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Premorbid childhood ocular alignment abnormalities and adult schizophrenia-spectrum disorder

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Abstract

This study examined the relation between childhood ocular alignment deficits and adult psychiatric outcomes among children at high-risk for schizophrenia and controls. A sample of 265 Danish children was administered a standardized eye exam assessing strabismus and related ocular alignment deficits. All children whose mothers or fathers had a psychiatric diagnosis of schizophrenia comprised the first group ($N=90$). Children who had at least one parent with a diagnosis other than schizophrenia comprised the first matched control group ($N=93$). The second control group consisted of children with no parental diagnoses ($N=82$). In 1992, adult psychiatric outcome data were obtained for 242 of the original subjects.

It was found that children who later developed a schizophrenia-spectrum disorder had significantly higher eye exam scale and strabismus scale scores compared to children who developed other non-psychotic psychopathology and children who did not develop a mental illness. The mean rank for children in the high-risk group (offspring of parents with schizophrenia) on the eye scale and the strabismus scale was greater than the mean rank for children in the matched control groups (both offspring of parents with other non-psychotic disorder and no mental illness), although the results failed to reach statistical significance.

Results from this study suggest a premorbid relation between ocular deficits and schizophrenia-spectrum disorders in childhood prior to onset of psychopathology in adulthood. Strabismus may serve as a premorbid marker for spectrum disorders and may have implications for the understanding of early aberrant neurological development related to later schizophrenia-spectrum disorders.

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1. Introduction

Previous research has established an association between eye movement abnormalities and schizophrenia (Brownstein et al., 2003; Ettinger et al., 2004; Hutton et al., 1998; Kathmann et al., 2003). The majority of research on eye deficits and schizophrenia has come from research on smooth pursuit functioning. Findings generally include lower pursuit gain and an increased frequency of inappropriate saccades during smooth pursuit tasks, as well as lower antisaccade gain and accuracy on antisaccade tasks. Global deficits appear to be stable over the course of schizophrenia (Clementz and Sweeney, 1990), and are hypothesized to represent an underlying genetic marker, and perhaps pre-existing neurobiological deficits (Kathmann et al., 2003; Tregellas et al., 2004). Similar findings have been reported among first episode patients (e.g., Hutton et al., 1998), among relatives of individuals with schizophrenia (Ettinger et al., 2004; Karoumi et al., 2001; Ross et al., 1996), and among the offspring of individuals with schizophrenia (Rosenberg et al., 1997; Schreiber et al., 1997). Despite a host of positive findings, however, there have been some non-replications of smooth pursuit deficits and schizophrenia particularly with respect to specificity to schizophrenia (Clementz and Sweeney, 1990; Kathmann et al., 2003).

Although less commonly studied than smooth pursuit functioning with respect to schizophrenia, some researchers have identified deficits in ocular alignment as a correlate of the disorder. Two studies report a high rate of ocular misalignment among adult patients with schizophrenia in relation to controls. Toyota et al. (2004) recently reported that patients with schizophrenia were nearly three times more likely than controls to demonstrate strabismus (the inability to align one eye in relation to the other). These authors contend that strabismus may represent an unstudied type of minor physical anomaly related to schizophrenia. A study by Flach et al. (1992) reported that in relation to controls, individuals with schizophrenia as well as individuals with affective disorders showed an increased rate of near point horizontal phoria, a deficit less severe but on a continuum with strabismus. The authors also noted an association between schizophrenia and a number of specific visual tasks including deficits of vergence

(rotation of eyes in opposite direction in order to maintain fusion), suppression (inhibition of perception of an image from one eye), perceptual integration (simultaneous use of multiple perceptual systems), and pursuit tracking. Flach et al. (1992) contend that these deficits might relate to difficulties with antisaccade and smooth pursuit tasks. Both of these studies included medicated adults with full schizophrenia and do not address issues related to the course of eye deficits in relation to development.

To our knowledge there have been no studies investigating eye deficits prospectively in childhood among individuals who later develop schizophrenia in adulthood. Prospective studies of high-risk individuals destined to develop schizophrenia might better address the issue of whether eye deficits are a function of schizophrenia or a precursor to the disorder. The present study investigates the relation between a prospectively administered eye examination in childhood and diagnostic outcome in adulthood among a group of children at high-risk for schizophrenia and controls. The eye examination specifically assessed strabismus (a.k.a., heterotropia) and related ocular alignment deficits (e.g., heterophoria, suppression, depth perception, visual acuity, pursuit movements). While the eye exam used in this study does not directly assess smooth pursuit or antisaccade functioning (the selection of the eye exam measures preceded the establishment of the modern smooth pursuit paradigm), several items on the current eye examination assess similar deviations as those measured in the smooth pursuit paradigm (e.g., visual pursuit movements) and possibly antisaccade tasks (e.g., Maddox Wing) (Flach et al., 1992).

