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Eye tracking dysfunction in families with multiple cases of schizophrenia

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Abstract There is increasing evidence that the genetic predisposition for schizophrenia in families affects more individuals than those fulfilling the criteria for schizophrenia. This finding is supposed to be one of the major problems in molecular genetic schizophrenia research, especially when linkage studies are employed. Eye-tracking dysfunction (ETD), which is conceived as a possible phenotypic marker for genetic liability to schizophrenia, may offer considerable advantages. However, there is only little information from families with multiple occurrence of schizophrenia. It is still unclear whether in these families ETD aggregates with diagnoses from the schizophrenia spectrum. This first report from an ongoing study presents the results of 48 individuals from 6 multiplex families. Smooth-pursuit eye movements were recorded by infrared reflectometry and assessed by quantitative measurement techniques. Along with the high degree of psychiatric morbidity in these families, in 56.3% of the individuals ETD was assessed. Reduced mean pursuit gain was present in 39.6%. The distribution of eye-tracking dysfunction resembles the distribution of schizophrenia-related psychiatry morbidity.

Key words Schizophrenia · Genetics · Liability · Vulnerability · Eye-tracking dysfunction · Eye movements · Smooth-pursuit eye movements

Introduction

Genetic–epidemiological studies have demonstrated consistently that genetic factors contribute substantially to the etiology of schizophrenia (Kendler and Diehl 1993). Molecular genetic methods based on recombinant DNA technology are supposed to have a major impact on the understanding of the genotype associated with genetic predisposition for schizophrenia. After early disappointment (Sherrington et al. 1988), linkage studies have recently yielded the first positive results, based on large numbers of families with multiple cases of schizophrenia (Moises et al. 1995; Straub et al. 1995; Wang et al. 1995). On the other hand, the linkage approach has been critically reviewed lately (Cardno and McGuffin 1994; Cloninger 1994; O'Donovan and Owen 1992; Rutter 1994) and possible pitfalls have been pointed out. The diffuse boundaries of the schizophrenic phenotype in families have turned out to be a major problem which might still handicap linkage analysis in large pedigrees (Hodge and Greenberg 1992). Yet genetic–epidemiological studies have provided some evidence for the understanding that genetic predisposition for schizophrenia results in phenotypic syndrome variety (Kendler 1988; Kendler and Diehl 1993). Thus it seems doubtful that this dilemma will be solved exclusively by means of psychopathology. One possible solution is the employment of phenotypic markers of genetic susceptibility (Holzman 1994).

As one of the most promising phenotypic markers, abnormal smooth-pursuit eye movements have been discussed extensivley (for reviews see Arolt et al. 1993; Clementz and Sweeney 1990; Holzman 1987, 1994; Levy et al. 1993). In affected individuals smooth-pursuit eye movements are frequently interrupted by small amplitude saccades. Such eye-tracking dysfunction (ETD) has been reported in different samples of schizophrenics with a mean prevalence of approximately 50%, but only in 4–8% of the normal population (Clementz and Sweeney 1990; Holzman 1987; Iacono 1985, 1988; Levy et al. 1993) and the first-degree relatives of normal subjects (Iacono et al. 1992). The neuro-ophthalmological techniques, as well as the reported deficits, vary widely across the numerous studies which have been carried out. In first-degree relatives of schizophrenics, ETD was also detected with a high degree of variation (between 14.0 and 50.0%; Levy et al. 1993). In

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most studies of first-degree relatives, their ascertainment was linked to single-index patients, regardless of single of multiple occurrence of schizophrenia in the related families. With two exceptions (Blackwood et al. 1991; Myles-Worsley 1992) ETD studies have not been based on a systematic recruitment of families with multiple cases of schizophrenia. Yet it is these families in whom a genetic susceptibly for schizophrenia can be assumed and who present a unique possibility for extensive studies of ETD and its implications for genetic research. In these families, however, it has neither been demonstrated whether ETD aggregates along with schizophrenia and schizophrenia-linked disorders, nor is much known (despite considerable research efforts) about whether psychopathology and oculomotor dysfunction distribute in a congruous manner. In this case ETD will be present in any family member with a disorder from the schizophrenia spectrum. However, it should not be regarded as contradictory if individuals without psychiatric disorders in such families are affected with ETD. This case would still be in line with the concept of a genetic marker, because it can be assumed that heritability needs not necessarily be expressed as schizophrenia spectrum disorder. It is of some importance in this respect that, in a review of previous studies, Holzman et al. (1987) reported a number of cases in which schizophrenic siblings were not affected by ETD, whereas parents were affected (approximately 30% of all cases). Such findings have provided the basis for the development of the latent trait model of genetic transmission of schizophrenia and ETD (Matthyse et al. 1986). It has been critically reviewed (Clementz and Sweeney 1990) that the psychiatric diagnoses in these previous studies were established inconsistently, and that only global neurophysiological measures were used.

