Vergence eye movements in patients with schizophrenia

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ABSTRACT

Previous studies have shown that smooth pursuit eye movements are impaired in patients with schizophrenia. However, under normal viewing conditions, targets move not only in the frontoparallel plane but also in depth, and tracking them requires both smooth pursuit and vergence eye movements. Although previous studies in humans and non-human primates suggest that these two eye movement subsystems are relatively independent of one another, to our knowledge, there have been no prior studies of vergence tracking behavior in patients with schizophrenia. Therefore, we have investigated these eye movements in patients with schizophrenia and in healthy controls. We found that patients with schizophrenia exhibited substantially lower gains compared to healthy controls during vergence tracking at all tested speeds (e.g. 0.25 Hz vergence tracking mean gain of 0.59 vs. 0.86). Further, consistent with previous reports, patients with schizophrenia exhibited significantly lower gains than healthy controls during smooth pursuit at higher target speeds (e.g. 0.5 Hz smooth pursuit mean gain of 0.64 vs. 0.73). In addition, there was a modest ($r \approx 0.5$), but significant, correlation between smooth pursuit and vergence tracking performance in patients with schizophrenia. Our observations clearly demonstrate substantial vergence tracking deficits in patients with schizophrenia. In these patients, deficits for smooth pursuit and vergence tracking are partially correlated suggesting overlap in the central control of smooth pursuit and vergence eye movements.

1. Introduction

Previous eye tracking studies in patients with schizophrenia have reported abnormalities in their eye movements; specifically, smooth pursuit and antisaccades (for reviews see Levy et al., 1994; Rommelse, Van der Stigchel, & Sergeant, 2008; Smyrnis, 2008; Turetsky et al., 2007). The smooth pursuit deficits associated with schizophrenia were first observed by Diefendorf and Dodge (1908) and, since then, smooth pursuit eye movement dysfunction has consistently been found in individuals with schizophrenia (O'Driscoll & Callahan, 2008; Smyrnis, 2008; Turetsky et al., 2007). However, under normal viewing conditions, targets move not only in the frontoparallel plane but also in depth, and tracking requires both smooth-pursuit eye movements, guided primarily by retinal slip velocity, as well as vergence eye movements guided primarily by binocular disparity, blur, and motion-in-depth signals. Psychophysical observation in humans (Rashbass & Westheimer, 1961; Regan,

Erkelens, & Collewijn, 1986; Semmlow, Yuan, & Alvarez, 1998), and electrophysiological studies in non-human primates (Gamlin & Clarke, 1995; Gamlin & Yoon, 2000; Gamlin, 2002) suggest that these two eye movement subsystems are relatively independent of one another. Nevertheless, the cortical substrates of vergence eye movements include areas such as the frontal eye fields (FEF) (e.g. Fukushima et al., 2002, 2004; Gamlin & Yoon, 2000; Gurler et al., 2011), which have been implicated in the smooth pursuit deficits in schizophrenia (Goldman-Rakic & Selemon, 1997; Holzman, 2000; Levy et al., 2010). Based on this, it seems plausible that patients with schizophrenia might exhibit vergence tracking deficits. However, to the best of our knowledge, there have been no reports on vergence tracking performance in patients with schizophrenia. Therefore, we investigated dynamic aspects of vergence tracking in healthy controls and patients with schizophrenia.

2. Methods

Twenty-four subjects with schizophrenia and schizoaffective disorder (SZ) were recruited from the outpatient psychiatry clinic

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at The University of Alabama at Birmingham to participate in this study. Twenty-three healthy controls (HC), matched on age, gender, ethnicity, and parental occupation, were recruited by advertisement in flyers and the university's newspaper. Exclusion criteria were major medical conditions, substance abuse within six months of examination, previous serious head injury, a neurological disorder, and loss of consciousness for more than 2 min. The study was approved by the Institutional Review Board of the University of Alabama at Birmingham in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, and all subjects gave written informed consent. Before signing consent, each SZ subject completed an Evaluation to Sign Consent Form.

Diagnoses were established using subjects' medical records and the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). General cognitive function was characterized by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998). The Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962) and its positive and negative subscales were used to assess mental status and symptom severity.