Given the literature suggesting oculomotor deficits among high-risk individuals, it was hypothesized that the offspring of parents with schizophrenia would show more eye deficits relative to offspring of parents without schizophrenia (i.e., high-risk versus non-high-risk). Additionally, given research indicating oculomotor and ocular alignment deficits among individuals with schizophrenia, it was hypothesized that individuals who eventually developed schizophrenia-spectrum disorders would show more eye deficits in childhood than those who did not develop schizophrenia-spectrum disorders (schizophrenia-spectrum versus no mental illness and other psychopathology).

2. Methods

The current study is part of a larger longitudinal high-risk project investigating the precursors of schizophrenia. The design of the study, the subject characteristics, and the premorbid and follow-up diagnoses are described in greater detail elsewhere (Schiffman et al., 2002).

2.1. Subjects

Subjects were drawn from a Danish birth cohort consisting of all children born between September 1, 1959, and December 31, 1961, at Rigshospitalet in Copenhagen (Zachau-Christiansen and Ross, 1975). In 1972, a sample of 265 children from this cohort was intensively examined (Mednick et al., 1971). All children whose mothers or fathers had a psychiatric hospital diagnosis of schizophrenia comprised the first group ($N=90$). A group of matched controls consisted of children who had at least one parent with psychiatric records other than schizophrenia ($N=93$). The remaining subjects were matched controls with no parental diagnoses ($N=82$). Both control groups were matched with the high-risk for schizophrenia birth cohort for gender ratio, mother's marital status at the time of conception, pregnancy number, social class, mother's height and weight, and mother's and father's age (Mednick et al., 1971). Two hundred forty-two participants were available for follow-up examinations in 1992. Diagnostic outcome information is presented in Table 1. After complete description of the study to the subjects, written informed consent was obtained. All procedures were in accordance with the ethical standards set forth by the school's committee on human experimentation and with the Helsinki Declaration of 1975.

2.2. Measures

The eye exam was performed by an experienced Danish pediatric neurologist in 1972 when subjects were between the ages of 11 and 13. The assessment occurred before any obvious signs of psychopathology in this sample, and therefore completely blind to adult psychiatric outcome. Additionally, the neurologist was blind to the diagnostic risk status of the parents of the children.

Table 1

Adult outcome diagnoses for offspring of parents with or without schizophrenia

Schizophrenia-spectrum disorders	Schizophrenia	16
	Schizotypal personality disorder	3
	Any psychosis or delusional disorder	5
	Paranoid personality disorder	2
	Other psychopathology	19
Other psychopathology	Non-psychotic mood or anxiety disorder	33
	Non-psychotic alcohol/drug abuse	1
	Non-hospitalized minor Axis I disorder	5
	Borderline personality disorder	1
	Schizoid personality disorder	1
	Antisocial personality disorder	4
	Personality disorder NOS	6
No mental illness	No diagnosis	146
	Total subjects	242

2.2.1. The eye examination

The eye examination directly assessed eye alignment and related deficits, specifically, heterophoria, heterotropia, suppression, depth perception, visual acuity, and pursuit movements. Flach et al. (1992) suggested that certain deficits in these domains may contribute to difficulties with smooth pursuit and antisaccade tasks. The assessment battery consisted of six tests yielding 9 items. The tests included: Maddox Wing Test (one item), monocular covering/uncovering (one item), Worth 4-Light Test (one item), the Titmus Fly Test (three items), visual acuity (left and right eye), and a measure of visual pursuit movements (one item).

2.2.2. Maddox Wing

Subjects viewed the Maddox Wing chart through horizontal slits enabling the right eye to see only white and red arrows, and the left eye only the white and red scales. Viewed simultaneously, the red arrow in the Maddox device corresponds to a number on the red (vertical) scale, the white arrow to a number on the white (horizontal) scale. Arrows appearing to point to zero indicate correct alignment in a fusion-free state. Arrows not appearing to point at zero indicate some degree of ocular misalignment. Scores were dichotomized. A score of one indicated the presence of some type and degree of phoria.

2.2.3. Monocular covering/uncovering

Subjects used both eyes to fixate on a visual target at a particular distance (near then far). The examiner then covered one eye, preventing binocular fusion, and observed the other eye for movement. The test was repeated for the other eye. Movement in the non-occluded eye occurs when that eye takes up fixation originally held by the occluded eye, indicating the presence of heterotropia. The presence or absence of movement indicating heterotropia was noted, and scores were dichotomized with a score of one indicating heterotropia.