During the past decade, techniques have been employed which adhere to neurophysiological standards. Based on infrared reflectometry, quantitative measures, such as the mean gain (the ratio of mean pursuit velocity: target velocity) or mean number of saccades, have only lately been used in ETD studies of schizophrenic patient samples (Abel 1992; Clementz and Sweeney 1990; Levy et al. 1993). Only three studies of first-degree relatives (Clementz et al. 1991, 1992; Grove et al. 1992) have employed such (or similar) methods. In the two studies of multiplex families cited previously (Blackwood et al. 1991; Myles-Worsley et al.1992), this technology has not been used, but only more global techniques based on conventional electro-oculography. Disregarding the importance of the observations of Holzman and coworkers (1988), their findings have not yet been systematically tested, neither in multiplex families nor with advanced technology.

In this article we present first results from an ongoing study of families with multiple occurrence of schizophrenia, based on infrared reflectometry and quantitative measures. It can be assumed that a genetically transmitted etiology of schizophrenia is very likely to be present in families with more than one schizophrenic member. It is our hypothesis that in such families, eye-tracking abnormalities will be present in any family member with a disorder of the schizophrenia spectrum, and will also, but to a lesser extent, be present in psychiatrically normal family members.

Methods

Psychiatric assessment

Six families with a suspected genetic liability to schizophrenia were recruited: Families were included if two or more schizophrenics had been diagnosed in one or two consecutive generation(s). In the six families with a total of 68 members, 51 individuals could be interviewed personally. Of these, 48 agreed to participate in the eye-tracking test. Eye-tracking data could not be assessed from three interviewed family members because of alcoholism, oligophrenia, and rejection of being tested. Although every possible effort had been made to obtain interviews and recordings, this was not successful in another 17 individuals because these persons had already died, suffered from severe dementia, lived too far away (>500 km), or the family had lost contact completely (so their address was unknown). Psychiatric diagnoses were established on the basis of the following principles:

1. Structured instruments used in German translations: (a) the Schedule for Affective Disorders and Schizophrenia/Lifetime Version (Endicott and Spitzer 1978); (b) the Structured Interview for Schizotypy/Version 1.6 (Kendler 1991); and (c) the Schedule for Affective Disorders and Schizophrenia/Personality Disorders (SCID-II; Spitzer and Williams 1985).
2. Operational definitions of psychiatric disorders as provided by DSM-III-R.
3. Blind interviews of family members.

A personality disorder (axis II) was diagnosed only in individuals without an axis-I disorder. As has been practiced in other genetic – epidemiological studies in this field, we distinguished between cases of schizotypal personality disorder (SPD), which fulfilled at least five of nine DSM-III-R criteria which were necessary for the diagnoses (definite SPD), and cases which fulfilled three or four of these criteria (probable SPD). For the purpose of this article and reasons of comparability, we collapsed these diagnostic subgroups into one category (SPD).

The following FH-RDC diagnoses were established in the cases of the 17 individuals who could not be interviewed personally: schizophrenia ($n = 2$), schizoaffective psychosis ($n = 1$), schizotypal or paranoid personality disorder ($n = 3$), substance abuse ($n = 3$), dementia ($n = 2$), other disorders ($n = 1$), and healthy ($n = 5$). In the case of the three family members who had to be excluded from eye-movement measuring because of substance abuse, one had a co-occurring psychiatric diagnosis (paranoid personality disorder).

Recording and measuring eye movements.

Eye movements were recorded by a mobile infrared light eye tracker (AMTech GmbH, Weinheim, Germany, and SKALAR, Delft, The Netherlands), which allowed us to examine probands at home, who whould have refused to participate otherwise. This high-resolution technique (Reulen et al. 1988) provides signal recordings with only few artifacts. The stimuli for eliciting smooth-pursuit eye movements were displayed by an array of red-light-emitting diodes (LED). The diodes (diameter 5.7 mm) were arranged as close as possible, so that the target traverse subtending 30° consisted of 186 diodes. To guarantee a quasi-continuous target motion two diodes might be energized during transition of the light signal. In a pilot study with five normal controls, we compared eye-tracking data which had been recorded with the mobile device to data recorded by a stationary infrared eye-tracker device which is supplied with an on-laser target. No significant differences could be observed, neither with respect to mean gain nor to saccade frequency. Subjects were seated in a portable armchair 2 m in front of

the LED array and were instructed not to move their head during the measurement. Visual acuity was normal or corrected by individual optical spectacles or contact lenses. Probands with a history of drug abuse of lithium treatment were excluded.

