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Schizophrenia and Vergence Eye Movements

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SCHIZOPHRENIA AND VERGENCE EYE MOVEMENTS

by

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A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

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2012

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2012

SCHIZOPHRENIA AND VERGENCE EYE MOVEMENTS

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VISION SCIENCE GRADUATE PROGRAM

ABSTRACT

Background: Compared to healthy controls (HC), patients with schizophrenia (SZ) have lower smooth pursuit gain and have been reported as having a higher prevalence of convergence insufficiency. To date, however, there have been no reports on vergence tracking gain in such patients. Therefore, we investigated both static and dynamic vergence behavior in healthy controls and patients with schizophrenia.

Methods: Eye movements were recorded in multiple tasks including antisaccades, triangular waveform smooth pursuit at multiple frequencies, and triangular waveform vergence tracking of a real target at multiple frequencies. Eye position data were collected at 500 Hz using a binocular video eye tracker.

Results: Consistent with previous reports, the SZ group exhibited lower gains than HC group during smooth pursuit tasks (0.5 Hz gain: HC=0.73, SZ=0.64, $p<0.05$; 1.0 Hz gain: HC=0.45, SZ=0.35, $p<0.05$). For vergence tasks, when compared to the HC group, the SZ group did not demonstrate a significantly greater incidence of convergence insufficiency, but did exhibit significantly lower gains during vergence tracking tasks (0.05 Hz: gain: HC=0.90, SZ=0.67, $p<0.05$; 0.1 Hz gain: HC=0.88, SZ=0.65, $p<0.05$; 0.25 Hz gain: HC=0.86, SZ=0.59, $p<0.01$). There was significant correlation between the smooth pursuit and vergence tracking gains in the SZ group. The HC group did not exhibit significant correlations between the smooth pursuit and vergence tracking gains.

Conclusions: We did not observe a significantly increased rate of convergence insufficiency in patients with schizophrenia. However, our observations clearly demonstrate previously unreported vergence tracking deficits in such patients.

Keywords: Vergence; Schizophrenia; Eye movement dysfunction; Convergence insufficiency

DEDICATION

This dissertation is dedicated to the light of my life, my wife Ann.

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My sincere and heartfelt thanks

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INTRODUCTION

This dissertation reports on studies of vergence, smooth pursuit, and antisaccade eye movements in one cohort of individuals with schizophrenia and another of matched controls. Previous eye tracking studies in schizophrenia have reported abnormalities in both smooth pursuit eye movements and in antisaccade eye movement tasks (Calkins, Iacono, & Curtis, 2003; Hutton et al., 2004; Rommelse, Van der Stigchel, & Sergeant, 2008; Sereno & Holzman, 1995; Trillenberg, Lencer, & Heide, 2004; Turetsky et al., 2007; Ulrich & Veena, 2003; Zanelli et al., 2005). These studies have suggested that eye movement abnormalities may represent valuable biomarkers associated with the illness (Bender, Weisbrod, & Resch, 2007; Calkins, Iacono, & Ones, 2008; Clementz & Sweeney, 1990; Copolov & Crook, 2000; Holzman, 1992; Hutton & Kennard, 1998; Lee & Williams, 2000; Szymanski, Kane, & Lieberman, 1991; Trillenberg et al., 2004). However, few previous studies have investigated vergence eye movements in subjects with this illness and, to my knowledge, none have investigated vergence tracking of targets moving in depth. The present study therefore used high-speed binocular eye tracking and a motion-in-depth target to investigate those vergence eye movements that had not yet been studied in schizophrenia as well as previously studied eye movements (e.g. smooth pursuit eye and antisaccade eye movement tasks). Overall, we confirmed previously

reported abnormalities in eye movements in this patient population including increased antisaccade error rate, increased intrusive and leading saccades and lowered gain during smooth pursuit. In addition, we were able to identify well-defined vergence eye movement abnormalities in this patient population, including decreased gain and tracking accuracy. We can conclude that in future studies it will be important to examine vergence eye movements, a major class of eye movements that had long been neglected in schizophrenia research.

Schizophrenia

Schizophrenia is a devastating and incurable disease affecting about 0.7% of the population worldwide (MacDonald & Schulz, 2009; Tandon, Keshavan, & Nasrallah, 2008a). The etiology of schizophrenia remains unknown and there are no known cures for the disease (Tandon, Nasrallah, & Keshavan, 2010; van Os & Kapur, 2009). It is a genetically complex and heterogeneous disease and is sometimes considered as best described as a group or spectrum of diseases (Greenwood et al., 2011). While schizophrenia is a highly heritable disease, both genetics and environment play a role in its development (Tandon, Keshavan, & Nasrallah, 2008a). It is believed that genetic factors contribute about 80% of the liability for developing the disease (MacDonald & Schulz, 2009; Sullivan, Kendler, & Neale, 2003; Tandon, Keshavan, & Nasrallah, 2008b). Some of the known environmental risk factors include (1) paternal age at the time of conception, suggesting genetic abnormalities, (2) perinatal difficulties (such as low birth rate),

(3) winter birth, suggesting maternal viral infection during pregnancy, (4) maternal stress and starvation during pregnancy, (5) cannabis abuse prior to developing the illness (MacDonald & Schulz, 2009).

Clinical schizophrenia is defined by criteria found in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) published by the American Psychiatric Association or the *International Classification of Diseases* (ICD) published by the World Health Organization. As a clinical disorder schizophrenia is identified by a pattern of symptoms that occur for a prescribed period of time. In schizophrenia research the criteria from the DSM-IV-TR are commonly used (see Box, page 4).

Schizophrenia diagnosis is based on these criteria using psychiatric assessments that encompass a range of information that is both qualitative and quantitative (van Os & Kapur, 2009). The information includes symptoms, self-reports of patients, reports of relatives, friends and coworkers combined with a clinical evaluation by a mental health professional (ibid.). The symptoms most commonly associated with schizophrenia are psychosis, cognitive impairment, and incongruous emotions, but schizophrenia affects each victim differently (Tandon, Nasrallah, & Keshavan, 2009).

Because schizophrenia is a heterogeneous disease, its symptoms are often divided into groups or classes (Picchioni & Murray, 2007). One scheme (Tandon, Keshavan, & Nasrallah, 2008b) classifies symptoms as positive, negative or

cognitive: Positive symptoms include auditory, visual or tactile hallucinations, delusions (paranoid, grandiose, religious, or bizarre), and disordered speech.

DSM-IV-TR diagnostic criteria for schizophrenia:

1. Characteristic symptoms: Two or more of the following, each present for much of the time during a one-month period (or less, if symptoms remitted with treatment).
 - Delusions
 - Hallucinations
 - Disorganized speech, which is a manifestation of formal thought disorder
 - Grossly disorganized behavior (e.g. dressing inappropriately, crying frequently) or catatonic behavior
 - Negative symptoms: Blunted affect (lack or decline in emotional response), alogia (lack or decline in speech), or avolition (lack or decline in motivation)

If the delusions are judged to be bizarre, or hallucinations consist of hearing one voice participating in a running commentary of the patient's actions or of hearing two or more voices conversing with each other, only that symptom is required above. The speech disorganization criterion is only met if it is severe enough to substantially impair communication.

2. Social or occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.
3. Significant duration: Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms (or less, if symptoms remitted with treatment).

If signs of disturbance are present for more than a month but less than six months, the diagnosis of schizophreniform disorder is applied.

Negative symptoms consist of social withdrawal, inability to experience pleasure, lack of emotion, and lack of initiative. These symptoms may reduce the quality of life even more than positive symptoms. Cognitive symptoms include deficits spanning various cognitive domains, such as attention, memory, concentration and learning. Schizophrenia patients typically score on the order of one standard

deviation below the mean of a normal population on many measures of cognition (van Os & Kapur, 2009). The severity of cognitive deficits is highly correlated with the functional (occupational and social) impairment of the patient and are a core aspect of the disease (Green, 2006). Symptoms of schizophrenia often overlap with other major mental illnesses, particularly mood disorders¹ or obsessive-compulsive disorder (Thaker, 2008). Despite the heterogeneity of symptoms, the disease evolves in a stereotypical way. The onset of schizophrenia is typically in late adolescence/early adulthood. The first schizophrenic episode typically occurs between the ages of fifteen and thirty. Onset of schizophrenia outside of this age range is rare (MacDonald & Schulz, 2009). Men develop the symptoms five to ten years earlier than women (ibid.).

It is important to appreciate that schizophrenia is a neurodevelopmental disorder and that the 'onset' and diagnosis occur after the disease has been present for many years (Insel, 2010). It has been shown that the longer psychosis remains untreated the poorer the prognosis (Mcglashan, 1999). Therefore, early detection and treatment should lead to a better prognosis and reduced treatment costs. Thus, diagnostic tools and biological markers that can identify schizophrenia very early in the course of the disease would be particularly valuable.

There are several biological markers that have been repeatedly and reliably associated with schizophrenia (Turetsky et al., 2007). Some of the most

¹ The term schizoaffective disorder is used when an individual has thought disorder symptoms of schizophrenia, combined with mood disorder symptoms associated with bipolar disorder or depression.

frequently studied biomarkers in schizophrenia research are eye movement deficits (Calkins, Iacono, & Ones, 2008; Haraldsson, 2007; Ross et al., 2003). Because eye movement dysfunction appears to be a stable trait it may be possible to use it for early detection of the disease in some populations (Rommelse et al., 2008).

Eye Movements

Eye movements enhance visual acuity. Eye movements keep images stabilized on the retina to reduce blur. Eye movements also direct or keep the **fovea**, the highest acuity central portion of the retina, on targets of interest (Kowler, 2011). Because most of us have two eyes and binocular vision, appropriate eye movements are made to keep the fovea of both eyes fixated on the same target (Blake & Wilson, 2011).

Eye movements can be classified in many ways. Perhaps the best classification scheme comes from Leigh and Zee (2006). In their book, *The Neurology of Eye Movements*, Leigh and Zee divide eye movements into the following functional classes:

- **Vestibular** eye movements, reflexive movements that stabilize images on the retina during sudden movements of the head.
- **Fixation**, a voluntary action that stabilizes the fovea on stationary objects or points of regard.

- **Optokinetic** eye movements, reflexive eye movements that stabilize large moving visual fields on the retina.
- **Smooth pursuit** eye movements that keep the fovea on moving targets. These movements are voluntary but cannot be performed without a visual target.
- **Nystagmus** eye movements, reflexive movements that reset the eye during prolonged rotation or optokinetic eye movements thus preventing the eye from becoming pinned at the end of its range of travel.
- **Saccades**, which allow the rapid shift of gaze from one target to another. Saccades can be voluntary or involuntary.
- **Vergence** eye movements that shift the gaze in depth and keep both foveae aligned on a target. Most vergence eye movements are voluntary, however large field looming stimuli and sudden forward translations of the head can induce short latency vergence eye movements.

Because eye movements vary in several important ways, many other distinctions can be made. Eye movements can be divided into **conjugate** (movement is the same in both eyes) and **disconjugate** (the eyes move a different distance or direction). Using conjugate eye movements we can look from one target to another that differs only in direction. However, targets at different distances require the eyes to change their relative orientations; looking from one target to another at a different distance requires disconjugate

movements (Straumann, 2007). Vergence eye movements are disconjugate movements that move the eyes between targets that vary in distance (Busetini, Davison, Gamlin, & Squire, 2009; Gamlin, 2002; Schor & Ciuffreda, 1983). Smooth pursuit is a conjugate eye movement that facilitates tracking of a small target against a background that differs in velocity from the target (Krauzlis, 2004) for example, watching a bird in flight against the clouds in the sky. This differs from saccades, the eye movements that are used to bring the fovea to a new target or location (McDowell, Dyckman, Austin, & Clementz, 2008). These rapid eye movements are ballistic in nature and are not generally subject to modification after initiation. The remaining eye movements, vestibular stabilization or optokinetic following responses, stabilize the view during movements of the head or the visual scene (Angelaki & Squire, 2009; Kheradmand & Zee, 2011; Mustari, Ono, & Squire, 2009).