Participants were also excluded during vision screening if they had acuity of less than 20/40 in either eye, more than 2 lines of difference in visual acuity between the eyes, or lack of stereopsis. Each subject was examined by the same doctor who was masked to the patient's psychiatric diagnosis. Three participants (SZ = 1) were excluded during vision screening and 4 (SZ = 3) withdrew or were lost to follow up. Forty participants, 20 SZ and 20 HC, completed the study and were included in the final analyses.

2.1. Binocular vision and vergence testing

All visual measures were taken with the subject's habitual prescription in place. Distance visual acuity was measured in each eye with a projected Snellen chart at 20 feet. Near visual acuity was screened in each eye with a 20/30 isolated line of letters. Binocular vision testing included fixation disparity (Saladin card), ocular alignment with cover test at distance and near, near point of convergence break (NPC) and recovery, positive fusional vergence at near break and recovery (prism bar), stereo acuity (Randot Stereo), accommodative amplitudes (push-up) for non-presbyopes, and distance and near auto-refraction.

Based on these static measures, we have previously reported for this cohort of patients that their mean NPC (5.5 cm) was not significantly different from healthy controls (4.4 cm), and that they did not exhibit convergence insufficiency more frequently than healthy controls (Bolding et al., 2012).

2.2. Eye tracking tasks

All of the eye tracking experiments were performed in a darkened room. Each task lasted 60 s and there was a 20 s gap between each task. The task order was randomized for each participant. A chin rest and pads placed against the temples were used to minimize head movement. The chin rest was adjusted so that the bridge of the participant's nose (midpoint between the eyes) was level with the vergence tracking target and the center of the CRT described below. Eye movement data was collected with a head mounted, dual camera, video eye tracker with a 500 Hz sample rate (Eyelink II, SR Research). Head movement was tracked so that residual head movement could be removed from the eye tracking signal. Eye tracking was calibrated at the start of the session using a 9-point calibration procedure and a 1-point drift correction was performed before each task.

For the smooth pursuit task in the frontoparallel plane, we used a CRT with a flat screen set at a refresh rate of 75 Hz. The screen

was 60 cm from the participant. The target was a 1° diameter white disk with a 0.2° black dot in the center (Fig. 1B). The target was presented on a black background and the brightness was matched to that of the vergence target described below. The smooth pursuit target moved horizontally with a constant speed, triangular waveform over a range of 14°. The speed of the target was 5.6°/s, 14°/s, or 28°/s.

The vergence tracking target was mounted on the carriage of an HP 7044A XY flatbed recorder. This recorder has a 28 × 43 cm range of travel, accuracy of 0.2% full-scale, acceleration of 5080 cm/s² and a slew rate of 104 cm/s. The target was a small disk of holographic diffuser material with a black dot inscribed in the center (Fig. 1A). It was illuminated with a white LED via a fiber optic bundle. In order to match the pursuit target, the vergence target was sized so that it would form a 1° disk at the distance of the CRT. The target moved along a line that passed through the bridge of the participants nose and the center of the CRT described above. During the vergence tracking task, the target motion had a constant speed, triangular waveform in depth over a range of 20 cm starting from 30 cm away from the subject. The speed of the target was 2 cm/s, 4 cm/s, or 10 cm/s. With this arrangement, because the target speed through space was constant, the angular speed varied with target distance. However, if the angular speed is held constant, the target appears to decelerate as it approaches the subject and accelerate as it recedes. The average angular speed of the target (i.e. the angular difference between 10 cm and 30 cm divided by half the period) was 2.2, 4.4, or 11°/s respectively for a subject with a 6 cm inter-pupillary distance.