In order to judge smooth-pursuit quality, we chose a triangular target movement paradigm with a constant velocity of 30°/s. This method was preferred because the discrimination between schizophrenics and healthy controls was best at a target velocity of 30°/s (our own unpublished data). One trial lasted 20 s plus 5 s of calibration (steps of 10° from the central point to the left and the right side each lasting 1 s at the beginning and the end of each trial. After calibration of the original recordings, saccades were detected and counted. The definition of a saccade was based on two requirements: firstly, the difference between the actual velocity of the eye movement and the mean velocity before and after the fast eye movement had to be > 30°/s, and secondly, the amplitude of the fast eye movement had to be larger than 0.5°. By this definition saccades in both directions of the target trajectory were detected. After having cut out saccades and artifacts, the mean eye velocity in each segment and the mean pursuit velocity gain (defined as ratio of the mean pursuit velocity to target velocity) were calculated in ten cycles (ten segments with target motion to the right and ten segments with target motion to the left side) 125 ms before and after the turning point were excluded from this procedure. To yield the average gain of the whole trial, the median was used.

A similar method was used in our pilot study (Moser et al. 1990), which also adheres to neurophysiological standards (Abel and Ziegler 1988). The quality of smooth pursuit was judged by the individual mean gain and the total number of saccades, after it had been compared with normal ranges for both parameters, established from a group of 47 controls (Table 1). As controls healthy students and medical staff members were chosen (demographic characteristics given in Table 2). In this sample the mean pursuit gain was 0.77 (± 0.10), and the mean number of saccades was n = 47.4 (± 20.2; our own unpublished data). In order to rule out an age effect on the assessment of smooth pursuit in the family members, the control sample was divided into three age groups: group 1 (G1), 20–39 years; group 2 (G2), 40–59 years; group 3 (G3), > 60 years. We defined the thresholds for a smooth-pursuit gain deficit as the arithmetic mean minus 2 SD for a target velocity of 30°/s (Table 1). This procedure was justified by the observation that the pursuit gains of schizophrenics, as well as of normal controls, were distributed binominally. This common definition of smooth-pursuit deficit was also used in other studies on ETD (Clementz et al. 1992; Iacono et al. 1992; Yee et al. 1987). Every performance with a mean gain below this threshold was rated as deviant. The threshold for an abnormal number of saccades was defined as arithmetic mean plus 2 SD; accordingly, every performance which led to a number of saccades above this threshold was rated as deviant.

For the purpose of this study and in order to assess the distributions of ETD and schizophrenia spectrum disorders, we assessed smooth-pursuit eye movements on two measurement levels:

1. In the case of gain deficit (GD) the mean pursuit gain is below the defined threshold (see above). We also included this procedure in this study because the respective results can easily be compared with other studies using mean eye movement gain.
2. In the case of saccade excess (SE), the number of saccades is on or beyond the threshold defined above, but the mean pursuit gain may still be within the normal range. All other cases were rated as non-deviant. Both GD and SE should not be understood as different categories of smooth-pursuit dysfunction; instead, they represent two different approaches of quantitative measurement. If GD and SE are combined to assess ETD in the afore mentioned manner, this procedure covers a range of dysfunctions which can be compard to the results of studies employing global qualitative judgment techniques, which are obviously more inclusive than the quantitative procedures (Levy et al. 1993).

All statistical procedures were performed by the SPSS-PC program. Sample differences were tested by the t-test, in case the samples were distributed normally (Shapiro-Wilk's test). If the normal distribution was rejected, the Mann-Whitney test was used (for independent samples). Differences in the distribution of dichotomous variables in independent samples were tested by the χ^2 test (or Fisher's exact test, if $n < 5$). In order to provide an estimation of the age-corrected morbidity risk of psychiatric disorders, the Weinberg/Strömgren method was used.

Table 1 Thresholds (in italics) for the assessment of eye-tracking dysfunction based on quantitative measures. MG mean pursuit gain; NS number of saccades/20 s

Age (years)	MG	*MG – 2SD*	NS	*NS + 2 SD*
20–39	0.82	*0.63*	45.26	*71.98*
30–59	0.75	*0.62*	55.83	*87.38*
> 60	0.72	*0.49*	67.60	*106.62*

NOTE: Target velocity 30°/s

Table 2 Sociodemographic characteristics of probands with schizophrenia, non-schizophrenic spectrum disorders, other axis-I diagnoses, healthy relatives, and controls

Samples	Gender		Age (years)	
	Male	Female	Mean	SD
Schizophrenics (n = 13)	9	4	37.4[a]	11.5
Non-schizophrenic spectrum (n = 8)	4	4	50.7	17.2
Other axis I diagnoses (n = 10)	3	7	54.1	20.1
No psychiatric diagnoses (n = 17)	4	13	44.7	21.1
Healthy controls (n = 47)	26	21	45.3	16.8

[a] Trend (P = 0.06) to younger age of schizophrenics as compared with controls.