Eye movements can also be broken down into reflexive or involuntary eye movements and non-reflexive or voluntary eye movements (Johnston & Everling, 2008; McDowell et al., 2008). Examples of reflexive eye movements are those driven by large field visual stimuli (optokinetic response) and those driven by the vestibular system (vestibulo-ocular reflex). These are movements that stabilize the visual scene on the retina (Angelaki, 2004; Crawford & Vilis, 1991; Lisberger, Miles, Optican, & Eighmy, 1981). Voluntary eye movements such as saccades are generally initiated by the desire to look at a particular location in space and they are indicative of overt attention (Kowler, 2011). Saccades can be executed to remembered or calculated locations (Pierrot-Deseilligny, Rivaud, Gaymard, &

Agid, 1991). Each eye movement can be driven by several signals or cues and various eye movements can interact. Thus, eye movements can range from reflexive to cognitively demanding.

Predictive eye movements are of particular interest. When target motions are predictable, accuracy can increase greatly and latencies can drop to zero if anticipatory motions can be made (Kowler, 2011; Stephen G Lisberger, 2010). In a repetitive task the subject forms an internal model or prediction of the target's motion and can use this to increase the accuracy and speed of eye movements (Barnes, 2008; Isotalo, Lasker, & Zee, 2005).

Antisaccades are saccades that require inhibition of a natural saccade to a novel target (Hutton & Ettinger, 2006). In an antisaccade task the subject is asked to fixate on a small target. He or she is instructed that a second small target will appear a small distance away on the left or right of the first target. When this target appears he or she should look in the opposite direction, but at an equal distance from the first target. This task requires the subject to suppress the natural saccade to the new target and execute a voluntary saccade to its mirror image location. Normal subjects will occasionally make an erroneous saccade to the new target and will follow this with the requested antisaccade (Ethridge, Brahmhatt, Gao, McDowell, & Clementz, 2009). Schizophrenic subjects make more of these errors (Calkins et al., 2003; Harris, Reilly, Keshavan, & Sweeney, 2006; Radant et al., 2007; Sereno & Holzman, 1995).

In this study we compared smooth pursuit, vergence, and antisaccade eye movements in individuals with schizophrenia to the same eye movements in healthy controls. Because schizophrenia is a neurological disorder and the eye movement deficits have a neuropathological basis (Clementz & Sweeney, 1990; Goldman-Rakic & Selemon, 1997; Holzman, 1991) we will briefly discuss the neural substrates of smooth pursuit, vergence, and antisaccades.

Neural Substrates of Eye Movement

The neural basis of oculomotor control has been studied extensively. Indeed it is the most studied and perhaps the best understood network in the brain (Kennard & Leigh, 2008; Beatriz Luna, Velanova, & Geier, 2008). Many of the neural substrates were initially investigated in non-human primates using electrophysiology (Johnston & Everling, 2008; Kowler, 2011; Lynch & Tian, 2006; Ramnani, 2011; Schutz, Braun, & Gegenfurtner, 2011; Tehovnik, Sommer, Chou, Slocum, & Schiller, 2000; Van Essen & Gallant, 1994). Lesion studies and clinical neurology have also provided much information about the neural substrates of eye movement in humans (Gaymard & Pierrot-Deseilligny, 1999; Müri & Nyffeler, 2008; Ramat, Leigh, Zee, & Optican, 2007). Studies have also been done in humans intraoperatively using stimulation, and non-invasively using TMS, EEG, and functional neuroimaging.

Figure 1 shows cortical areas important for smooth pursuit, antisaccades, and vergence include the dorsolateral prefrontal cortex (DLPFC), frontal eye fields (FEF), supplementary eye fields (SEF), posterior eye fields (PEF) and middle

temporal areas (MT/MST) (Luna & Sweeney, 1999). Since attention, volition, and eye movements are so entwined, these areas are also crucially involved in attention and cognition (Bisley, 2011; Carrasco, 2011; Roitman, Keefe, Harvey, Siever, & Mohs, 1997; Sweeney, Clementz, et al., 1994). Because the neural substrates of eye movement have been so extensively investigated, the study of eye movement deficits may provide profound insights into the neuropathology of schizophrenia (Campanella & Guerit, 2009; Kennard & Leigh, 2008; Gaebel, 1989; Hutton, 2008; Leigh & Kennard, 2004).

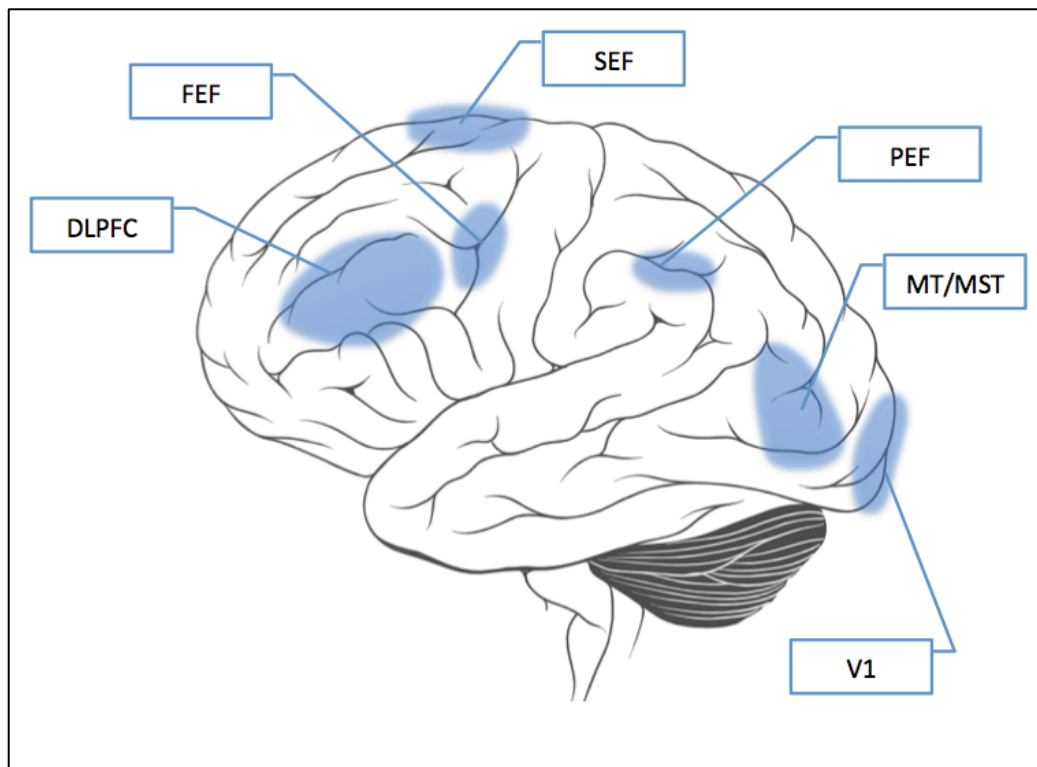


Figure 1 Cortical areas important for smooth pursuit, antisaccade, and vergence eye movements. DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; SEF, supplementary eye fields; PEF, parietal eye fields; MT/MST, human analog of macaque middle temporal and middle superior temporal areas; V1, primary visual cortex.

Eye Movement Dysfunction in Schizophrenia

There are many compelling reasons to investigate the vergence eye movements of individuals with schizophrenia. Abnormalities of eye movement related to schizophrenia have been studied for over one hundred years. Some kinds of eye movement are affected by schizophrenia and some are not (Levin et al., 1982; Levy et al., 1994).

The two classes of eye movement most frequently studied in schizophrenia are antisaccades and smooth pursuit (Sereno & Holzman, 1995). Smooth pursuit eye movements have been shown to be abnormal often with decreased gain in numerous studies of patients with schizophrenia (Smyrnis 2008; Rommelse et al. 2008; Turetsky et al. 2007; Reuter & Kathmann 2004; Trillenberget al. 2004; McDowell & Clementz 2001; Holzman 2000; Hutton & Kennard 1998; Levy et al. 1994; Abel et al. 1992; Gaebel 1989; Holzman 1985). Patients with schizophrenia have also been shown to have difficulty in the antisaccade eye movement task with a significantly greater number of errors than normal subjects (Calkins et al., 2003; Harris et al., 2006; Radant et al., 2007; Sereno & Holzman, 1995). Less extensively studied, but also observed, are deficits in memory guided saccade tasks (Gooding & Basso, 2008; Levy et al., 2009). Such oculomotor abnormalities are reported at rates of 40 to 80% in schizophrenia (Holzman, 2000), with some of the variation in reported rates due to variation in experimental procedures (Smyrnis 2008; Gooding & Basso 2008; Levy &

Sweeney 2009). The basis of these eye movement abnormalities is not currently known, but they are present in both medicated and unmedicated patients (Reilly et al., 2008; Ulrich & Veena, 2003).

Some types of eye movement, however, are not disturbed in schizophrenia. Vestibulo-ocular responses are not affected (Levy, Holzman, & Proctor, 1978). However patients have difficulty overriding this response with fixation (Warren & Ross, 1998; Yee et al., 1987). Full field optokinetic responses are not disturbed (Latham, Holzman, Manschreck, & Tole, 1981). In general, reflexive eye movements are not disturbed in patients with schizophrenia, while voluntary eye movements are affected.

While these deficits are robust and reliable, they have failed to identify abnormalities that are specific to schizophrenia (Rommelse et al., 2008; Szymanski et al., 1991). Even though these abnormalities are not specific to schizophrenia, recent studies have shown that combined measures of eye movements and other anomalies can be used to distinguish schizophrenia from other populations with good sensitivity and specificity (Chapelle et al., 2005; Price et al., 2006; Sponheim, Iacono, Thuras, & Beiser, 2001). Thus, any observed deficits in a combination of traditional and novel vergence eye movement measures could form an additional biomarker that reliably separates schizophrenics from normal volunteers.

Furthermore, schizophrenia is a genetically complex disease. Using eye movement dysfunction as a biomarker for risk factors and endophenotypes can

help deal with the complexity of the disease. Eye movement dysfunction can serve as a biomarker for risk factors, allowing investigators to reduce the heterogeneity of the disease (Bender et al. 2007; Trillenberget al. 2004; Lee & Williams 2000; Copolov & Crook 2000; Calkins & Iacono 2000; Hutton & Kennard 1998; Holzman 1994; Holzman 1992; Szymanski et al. 1991; Clementz & Sweeney 1990). Characterizing the eye movement function in detail can also provide information about the underlying neurological disorder that leads to and springs from schizophrenia (Büttner-Ennever, 2008; Leigh & Kennard, 2004). Because eye tracking measures tap into cognitive operations that are abnormal in schizophrenia, such as attention and working memory, they may be key to providing biomarkers that could be used to identify new drugs that treat more than just the psychosis and positive symptoms. For these reasons, there has been extensive research into the effect of schizophrenia on eye movements. In fact, all but one of the basic classes of eye movement (saccades, smooth pursuit, vestibular, optokinetic, nystagmus, and fixation) have been examined rigorously. The exception is vergence eye movements.

Vergence and Schizophrenia

Vergence eye movements have not previously been rigorously characterized in schizophrenics, but the following abnormalities have been reported. Levin et al. (1982) reported that they observed a higher rate of intrusive saccades in vergence tracking in patients than in controls. However, they did not report the

actual rates or the statistical significance of the difference. Buchanan & Heinrichs (1989) and Flach et al. (1992) reported a higher incidence of convergence insufficiency and ocular alignment issues. Both of these reports are based on subjective, unquantified judgments of convergence insufficiency and no measures of eye position, near point of convergence, phoria, or positive fusion vergence ranges were made. In a prospective study of high-risk individuals, Schiffman et al. (2006) reported a higher rate of ocular alignment abnormalities in individuals who went on to develop schizophrenia.

In addition to these reports, known deficits in other classes of eye movements suggest that vergence may be disturbed too. A large body of evidence suggests that smooth pursuit eye movements are impaired in schizophrenia (Calkins, Iacono, & Curtis, 2003; Hutton et al., 2004; Rommelse, Van der Stigchel, & Sergeant, 2008; Sereno & Holzman, 1995; Trillenberg, Lencer, & Heide, 2004; Turetsky et al., 2007; Ulrich & Veena, 2003; Zanelli et al., 2005). Since some structures such as the FEF participate in the control of both vergence eye movements and smooth pursuit (Gamlin, 2002), it is possible that vergence eye movements will be impaired as well.