2.3. Data analyses

For initial analysis, eye movements were decomposed into saccadic and slow components. Saccades were identified using velocity, and acceleration thresholds of 22°/s and 4000°/s² respectively. Since we were interested in saccades that occurred during pursuit and tracking eye movements that could exceed 22°/s, the velocity threshold was increased by the average velocity of the eye over the preceding 40 ms (up to a limit of 60°/s).
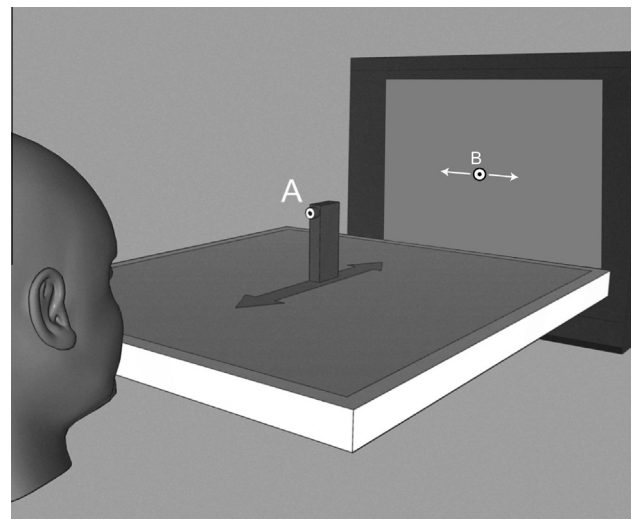

Fig. 1. Illustration of vergence pursuit and smooth pursuit stimuli used in the dynamic eye movement experiment. The arrows represent the direction of target motion and were not presented to the participant during the experiment. (A) Vergence tracking target. The white circle represents the holographic diffuser with inscribed black dot backlit by a white LED. The vergence target is mounted on the moving chassis of an X–Y plotter. (B) Smooth pursuit target. The white circle with a centered black dot represents the smooth pursuit target, which was presented on the flat screen monitor. Vergence tracking and smooth pursuit targets were presented in separate trials.

After saccades were identified, the eye movements were separated into a saccadic component and a pursuit component. In the missing parts of each component, the velocity was set to zero. Because participants tended to make saccades in one direction more than the other, the pursuit component was detrended. The saccadic component was used to calculate saccade frequency, mean duration, and mean velocity. The pursuit component was compared to the target motion to estimate the gain and error of eye position with respect to the target. Eye movement error was calculated by subtracting the target motion from the eye motion. The phase and amplitude of the pursuit component was estimated by fitting a parameterized target waveform to the actual eye motion. Gain was calculated as the ratio of the peak-to-peak amplitudes of the fitted eye motion and the actual target motion (in degrees). Tracking error for a trial was defined as the standard deviation of the difference between the target position and gaze position (gaze error, in degrees) over the course of the task trial.

2.4. Medication

None of the healthy controls were taking antipsychotics or antidepressants. Eighteen patients with schizophrenia were taking atypical antipsychotics and two were taking no antipsychotics. Ten patients with schizophrenia were taking antidepressants. There were no significant differences in the eye movement measures between the ten patients with schizophrenia taking antidepressants and the ten who were not. Four patients with schizophrenia were taking anticholinergic medication, but there were no significant differences in their eye movement measures compared to the other patients.

3. Results

There were no significant differences between the patients with schizophrenia and healthy controls for their age, gender, race, smoking, or parental socioeconomic status (Table 1).

3.1. Vergence tracking

Fig. 2 shows example eye movement traces for 0.1 Hz, 4 cm/s vergence tracking trials. Compared to the healthy control subject, the patient with schizophrenia is clearly unable to track the target effectively. When compared to healthy controls, patients with schizophrenia exhibited significantly lower gains during vergence tracking at all speeds (Fig. 3A). The difference in gains between the patients with schizophrenia and healthy controls became larger with higher target speeds (Fig. 3A; Table 2). Furthermore, the patients with schizophrenia showed larger tracking errors than healthy controls at all target speeds (Fig. 3B).

3.2. Smooth pursuit

Consistent with previous reports, the patients with schizophrenia exhibited lower gains than healthy controls during smooth pursuit. The difference increased with higher target speeds (Table 2). The patients with schizophrenia showed larger tracking errors than healthy controls at all target speeds. Gain decreased and tracking error increased with higher target speeds (Fig. 3B and D).

