
Blink Rate in Childhood-Onset Schizophrenia: Comparison with Normal and Attention-Deficit Hyperactivity Disorder Controls

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Several lines of evidence have implicated central dopaminergic pathways in the modulation of blink rate. In the present study, blink rate during smooth pursuit was examined in 17 children with childhood-onset schizophrenia, on and off of clozapine, and compared to that of age-matched normal children and unmedicated children with attention-deficit hyperactivity disorder (ADHD). As has been observed in adolescent and adult schizophrenics, blink rate was significantly higher in schizophrenic children relative to normal and ADHD controls. Within the schizophrenic group, blink rate did not significantly change with the introduction of clozapine and was not related to clinical variables. Blink rate was positively correlated with deterioration in smooth pursuit in normal subjects. © 1996 Society of Biological Psychiatry

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Introduction

Spontaneous blinking, first noted to be elevated in psychotic patients by Ostow and Ostow (1945), has since been found to be increased in chronic adult schizophrenic patients withdrawn from neuroleptic medications (Karson et al 1981a; Stevens 1978) and in medication-naïve adolescent (Karson et al 1986) and adult schizophrenics

(Mackert et al 1990). Administration of typical neuroleptics reduces blink rate in schizophrenics and the degree of blink rate reduction has been found to be correlated with reduction in brief psychiatric rating scale (BPRS) (Overall and Gorham 1962) anxiety, hostility, and unusual thought content items (Mackert et al 1990) and a thought disturbance subscale (Karson et al 1982). Blunted affect in schizophrenia has been found to be negatively correlated with blink rate (Kitamura et al 1984).

Although blinking maintains corneal lubrication, humans, on average, blink 5-10 times more frequently than is necessary to achieve this (Karson 1988). Further indication of a central contribution to blink rate comes from the fact that blink rate is largely independent of ambient humidity, light, temperature, and of deafferentation of the fifth cranial nerve (Ponder and Kennedy 1928). Central

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dopaminergic pathways have been implicated in the modulation of blink rate by observations of decreased blink rates in patients with Parkinson's disease, which increase with levodopa-induced dyskinesia (Karson 1983); increased blink rates observed in nonhuman primates administered D_1 or D_2 agonists, the effects of which are blocked by pretreatment with D_1 or D_2 antagonists (Elsworth et al 1991); and reduction of blink rate in schizophrenics with administration of dopamine receptor blocking agents (Karson et al 1981a).

In contrast to the findings of increased blink rate in unmedicated adolescent and adult patients with schizophrenia, Caplan and Guthrie (1994) have found that blink rate in unmedicated schizophrenic spectrum children was significantly lower than that of similarly aged normal children. Schizophrenic spectrum children receiving neuroleptic medication, on the other hand, did not differ from normals in terms of blink rate. This finding is unexpected particularly in view of the similarities in clinical features (Green et al 1984; Werry et al 1994; Beitchman 1985) and smooth pursuit abnormalities (Jacobsen et al in press) between children and adults with schizophrenia. Blink rate was not significantly related to measures of thought disorder in schizophrenic children, but did increase with increasing processing demand of the task in both schizophrenic and normal children (Caplan and Guthrie 1994), as has been observed in normal adults (Karson et al 1981b).

The importance of age-matched controls for studies of blink rate in children was underscored by Zametkin and colleagues (1979), who demonstrated the developmental progression for spontaneous blink rate in normal children, from very low rates in infancy, steadily increasing during childhood and adolescence, reaching adult rates by age 20.