Results

A diagnosis of schizophrenia was established in 13 of 48 (27.1%) personally interviewed family members from six multiplex families. Of the relatives of the six schizophrenic index patients, seven secondary cases (16.7%) suffer from schizophrenia. Accordingly, of the six families, five had one secondary case of schizophrenia, and one family had two cases. Eight (19.0%) of the relatives had a diagnosis of schizoaffective, schizotypal, or paranoid personality disorder (schizophrenia spectrum). Other axis-I diagnoses were given to two (4.8%) of the relatives; eight individuals (19.0%) had other axis-II diagnoses. In 17 relatives (40.5%) no psychiatric diagnosis could be established (Table 3). If the distribution of psychiatric diagnoses in personally interviewed family members is compared with the diagnoses of those family members which could not be reached and had to be assessed by the FH-RDC method, no significant differences are observed.

In order to assess ETD in different diagnostic samples from the family members, we first calculated mean gain (MG) and number of saccades (NS). In the schizophrenic, as well as in the non-schizophrenic spectrum individuals, group means of MG were significantly lower than in the case of the control sample (Table 4). Furthermore, in the samples with other axis-I disorders and without psychiatric morbidity, MG was also lower than in controls. The

Table 3 Lifetime psychiatric diagnoses (DSM-III-R) and relative risks of lifetime morbidity of 42 personally interviewed relatives of six index patients with schizophrenia from six families with multiple occurrence of schizophrenia. MR age-corrected relative morbidity risk

Diagnoses	*n*	%	MR
Schizophrenia	7	16.7	28.6
Schizoaffective disorder	4	9.5	16.3
Schizotypal personality disorder[a]	3	7.1	12.2
Paranoid personality disorder	1	2.4	4.1
Other axis-I diagnoses	2	4.8	8.2
Other personality disorders	8	19.0	28.6
No psychiatric diagnosis	17	40.5	
Total	42	100.0	

[a] "Definite" cases: $n = 1$; "probable" cases: $n = 2$ (see Methods)

Table 4 Mean pursuit gain (MG) and mean number of saccades (NS) in members of six families with multiple occurrence of schizophrenia and healthy controls during a smooth-pursuit task with a constant target velocity of 30°/s (triangular movement)

Samples	MG	SD	NS	SD
Schizophrenics ($n = 13$)	57.8***	21.4	67.4****	10.6
Non-schizophrenic spectrum ($n = 8$)	51.9***	22.4	57.3**	10.9
Other diagnoses ($n = 10$)	65.4*	18.4	54.7	14.5
No psychiatric diagnoses ($n = 17$)	62.2*	25.8	55.3**	20.2
Healthy controls ($n = 47$)	77.4	9.6	47.4	20.2

*$P \leq 0.10$ (trend), **$P \leq 0.05$, ***$P \leq 0.01$, ****$P \leq 0.001$.
NOTE: The family samples were tested against the healthy controls by *t*-test after controlling for normal distribution by Shapiro-Wilk's test and for homogenetiy of variance by Levene's test (with the exception of MG in the case of the family sample without psychiatric diagnoses, which was not normally distributed; in this case the Whitney-Mann test was employed). The differences between the family samples were non-significant

Table 5 Eye-tracking dysfunction (*n*; numbers in parentheses are percentages) in schizophrenic index patients, 1st-, 2nd-, and 3rd-/4th-degree relatives from six families with multiple occurrence of schizophrenia. ETD eye-tracking dysfunction; I index patients; R1 first-degree relative; R2 second-degree relative; R3+ third- and fourth-degree relative; GD gain deficit (i.e., mean pursuit gain below threshold) SE saccad excess (i.e., number of saccades above threshold)

	I ($n = 6$)	R1 ($n = 22$)	R2 ($n = 11$)	R3+ ($n = 9$)
ETD	5 (83)	14 (64)	5 (46)	3 (33)[a]
GD	5 (83)	7 (32)	5 (46)	2 (22)[a]
SE	0 (0)	7 (32)	0 (0)	1 (11)
No ETD	1 (17)	8 (36)	6 (55)	6 (67)[a]

[a] $P \leq 0.05$ (vs index patients)