There are two compelling reasons to study vergence eye movements in particular in patients with schizophrenia. First, there are many standardized clinical tests of binocular vision and vergence eye movements. These clinical tests are already regularly used in standard eye exams. There are no such standardized tests of smooth pursuit. So, identifying and characterizing vergence eye movement dysfunction will make large scale, multisite studies of the eye

movement dysfunction endophenotype easier to design and execute. It will also make possible retrospective studies that are based on a large body of previously collected clinical data. Second, oculomotor dysfunction, particularly binocular vision problems, could negatively impact cognitive therapy (Reding et al, 1988; Grosswasser et al, 1990). Vision therapy could enhance cognitive therapy and thus help alleviate the greatest contributor to negative functional outcomes in schizophrenia.

Finally, vergence eye movements are the only class of eye movements that have not been investigated quantitatively in schizophrenia.

Note on Dissertation Format

The body of the dissertation consists of this introduction, two independent manuscripts reporting results from experiment one and two, and a discussion. In the first paper, we examine subjective and objective aspects of binocular vision dysfunction and convergence insufficiency in patients with schizophrenia. In the second paper, we examine the dynamics of vergence eye movements in patients with schizophrenia.

OCULAR CONVERGENCE DEFICITS IN SCHIZOPHRENIA

by

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and Paul D. Gamlin

In preparation for *Schizophrenia Research*
Format adapted for dissertation

Ocular convergence deficits in schizophrenia

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Abstract

Individuals with schizophrenia have been reported to exhibit a higher prevalence of convergence insufficiency than the “normal” adult population. The purpose of this study was to determine if individuals with schizophrenia exhibit clinical signs of convergence insufficiency (CI) and to determine if the Convergence Insufficiency Symptom Survey (CISS) is an effective instrument for identifying CI in this population.

Twenty participants with schizophrenia (SZ) and 20 healthy controls (HC) completed the study. The prevalence of CI (15%) was slightly higher than reported norms in the SZ group, but the difference was not significant. The SZ group had significantly higher scores on the CISS than the HC group, but the CISS scores did not correlate with clinical measures of CI in individuals with schizophrenia. Further study is needed to determine why individuals with schizophrenia reported symptoms associated with CI even though clinical measures did not support this diagnosis.

Keywords: convergence insufficiency, schizophrenia, vergence, oculomotor, endophenotype, eye movement dysfunction

1. Introduction

The neural changes underlying schizophrenia are not well understood. One strategy for discerning the underlying neuropathology has been investigation of the subtle neurophysiological anomalies associated with schizophrenia (Ritsner, 2009; Turetsky et al., 2007). Eye movement dysfunctions in particular have received much attention because the neural substrates of oculomotor function are some of the best understood systems in the brain and because the eye movement impairments are associated with other neurocognitive measures (Donohoe et al., 2006; Hutton et al., 2004; Levy, Mendell, & Holzman, 2004).

Smooth pursuit and saccades have been extensively studied in patients with schizophrenia (Levy et al., 1994; O'Driscoll & Callahan, 2008). The smooth pursuit deficits associated with schizophrenia were first reported by Diefendorf and Dodge (1908). Later deficits in the antisaccade task were identified as well (Fukushima et al., 1990). Specifically, individuals with schizophrenia demonstrate lowered smooth pursuit gain and an increased rate of errors during antisaccade tasks. These deficits persist during treatment (Levy, Lipton, Holzman, & Davis, 1983) and are also found in asymptomatic relatives (Calkins et al., 2003; Kathmann, Hochrein, Uwer, & Bondy, 2003; Ross et al., 2002) but they differ in their relationship to other cognitive deficits (Zanelli et al., 2009). There are competing theories as to the etiology of the eye movement deficits, but there has been no definite determination of the cause of either the smooth pursuit or the antisaccade deficit. Other eye movement and visual perceptual deficits have also

been investigated, albeit not as thoroughly as the smooth pursuit and antisaccade deficits. In particular, even though there are suggestions that vergence eye movements may be disturbed, there have been no rigorous studies of the deficit.

Levin et al. (1982) reported that they observed a higher rate of intrusive saccades in vergence tracking in patients than in controls. However, they did not report the rates of intrusive saccades or the statistical significance of the difference. Also, in a prospective study of high-risk individuals, Schiffman et al. (2006) reported a higher rate of ocular alignment abnormalities in individuals who went on to develop schizophrenia. They suggested that there may be a pre-morbid relationship between oculomotor disorders and schizophrenia spectrum disorders, but their study did not examine convergence insufficiency or any specific vergence eye movement deficit.

One specific deficit of vergence eye movements that has been examined in several studies is convergence insufficiency (CI). CI is a deficit in the ability to converge the eyes to near targets. Suggestions that CI may be present in individuals with schizophrenia derive from perceptual tests that were included in a study by Flach (1992) and from tests of convergence facility that are included in a battery of tests measuring neural soft signs (NSS) and that have been administered to individuals with schizophrenia in several studies (Chan, Xu, Heinrichs, Yu, & Wang, 2009; Hobart, Goldberg, Bartko, & Gold, 1999). However, these reports were based on subjective judgments of convergence insufficiency and no measures of eye position, near point of convergence, phoria,

or positive fusion vergence ranges were made. To date, there have been no definitive studies of CI in individuals with schizophrenia.

Known deficits in other classes of eye movements also suggest that vergence may be disturbed. A large body of evidence shows that smooth pursuit eye movements are impaired in schizophrenia (Calkins, Iacono, & Curtis, 2003; Hutton et al., 2004; Rommelse, Van der Stigchel, & Sergeant, 2008; Sereno & Holzman, 1995; Trillenber, Lencer, & Heide, 2004; Turetsky et al., 2007; Ulrich & Veena, 2003; Zanelli et al., 2005). Since many structures such as the FEF participate in the control of both vergence eye movements and smooth pursuit (Gamlin, 2002), it is possible that vergence eye movements will be impaired as well.

The current study was designed to measure clinical, objective signs of CI in a population of individuals with schizophrenia and age matched healthy controls. A secondary goal of the study was to test the validity of the Convergence Insufficiency Symptom Survey (CISS) for detecting symptoms associated with CI in both study groups. The CISS is an instrument to measure the symptoms of CI and it has been validated in adults 19-30 years of age (Rouse et al., 2009). The validity of the CISS has not been previously been tested for individuals with schizophrenia.

2. Experimental materials and methods

Twenty-four subjects with schizophrenia and schizoaffective disorder (SZ) were recruited from the outpatient psychiatry clinic 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 two minutes. The study was approved by the Institutional Review Board of The University of Alabama at Birmingham, 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, Tierney, Mohr, & Chase, 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 two 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. Clinical assessment

All visual measures were obtained 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 vergences at near break and recovery (prism bar), stereo acuity (Randot Stereo), accommodative amplitudes (push-up) for non-presbyopes, and distance and near auto-refraction.

Near point of convergence was measured three times with the Astron International (ACR/21) Accommodative Rule (Gulden Ophthalmics, Elkins Park, PA) using a printed fixation target with a single column of 20/30 letters. The target was initially positioned at eye level, 40 cm from the patient's bridge. The target was moved toward the subject's eyes until either the subject reported seeing that the target doubled or the examiner noticed a break in fusion (one eye drifted off target). If the subject was not able to regain fusion, the distance from the eyes where fusion was lost was noted as the NPC break point. The target was then pulled away from the participant's eyes until fusion was regained and this distance was documented as the recovery point. The three NPC measures were averaged for analysis.

Positive fusional vergences were measured three times with a horizontal prism bar (Gulden B-16 horizontal prism bar) while the patient fixated a hand-held fixation target (Gulden fixation stick #15302) with a single column of 20/30

letters held at eye level at a distance of 40 cm. Base out prism was introduced in gradient steps on the prism bar while the patient was asked to report if the target became blurred or double. The prism amounts where blur and then double vision were reported were recorded as the blur and break values respectively. Once fusion had been lost, the prism amount was decreased until fusion was recovered and this prism amount was recorded as the recovery value. If the examiner noticed a loss of fusion without the report of double vision, this value was also recorded as the break value. Three fusional vergence measures were taken and the results were averaged.

The Convergence Insufficiency Symptom Survey (CISS) was administered to each subject at the beginning of the visit before any other testing and again at the conclusion of the examination. The survey contains 15 questions regarding how the subject's eyes feel when reading or doing close work. The examiner asked each question verbally and the participants were asked to respond with one of the phrases/words printed on a hand held card (never, infrequently, sometimes, fairly often, or always). Each response was scored between 0 (never) and 4 (always) to give a final symptom score range of 0-60. For analysis, the two symptom scores were averaged.

2.2. Classification of CI

Participants were categorized as having convergence insufficiency if they met the following three criteria: phoria at near 4 prism diopters or more greater exo than at distance, an NPC break greater than 5.5 cm, and near positive fusional

vergences (PFV) less than 15 prism diopters or failing Sheard's criteria (PFV less than twice the near phoria). Participants were classified as symptomatic if the CISS average was 21 or greater. Results for the participants with schizophrenia were compared to published norms (Daum, 1988; Rouse et al., 2004; Rouse et al., 2009). Statistics were calculated in R (the R project for statistical computing). Group means were compared using t-tests (two-tailed, Welch correction for unequal variance) unless otherwise noted.

3. Results

3.1. Group matching

There were no significant differences in age, race, gender, smoking status, or parental SES between SZ and HC participant groups (Table 1).

3.2. CISS

Eight SZ and one HC met or exceeded the cutoff score of 21 on the CISS (Figure 1). The mean CISS score (18.6 ± 9.9) for the SZ group was significantly higher than that of the HC group (9.9 ± 5.5). In addition, as a group, the SZ group exhibited significantly ($p=0.002$) higher CISS scores than those reported for normal binocular volunteers (11.0 ± 8.2) (Rouse, 2004).

3.3. Clinical measures

3.3.1. CI criteria measures

Three of the SZ participants and one of the HC participants met all three of the diagnostic criteria and were classified as convergence insufficient (Table 2). Seven SZ and 6 HC had a receded NPC. The mean NPC for the SZ and HC groups were 5.5 cm and 4.4 cm respectively, which was not a significant difference ($p=0.207$). Eight SZ and 9 HC met the cover test criteria for CI. The mean phoria difference in the cover test for the SZ group was -3.95 prism diopters while the HC group was -2.35 prism diopters. The phoria differences between groups were also not significant ($p=0.626$). Seven SZ and 1 HC failed Sheard's criteria. This difference was significant ($p=0.022$). With our cut off values, the chi-square test for differences between NPC and phoria classifications were not significant ($p=0.736$, $p=0.749$ respectively).

3.3.2. Interrelation of CI clinical measures

In the 40 participant cohort as a whole, highly significant correlations were found between all of the measures used to form the CI criteria (all $p<0.0005$). In the 20 SZ participants, significant correlations were found between all of the measures used to form the CI criteria (all $p<0.05$). Thus, for example, if patients were to have receded NPC then they were more likely to have reduced PFVs. In the 20 HC, significant correlations were found between all of the measures used to form the CI criteria (all $p<0.05$).

3.3.3. Relationship of CISS scores and clinical measures in the SZ group

Eight SZ participants exceeded the cutoff score of 21 on the CISS (Table 2) indicating that they experienced symptoms consistent with CI. There were no significant differences in near point of convergence break or recovery, vergence break or recovery, distance or near phoria, phoria differences at near vs. distance, stereo acuity, or fixation disparity between the SZ participants who scored at or above the CISS cutoff and those who scored below the cutoff.

The mean CISS score for the SZ participants with CI was 15.83 while the mean score for the SZ participants without CI was 19.06, which was not a significant difference (Table 3). The three SZ participants who met the clinical criteria for CI all scored below 21 on the CISS (Table 3). There was no significant relationship between the CISS scores and the clinical measures of convergence insufficiency.

3.3.4. Relationship of CISS and clinical CI measures with psychometric tests

SZ and HC had significantly different scores on the RBANS ($p=0.002$). In the SZ group there was no significant difference between those who scored 21 or above and those who did not in the BPRS total, BPRS negative subscale, BPRS positive subscale, the RBANS total or its subscales. There was no significant correlation between the CISS mean score and any of the psychometric total scores or sub scores in either group.

There was no significant difference between SZ with CI and those without and any of the psychometric total scores or sub scores. There was no significant correlation between the NPC break, phoria measures, or vergence ductions and any of the psychometric total scores or sub scores.

4. Discussion

In this study, we looked at two different aspects of convergence insufficiency (CI) in a population of patients with schizophrenia. We evaluated clinical measures of CI as well as subjective self-reports of symptoms associated with CI. To evaluate the performance of the participants with schizophrenia, we compared their vergence eye movements to that of a group of healthy controls.