2.2.4. Worth 4-Light or 4-Dot Test

The four lights of the Worth 4-Dot Test are orientated in a diamond-shaped configuration: a red light at the top point, white light at the bottom point, and a green light at both left and right points. Subjects viewed the lights through glasses with one green and one red lens, and noted the number and color of the dots. Seeing four dots indicated that the subject was successfully able to fuse two retinal images together into a single image. Seeing only two or three dots indicated suppression of one of the eyes. The presence or absence of suppression was noted, and scores were dichotomized with a score of one indicating suppression.

2.2.5. Titmus Fly Test

This test determines the presence or absence of binocular depth perception and consists of three sections: the housefly, animals, and circles. Each section uses vectographs to present identical or slightly different variations of objects or patterns to each eye. When viewed through a Polaroid visor, disparities in the images can be fused and viewed in depth. Subjects noted whether the housefly is seen in depth, and which animals or circles appeared three dimensional, and were scored as either normal (perceived depth) or abnormal (only perceived two dimensionally). There are three trials for the animals and nine trials for the circles. Subjects received a total error score for each subtest, with higher scores indicating worse depth perception. To be consistent with the other eye measures, these scores were dichotomized with the extreme 20% (approximately) considered abnormal.

2.2.6. Visual pursuit movements

Pursuit movements were assessed by direct observation of the eyes as they followed a moving target. The eyes were assessed for fast, smooth, accurate, and parallel motion that mirrored the velocity of the target. Jerky movements and fixation losses or inaccurate speed indicated abnormal conjugated movements. Pursuit was scored as either normal or abnormal.

2.2.7. Visual acuity: right and left

Visual acuity was measured using the Stycar Vision Test. Standing 3 m from the chart, subjects kept both eyes open, gently covering one eye. They then identified the smallest line of letters that they were able to see. The procedure was repeated with the opposite eye. The Stycar Test does not require the ability to read, as only identification of the shape of the letter is necessary as subjects are able to match the shapes on a card held by the examiner next to the subject. Subjects were categorized into either normal or abnormal acuity for both eyes.

3. Statistical analyses

In order to create an “eye exam” scale, we summed the variables and divided the summed score by the number of variables available per subject to account for missing data (missing data were rare). Cronbach’s alpha was .69, suggesting adequate internal reliability for the scale. To specifically assess the potential link between strabismus and schizophrenia, we created a “strabismus” scale by summing the scores of monocular covering, Worth Four-Dot, and the three Titmus Fly subtests and dividing the sum by the total number of items for each subject. Cronbach’s alpha was .70. It is relevant to note that the tests used in the strabismus scale may indicate, but do not guarantee, strabismus. Additionally, the Maddox Wing Test is also sometimes used to assess for strabismus, but may not be sensitive enough to distinguish heterophoria from full heterotropia (i.e., strabismus), and was thus not included in the strabismus scale.

Given that neither scale was normally distributed (eye scale skewness=2.06, SE=.15, kurtosis=4.11, SE=.30; strabismus scale skewness=1.86, SE=.15; kurtosis=3.65, SE=.30), we employed the Mann–

Whitney *U* tests to assess for hypothesized group differences in rank using the Statistical Package for the Social Sciences (SPSS) version 11.5. To test for the impact of genetic risk for psychopathology on the two eye exam scales, we used a Mann–Whitney *U* test to compare the eye exam scale and strabismus scale between subjects who had at least one parent with schizophrenia compared to subjects who did not have a parent with schizophrenia (one or both parent with a non-psychotic disorder or both parents with no diagnosed mental illness). We also used a Mann–Whitney *U* test to determine differences between the adult follow-up diagnostic outcome groups (schizophrenia-spectrum versus other psychopathology or no diagnosable mental illness). All tests were two-tailed; alpha levels were set at $p=.05$. Given the concern for Type II error and our hypothesis-driven analyses, we did not correct the alpha level for multiple testing.

4. Results

We first tested for the potential confounding effect of sex on the eye examination. Males and females did not significantly differ on the eye examination scale (Fig. 1).

Results from the Mann–Whitney *U* test assessing for differences on the eye scale and the strabismus scale among genetic risk groups (offspring of parents with schizophrenia compared to offspring of parents with some non-psychotic disorder and offspring of parents without a diagnosed mental illness) failed to reach statistical significance (eye exam scale, high-risk mean rank = 127.81, comparison group mean rank = 118.32, $z = 1.03$, $p = .301$; strabismus scale, high-risk mean rank = 129.72, comparison group mean rank = 117.36, $z = 1.51$, $p = .132$). While not significant, the mean rank was higher in the high-risk group for both scales.