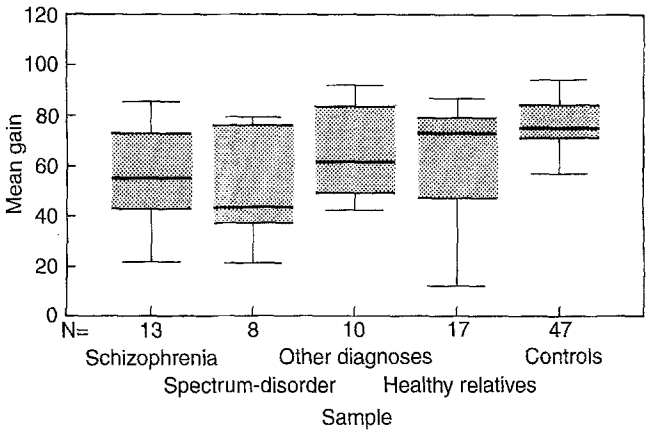

Fig. 1 Mean pursuit gain in samples of different diagnostic categories from six families with multiple cases of schizophrenia

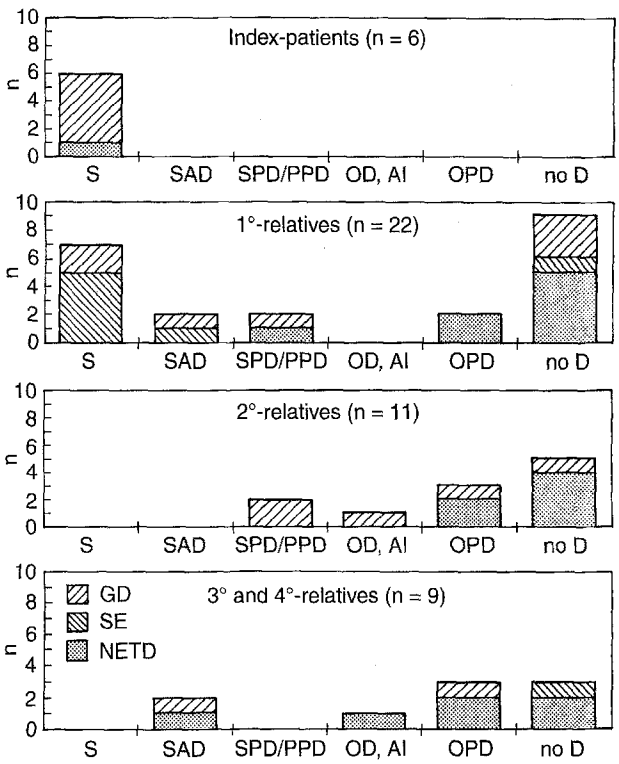

Fig. 2 Distribution of eye-tracking dysfunction in the members of six families multiply affected with schizophrenia. GD gain deficit; SE saccade excess; NETD no eye-tracking dysfunction; S schizophrenia; SAD schizoaffective disorder; SPD/PPD schizotypal or paranoid personality disorder; OD, AI other axis-I diagnosis; OPD other personality disorder; no D no psychiatric diagnosis

individuals from these samples performed with less-disturbed smooth-pursuit eye movements than family members with schizophrenia and related disorders, although the respective differences in group means were not significant (Fig. 1) A complementary pattern can be observed if NS is measured (Table 4).

In a next step we dichotomized the smooth-pursuit performance into presence and absence of ETD according to our definition (see Methods). In the families the aggregation of schizophrenia and schizophrenia-related disorders is paralleled by an aggregation of ETD (Fig. 2). The ETD was frequently observed with no gender differences in all six multiplex families, the affected individuals following each other in every consecutive generation. Of all family members, 56.3% were affected, 39.6% with GD. Of the six schizophrenic index probands, five (83.3%) performed with ETD. The smooth-pursuit eye movements of the sixth index proband represented a borderline case: Although they

were rated as normal according to our definitions, the number of saccades was only just below the required threshold. In the 22 first-degree relatives (R1) of the index probands, ETD of some form was present in 14 of 22 (63.6%) individuals; if restricted to GD, this form of deviance was calculated for 7 of 22 (31.8%) R1. If only the R1 individuals without a diagnosis of schizophrenia are counted, 7 of 15 (46.7%) have ETD (5 GD, 2 SE). The ETD was also prevalent in the second-degree relatives (R2): 5 of 11 (45.5%) had ETD (all GD). In 3 of 9 (33.3%) of the third- and fourth-degree relatives (R3+) ETD was present, and in 2 of 9 (22.2%) it was the GD subtype. All seven schizophrenic R1 revealed ETD (5 SE, 2 GD). If all schizophrenic individuals from the six families are taken together, 12 of 13 (92.3%) of the schizophrenic individuals had ETD and 7 of 13 (53.8%) performed with the GD subtype. All schizoaffective individuals, with the exception of one R4 individual, revealed ETD. All 3 R1/R2 relatives with a schizotypic personality disorder revealed ETD (all GD). However, one individual with a paranoid personality disorder had normal smooth pursuit. Three of 10 (30%) relatives with other psychiatric disorders showed ETD, all of the GD form. Concerning the relatives without psychiatric disorders, 6 of 17 (35.3%) family members had ETD (4 GD, 2SE). In the whole sample of family members, the rates of ETD decline with the degree of relationship (Table 5); however, only the difference between the index patients and the R3/R4 is significant (ETD: $\chi^2 = 3.61$, $df = 1$, $P \leq 0.05$).