We found that SZ scored significantly worse on the CISS than HC, suggesting more prevalent convergence deficits. However, except for Sheard's criteria, we did not find a statistically significant difference between the groups in any of the measures of CI.

4.1. Sheard's criteria

Sheard's criteria states that patients should have 'a fusional vergence reserve at least twice the magnitude of [their] heterophoria' (Sheard, 1938). Failure of the criteria predicts binocular vision discomfort particularly when the patient is fatigued. Proposed by Sheard in the 1930s, this rule is frequently used by optometrists to prescribe prism. As yet, there have been few studies to test its validity. The studies that have been done generally support Sheard's criteria, but suggest that it may not detect some patients who are symptomatic (Daum,

Rutstein, Houston, Clore, & Corliss, 1989). Studies also suggest that this test is better at predicting discomfort in exophores than esophores (Sheedy & Saladin, 1978). The significant difference between the groups may indicate that, even though the patients with schizophrenia have normal ranges of convergence, they have less reserve capacity and may experience binocular vision problems when fatigued.

4.2. Relationship of CISS scores and CI clinical measures in patients with schizophrenia

There was no correlation between the CISS ratings and CI clinical measures in the SZ group. Of the three SZ participants diagnosed with CI, none had a CISS score greater than or equal to 21. In presumed non-schizophrenic adults, the CISS has shown good sensitivity (97.8%) for identifying symptomatic CI individuals (Rouse et al., 2004). In this study, the CISS did not discriminate SZ participants who had clinical findings indicating CI from those who did not.

Of the SZ participants who did not have CI, 8 of them scored 21 or greater on the CISS. The large number of false positives on the CISS in the SZ group may suggest that the participants with schizophrenia experience visual difficulties causing symptoms related to CI. It is also possible that patients failed to understand the questions listed in the scale. Patients with schizophrenia have cognitive deficits in several domains. If this were the case then we would expect the CISS scores to correlate with the RBANS scores because the RBANS is a sensitive and well validated indicator of cognitive deficits associated with schizophrenia (Gold, Queern, Iannone, & Buchanan, 1999; Wilk et al., 2002).

However, the CISS scores did not correlate with the RBANS scores or any of its subscales. Therefore, while the two groups have significantly different results on both the CISS and the RBANS, they seem to be measuring different underlying problems.

A second possibility is that while the clinical measures of CI are objective tests, the scores on the CISS are based on subjective self-reports of symptoms consistent with CI. It is possible that the SZ group scored higher because they rate the same symptoms differently than the HC group. One way to address this possible self-report bias would be to embed the CISS questions in a larger battery of similarly phrased questions on an unrelated topic. This might allow one to separate the response bias and the effect due to the CI symptoms.

A final consideration is that the CISS may be sensitive to visual deficits that are not detected by the clinical measures of CI, possibly some dynamic aspect of vergence eye movements that is not measured well by the clinical tests of CI. It has been observed that patients with schizophrenia exhibit an increased incidence of visual dysfunction in some eye movement tasks, but not in others. Patients with schizophrenia exhibit problems in cognitively demanding eye movement tasks, but not with reflexive eye movements such as vestibular ocular response and simple voluntary eye movements such as saccades to novel targets (Latham et al., 1981; Yee et al., 1987). In fact, in our laboratory we have observed that schizophrenia patients have lowered vergence tracking gain compared to controls (Bolding et al., 2012).

4.3. Vergence eye movement deficits in schizophrenia

The two eye movement deficits that have been studied most extensively, smooth pursuit gain and increased errors on the antisaccade task, are not specific to schizophrenia and are not present in all patients with schizophrenia (Holzman, 2000). Therefore, they are not a useful tool, as yet, for the diagnosis of schizophrenia. However, they do however provide insights into the neuropathology of schizophrenia and have been useful endophenotypes to reduce heterogeneity in studies of the complex genetics of schizophrenia (Calkins et al., 2008). Examining additional classes of eye movements to characterize what is and is not affected by the disease may refine our understanding of the neural basis of the eye movement dysfunctions in schizophrenia. Because the neural substrates of vergence overlap with those of smooth pursuit (Lynch & Tian, 2006), they are a particularly interesting class of eye movements to investigate in patients with schizophrenia.

There are at least two additional compelling reasons to study CI in patients with schizophrenia. First, there are many standardized clinical tests of CI. These clinical tests are regularly used in standard eye exams. In contrast, there are no such widely used clinical tests of smooth pursuit or antisaccades. Thus, identifying and characterizing vergence eye movement dysfunction will make large scale, multisite studies of the eye movement dysfunction endophenotype easier to design and execute. It will also make possible retrospective studies that are based on a large body of previously collected clinical data. Second, oculomotor dysfunction, particularly binocular vision problems such as

convergence insufficiency, could negatively impact cognitive therapy (Groswasser, Cohen, & Blankstein, 1990; Reding & Potes, 1988). Vision therapy could enhance cognitive therapy and thus help alleviate the greatest contributor to negative functional outcomes in schizophrenia.

In conclusion, contrary to previous reports, patients in this study with schizophrenia did not exhibit a higher prevalence of CI. However, 40% of the individuals in this study with schizophrenia did report symptoms associated with CI. The CISS may not be an appropriate tool to assess prevalence of convergence insufficiency in individuals with schizophrenia. Further study is needed to determine why individuals with schizophrenia are reporting symptoms associated with CI even though clinical measures do not reveal the deficit.

5. Author Disclosure

5.1. Contributors

M.S.B, K.B.H., P.D.G., and A.C.L. designed the experiments. M.S.B. and K.B.H. performed the experiments and analysed the data. M.S.B, T.J.G., K.B.H., P.D.G., and A.C.L. wrote the paper.

5.2. Conflict of Interest

No authors have conflicts of interest to report in association with this manuscript.

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Tables

Table 1. Demographics and clinical measures^a

Characteristic	HC (n = 20) ^f	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 unless indicated otherwise; SZ, schizophrenia; HC, healthy control

^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

^f 18 SZ were treated with second generation antipsychotics and 2 SZ were not taking antipsychotics

Table 2. CISS scores and CI clinical measures, between group comparisons^a

Criterion Measure	HC (N = 20)	SZ (N = 20)	t/ χ^2	p-value
CISS	9.9 \pm 5.5	18.6 \pm 9.9	t=3.43	0.001
< 21	19	12		
\geq 21	1	8		
CI				
<i>CI negative</i>	19	17	Fischer	0.60
<i>CI positive</i>	1	3	Exact Test	
NPC criteria				
\leq 5.5 cm	14	13	$\chi^2=0.11$	0.73
$>$ 5.5 cm	6	7		
Sheard's criteria				
<i>True</i>	1	7	Fischer	0.02
<i>False</i>	19	13	Exact Test	
Phoria criteria				
<i>True</i>	9	8	$\chi^2=0.10$	0.75
<i>False</i>	11	12		
NPC break (cm)	4.4 \pm 2.37	5.5 \pm 2.95	t=1.30	0.20
NPC recover (cm)	6.88 \pm 3.28	8.45 \pm 3.02	t=1.57	0.12
Cover test (PD^b)	-2.35 \pm 3.45	-3.95 \pm 6.76	t=0.94	0.35

Note: χ^2 statistic includes Yate's correction. Fischer's exact test was used when there were less than 5 cases in a cell in a given contingency table.

^a Mean \pm SD unless indicated otherwise; SZ, schizophrenia; HC, healthy control

^b PD prism diopters, near phoria – distance phoria

Table 3. SZ CISS Scores and CISS Classification Frequency by CI diagnosis^a

CISS Scores	CI positive	CI negative
<i>mean</i>	15.83 ±1.25	19.06 ±10.72
<i>n < 21</i>	3	9
<i>n ≥ 21</i>	0	8

^a Mean ± SD unless indicated otherwise; SZ, schizophrenia; CISS, Convergence Insufficiency Symptom Survey

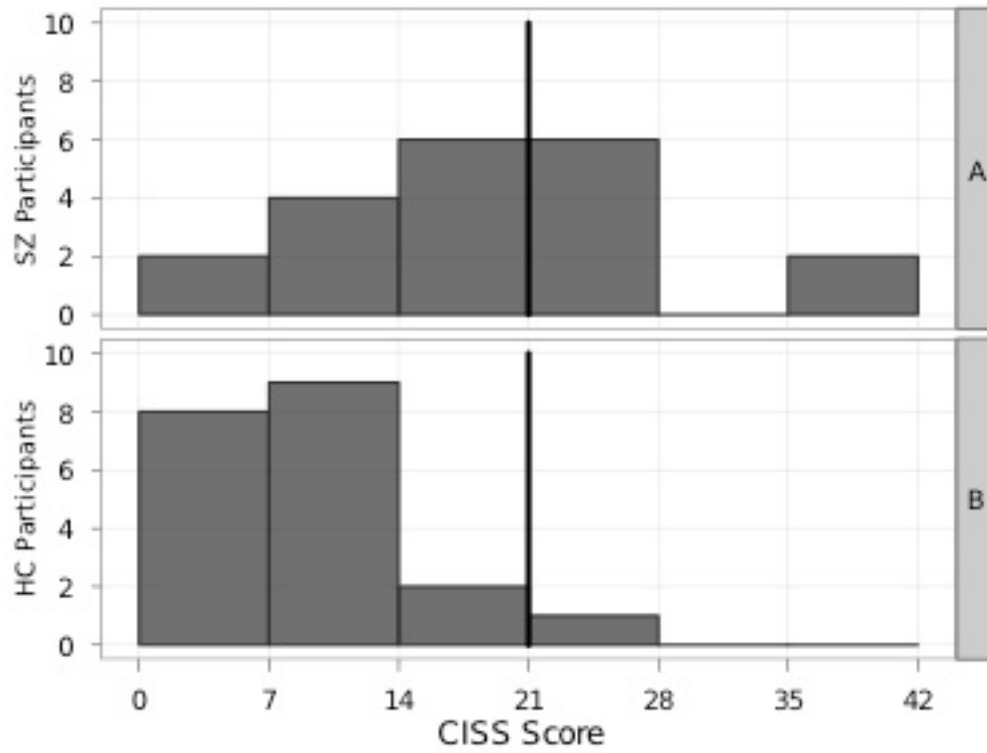
Figure Legends

Figure 1.

Distribution of mean CISS scores in each participant group. Bold vertical line indicates the cutoff score of 21. Individuals scoring ≥ 21 on the CISS were considered as having symptoms consistent with CI. **A**: SZ, schizophrenia patients. **B**: HC, healthy controls. CISS, Convergence Insufficiency Symptom Survey.

Figures

Figure 1. Distribution of CISS mean scores for each participant group.



VERGENCE TRACKING DEFICITS IN SCHIZOPHRENIA

by

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Vergence Tracking Deficits in Schizophrenia

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ABSTRACT

Background: Compared to healthy controls (HC), patients with schizophrenia (SZ) have lower smooth pursuit gain (O'Driscoll & Callahan, 2008) and have been reported as having a higher prevalence of convergence insufficiency (Flach et al., 1992). To date, however, there have been no reports on vergence tracking gain in such patients. Therefore, we investigated both static and dynamic vergence behavior in healthy controls and patients with schizophrenia.

Methods: Eye movements were recorded in multiple tasks including antisaccades, triangular waveform smooth pursuit at multiple frequencies, and triangular waveform vergence tracking of a real target at multiple frequencies. Eye position data were collected at 500 Hz using a binocular video eye tracker.

Results: Consistent with previous reports, the SZ group exhibited lower gains than HC group during smooth pursuit tasks (0.5 Hz gain: HC=0.73, SZ=0.64, $p<0.05$; 1.0 Hz gain: HC=0.45, SZ=0.35, $p<0.05$). For vergence tasks, when compared to the HC group, the SZ group did not demonstrate a significantly greater incidence of convergence insufficiency, but did exhibit significantly lower gains during vergence tracking tasks (0.05 Hz: gain: HC=0.90, SZ=0.67, $p<0.05$; 0.1 Hz gain: HC=0.88, SZ=0.65, $p<0.05$; 0.25 Hz gain: HC=0.86, SZ=0.59, $p<0.01$). There was significant correlation between the smooth pursuit and vergence tracking gains in the SZ group. The HC group did

not exhibit significant correlations between the smooth pursuit and vergence tracking gains.

Conclusions: We did not observe a significantly increased rate of convergence insufficiency in patients with schizophrenia. However, our observations clearly demonstrate previously unreported vergence tracking deficits in such patients.