Smooth pursuit has also been found to be abnormal in adult schizophrenics (Abel et al 1992; Levy et al 1993). Unlike blink rate, smooth pursuit dysfunction in schizophrenia does not normalize with the introduction of dopamine blocking agents (Kufferle et al 1990; Levy et al 1983; Litman et al 1989) or improvements in clinical state (Levy et al 1983; Rea et al 1989; Saletu et al 1986). Smooth pursuit, which also demonstrates developmental changes in normal children, who typically achieve adult levels of pursuit performance by age 14 (Ross et al 1993), was recently examined in a sample of children and adolescents with childhood-onset schizophrenia (Jacobsen et al in press). Schizophrenic subjects exhibited significantly lower gain (ratio of eye to target velocity) and increased saccades relative to both normal children and children with attention-deficit hyperactivity disorder (ADHD), thus demonstrating a pattern of eye movement abnormalities similar to that seen in adult-onset schizophrenia. ADHD subjects performed as well as normals on

all measures of eye tracking with the exception of the global measure, root mean square error (RMSE).

Preliminary evidence suggests that blink rate may normally be suppressed during smooth pursuit (Evinger 1984); however, adult schizophrenics blink more frequently than normals while visually tracking a target (Cegalis and Sweeney 1979). This observation, together with the fact that the smooth pursuit and blink rate abnormalities seen in schizophrenia both may subtly interfere with visual perception by decreasing the time that images are on the fovea (Volkman 1986), suggests that there may be a common neurobiologic basis to the dysregulation of pursuit and blinking in schizophrenia. Yet, the relationship between smooth pursuit abnormalities and blink rate in schizophrenia has not been examined in detail.

In the present study, blink rate was examined in a sample of 17 children with childhood-onset schizophrenia, on and off of clozapine, and compared to that of age-matched normal children and children with ADHD. The relationship between blink rate and smooth pursuit gain was examined and, within the schizophrenic group, relationships between blink rate and clinical variables were assessed. We hypothesized that schizophrenics would exhibit higher blink rates than both normal and ADHD children and that clozapine, due to its relatively high dissociation constants at both D_1 and D_2 receptors (Seeman 1990), would not be associated with decreased blink rates in the schizophrenic subjects. Based on observations in adult schizophrenics of positive correlations between changes in positive symptoms and changes in blink rate (Mackert et al 1990; Karson et al 1982), we further hypothesized that blink rate would be positively correlated to Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984) and BPRS total and anxiety subscale scores within the schizophrenics. We hypothesized that blink rate would be negatively correlated to Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1983) on the basis of negative correlations between blink rate and blunted affect in adult schizophrenic patients (Kitamura et al 1984) and parkinsonian symptoms in patients with Parkinson's disease (Karson 1988).

Methods

Subjects

SCHIZOPHRENIC GROUP. Schizophrenic subjects were 10 boys and 7 girls, age 10–18 (mean 14.5 ± 1.8), who met DSM-III-R (American Psychiatric Association 1987) criteria for schizophrenia, with onset of psychotic symptoms prior to age 12, and were participants in an ongoing study of childhood-onset schizophrenia described else-

where (Frazier et al 1994; Gordon et al 1994). Other inclusion criteria were absence of active medical or neurologic disease and, because this study involves a trial of clozapine, history of poor response to or intolerance of treatment with at least two different neuroleptics. Diagnosis was determined using previous records and clinical and structured interviews of the children and parents using portions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version (Orvaschell et al 1980) and of the Diagnostic Interview for Children and Adolescents Revised (DICA-R) (Reich and Welner 1988).

Eye tracking data and blink rates were obtained from most schizophrenic subjects at the end of a 4-week medication washout phase and at the end of 6-week trials of haloperidol or clozapine. Five subjects could not be studied in the unmedicated state. Since only 4 subjects were studied following randomization to haloperidol, only data collected from subjects while medication free (10 subjects) or on clozapine (14 subjects) will be reported here. A total of 7 subjects were studied both while unmedicated and while on clozapine.

ADHD CONTROL GROUP. Subjects with ADHD were 17 boys and 1 girl, age 9–15 (mean 12.4 ± 2.5), and were participating in a 9-week double-blind, placebo-controlled trial of methylphenidate and dextroamphetamine described elsewhere (Elia et al 1991). All were screened for medical and neurologic disease, and all met DSM-III-R criteria for ADHD, determined via structured interviews with parent and child using the DICA-P (parent) and the DICA-C (child) (Herjanic and Campbell 1977), and via cut off scores on parent and teacher ratings. ADHD subjects were studied while medication free.