Discussion

There is considerable evidence from controlled family studies that schizophrenia and schizophrenia-related disorders aggregate in families (Kendler and Diehl 1993). Although the question of familial aggregation of schizophrenia and schizophrenia-related disorders was not addressed primarily in this study, obviously not only cases of schizophrenia cluster in the families, but also other disorders from the schizophrenia spectrum: A total of 21 of the 48 individuals (43.8%) were given a diagnosis within the schizophrenia spectrum. In 31.3% of the relatives of the six index patients (Table 2) a diagnosis of the schizophrenia spectrum was established. The age-corrected moribidity risks in the relatives (Table 3) are higher than in most controlled family studies in which both single-case and multiple-case families have been investigated (Kendler and Diehl 1993). The higher relative risk of schizophrenia is directly explained by the inclusion criteria for this study (families with two or more schizophrenic relatives). With regard to non-schizophrenic spectrum disorders, higher risks probably reflect the fact that a comparatively high genetic load is present in families with multiple occurrence of schizophrenic psychoses. We have not been able to recruit all living family members, due mostly to their refusals to take part in the investigation. However, the psychiatric FH-RDC diagnoses in these individuals resemble those of the personally interviewed family members. It therefore seems unlikely that our results were biased by differing distributions of psychiatric morbidity which might have been caused by our recruitment procedures.

With respect to ETD, this is one of the few studies (e.g., Whicker et al. 1985; Clementz et al. 1991; Clementz et al. 1992; Iacono et al. 1992) in which precise quantitative measurement techniques were employed not only in a schizophrenic sample, but also in relatives. This is the first study in which these techniques were used in families with multiple occurrence of schizophrenia, and in which not only first-degree relatives were investigated, but also less closely related individuals. Guided by neurophysiological considerations (Abel and Ziegler 1988; Abel 1992), we did not choose global measures of ETD, which had been employed in numerous studies; instead, we preferred quantitative measures, reasonably based on an experimental design with constant target velocity. Such procedures have only lately been introduced into schizophrenia research (Clementz and Sweeney 1990; Levy et al. 1993).

It has been demonstrated that ETD aggregates in the multiplex families which we investigated (Fig. 2). With respect to quantitative measures MG and NS, in the samples of family members with schizophrenia and with non-schizophrenic spectrum disorders, the lowest group means of MG and the highest means of NS, respectively, were found (Table 4). Relatives form the two other diagnostic samples (other axis-I disorders, no psychiatric diagnoses) tend to perform worse than normal controls, but tend to have higher MG and lower NS than the samples with schizophrenia and schizophrenia-related disorders (Fig. 1). However, due probably to the low number of individuals in the subsamples, these latter differences are not statistically significant. These results indicate that there are significant deficits in smooth-pursuit eye movements in members of families with multiple cases of schizophrenia, even in individuals without schizophrenia spectrum disorders. It seems possible that some of these individuals carry a genetic predisposition for schizophrenia, although they are not affected phenotypically.

When the eye-tracking performance is dichotomized according to our definition, the familiar aggregation of ETD becomes more obvious. If all family members are taken together, 56.3% had deviant eye tracking; ETD was present in 92.3% of all schizophrenic individuals, in 63.6% of the R1 inlcuding cases of schizophrenia, and in 46.7% of non-schizophrenic R1 (Fig. 2). The prevalence of any form of ETD in the sample of schizophrenics from our families is considerably higher than the rate reported from schizophrenic patient samples investigated with qualitative measures (which compare to our overall ETD), as is the prevalence of ETD in first-degree relatives (Clementz and Sweeney 1990; Levy et al. 1993). It is noteworthy, however, that similar results were obtained by Myles-Worsley et al. (1992) from one of the two ETD studies in multiplex families; using global ETD ratings they reported a rate of 63% ETD in R1 affected with schizophrenia, and 53% ETD in non-affected R1. On the other hand, Blackwood et al. (1991), using a semi-quantitative measure (1n S/N), detected ETD in only 15.4% of their schizophrenic