Results of the Mann–Whitney *U* test assessing differences between diagnostic outcome indicated significant differences between adult diagnostic outcome groups (schizophrenia-spectrum versus all other subjects) on childhood eye examination scale and strabismus scale (eye exam scale, schizophrenia-spectrum mean rank = 147.90, comparison group mean rank = 118.32, $z = 2.11$, $p = .035$; strabismus scale, schizophrenia-spectrum mean rank = 152.88, comparison group mean rank = 117.72, $z = 2.81$, $p = .005$). In an effort to assess for specificity, we undertook additional analyses revealing that children who later developed a schizophrenia-spectrum disorder had a significantly higher eye examination and strabismus scales scores relative to children who did not develop a mental illness (eye exam scale,

schizophrenia-spectrum mean rank = 104.98, no mental illness mean rank = 83.21, $z = 2.13$, $p = .033$; strabismus scale, schizophrenia-spectrum mean rank = 107.69, comparison group mean rank = 82.73, $z = 2.71$, $p = .007$). Additionally, children who later developed a schizophrenia-spectrum disorder had higher eye exam and strabismus scores in relation to those who developed other non-psychotic psychopathology (eye exam scale, schizophrenia-spectrum mean rank = 56.42, other psychopathology mean rank = 45.56, $z = 1.75$, $p = .080$; strabismus scale, schizophrenia-spectrum mean rank = 58.69, comparison group mean rank = 44.71, $z = 2.47$, $p = .013$). The other psychopathology group did not significantly differ from the group that did not develop a diagnosable mental illness on either scale (eye exam $p = .596$; strabismus $p = .999$).

To test for a possible interactive effect of ocular alignment deficits with high-genetic-risk status for schizophrenia-spectrum disorders, we selected only subjects with a parent with schizophrenia. Among high-risk subjects only, we then compared eye scores between youth who eventually developed a schizophrenia-spectrum disorder to those who did not (schizophrenia-spectrum, $n = 17$; no mental illness or other psychopathology, $n = 64$). Results from the Mann–Whitney *U* test assessing for differences on the eye scale and the strabismus scale failed to reach statistical significance (eye exam scale, high-risk schizophrenia-spectrum

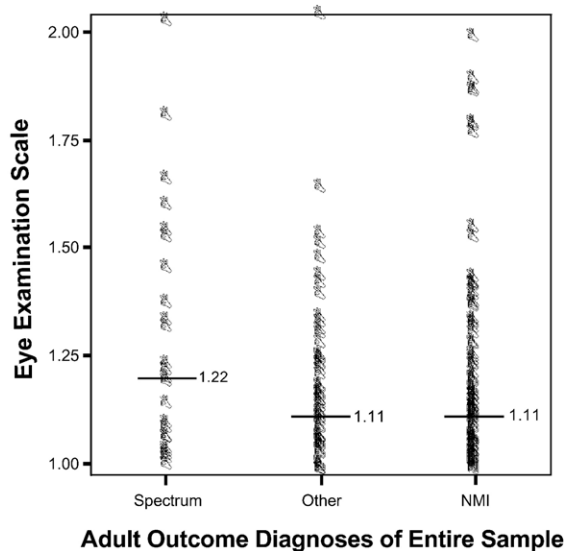


Fig. 1. Childhood eye examination scale scores across adult diagnostic outcome (Scatterplot). Horizontal lines represent median eye examination scale score for each diagnostic group. “Spectrum” equals schizophrenia-spectrum group. “Other” equals other psychopathology group. “NMI” equals no mental illness group.

mean rank=48.35, comparison group mean rank=39.05, $z=1.50$, $p=.134$; strabismus scale, high-risk schizophrenia-spectrum mean rank=47.47, comparison group mean rank=39.28, $z=1.43$, $p=.152$).

A significant relation between schizophrenia-spectrum disorders and MPAs has previously been described in this sample (Schiffman et al., 2002). To test for a relation between the eye exam and traditional MPAs, a Spearman rho correlation was performed. Results did not suggest a significant association between the eye exam and MPAs (Spearman rho=.06, $p=ns$).