3.3. Relationship between vergence tracking and smooth pursuit performance

Healthy controls exhibited no significant correlation between their performance on smooth pursuit and vergence tracking tasks (Fig. 4A–C). In contrast, the patients with schizophrenia exhibited

Table 1
Demographics and clinical measures.[a]

Characteristic	HC (n = 20)	SZ (n = 20)	t/χ^2	p-Value
Age, years	36.3 ± 11.3	39.0 ± 11.4	0.75	0.46
Gender, F/M	8/12	9/11	0.10	0.75
Ethnicity, AA/C[b]	10/10	14/6	0.94	0.33
Parental SES[c]	6.7 ± 5.1	6.8 ± 5.0	0.07	0.94
RBANS[d]				
Total index	87.2 ± 12.5	73.7 ± 10.2	6.16	0.002
Immediate memory	88.6 ± 15.3	77.5 ± 12.3	6.43	0.03
Visuospatial	79.9 ± 15.7	79.9 ± 15.7	2.31	0.69
Language	95.5 ± 14.4	87.3 ± 13.7	2.95	0.11
Attention	96.4 ± 20.8	82.3 ± 12.9	4.58	0.03
Delayed memory	91.8 ± 8.4	72.5 ± 20.7	5.38	0.001
BPRS[e]				
Total	–	29.2 ± 6.8	–	–
Positive	–	4.5 ± 2.6	–	–
Negative	–	4.3 ± 2.0	–	–

Notes: χ^2 includes Yate's correction.
[a] Mean ± SD; SZ, patients with schizophrenia; HC, healthy controls.
[b] AA, African American; C, Caucasian.
[c] Socioeconomic status; ranks determined from Diagnostic Interview for Genetic Studies (1–18 scale); higher rank (lower numerical value) corresponds to higher socioeconomic status; information not available for 1 SZ.
[d] Repeatable Battery for the Assessment of Neuropsychological Status; data not available for 2 SZ and 2 HC.
[e] Brief Psychiatric Rating Scale (1–7 scale); positive (conceptual disorganization, hallucinatory behavior, and unusual thought content); negative (emotional withdrawal, motor retardation, and blunted affect); data not available for 2 SZ.
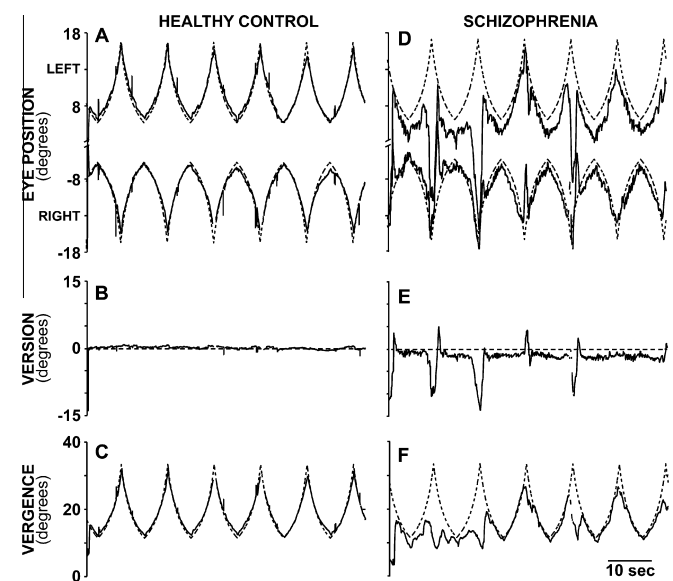

Fig. 2. Sixty seconds vergence tracking showing examples of the performance of a healthy control (A–C) and a patient with schizophrenia (D–F) (0.1 Hz; target speed = 4 cm/s). (A and D) Plots of left and right eye positions during vergence tracking. (B and E) Plots of versional (horizontal average) eye position during vergence tracking. (C and F) Plots of vergence angle during vergence tracking. Solid lines, eye position; dashed lines, target position.

a significant, albeit modest, correlation in their performance on smooth pursuit and vergence tracking tasks at all tested speeds (Fig. 4D–F).