individuals and in only 14.0% of their sample of non-schizophrenic relatives. However, it has to be considered that these latter prevalence rates are not in accordance with studies employing similar technology (Levy et al. 1993) and number among the lowest rates yet reported. If our results are restricted to the GD subtype of ETD, which equals low mean pursuit gain (which is the common quantitative measure), 53.8% of all schizophrenic family members and 31.8% of the R1 (including cases of schizophrenia) are affected. If these results are compared with studies which employ reduced gain, it again shows that in samples of schizophrenics as well as in the R1, our prevalence rates are considerably higher (Clementz and Sweeney 1990; Levy et al. 1993). In their extensive studies of schizophrenics and their R1, in which they used quantitative measures, Iacono et al. (1992) and Clementz et al. (1992) found reduced gain in 20% and 37%, respectively, of the schizophrenics, and in 21% and 22%, respectively, of the R1.

Concerning the comparatively high prevalence of ETD schizophrenics and R1 in our families, and also regarding the fact that ETD was prevalent in all of the six families, it is noteworthy that, with the two exceptions mentioned (see above), in other ETD studies schizophrenics and relatives were recruited regardless of multiple or single occurrence of schizophrenia in their families; instead, they were taken from family samples in which single and multiple occurrence of schizophrenia were mixed. It can be concluded that higher prevalence rates in our families are due to the assumption that a genetic trait (indicated by ETD) underlies only the proportion of the schizophrenic and schizophrenia-linked phenotype which aggregates in families, whereas it is not present in other (possibly sporadic) cases of schizophrencis and their relatives. It is of considerable importance in this respect that Clementz et al. (1992) reported evidence for a bimodal distribution of ETD in families with a schizophrenic individual.

It could be argued that our measurement procedure yields overly inclusive results. However, this seems unlikely for several reasons:

1. We used the same method and techniques in former investigations with normal controls and found a prevalence of GD in 6.3% (Nolte et al., in preparation), a result which is in remarkable accordance with other studies (Clementz et al. 1992; Iacono 1992; Sweeney et al. 1992).
2. Because our investigation of normal controls revealed a slight age effect, we corrected our results for age, which may even have resulted in comparatively lower rates of ETD.
3. In our pilot study of ETD in consecutively admitted schizophrenic hospital patients (Moser et al. 1990) in which the same techniques were applied as in this study, we found reduced gain in 20–40% (depending on the experiment) of the cases, a finding which corresponds to those of other authors (Levy et al. 1993; Clementz and Sweeney 1992). Thus, it seems unlikely that the comparatively high rates of ETD in our study are caused by a specific set of methods; instead, it is supposed that a high familial genetic load is associated with a high prevalence of ETD.

This assumption is supported by a considerable degree of congruity between ETD and diagnoses from the schizophrenia spectrum which can be observed in our families. With two exceptions ETD is present in all cases of schizophrenia and schizoaffective psychosis. In analyzing these exceptions it becomes clear that both cases represent only a weak argument against congruity: The schizophrenic individual is a borderline case of ETD, and the schizoaffective individual with normal ETD is a fourth-degree relative and therefore farther removed from the proposed genetic trait in the family. However, it must not be neglected that one individual with paranoid personality disorder has normal eye tracking; a finding the meaning of which remains unclear. Because ETD is suppossed to represent a marker of genetic predisposition for schizophrenia, the occurrence of ETD in individuals without a schizophrenia spectrum diagnosis does not contradict congruity.

Concerning the one index proband with only borderline ETD, Holzman (1987) reviewed a considerable number of cases in which the schizophrenic sibling had undisturbed eye movements while both healthy parents had ETD. This puzzling observation led to the development of the latent trait model (Holzman et al. 1988; Matthysse et al. 1986). In this model a latent trait is transmitted in a modified Mendelian fashion and is determined by a single major locus. The trait can occur without the allele that is responsible for it as a phenocopy or the allele can be present without the trait, as in partial penetrance. We found this to be the case in only 1 of 13 schizophrenic individuals, but, as a borderline case, the affected individual did not have completely undistributed smooth pursuit. It may therefore be questioned if latent trait model is applicable in multiplex families. The differences between the results of the Holzman group and ours might also be due to technical reasons: Holzman and coworkers used conventional electro-oculography with global measurement techniques. Because global measures obscure the nature of the saccades interrupting smooth pursuit (Abel and Ziegler 1988), the typology of saccades interrupting smooth pursuit in Holzman's cases could not be assessed. It may be possible, however, that the parents produced a high amount of anticipatory saccades due to old age; which would be in line with the observation of Whicker et al. (1985). However, this structural abnormality differs markedly from the impairment found in schizophrenia, in which cases of an excess of catch-up saccades are observed (Friedman et al. 1992; Moser et al. 1990; Radant and Hommer 1992; Sweeney et al. 1992). Thus, if the structure of the eye-movement dysfunction is analyzed in detail, the findings of Holzman and coworkers possibly do not indicate incongruity between the levels of ETD and cases of schizophrenia.