NORMAL CONTROL GROUP. Normal subjects included 16 boys and 6 girls, age 9–18 (mean 13.5 ± 2.2), who were recruited through advertisement and were free of medical, neurologic, and psychiatric illness and learning disabilities as determined by history from parents, the Conners Preliminary Parent Report and the Achenbach Child Behavior Checklist (Achenbach and Edelbrock 1983) completed by parents, Conners Teacher Preliminary School Report and Conners Teacher Questionnaire (Goyette et al 1978; Werry et al 1975), physical and neurologic exam of the child, and structured interview of the child and parent using the DICA-R. Any history of psychiatric illness in a first-degree relative, per parent report, was exclusionary.

Parents of all subjects provided written informed consent and subjects provided written assent for participation in the study. This study was approved by the NIMH Institutional Review Board.

Eye Movement Procedure and Task

Details of the eye movement procedure, task, analysis, and smooth pursuit and saccade classification criteria used in this study are described in a separate report on the eye tracking of these subjects (Jacobsen et al in press). Briefly, subjects' heads were stabilized with a bite bar and a head rest 43 cm in front of a video monitor on which a bright square target subtending less than 0.25° of visual angle was displayed against a black background. The room was darkened during eye movement tasks. Horizontal eye movements of 39 subjects (10 schizophrenics, 11 ADHD, 18 normals) were recorded using an infrared photoelectric limbus detection eye tracking device [Eye-trac model 210, Applied Sciences Laboratories (ASL), Waltham, MA], which is accurate to within 0.25° of visual angle, and has a time constant of 4 msec. The analog output was sampled at 1000 Hz using a 12-bit analog-to-digital converter. During the course of this study, eye movement recording equipment was upgraded. Thus, 18 subjects (7 schizophrenics, 7 ADHD subjects, 4 normals) were studied using the Ober2 infrared orbital scanning system. This system uses extremely brief pulses of infrared light (pulse rate 600 Hz), and collects data over a few microseconds. Thus, it has a time constant of well under 1 msec. Calibration of the two systems was performed independently.

Data from an approximately 60-sec smooth pursuit task, during which the target moved horizontally back and forth over 30° with a constant velocity of $11.0^\circ/\text{sec}$ and a 1.4-sec fixation period between ramps (a "trapezoidal" pattern), were included in the present analysis. Subjects were instructed to keep their eyes on the target, to follow it as closely as possible, and to avoid blinking during the entire task. Subjects were permitted to wear corrective lenses, but not contact lenses, during the eye movement procedure.

Eye Movement Analysis and Blink Rate Determination

Data obtained from the ASL and Ober2 systems were analyzed identically. Following data collection, superimposed tracings of eye and target movement were displayed graphically on a computer screen. Sections of the records during which subjects were not attempting to perform the task (i.e., were not looking at the screen) were identified by visual inspection and were excluded from all analysis.

Eye movement data were analyzed with a computerized pattern recognition system that has been described elsewhere (Nickoloff et al 1991; Radant and Hommer 1992). Blinking produces a morphologically distinct pattern in the eye position record consisting of two intervals of high-velocity artifact. These intervals are not separated by a period of fixation as is usually the case with sequential

saccades. Blinks were excluded from the eye tracking analysis by the pattern recognition software. Smooth pursuit gain was calculated by summing the amplitude of all smooth pursuit intervals and dividing this value by the total amplitude traveled by the target during all smooth pursuit intervals.

Blink rate was determined by a rater blind to diagnosis (LKJ) who counted episodes of blink artifact occurring while subjects were engaged in the smooth pursuit task. To ensure that only artifacts with morphology consistent with being blinks were counted, eye tracking records were examined at two magnifications (16 sec/computer screen and 2 sec/computer screen). The resulting number was divided by total task time in seconds and multiplied by 60 to obtain blinks per minute.

