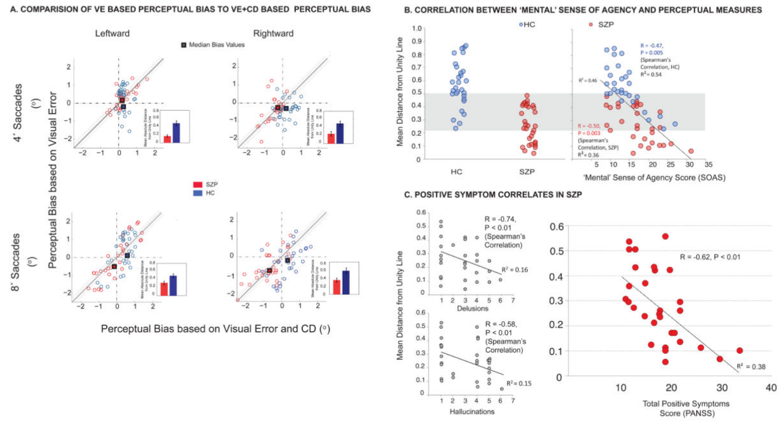

Figure 4. Clinical correaltions to behavioral measures

(A) Individual data points (light circles, red for SZP and blue for HC) for perceptual bias. Estimates for visual error-based (ordinate) vs. visual error + CD-based (abscissa) are plotted for each target amplitude and direction. Square symbols with the thick black outline represent the mean values across the respective groups. We obtain a distance from the unity line measure as an assay of how closely the two estimates of perceptual bias matched. Points along the unity line designate subjects for whom the two biases are closely related, thus indicating the lack of CD utilization in the estimate of the pre-saccadic target location and an incorrect reliance on post-saccade sensory information. The distance of points lying above or below the line indicate the magnitude of misalignment between the two measures. The bar charts show mean absolute values indicating the magnitude of the distance from the unity line across the respective group. **(B)** Scatter plot showing correlations between mean distance from the unity line (across the two directions and movement amplitudes) and "Mental" SoA for SZP (Red circles) and HC (Blue circles), respectively with Spearman's R and p-values displayed, as well as the R^2 value for the regression line over the entire sample (SZP and HC combined). The grey shaded area shows overlap between HC and SZP subjects—across groups these subjects had similar mean distance-from-unity-line values. The HC within this range demonstarted perceptual judgments that were closely related to the hypothetical judgments derived from the experienced visual error, similar to most SZP. Thus, these HC had lower values for distance-from-unity-line measure and also demonstrated a disturbed subjective sense of mental agency. **(C)** Scatter plots showing significant correlation between mean distance from the unity line and Hallucinations, Delusions and Total PANSS score.

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Table 1

Participant demographics. Means (SD) are displayed, along with statistical values for comparison between groups. We based premordbid IQ on word reading from the WRAT 4 (Wide Range Achievement Test). CPZ, Chlorpromazine; PANSS, Positive and Negative Syndrome Scale.

	HC, N=31	**SZP, N=31**		
	Mean (SD)	**Mean (SD)**	**Statistic**	**p**
Age	54.81(9.01)	56.25 (9.84)	*t = 0.06*	*0.95*
Gender	3 F /28 M	2 F /29 M	*φ =0.22*	*0.65*
Years of education	14.89 (0.33)	13.66 (0.41)	*t = 2.35*	*0.07*
Standard WRAT Scores (Estimation of IQ)*	100.19 (8.82)	93.75 (12.80)	*t = 3.12*	*0.03*
Handedness	3 L /28 R	6 L /25 R	*φ =1.17*	*0.28*
Duration of illness		28.11(10.04)		
CPZ Equivalent Dose		454.37 (277.51)		
PANSS Total		57.14 (11.54)		
PANSS Positive		16.42 (5.43)		
PANSS Negative		15.67 (6.49)		
PANSS General		26.29 (6.51)		

Table 2

Saccade Kinematics

Saccade and manual response metrics. Means and SDs for each measure are displayed, separated by group, target amplitude and direction.

		Leftward		Rightward	
		4°	**8°**	**4°**	**8°**
Saccade Amplitude	**HC**	3.54 (0.25)	7.03 (0.48)	3.56 (0.21)	7.22 (0.5)
	SZ	3.43 (0.33)	6.89 (0.67)	3.36 (0.38)	7.07 (0.63)
Saccade Variability (SD)	**HC**	0.70 (0.03)	1.16 (0.12)	0.71 (0.11)	1.17 (0.13)
	SZ	0.79 (0.12)	1.19 (0.18)	0.81 (0.09)	1.24 (0.16)
Saccade Latency (ms)	**HC**	242.58 (34.6)	257.64 (37.84)	246.3(35.28)	260.63 (38.2)
	SZ	265.79 (46.24)	286.27 (38.77)	262.59 (52.2)	275.45 (43.62)
Manual Response RT (ms)	**HC**	559.16 (152.42)	578.82 (159.42)	546.12 (153.28)	572.46 (154.71)
	SZ	714.93 (226.94)	761.76 (261.1)	720.55 (227.73)	769.85 (256.99)
Corrective Saccades (% of trials)	**HC**	42.28 (2.29)	44.33 (2.02)	42.97 (2.10)	44.59 (2.16)
	SZ	38.02 (2.54)	42.95 (3.82)	40.84 (2.91)	43.78 (2.86)