5. Discussion

Results from this standardized eye examination suggest childhood differences between those who do and who do not develop schizophrenia-spectrum disorders in adulthood. Specifically, subjects who eventually developed schizophrenia-spectrum disorders demonstrated poorer pre-morbid eye exam and strabismus scores in relation to comparison subjects with an outcome of other psychopathology and those with no psychiatric diagnosis in adulthood. These findings suggest a specific relation between deficits in eye functioning and schizophrenia-spectrum disorders observed in childhood prior to diagnosis. Findings from this study add significantly to previous reports as the eye exam employed in this study was administered in childhood prior to onset of diagnosable psychopathology assessed in adulthood 20 years later.

Results from this report extend the recent work of Toyota et al. (2004) who reported increased strabismus among adults with schizophrenia. Identifying ocular alignment deficits in childhood among individuals who later developed schizophrenia-spectrum disorders in relation to those who did not develop schizophrenia-spectrum disorders suggests that strabismus may serve as an early marker for schizophrenia identifiable in childhood prior to illness.

Speculation regarding neurological impairment responsible for the observed deficits from this study should be made with caution as the exact neurological substrates subserving the eye examination are not completely understood (Leigh and Zee, 1999). Toyota et al. (2004) consider strabismus a minor physical anomaly (MPA) with neurodevelopmental origins in the first or second trimester of gestation. A previous

study (Schiffman et al., 2002) investigating Waldrop scale MPAs (Waldrop and Halverson, 1971) in the same sample used for this study noted an increase in MPAs among individuals who later developed a schizophrenia-spectrum disorder. While analyses assessing the relation between the eye examination scale and MPAs in this sample did not reveal a significant association, it is possible that ocular alignment deficits represent a relevant disruption in pre-natal neurodevelopment not captured in the Waldrop scale. The relation between Waldrop scale MPAs and strabismus will be an important area for continued research. Regardless as to whether strabismus should be considered an MPA, the timing and cause of potential insults resulting in strabismus may provide insight into neurodevelopmental disruption contributing to schizophrenia.

In their study, Toyota et al. (2004) linked a mutation of the *PMX2B* gene to patients with schizophrenia and strabismus, and suggested that strabismus may result from *PMX2B* mutations in conjunction with additional genetic or environmental factors. It is interesting to note that mutation of *PMX2B* may influence the synthesis of dopamine and noradrenaline. These neurotransmitters are implicated in the expression of schizophrenia, and dopaminergic modulation of the oculomotor system occurs at the level of the basal ganglia (Hikosaka et al., 2000).

Contrary to other studies of eye functioning in the offspring of parents with schizophrenia, we did not detect a significant group difference between the genetic psychiatric risk groups in this study (offspring of parents with schizophrenia compared to offspring of parents with other non-psychotic psychopathology and offspring of parents without a diagnosable mental illness). Additionally, while in the expected direction, among genetically at risk subjects, no significant differences on the eye exam scales were detected between individuals who developed schizophrenia-spectrum disorders in relation to those who did not. This finding is puzzling as ocular deficits significantly distinguished subjects when the entire sample was considered. Several factors, however, make it difficult to make strong conclusions regarding the relation between genetic risk and the eye examination based on this study. Such factors include a potential lack of statistical power to detect existing differences as a result of using non-para-

metric analyses and the relatively low sample size due to selecting the sample based on genetic risk. Additionally, as suggested by Toyota et al. (2004), strabismus might result from the interaction of genetic effects and other schizophrenia-relevant risk factors.

5.1. Limitations

The measure of eye dysfunction used in this study was not the same as more traditional eye paradigms investigated in schizophrenia such as smooth pursuit and antisaccade tasks. Rather, the eye examination employed in this project tapped various constructs related to the functioning of the eyes (including movement and alignment). As a result, findings from our study may be more in line with a recent study regarding ocular alignment (Toyota et al., 2004) rather than with more traditional studies of eye functioning and schizophrenia such as smooth pursuit and antisaccade tasks. It is relevant to note, however, that the ocular systems measured in this study are related to general ocular functioning and some of the tasks included in the eye examination scale likely relate to smooth pursuit tasks (e.g., visual pursuit movements) and others likely measure deficits that contribute to difficulties with antisaccade tasks (e.g., Maddox Wing) (Flach et al., 1992). Unfortunately for the purposes of ensuring reliability, only one neurologist administered the eye examination. He was, however, a leading pediatric neurologist in Denmark and well trained in the assessment of the eye examination.

General eye deficits and deficits related specifically to strabismus among children predicted later development of schizophrenia-spectrum disorders. Eye examinations similar to the one employed in this study are relatively brief and common. Eye exams noting eye deficits such as those related to strabismus, may be a useful tool in conjunction with other predictors to identify youth at increased risk for schizophrenia. Future study should pursue this relation.

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