INTRODUCTION

Previous eye tracking studies in schizophrenia have found abnormalities in the control of eye movements; specifically, smooth pursuit and antisaccades (for reviews see Levy et al. 1994; Turetsky et al. 2007; Rommelse et al. 2008; Smyrnis 2008). These studies have suggested that eye movement abnormalities may provide valuable information about the pathophysiology of schizophrenia (Clementz & Sweeney 1990; Szymanski et al. 1991; Holzman 1992; Holzman 1994; Hutton & Kennard 1998; Lee & Williams 2000; Copolov & Crook 2000; Calkins & Iacono 2000; Trillenberg et al. 2004; Bender et al. 2007).

The smooth pursuit deficits associated with schizophrenia were first observed by Diefendorf and Dodge in 1908 and have been investigated for several decades. Over that time smooth pursuit eye movement dysfunction has consistently been found in individuals with schizophrenia (O'Driscoll & Callahan, 2008; Smyrnis, 2008; Turetsky et al., 2007). More recently, deficits in the antisaccade task have been found in patients with schizophrenia (Fukushima et al., 1990). Studies have consistently found that patients with schizophrenia commit errors on this task more frequently than healthy controls (Hutton & Ettinger, 2006; Levy et al., 2004; Nikolaos Smyrnis, 2008). Both of these deficits persist during treatment (Levy, Lipton, Holzman, & Davis, 1983) and are also found in asymptomatic relatives (Calkins, Iacono, & Curtis, 2003; Kathmann, Hochrein, Uwer, & Bondy, 2003; Ross et al., 2002).

Some types of eye movement, however, are not disturbed in schizophrenia. Vestibulo-ocular responses are not affected (Levy, Holzman, &

Proctor, 1978), though patients have difficulty overriding this response with fixation (Warren & Ross, 1998; Yee et al., 1987). Full field optokinetic responses are not disturbed (Latham et al., 1981), though partial field optokinetic responses are (Latham et al., 1981). Fixation may be disturbed, but there are conflicting reports (Gooding, Grabowski, & Hendershot, 2000; Smyrnis et al., 2004). Overall, it seems that lower level, reflexive eye movements are not disturbed in patients with schizophrenia, but that higher level, voluntary eye movements that rely more on cortical substrates are affected.

The cortical substrates of vergence eye movements include the frontal eye fields (Gamlin & Yoon, 2000) and motion processing areas (Lynch & Tian, 2006; Pierrot-Deseilligny, Milea, & Mu, 2004). These cortical areas have been implicated in the smooth pursuit deficits in schizophrenia (Goldman-Rakic & Selemon, 1997; Holzman, 2000; Levy, Sereno, Gooding, & O'Driscoll, 2010). This suggests that patients with schizophrenia who exhibit smooth pursuit deficits may exhibit vergence tracking deficits too.

Vergence tracking eye movement deficits have not been demonstrated in schizophrenia, but the following abnormalities have been reported. Levin et al. (1982) reported that they observed a higher rate of intrusive saccades in vergence tracking in patients than in controls. However, they did not report the actual rates or the statistical significance of the difference. Buchanan & Heinrichs (1989) and Flach et al. (1992) reported a higher incidence of convergence insufficiency (CI) and ocular alignment issues. Both of these reports are based on subjective, unquantified judgments of CI and no measures of eye position,

near point of convergence, phoria, or positive fusion vergence ranges were made. In a prospective study of high-risk individuals Schiffman et al. (2006) reported a higher rate of ocular alignment abnormalities in individuals who went on to develop schizophrenia.

There are at least two compelling reasons to study vergence eye movements in patients with schizophrenia. First, there are many standardized clinical tests of binocular vision and vergence eye movements. These clinical tests are already regularly used in standard eye exams. Standardized tests of smooth pursuit are uncommon. Therefore, identifying and characterizing vergence eye movement dysfunction may make multisite studies of eye movement dysfunction in schizophrenia easier to design and execute and may also make possible retrospective studies that are based on a large body of previously collected clinical data. Second, oculomotor dysfunction, particularly binocular vision problems, could negatively impact cognitive therapy (Groswasser, Cohen, & Blankstein, 1990; Reding & Potes, 1988). Vision therapy could enhance cognitive therapy and thus help alleviate one of the major contributors to negative functional outcomes in schizophrenia.

Because of these potential benefits, and because there have been no definitive reports on vergence in schizophrenia, we investigated static and dynamic aspects of vergence in healthy controls and patients with schizophrenia.

METHODS

Twenty-four subjects with schizophrenia and schizoaffective disorder (SZ) were recruited from the outpatient psychiatry clinic 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 two minutes. The study was approved by the Institutional Review Board of The University of Alabama at Birmingham, 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 (K.B.H.) 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 analysis.

Binocular Vision 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 vergences at near break and recovery (prism bar), stereo acuity (Randot Stereo), accommodative amplitudes (push-up) for non-presbyopes, and distance and near auto-refraction.

The NPC measures were the average of 3 trials. The fusional vergence measures were the average of 3 trials. Autorefraction was performed using a Grand Seiko (WR5100-K, Grand Seiko, Ltd.) open field autorefractor. Five refractions were taken and averaged at each distance.

A diagnosis of convergence insufficiency was based on three measures. 1) NPC receded more than 5.5 cm, 2) a deficit in positive fusional vergence at near as determined using Sheard's criterion, and 3) near exophoria 4 prism diopters greater than distance phoria. Sheard's criteria states that patients should have "a fusional vergence reserve at least twice the magnitude of [their] heterophoria" (Sheard, 1938). Failure of the criteria predicts binocular vision discomfort particularly when the patient is fatigued. Participants had to meet all three criteria to be classified as having CI.

Eye Tracking Tasks

All of the eye tracking experiments were performed in a darkened room. Each task lasted 60 seconds and there was a 20 second 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 and antisaccade tasks in the fronto-parallel 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 (Figure 1, B). 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 triangular waveform over a range of 14°. The speed of the target was 5.6°/sec, 14°/sec, or 28°/sec.

The vergence tracking target was mounted on the carriage of an HP 7044A XY flatbed recorder. This recorder has a 28x43 cm range of travel, accuracy of 0.2% full-scale, acceleration of 5080 cm/s² and a slew rate of 104

cm/sec. The target was a small disk of holographic diffuser material with a black dot inscribed in the center (Figure 1, A). 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. During the vergence tracking task, the target motion had a triangular waveform in distance so that the angular velocity of the eyes was not constant over time. The target moved along a line that passed through the bridge of the participants nose and the center of the CRT described above. The target moved with constant speed over a range of 10 to 30 cm with periods of 20, 10, or 4 seconds. A 10 cm minimum distance was chosen so that all subjects should be able to converge to the target at its closest approach. The average angular speed of the target was 1.1, 2.2, or 5.5°/seconds respectively for a subject with a 6 cm interpupillary distance (ipd). Because the speed through space was constant, the angular speed varied over time as the derivative of the inverse tangent, $ipd/(ipd^2+distance^2)$. Had the angular speed been held constant, the target would have decelerated as it approached and accelerated as it receded.

Data Analysis

For analysis, eye movements were decomposed into saccadic and slow components. Saccades were identified using velocity, and acceleration thresholds of 22°/seconds and 4000°/seconds² respectively. Since we were interested in saccades that occurred during pursuit and tracking eye movements that could exceed 22°/seconds, the velocity threshold was increased by the

average velocity of the eye over the preceding 40 ms (up to a limit of 60°/seconds).

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 saccade 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.

It is important to note that in both smooth pursuit and vergence tracking, we define gain as the ratio of the gaze angle velocity to target angle velocity.

RESULTS

There were no significant differences between the groups in their age, gender, race, smoking, or parental socioeconomic status (Table 1).

Convergence Insufficiency

Three of the SZ subjects and one of the HC subjects met all three criteria for the CI diagnosis and were classified as convergence insufficient, which was not significantly different (Fischer's exact test, $p=0.6$). The mean NPC for the SZ and HC groups were not significantly different (SZ=5.5 cm; HC=4.5 cm; $p=0.207$). The phoria differences between groups were not significant (SZ=-3.95 p.d.; HC=-2.35 p.d.; $p=0.626$). Seven SZ and one HC failed Sheard's criteria. This difference was significant (Fischer's Exact Test, $p=0.022$).

Smooth Pursuit and Antisaccades

Consistent with previous reports, the SZ group exhibited lower gains than the HC group during smooth pursuit. The difference increased with higher target speeds (Table 2). The SZ group showed larger tracking errors than the HC group at all target speeds. Gain decreased and tracking error increased with higher target speeds (Figure 2). Also consistent with previous reports, the SZ group made errors more frequently than the HC group in the antisaccade task (SZ=47%, HC=21%, $p=0.001$).

Vergence Tracking

For vergence tasks, when compared to the HC group, the SZ group exhibited significantly lower gains during all vergence tracking tasks.

For example, Figure 2 shows example eye movement traces from 0.1 Hz vergence tracking trials. Panels A and B show vergence tracking from a healthy control. Version matches the target direction and vergence matches the target

depth accurately throughout the trial. Panels C and D show vergence tracking from a schizophrenia patient. This participant is not able to follow the target as it approaches closely. On some target motion cycles fusion is lost and one eye deviates outward resulting in a change of gaze direction. Asterisks indicate loss of fusion and gaze direction change.

The difference in gains became larger with higher target speeds (Table 2). The SZ group showed larger tracking errors than the HC group at all target speeds and gain decreased with higher target speeds (Figure 3).

HC subjects exhibited no significant correlation between the smooth pursuit and the vergence tracking tasks (Figure 4 A-C). In contrast, SZ subjects did exhibit significant correlation in gain and between the smooth pursuit and vergence tracking tasks (Figure 4 D-F).

Medication

Eighteen SZ participants were taking atypical antipsychotics and two were taking no antipsychotics. None of the HC group was taking antipsychotics. Ten of the SZ were taking antidepressants. None of the HC group was taking antidepressants. There were no significant differences in the eye movement measures between the ten SZ subjects taking antidepressants and the ten who were not. Four SZ participants were taking anticholinergic medication. There were no significant differences in the eye movement measures between the four SZ subjects taking anticholinergic medication and the sixteen who were not.

DISCUSSION

In this study, we evaluated static and dynamic aspects of vergence eye movements in a population of chronic, medicated patients with schizophrenia. To evaluate the performance of the participants with schizophrenia, we compared their vergence eye movements to that of a group of matched healthy controls. We found one statistically significant difference between the groups in measures of convergence insufficiency. In addition, we found statistically significant differences between the groups on measures of vergence tracking gain and vergence tracking accuracy.

Convergence Insufficiency

The only CI measure that differed significantly between the groups was Sheard's criteria. Sheard's criteria states that patients should have "a fusional vergence reserve at least twice the magnitude of [their] heterophoria" (Sheard, 1938). Failure of the criteria predicts binocular vision discomfort particularly when the patient is fatigued. The significant difference between the groups may indicate that, even though the patients with schizophrenia have normal ranges of convergence, they have less reserve capacity and may experience binocular vision problems when fatigued.

Lowered vergence tracking gain

We observed that vergence tracking gain and smooth pursuit gain were correlated in individuals with schizophrenia. The correlation in the eye movement performance in individuals with schizophrenia and not in controls suggests that

there is a common deficit that is affecting the two eye movements. One possibility is that the deficit is related to a final common pathway such as the motor output, an initial common pathway such as lateral geniculate nucleus of the thalamus. However a deficit of one of the common pathways seems unlikely because many reflexive eye movements such as VOR, full-field OKN and prosaccades to novel targets are not affected in schizophrenia (Latham, Holzman, Manschreck, & Tole, 1981; Levy, Holzman, & Proctor, 1978; Yee et al., 1987).

The finding of significant differences in vergence tracking gain and accuracy but not in convergence insufficiency (CI) between individuals with schizophrenia and healthy controls agrees with previous studies showing schizophrenia affects high level, voluntary eye movements such as antisaccades, memory guided saccades and smooth pursuit (Calkins, Iacono, & Curtis, 2003; Calkins, Iacono, & Ones, 2008; Landgraf, Amado, Bourdel, Leonardi, & Krebs, 2008; Sereno & Holzman, 1995; Zanelli et al., 2005), but that more basic sensory driven and reflexive eye movements are still intact (Latham et al., 1981; Yee et al., 1987).