4. Discussion

In this study, we evaluated dynamic aspects of vergence eye movements in a population of patients with schizophrenia. To evaluate their performance, we compared their vergence eye movements to that of a group of matched healthy controls. We
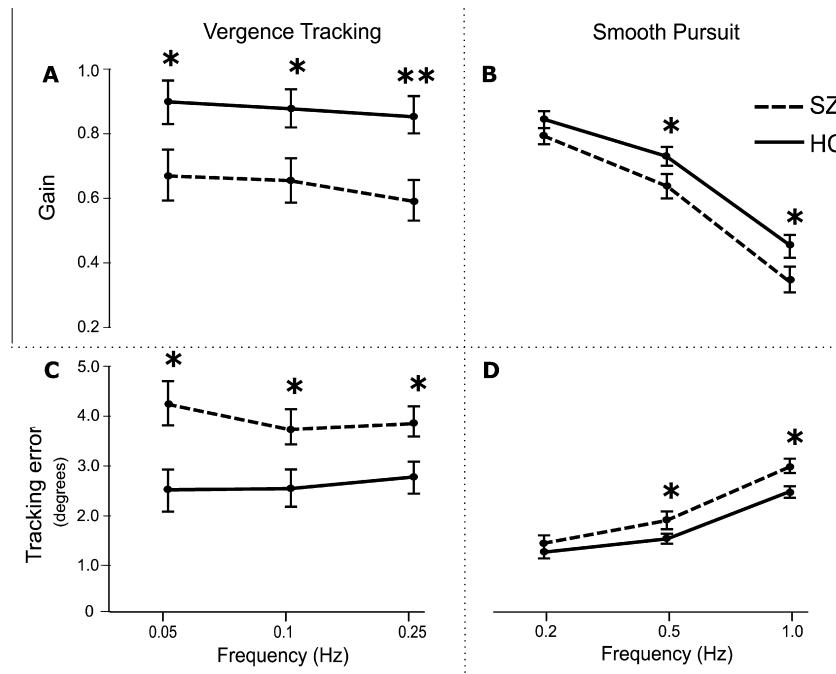
Fig. 3. Vergence tracking and smooth pursuit performance measures for healthy controls and patients with schizophrenia showing impaired performance in the patient population. Panels (A and B) show the gain for each group (mean ± SE) during vergence tracking and smooth pursuit respectively. Patients with schizophrenia exhibited reduced gain compared to healthy controls in all conditions. Panels (C and D) show the tracking error for each group (mean ± SE) during the vergence tracking and smooth pursuit respectively. Patients with schizophrenia exhibited increased tracking error compared to healthy controls in all conditions. $^*p < .05$; $^{**}p < .005$.

Table 2
Smooth pursuit and vergence tracking gains.

Eye tracking performance measure	HC mean	SZ mean	t	p-Value
Smooth pursuit gain				
0.2 Hz, 5.6°/s	0.84 ± 0.11	0.80 ± 0.16	1.12	0.133
0.5 Hz, 14°/s	0.73 ± 0.14	0.64 ± 0.18	1.94	0.029
1.0 Hz, 28°/s	0.45 ± 0.17	0.35 ± 0.19	1.92	0.030
Vergence tracking gain				
0.05 Hz, 2 cm/s	0.90 ± 0.32	0.67 ± 0.39	2.17	0.036
0.1 Hz, 4 cm/s	0.88 ± 0.28	0.65 ± 0.34	2.46	0.018
0.25 Hz, 10 cm/s	0.86 ± 0.27	0.59 ± 0.31	3.10	0.003

Mean ± SD; SZ, patients with schizophrenia; HC, healthy controls.

found statistically significant differences between these groups both in measures of vergence tracking gain and vergence tracking accuracy. Importantly, this cohort of patients were not significantly different from healthy controls in their ability to converge to static targets (Bolding et al., 2012).

4.1. Reductions in gain of tracking eye movements in patients with schizophrenia

We observed, as others have (Cerbone et al., 2003; Ettinger et al., 2003; Hong, Avila, & Thaker, 2005; Hutton et al., 2001; Smyrnis et al., 2007; Sweeney et al., 1998), that the smooth pursuit gain deficit was dependent on target velocity and that the difference between the schizophrenia group and healthy controls grew as velocity increased. Similarly, vergence tracking gain was dependent on target velocity and the difference between the groups increased as target velocity increased. Overall, the vergence tracking gain deficit was: (1) more pronounced than the deficit in smooth pursuit gain and, (2) these deficits were seen at lower target speeds. The first observation might be explained by difference in difficulties of the two tasks. For a target moving at a constant velocity through space, the angular velocity is

approximately constant for smooth pursuit but a tangent function for vergence tracking. On the other hand, the speed of the target through 3D space was linear for both conditions, so it is not clear that one of these two tasks is more difficult than the other, especially since normal individuals were able to perform the vergence task with a gain of close to 1.0.