Behavioral and Cognitive Assessments

BPRS, SANS, and SAPS scores were obtained on schizophrenic subjects as described previously (Frazier et al 1994), and the scores in closest temporal proximity to the dates on which eye tracking data and blink rate were collected (usually the week of testing) were used in this analysis. A BPRS anxiety subscale score was also constructed by summing scores on the anxiety (#2) and tension (#6) items. Interrater reliabilities (intraclass correlation coefficients) for BPRS ranged from 0.64 to 0.90, for SANS they ranged from 0.81 to 0.92, and for SAPS they ranged from 0.87 to 0.91.

Five schizophrenic subjects were too symptomatic during the course of this study to permit valid assessment of intelligence. With the remaining 12 subjects, IQ was measured using the Wechsler Intelligence Scale for Children—Revised (WISC-R) (Wechsler 1974). The IQ of ADHD subjects was obtained from the full WISC-R, while the IQ of the normal subjects was estimated using the vocabulary and block design subtests (Sattler 1992).

Data Analysis

Data were analyzed using two-tailed *t* tests for independent samples, paired *t* tests, Pearson's correlation coefficient, analysis of variance, and analysis of covariance. Examination of all of the variables in this study using data plots and the Kolmogorov-Smirnov test for normality revealed that only blink rate of the schizophrenic group had a skewed distribution. Thus, all analyses were performed using log transformed blink rate, which normalized the distribution of this variable.

Although age was not significantly correlated with log transformed blink rate within normal or ADHD groups, the correlation between these two variables within the schizophrenic group exhibited a trend toward significance.

Thus, age was used as a covariate in the analysis of covariance. Duncan Multiple Range post hoc tests were used to determine whether significant differences existed between groups. The relationship between log transformed blink rate and gain within each of the groups was examined using partial correlation coefficients controlling for age. Exploratory correlation analyses examining the relationship between log transformed blink rate and clinical variables within the schizophrenic group were also performed using partial correlation coefficients controlling for age. Although the schizophrenics differed significantly from the control groups in IQ, adjustment for IQ was not performed, as this difference may reflect an aspect of the schizophrenic disease process itself. All *p* values are two tailed.

Results

All subjects completed the task. *T* tests with Bonferroni correction for multiple comparisons revealed no significant differences across eye movement variables and log transformed blink rate between subjects studied with the ASL system and subjects studied using the Ober2 system. Paired *t* tests using data from 6 subjects (4 normals and 2 schizophrenics) studied on both systems also revealed no significant differences between the two systems across eye movement variables and log transformed blink rate. Thus, data from the two systems were combined.

Within the subgroup of 7 schizophrenics studied both on and off of medication, log transformed blink rate on clozapine was not significantly different from blink rate while off of medication ($t = -0.65$, $df = 6$, $p = .69$). Given the absence of significant differences in blink rate and smooth pursuit performance between unmedicated schizophrenics and schizophrenics on clozapine (Jacobsen et al in press), all subsequent analyses were conducted using the eye tracking record associated with the highest average gain for each schizophrenic subject. This more conservative criterion was used as a means of selecting the record representing the best smooth pursuit performance for each schizophrenic subject. This resulted in selecting 8 records obtained while subjects were unmedicated and 9 while subjects were on clozapine.

Schizophrenic, ADHD subjects, and normals differed significantly in both age [$F(2, 54) = 3.41$, $p < .05$] and IQ [$F(2, 49) = 13.54$, $p < .0001$]. Post hoc tests indicated that ADHD subjects were significantly younger than schizophrenic subjects, but not different in age from normals, who did not differ in age from schizophrenics. The schizophrenic group had a significantly lower IQ than both ADHD and normal groups, who did not differ from one another in IQ.