There are two important differences between the smooth pursuit and vergence tracking deficits. 1) The angular velocity required for the eye to accurately follow the target was much lower for vergence targets and 2) saccades could not be used to compensate for poor vergence tracking.

First, we observed, as others have (Cerbone et al., 2003; Ettinger et al., 2003; Hong, Avila, & Thaker, 2005; S B 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. However, it is important to note that the average angular velocity required to track the target in the fastest vergence task ($5.5^\circ/\text{sec}$) was equivalent to that required in the slowest smooth pursuit task ($5.6^\circ/\text{sec}$), even though the difference in gains was greater for the fast vergence task than for the slow pursuit task. Thus, while task performance degrades with increasing target angular velocity within the smooth pursuit or within the vergence tracking tasks, this is not true when the two tasks are compared. One way to explain this is to assume that the gain degradation does not depend on the angular velocity of the target but rather on the speed of the target through space. This would suggest that the gain deficit might occur in a brain region in which the target velocity is encoded in 3D rather than a region in which the target velocity is encoded in separate depth and fronto-parallel channels. In order to test this hypothesis it will be necessary to perform experiments in which the target moves along oblique or curved trajectories that are not confined to the fronto-parallel or median plane.

Second, we observed catch up saccades during low-gain pursuit and several other studies have also reported that catch-up saccades are used to compensate for poor smooth pursuit gain (Flehtner, Steinacher, Sauer, & Mackert, 1997; Friedman, Jesberger, & Meltzer, 1991; Haarmeier, 1999; Levin et

al., 1988). In contrast, we and others have observed that under such vergence tracking conditions there may be no corresponding “saccadic vergence” (Rambold, Sander, Sprenger, & Helmchen, 2009; Semmlow, Pedrono, & Alvarez, 2007). The fact that vergence tracking lacks (or has a largely absent version of) this compensatory mechanism while vergence gain is still impaired in schizophrenia suggests that the gain deficit in smooth pursuit is a deficit of pursuit itself and not a consequence of saccadic disinhibition.

Medication

It is important point to note that eighteen of the participants with schizophrenia in this study were taking atypical antipsychotics. Smooth pursuit deficits have been observed in medicated, unmedicated, and medication naïve patients with schizophrenia (Friedman, Jesberger, & Meltzer, 1992; Holzman, Levy, Uhlenhuth, Proctor, & Freedman, 1975; Ross et al., 1998; Sweeney, Haas, Li, Weiden, & Sweeley, 1994). However, the effect of atypical antipsychotics has not been systematically evaluated (Reilly et al., 2008). Therefore, while atypical antipsychotics do not cause the pursuit deficits observed in schizophrenia, we cannot rule out the possibility that atypical antipsychotics have some effect on smooth pursuit or vergence eye movements. Future studies of vergence tracking in unmedicated and medication naïve patients with schizophrenia are needed.

Conclusion

In conclusion, we did not observe a significantly increased rate of convergence insufficiency in this group of chronic, medicated patients with schizophrenia. However, our observations clearly demonstrate, for the first time

to our knowledge, substantial deficits in vergence tracking in these patients. These deficits seem not to be due to saccadic disinhibition and for a given average target angular velocity the gain deficit is more pronounced for vergence than for smooth pursuit.

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The authors report no biomedical financial interests or potential conflicts of interest.

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TABLES

Table 1. Demographics and clinical measures^a

Characteristic	HC (n = 20) ^f	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 unless indicated otherwise; SZ, schizophrenia; HC, healthy control

^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

^f 18 SZ were treated with second generation antipsychotics and 2 SZ were not taking antipsychotics

Table 2. Pursuit and Tracking Gains^a

Eye Tracking Performance Measure	HC Mean	SZ Mean	t	p-value
Smooth Pursuit Gain				
Slow, 0.2 Hz, 5.6°/s	0.84 ± 0.11	0.80 ± 0.16	1.12	0.133
Medium, 0.5 Hz, 14°/s	0.73 ± 0.14	0.64 ± 0.18	1.94	0.029
Fast, 1.0 Hz, 28°/s	0.45 ± 0.17	0.35 ± 0.19	1.92	0.030
Vergence Tracking Gain^b				
Slow, 0.05 Hz	0.90 ± 0.32	0.67 ± 0.39	2.17	0.036
Medium, 0.1 Hz	0.88 ± 0.28	0.65 ± 0.34	2.46	0.018
Fast, 0.25 Hz	0.86 ± 0.27	0.59 ± 0.31	3.10	0.003

^a Mean ± SD unless indicated otherwise; SZ, schizophrenia; HC, healthy control

^b Vergence tracking range: 10-30 cm.

FIGURE LEGENDS

Figure 1. Illustration of vergence tracking and smooth pursuit stimuli used in the dynamic eye movement experiment. The blue 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 CRT. The vergence and pursuit targets were presented in separate trials; they were not presented simultaneously during the experiment.

Figure 2. Examples of 60 seconds vergence tracking trials showing good and poor vergence tracking at the medium target speed (0.1 Hz, 10-30 cm). Solid lines, eye; Dashed lines, target. Upper traces (A,C) show target direction and eye version angle (gaze direction) in degrees. Lower traces (B,D) target vergence angle and eye vergence angle in degrees. **A,B**: example of good vergence tracking from a healthy control. **C,D**: example of poor vergence tracking from schizophrenia patient. Asterisks indicate loss of fusion ('breaking').

Figure 3. Vergence tracking and smooth pursuit performance measures for the HC and SZ groups showing impaired performance in the SZ group. Upper plots (A,B) show the gain for each group (mean \pm SE) during the vergence

tracking (left column) or smooth pursuit (right column) tasks. The SZ group exhibited reduced gain compared to the HC group in all task conditions. Lower plots (C,D) show the tracking error for each group (mean \pm SE) during the vergence tracking (left column; A,C) or smooth pursuit (right column; B,D). Tracking error was defined as the SD of the difference between the target position and gaze position (in deg) over the course of the task trial. The SZ group exhibited increased tracking error compared to the HC group in all task conditions.

Figure 4. Correlation of vergence tracking gain and smooth pursuit gain in HC and SZ groups. Panels **A-C** (HC group) show the correlation between vergence tracking gain and smooth pursuit gain for: **A**. 0.2 Hz smooth pursuit, 0.05 Hz vergence tracking; **B**. 0.5 Hz smooth pursuit, 0.1 Hz vergence tracking; **C**. 1 Hz smooth pursuit, 0.25 Hz vergence tracking. Overall, there was no significant correlation between vergence tracking gain and smooth pursuit gain in the HC group. Panels **D-F** (SZ group) show the correlation between vergence tracking gain and smooth pursuit gain for: **D**. 0.2 Hz smooth pursuit, 0.05 Hz vergence tracking; **E**. 0.5 Hz smooth pursuit, 0.1 Hz vergence tracking; **F**. 1 Hz smooth pursuit, 0.25 Hz vergence tracking. Overall the SZ group exhibited significant correlations between vergence tracking gain and smooth pursuit gain during all conditions.

FIGURES

Figure 1. Illustration of vergence tracking and smooth pursuit stimuli used in the dynamic eye movement experiment.

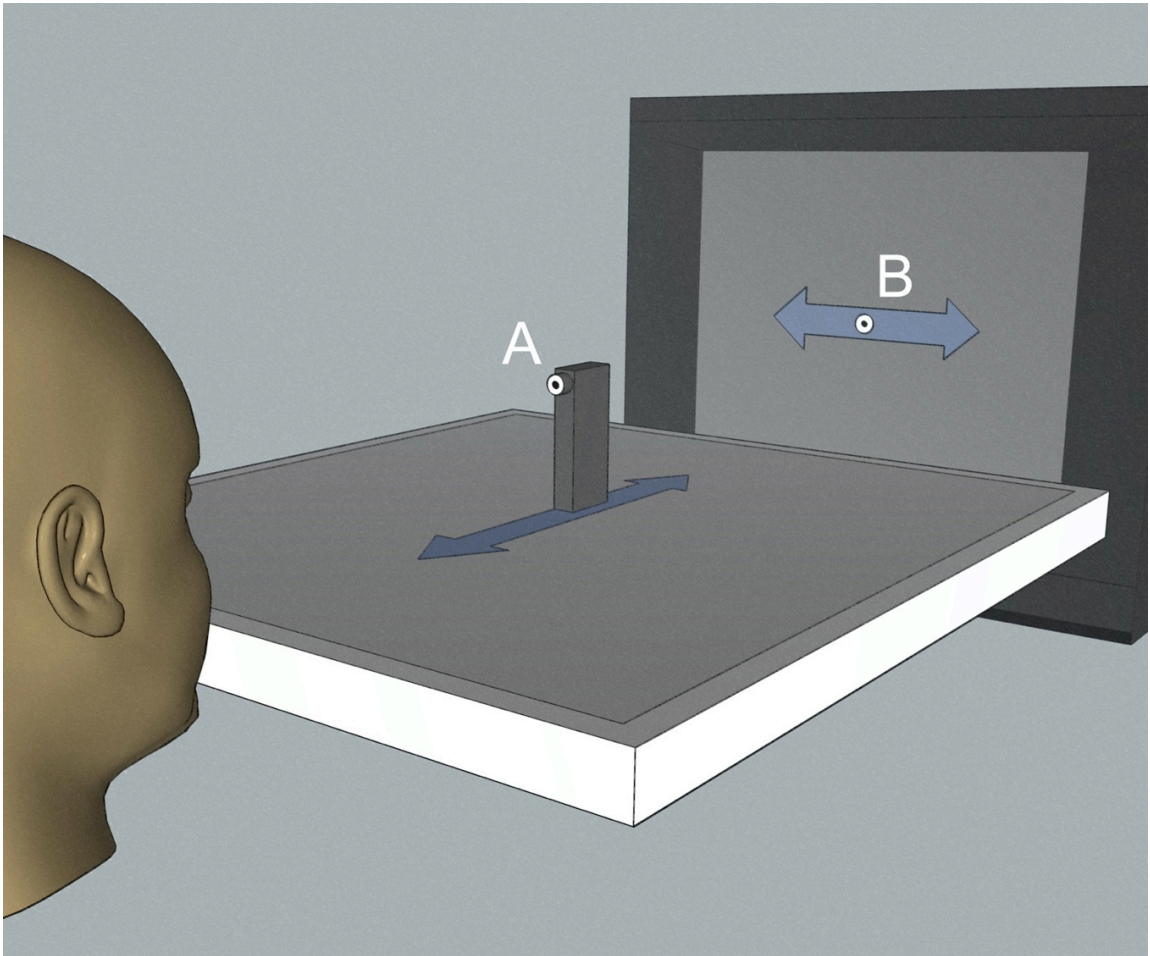


Figure 2. Examples of 60 second vergence tracking trials showing good and poor vergence tracking.