The first observation might also be explained by the inability of the subjects to perform compensatory "catch up" vergence eye movements. During periods of low gain smooth pursuit, "catch up" saccades are used to compensate for poor smooth pursuit gain (Flechtner et al., 1997; Friedman, Jesberger, & Meltzer, 1991; Haarmeier, 1999; Levin et al., 1988). In contrast, during low gain vergence tracking we and others have observed few, if any, "catch up" vergence eye movements (Rambold et al., 2009; Semmlow, Pedrono, & Alvarez, 2007). However Semmlow, Hung, and Ciuffreda (1986) originally reported that under these conditions when the vergence angle fails to match target vergence angle, transient "catch up" vergence responses occur that effectively increase vergence gain and reduce vergence tracking error. The differences between the results of these various studies have not been resolved.

The second observation that vergence tracking gain was reduced at lower target speeds than smooth pursuit is consistent with what is known about the visuomotor control of these eye movements. Early studies showed that the frequency response of vergence eye movements was substantially lower than that of smooth pursuit eye movements (Rashbass & Westheimer, 1961). Later studies showed that while smooth vergence tracking eye movements saturated at disparity velocities of 5–7°/s (Semmlow, Hung, & Ciuffreda, 1986), smooth pursuit eye movements saturated at target velocities of ~100°/s (Leigh & Zee, 2006).

4.2. Vergence tracking and smooth pursuit deficits are correlated

We observed that vergence tracking gain and smooth pursuit gain were modestly correlated in individuals with schizophrenia.
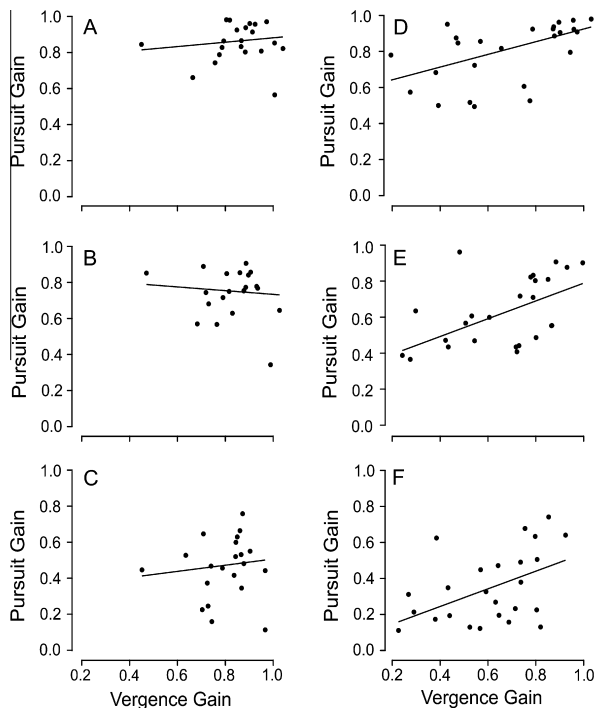
Fig. 4. Correlation of vergence tracking and smooth pursuit gain. The relationship between vergence tracking and smooth pursuit gain for healthy controls at target speeds of: (A) 5.6°/s smooth pursuit; 2 cm/s vergence tracking ($r = 0.08$; $p = 0.73$); (B) 14°/s smooth pursuit; 4 cm/s vergence tracking; ($r = 0.18$, $p = 0.41$); (C) 28°/s smooth pursuit; 10 cm/s vergence tracking ($r = 0.08$, $p = 0.71$). Overall, there was no significant correlation between vergence pursuit gain and smooth pursuit gain in healthy controls. The relationship between vergence tracking and smooth pursuit gain for patients with schizophrenia for target speeds of (D) 5.6°/s smooth pursuit; 2 cm/s vergence tracking ($r = 0.53$, $p = 0.006$); (E) 14°/s smooth pursuit; 4 cm/s vergence tracking ($r = 0.52$, $p = 0.007$); (F) 28°/s smooth pursuit; 10 cm/s vergence tracking ($r = 0.45$, $p = 0.03$). Overall the patients with schizophrenia exhibited significant correlations between vergence tracking gain and smooth pursuit gain.