Table 1. Medication Status, Gender, Age, Full Scale IQ, and Raw Blink Rates of Schizophrenic, ADHD, and Normal Subjects

Diagnosis/medication status	N	Gender (M/F)	Age ^a [mean (SD), years]	IQ ^b [mean (SD)]	Blink rate ^c [mean (SD) per minute]
Schizophrenic (unmedicated/clozapine)	8/9	10/7	14.5 (1.8)	84.7 (16.8)	15.1 (16.5)
ADHD (unmedicated)	18	17/1	12.6 (2.5)	110.6 (16.6)	3.4 (3.7)
Normals (unmedicated)	22	16/6	13.5 (2.2)	116.0 (17.9)	3.9 (4.4)

SD = standard deviation.

^aAttention-deficit hyperactivity disorder (ADHD) subjects were significantly younger than schizophrenics ($p < .05$).

^bIQ of 12 schizophrenics, 18 ADHD, and 22 normal subjects; schizophrenics had a lower mean IQ than ADHD and normal subjects ($p < .0001$).

^cSchizophrenics had a higher mean blink rate than ADHD and normal subjects after log transformation and adjusting for age ($p < .001$).

Blink Rate, Smooth Pursuit, and Clinical Variables

Analysis of covariance, using age as a covariate, revealed a significant main effect of log transformed blink rate [$F(2, 53) = 8.40, p < .001$], with post hoc tests indicating that schizophrenics blinked significantly more frequently than both ADHD and normal subjects, while the latter two groups did not differ from one another. Medication status, gender, and mean age, IQ, and unadjusted, raw blink rate for each of the three groups are shown in Table 1.

The partial correlation between log transformed blink rate and gain did not achieve significance within schizophrenic and ADHD groups ($r = -0.04, n = 17, p = .88$ and $r = -0.14, n = 18, p = .60$, respectively); however, log transformed blink rate was significantly negatively correlated with gain within the normal group ($r = -0.49, n = 22, p < .05$).

Examination of the relationship between log transformed blink rate and clinical variables within the schizophrenic group revealed the following partial correlations: $r = -0.19$ (with BPRS anxiety subscale score), $r = -0.19$ (with total BPRS score), $r = -0.21$ (with total SANS score), and $r = -0.36$ (with total SAPS score). None of these partial correlations achieved significance. As noted above, the relationship between log transformed blink rate and age approached significance only within the schizophrenic group ($r = -0.42, n = 17, p = .09$). Similarly, the correlation between IQ and log transformed blink rate approached significance only within the normal group ($r = -0.40, n = 22, p = .06$).

Discussion

Consonant with observations in adolescent (Karson et al 1986) and adult (Karson et al 1981a; Stevens 1978; Mackert et al 1990) schizophrenics, and in contrast to the one previous study of blink rate in schizophrenic children (Caplan and Guthrie 1994), we found that blink rate was significantly higher in schizophrenic children relative to normal and ADHD controls. Although this finding supports continuity between childhood- and later-onset forms of schizophrenia in terms of abnormalities in blink rate,

limitations of this study necessitate replication of these results before confidence can be placed in this conclusion.

In the present study, blink rate was measured via infrared oculography in a standardized setting while subjects were engaged in a brief, simple, oculomotor task. Although this design does not permit examination of variation within subjects, it does permit examination of variation between subjects. We note that a substantial minority (5) of schizophrenic subjects blinked more than 20 times per minute; much more frequently than any of the normal or ADHD subjects. Given evidence linking increased activity at central nervous system dopamine receptors with increased blink rate (Elsworth et al 1991), this subgroup of schizophrenic subjects might be expected to differ in treatment response from the remaining schizophrenics whose rate of blinking was within the range of normals; however, these 5 subjects did not differ from the remaining 12 in response to treatment with clozapine, as reflected by change in SANS, SAPS, or total BPRS score.

Our failure to replicate Caplan and Guthrie's (Caplan and Guthrie 1994) previous finding of lower blink rate, measured by counting blinks from videotapes of subjects undergoing language assessment, in unmedicated schizophrenic children relative to normal children may be primarily due to the methodologic differences between these two studies. Other potentially important differences between the two studies include differences in the ages of the children studied and differences in inclusion criteria. Our criterion that schizophrenic children be neuroleptic nonresponders, for example, may have selected for a subgroup of schizophrenic children with greater brain abnormalities (Crow 1985).