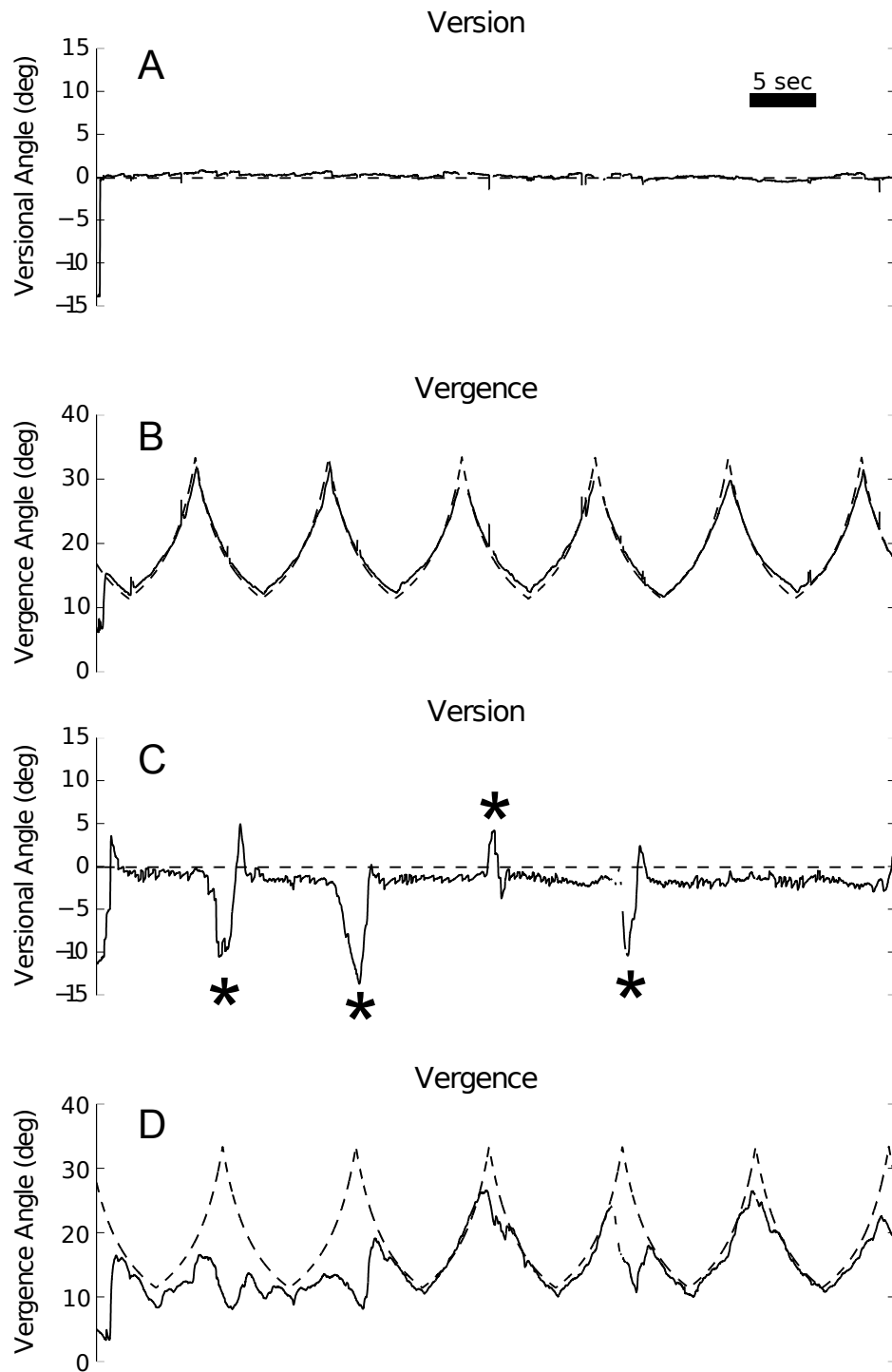


Figure 3. Vergence tracking and smooth pursuit performance measures.

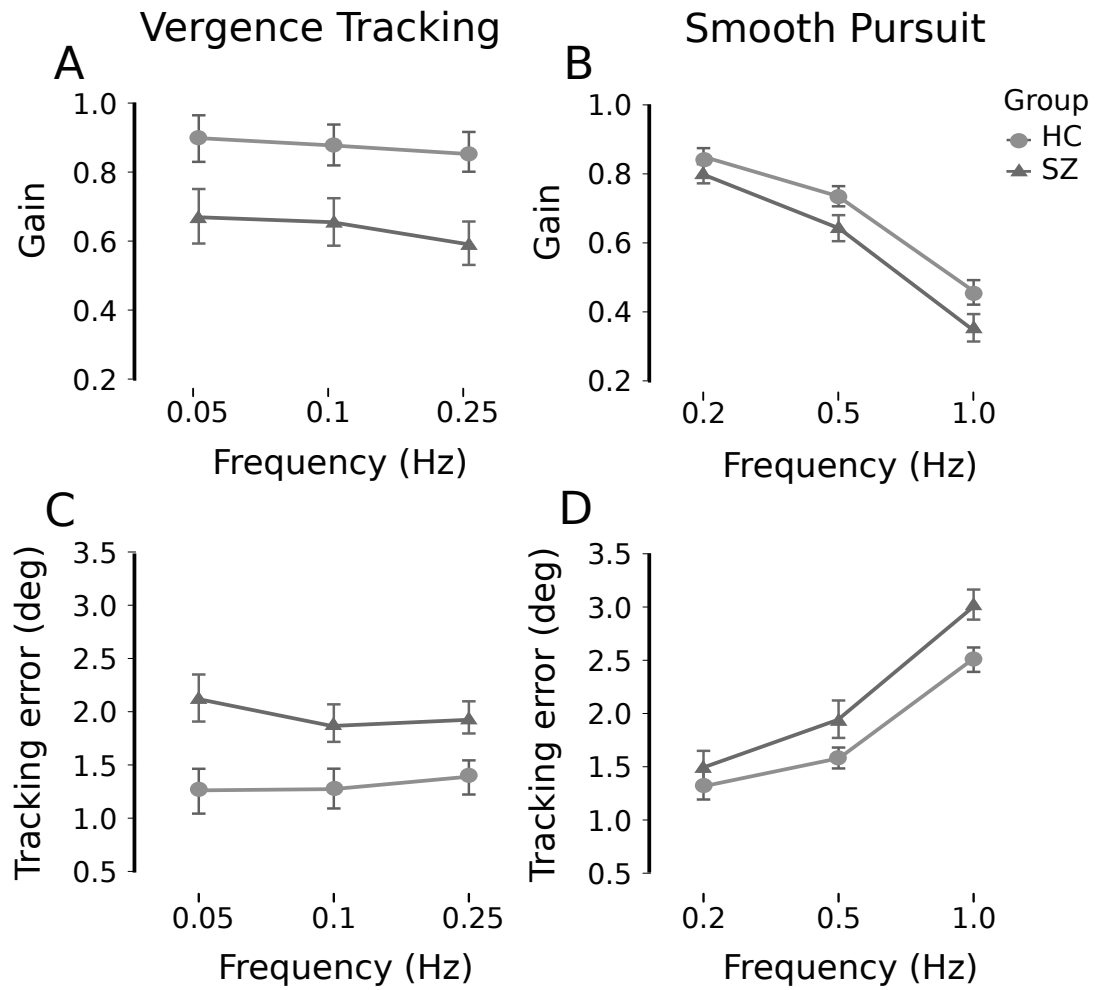
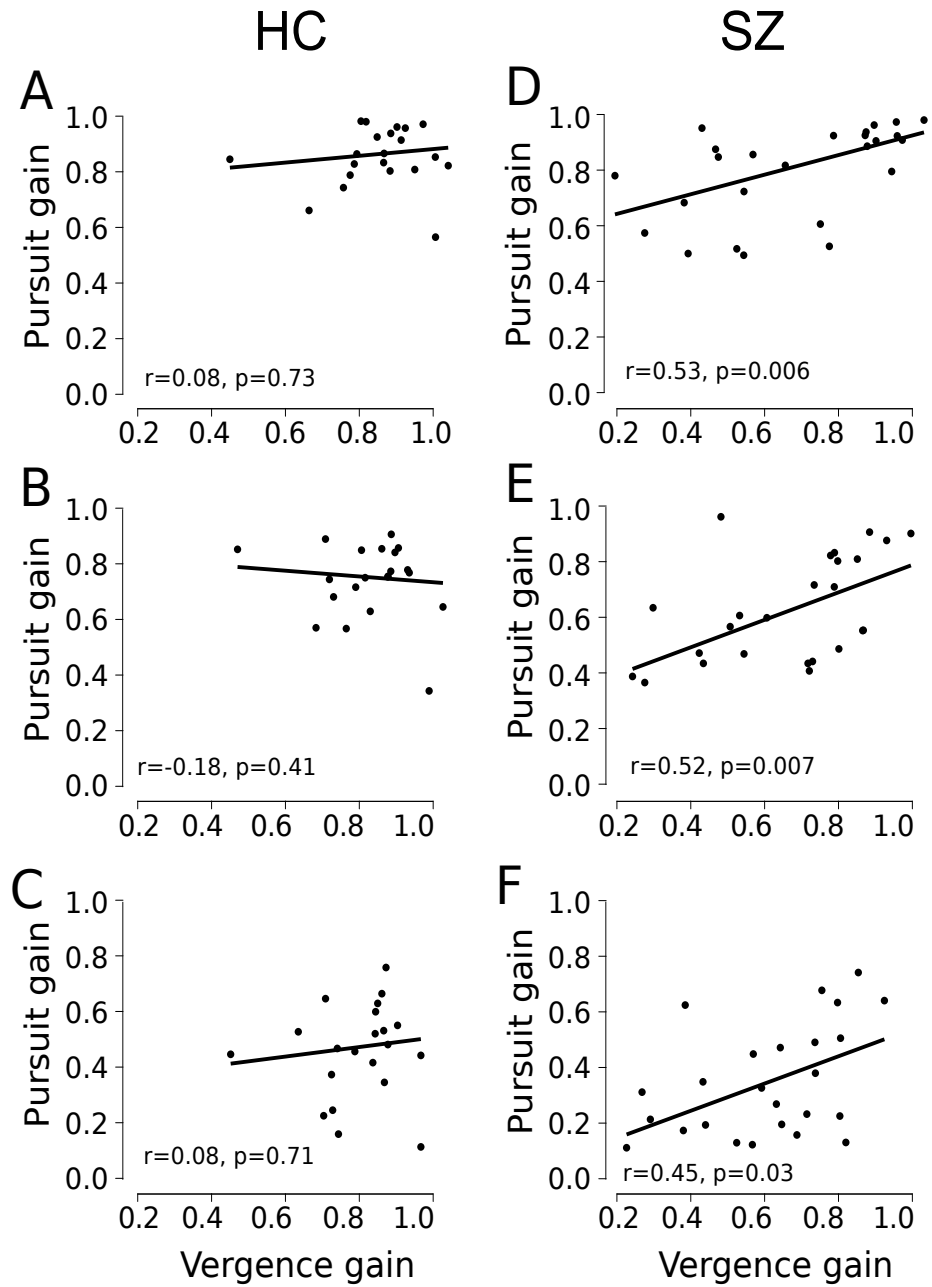


Figure 4. Correlation of vergence tracking gain and smooth pursuit gain in HC and SZ groups.



GENERAL DISCUSSION

In this study, we looked at static and dynamic aspects of vergence eye movements in a population of patients with schizophrenia. To evaluate the performance of the participants with schizophrenia, we compared their vergence eye movements to that of a group of healthy controls.

We found statistically significant differences between the groups on measures of vergence tracking gain and vergence tracking accuracy. Performance measures of vergence tracking and smooth pursuit were correlated in the schizophrenia group but not in the healthy controls.

We did not find a statistically significant difference in the prevalence of convergence insufficiency (CI) between the individuals with schizophrenia and the healthy controls. Even though we did not find a difference in CI between the groups, we found a highly significant difference in reports of CI associated symptoms. Unexpectedly, the results on the CI symptom survey (CISS) were uncorrelated with the results of the CI clinical measures in the SZ group and so the CISS did not discriminate SZ participants who had clinical findings consistent with CI from those who did not.

Consistent with other reports, we observed eye movement dysfunction in the individuals with schizophrenia during smooth pursuit and antisaccade tasks. This

study contributes to the schizophrenia literature by reporting on a deficit of dynamic vergence eye movements in individuals with schizophrenia, reporting on the prevalence of convergence insufficiency in the same group, and demonstrating that the CISS may not be appropriate for use in individuals with schizophrenia.

Neural Substrates of Vergence Tracking Deficits in Schizophrenia

We observed that vergence tracking gain, smooth pursuit gain and antisaccade error rate were correlated in the individuals with schizophrenia. Other groups have also observed correlation of eye pursuit performance and antisaccade performance (Matsue et al., 1994; Sereno & Holzman, 1995; Zanelli et al., 2005). The high correlation in the eye movement performance across smooth pursuit, vergence tracking, and antisaccades in individuals with schizophrenia and not in controls suggests that there is a common deficit that is affecting the three distinct eye movements. One possibility is that the deficit is related to a final common pathway such as the motor output, an initial common pathway such as lateral geniculate nucleus of the thalamus. However a deficit of one of the common pathways seems unlikely because many reflexive eye movements such as VOR, full-field OKN and prosaccades to novel targets are not affected in schizophrenia (Latham, Holzman, Manschreck, & Tole, 1981; Levy, Holzman, & Proctor, 1978; Yee et al., 1987).

The finding of significant differences in vergence tracking gain and accuracy but not in convergence insufficiency (CI) between individuals with schizophrenia and healthy controls also suggests that basic eye movement mechanisms are intact, but that some other component required to follow a moving target is disturbed. A basic pattern seems to be that schizophrenia affects eye movements requiring higher cognitive functions (e.g. working memory or internal representations of targets) such as antisaccades, memory guided saccades and smooth pursuit (Calkins, Iacono, & Curtis, 2003; Calkins, Iacono, & Ones, 2008; Landgraf, Amado, Bourdel, Leonardi, & Krebs, 2008; Sereno & Holzman, 1995; Zanelli et al., 2005), but not purely sensory guided eye movements such as vestibular ocular response or saccades to novel targets (Latham et al., 1981; Yee et al., 1987).