These values were not correlated in healthy controls, but their vergence tracking and smooth pursuit gain varied much less, so any potential correlation was obscured. The observation of a correlation between vergence tracking gain and smooth pursuit gain in individuals with schizophrenia is consistent with our current knowledge of the visuomotor control of these eye movements. Psychophysical observation in humans (Rashbass & Westheimer, 1961; Regan, Erkelens, & Collewijn, 1986; Semmlow, Yuan, & Alvarez, 1998), and electrophysiological studies in non-human primates (Gamlin & Clarke, 1995; Gamlin & Yoon, 2000; Gamlin, 2002) suggest that these two eye movement subsystems are relatively independent of one another. However, they are not entirely independent since some neurons in the FEF (Akao et al., 2005b; Fukushima et al., 2002), MST (Akao et al., 2005a), and cerebellum (Nitta et al., 2008) of macaques are sensitive to both vergence tracking and smooth pursuit eye movements. In addition, our recent fMRI studies in normal subjects show that there is partial overlap in the FEF regions controlling vergence tracking and smooth pursuit eye movements (Gurler et al., 2011). Thus, from these data, we might expect a modest correlation between the performance of vergence tracking and smooth pursuit in patients with schizophrenia.

4.3. Medication

Eighteen of the participants with schizophrenia in this study were taking atypical antipsychotics. However, although the effect of medication has not been systematically evaluated, smooth pursuit deficits have been observed not only in medicated patients with schizophrenia, but also in unmedicated and medication naïve patients (Friedman, Jesberger, & Meltzer, 1992; Holzman et al., 1975; Reilly et al., 2008; Ross et al., 1998; Sweeney et al., 1994). Therefore, while atypical antipsychotics do not cause the smooth pursuit deficits observed in schizophrenia, we cannot rule out the possibility that atypical antipsychotics have some affect on vergence eye movements. Additional studies are needed to investigate the effect of commonly prescribed antipsychotics on vergence eye movements and binocular vision.

4.4. Etiology of vergence tracking and smooth pursuit deficits

Previous psychophysical studies have suggested that the deficits seen in smooth pursuit eye movements in patients with schizophrenia are due to deficits in visual motion processing, especially velocity discrimination (e.g. Butler & Javitt, 2005; Chen et al., 1999, 2003; Clementz, McDowell, & Dobkins, 2007; Tadin et al., 2006). Further, recent fMRI studies in patients with schizophrenia have reported that there is reduced activity in the human motion-selective complex (hMT+) and the parietal regions that subserve the processing of visual motion information for smooth pursuit eye movements (Lencer et al., 2011; Nagel et al., 2012). Given that these same cortical regions process not only visual motion signals but also the disparity and motion-in-depth signals that guide vergence tracking (e.g. Cottereau, McKee, & Norcia, 2014; Huk 2012; Cottereau et al., 2011; Likova & Tyler, 2007; Rokers, Cormack, & Huk, 2009), our finding that the gain in vergence tracking is reduced in patients with schizophrenia is consistent with these previous findings. Further studies are therefore clearly needed that use psychophysics and fMRI to investigate the processing of both cyclopean and non-cyclopean disparity and motion-in-depth signals in patients with schizophrenia.

In addition, other studies indicate the deficits seen in smooth pursuit eye movements in patients with schizophrenia are due to deficits in the integration of the retinal and extra-retinal (efference copy) signals that are required for predictive, closed-loop smooth pursuit (e.g. Hong et al., 2008; Spering et al., 2013; Sweeney et al., 1998; Thaker et al., 1999). The appropriate neural signals for such sensorimotor integration are found in the frontal eye fields of non-human primates (e.g. Gottlieb, Bruce, & MacAvoy, 1993; MacAvoy, Gottlieb, & Bruce, 1991; Mahaffy & Krauzlis, 2011; Tanaka & Lisberger, 2001). Given that the frontal eye fields also contain neurons related to vergence eye movements (e.g. Fukushima et al., 2002, 2004; Gamlin & Yoon, 2000), the reduction in the gain of vergence tracking in patients with schizophrenia might similarly be due to deficits in the integration of the disparity and extra-retinal vergence signals required for closed-loop vergence tracking. Further studies are therefore needed that investigate the ability of patients with schizophrenia to integrate the disparity and extra-retinal vergence signals required for closed-loop vergence tracking.

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