As predicted, clozapine treatment was not associated with a significant change in blink rate in schizophrenic children, consistent with clozapine's relatively weak affinity for D₁ and D₂ receptors (Seeman 1990). As observed previously in children with ADHD engaged in low processing demand tasks (Caplan et al in press), blink rate of subjects with ADHD did not differ from that of normals during smooth pursuit, a task involving minimal cognitive processing.

The fact that the relationship between blink rate and gain did not even approach significance within schizophrenic and ADHD groups may be due to the relatively small size of these groups, or may reflect deficient integration of neural circuits that regulate blinking and pursuit eye movements in schizophrenics. In contrast, gain was closely related to blink rate in normals such that blink rate increased as smooth pursuit deteriorated, as reflected by decreasing gain.

Given the evidence that central dopaminergic neural pathways regulate blink rate (Karson 1983; Elsworth et al 1991; Karson et al 1981a), these relationships suggest that increased activity in these pathways may also disrupt smooth pursuit. Candidate structures known to modulate both blinking and saccades include the substantia nigra and the superior colliculus (Karson et al 1984; Hikosaka and Wurtz 1983, 1985a, 1985b; Waitzman et al 1991). Fixation cells in the superior colliculus are active both during fixation and during smooth pursuit, and inhibit the activity of saccade-generating cells (Munoz and Wurtz 1993). The fact that blinking is also suppressed during fixation and smooth pursuit (Evinger 1984) suggests that fixation cells may coordinate blink and smooth pursuit modulation. If this were the case, disruption of these cells could be the basis for our failure to observe a relationship between gain and blink rate in the schizophrenic and ADHD groups.

Although relationships between the clinical measures and blink rate within the schizophrenic group did not achieve significance, the relationship between blink rate and SAPS scores was fairly strong, suggesting that the lack of significance may primarily have been due to small sample size. This relationship was not in the expected direction, however; blink rate increased as SAPS score decreased, contrary to our expectation based upon observations in later-onset schizophrenia (Mackert et al 1990; Karson et al 1982; Kitamura et al 1984). Notably, Caplan and Guthrie (1994) failed to find a significant relationship between blink rate and measures of thought disorder in their sample of schizophrenic spectrum children. Although the small size of the schizophrenic sample in the present study precludes conclusive interpretation of these data, these observations, together with those of Caplan and Guthrie (1994), may suggest that blink rate in childhood-onset schizophrenia is not linked to positive and negative symptoms in the same way or as closely as it is in later-onset schizophrenia.

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- Zametkin and colleagues (1979) noted that the greatest increases in blink rate occurred between the ages of 1 and 15 years. Our sample may not have included enough subjects from the lower part of this age range to detect the relationship between blink rate and age.

Notably, the blink rates of our ADHD and normal subjects are lower than that observed by Zametkin and colleagues (1979) in normal 11-15-year-old children (10.3 blinks per minute). This may indicate that the suppression of blinking possibly occurring during smooth pursuit in adults also occurs in children and adolescents (Evinger 1984); however, this may also reflect methodologic differences between the two studies. In particular, both using infrared oculography to measure blink rate and instructing subjects to avoid blinking during the task may have led to underestimation of blink rate.

In conclusion, blink rate was significantly higher in a sample of children with schizophrenia relative to normal children and unmedicated children with ADHD, suggesting continuity between childhood- and later-onset schizophrenia along this dimension. Clozapine did not alter blink rate in schizophrenic children and, although blink rate was not significantly related to clinical variables in schizophrenics, blink rate was positively related to poorer smooth pursuit performance in normal subjects. Limitations of this study include small sample sizes and our inability to assess modulation of blink rate across different processing loads, or to assess the effect of stimulant medication on blink rate in ADHD subjects; the latter will be addressed in future studies. In addition, two eye movement recording systems were used to collect data and comparability to blink rates measured via videotape recording was not established. Future studies of larger samples of subjects are planned to address these weaknesses.

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