The neural substrates of vergence eye movements (Busettoni, Davison, Gamlin, & Larry R. Squire, 2009; Lynch & Tian, 2006; Maxwell & Schor, 2006; Pierrot-Deseilligny, Milea, & Mu, 2004; Serra, Chen, & Leigh, 2011) and of smooth pursuit eye movements (Lencer & Trillenber, 2008; Lynch & Tian, 2006; Thier & Ilg, 2005) extend throughout many regions of the brain including the thalamus, brainstem, subcortical nuclei, occipital, parietal, and temporal lobes, and the cerebellum. Cortical areas involved in both kinds of eye movement include the FEF, SEF, and MT/MST (Akao, Mustari, Fukushima, Kurkin, & Fukushima, 2005; Fukushima et al., 2002; Gamlin & Yoon, 2000).

Lesion studies in humans and non-human primates have identified cortical areas in which pathology results in smooth pursuit eye movement deficits. The

most commonly identified areas in these focal lesion studies are FEF, V5/MT/MST, and the parieto-temporo-occipital junction (see Sharpe, 2008). Specific lesions of the brainstem and cerebellum are also known to cause vergence eye movement deficits (Serra, Chen, & Leigh, 2011) and vergence eye movement dysfunction is the most frequent oculomotor abnormality found in patients suffering from mild traumatic brain injury (Thiagarajan, Ciuffreda, & Ludlam, 2011), but few studies have reported on the affect of localized cortical lesions on dynamic vergence eye movements. So, based on lesion studies, it is difficult to draw conclusions about specific cortical regions that might be involved in vergence gain deficits.

Cortical regions that may specifically be involved in eye movement dysfunction in schizophrenia have been identified using neuroimaging, lesion studies and neuropathology. Neuroimaging has been used by several groups to investigate the neural correlates of smooth pursuit dysfunction in schizophrenia. The most consistent findings in studies comparing schizophrenia patients to healthy controls are reduced activation in FEF and in motion processing areas (human MT/MST). See Levy et al. (2010) for an excellent review. But, as Levy et al. point out, since studies consistently compare patients to healthy controls instead of patients with eye movement dysfunction to patients without, separating effects due to diagnosis from effects due to eye tracking dysfunction is difficult. To our knowledge, no neuroimaging studies of vergence in schizophrenia have been published.

Taken together, current evidence suggests that the FEF and MT/MST are candidates for a common region that is involved in vergence and smooth pursuit deficits in schizophrenia.

Smooth Pursuit and Vergence Tracking

In contrast to the similarities in the cortical regions involved in vergence and smooth pursuit eye movements there are two important and informative differences between the two deficits. 1) The angular velocity required for the eye to accurately follow the target. 2) Saccades may be used to compensate for poor smooth pursuit, but not poor vergence tracking.

First, we observed, as others have (Cerbone et al., 2003; Ettinger et al., 2003; Hong et al., 2005; Hutton et al., 2001; Nikolaos 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 of the target increased. Similarly, vergence tracking gain was dependent on target velocity and the difference between the groups increased as target velocity increased. However, it is important to note that the difference in gains was greater for the fast vergence task than for the slow pursuit task even though the average angular velocity required to track the target in the fast vergence task (mean angular velocity 5.5°/sec, peak angular velocity 15°/sec)

was similar to that required in the slow smooth pursuit task ($5.6^\circ/\text{sec}$)². Thus, while task performance degrades with increasing target velocity within the smooth pursuit or within the vergence tracking tasks, the relationship does not necessarily hold when the two tasks are compared. One way to explain this is to assume that the gain degradation does not depend on the angular velocity of the target but rather on the speed of the target through space. This would suggest that the gain deficit might occur in a brain region in which the target velocity is encoded in 3D rather than a region in which the target velocity is encoded in separate depth and fronto-parallel channels. In order to test this hypothesis it will be necessary to perform experiments in which the target moves along oblique or curved trajectories that are not confined to the fronto-parallel or median plane.

Second, we also observed, as others have, that catch-up saccades can be used to compensate for poor smooth pursuit gain (Flechner et al., 1997; L. Friedman et al., 1991; Haarmeier, 1999; Levin et al., 1988). In contrast, we and others have observed that there is no corresponding “saccadic vergence” that is used to compensate for vergence errors (Rambold et al., 2009). The fact that vergence tracking lacks this compensatory mechanism and yet vergence gain is still impaired in schizophrenia suggests that the gain deficit in smooth pursuit is deficit of pursuit itself and not a consequence of saccadic disinhibition.

² Note that since vergence angle is traditionally defined as the left eye angle minus the right eye angle, vergence angle and vergence velocity are twice the eye angle and angular velocity, respectively, for targets moving on the midline. i.e. for an angular velocity of $5.5^\circ/\text{sec}$ the vergence velocity will be $11^\circ/\text{sec}$.

CISS scores and the clinical measures of CI

Of the SZ participants who did not have CI, eight of them scored 21 or greater on the CISS. The large number of false positives on the CISS in the SZ group suggests that the participants with schizophrenia may suffer from a visual impairment that is causing symptoms similar to those suffered by individuals with CI. In fact, in the dynamic tracking experiment we observed that schizophrenia patients have lowered vergence tracking gain compared to controls. Possibly some dynamic aspects of vergence eye movements are not measured well by the clinical tests of CI. Thus, the CISS may be sensitive to visual deficits that are not detected by the clinical measures of CI.

A final consideration is that while the clinical measures of CI are objective tests, the scores on the CISS are based on subjective self reports of symptoms consistent with CI. It is possible that the SZ group scored higher because they rate the same symptoms differently than the HC group. One way to address this possible self-report bias would be to embed the CISS questions in a larger battery of similarly phrased questions on an unrelated topic. This might allow one to separate the response bias and the effect due to the CI symptoms.

Study Limitations

It is important point to note that participants with schizophrenia in this study were taking an atypical antipsychotic (risperidone, quetiapine, olanzapine, or aripiprazole), while the controls were not. Smooth pursuit has been previously

studied using medicated, unmedicated, or medication naïve populations in various studies and deficits have been found in each of these studies. However, the affects of atypical antipsychotics on smooth pursuit have not been systematically evaluated in studies comparing medicated and unmedicated patients (Reilly et al., 2008). Therefore, while atypical antipsychotics are not the cause of the smooth pursuit deficits observed in schizophrenia, we cannot rule out the possibility that they have some affect on smooth pursuit or vergence eye movements. Studies that include off-medication and medication naïve individuals with schizophrenia are needed to determine that role medication plays in the vergence tracking deficits we observed.

Future Studies

Prior to these current studies, two eye movement deficits in particular had been studied extensively in patients with schizophrenia: smooth pursuit gain and increased errors on the antisaccade task. These deficits are not specific to schizophrenia and are not present in all patients with schizophrenia (Holzman, 2000). Therefore, as yet, these two classes of eye movement deficits do not provide a useable tool for the diagnosis of schizophrenia; they may yet provide useful insights into the disease process and the underlying neural deficits.

Examining other classes of eye movements to characterize what is and is not affected by the disease will likely lead to a better understanding of the basis of the currently known eye movement dysfunctions. Because the neural substrates

of vergence overlap with those of smooth pursuit, they are a particularly interesting class of eye movements to investigate in patients with schizophrenia. Identifying what deficits are present or absent in vergence and comparing them to the deficits found in smooth pursuit may shed light on the location or mechanism of the eye movement dysfunction in schizophrenia.

There are two additional compelling reasons to study vergence eye movements in patients with schizophrenia. First, there are standardized clinical tests of dynamic vergence eye movements (i.e. assessment of dynamic vergence with prism flipper testing, see Cooper et al., 2010). These clinical tests have been used in a retrospective study of oculomotor dysfunction in acquired brain injury (Ciuffreda et al., 2007). Therefore, identifying and characterizing vergence eye movement dysfunction may make large scale, multisite studies of the eye movement dysfunction endophenotype easier to design and execute and may also make possible retrospective studies that are based on a large body of previously collected clinical data. Second, oculomotor dysfunction, particularly binocular vision problems, could negatively impact cognitive therapy (Groswasser et al., 1990; Reding & Potes, 1988). Vision therapy could enhance cognitive therapy and thus help alleviate the greatest contributor to negative functional outcomes in schizophrenia.

Conclusion

In conclusion, our observations clearly demonstrate previously unreported vergence tracking deficits in schizophrenia patients. Contrary to previous reports, we did not observe a higher prevalence of CI in individuals with schizophrenia even though 40% of the individuals with schizophrenia reported symptoms associated with CI. Further study is needed to determine why individuals with schizophrenia have dynamic vergence deficits and are reporting symptoms associated with CI even though clinical measures do not reveal static deficits.

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doi:10.1016/j.psychres.2004.12.008

APPENDIX A

IRB APPROVAL

MEMORANDUM

TO: Mark S Bolding
Principal Investigator **FAX:** 975-4879 (David White)

FROM: Leslie Cooper, CIP *Leslie Cooper*
On behalf of IRB 02

DATE: September 16, 2011

RE: F081030002
Characterization of Vergence Eye Movements in Schizophrenia, Schizoaffective Disorder, and Bipolar Disorder

The IRB 02 met on **September 14, 2011** and **approved** the protocol referenced above. The approval form and IRB-stamped consent form are enclosed. **This approval will expire and no longer be valid on September 14, 2012.**

Please note the following as related to this review:

- The IRB reviewed and approved the personnel changes to the protocol.
- The next time you need to make changes to the consent form for this protocol, please update the text in the Refusal or Withdrawal without Penalty section regarding UAB students and employees and the Questions section about when and how to contact the Office of the IRB, as shown in the sample consent form. The sample consent form is available at www.uab.edu/irb/forms/sample-consent-form.doc.

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Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on August 29, 2016. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator: BOLDING, MARK S
Co-Investigator(s): GAMLIN, PAUL D
LAHTI, ADRIENNE C.
Protocol Number: **F081030002**
Protocol Title: *Characterization of Vergence Eye Movements in Schizophrenia, Schizoaffective Disorder, and Bipolar Disorder*

The IRB reviewed and approved the above named project on 9/14/2011. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received FULL COMMITTEE review.

IRB Approval Date: 9/14/2011

Date IRB Approval Issued: 9-16-11

Identification Number: IRB00000726

Ferdinand Urthaler, MD/AC

Ferdinand Urthaler, M.D.

Chairman of the Institutional Review
Board for Human Use (IRB)

Partial HIPAA Waiver Approved?: Yes

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

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**UAB IRB Approval of
Partial Waiver of HIPAA Authorization
to Use PHI in Screening for Research**

Patient Authorization: Approval of Partial HIPAA Waiver to Use PHI in Screening for Research. The IRB reviewed the proposed research and granted the request for a "partial HIPAA waiver," to allow the proposed use of protected health information (PHI) in screening for research, based on the following findings:

1. The use/disclosure of PHI to screen candidates for research involves no more than minimal risk to the privacy of individuals
 - a. There is an adequate plan to protect the identifiers from improper use and disclosure.
 - b. There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.
 - c. The PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted.
2. The screening cannot practicably be conducted without the waiver or alteration.
3. The screening cannot practicably be conducted without access to and use of the PHI.

—OR—

Full Review

The IRB reviewed the proposed research at a **convened meeting** at which a majority of the IRB was present, including one member who is not affiliated with any entity conducting or sponsoring the research, and not related to any person who is affiliated with any of such entities. The partial waiver of authorization for screening was approved by the majority of the IRB members present at the meeting.

9-14-11
Date of Meeting

Ferdinand Uthaler, MD/AC
Signature of Chair, Vice-Chair or Designee

9-16-11
Date

Expedited Review

The IRB used an **expedited review procedure** because the research involves no more than minimal risk to the privacy of the individuals who are the subject of the PHI for which use or disclosure is being sought. The review and approval of the partial waiver of authorization for screening was carried out by the Chair of the IRB, or by one of the Vice-Chairs of the IRB as designated by the Chair of the IRB.

Date of Expedited Review

Signature of Chair, Vice-Chair or Designee

Date