The rate of ETD in our sample seems to decline with the degree of relationship (Table 5), although the differences between the subsamples were only significant in the case of index patients vs third- or more-degree relatives, due probably to the small number of individuals in the sub-

samples. However, no similar observation has been demonstrated previously for ETD. If this finding can be replicated in a larger number of families, it would increase the evidence for ETD to represent a phenotypic genetic marker for liability to schizophrenia, because a decline of prevalence rates in association with the degree of relationship indicates genetic transmission of phenotypic variables. Moreover, with regard to a possible mode of inheritance, it must be considered that in the families reported upon, ETD was present in one affected individual followed by the next in every generation, in male as well as in female family members. Thus, our results are in line with an autosomal dominant major gene model which might support the understanding of the genetic transmission of ETD families with schizophrenia (Grove et al. 1992; Holzmann et al. 1988).

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References

Abel LA, Ziegler S (1988) Smooth pursuit eye movements in schizophrenics – what constitutes quantitative assessment? Biol Psychiatry 24:747–761

Abel LA, Levin S, Holzman PS (1992) Abnormalities of smooth pursuit and saccadic control in schizophrenia and affective disorders – minireview. Vision Res 32(6):1009–1014

Arolt V, Steege D, Nolte A (1993) Störungen der Augenbewegungen bei Schizophrenen – Kritische Übersicht und zukünftige Perspektiven. Fortschr Neurol Psychiatrie 61:90–105

Blackwood DHR, St. Clair DM, Muir WJ, Duffy JC (1991) Auditory P300 and eye tracking dysfunction in schizophrenic pedigrees. Arch Gen Psychiatry 48:899–909

Cardno AG, McGuffin P (1994) The molecular genetics of schizophrenia. Neuropathol Appl Neurobiol 20:344–349

Clementz BA, Sweeney JA (1990) Is eye movement dysfunction a biological marker for schizophrenia? A methodological review. Psychol Bull 108:77–92

Clementz BA, Sweeney JA, Hirt M, Haas G (1991) Phenotypic correlations between oculomotor functioning and schizophrenia-related characteristics in relatives of schizophrenic probands. Psychophysiology 28:570–578

Clementz BA, Grove WM, Iacono WG, Sweeney JA (1992) Smooth pursuit eye movement dysfunction and liability for schizophrenia: implications for genetic modeling. J Abnorm Psychol 101:117–129

Cloninger R (1994) Turning point in the design of linkage studies in schizophrenia. Am J Med Genetics 54:83–92

Endicott J, Spitzer RL (1978) A diagnostic interview: the Schedule of Affective Disorders and Schizophrenia. Arch Gen Psychiatry 35:837–844

Friedman L, Jesberger JA, Meltzer HY (1992) A model of smooth pursuit performance illustrates the relastionship between gain, catch-up saccade rate, and catch-up saccade amplitude in normal controls and patients with schizophrenia. Biol Psychiatry 30:537–556

Grove WM, Clementz BA, Iacono WG, Katsanis J (1992) Smooth pursuit ocular motor dysfunction in schizophrenia: evidence for a major gene. Am J Psychiatry 149:1362–1368

Hodge SE, Greenberg DA (1992) Sensitivity of lod scores to changes in diagnostic status. Am J Hum Genet 50:1053–1066

Holzman PS (1987) Recent studies of psychophysiology in schizophrenia. Schizophr Bull 13:49–75

Holzman PS (1994) The role of psychological probes in genetic studies of schizophrenia. Schitzophr Res 13:1–9

Holzman PS, Kringlen E, Matthysse S, Flanagan SD, Lipton RB, Cramer G, Levin S, Lange K, Levy DL (1988) A single dominant gene can account for eye tracking dysfunctions and schizophrenia in offspring of disconcordant twins. Arch Gene Psychiatry 45:641–647

Iacono WG (1985) Psychophysiologic markers of psychopathology: a review. Can Psychol 26:96–107

Iacono WG (1988) Eye movement abnormalities in schizophrenic and affective disorders. In: Johnston CW, Pirozzolo FJ (eds) Neuropsychology of eye movements. Erlbaum, Hillsdale, New York, pp 115–145

Iacono WG, Moreau M, Beiser M, Fleming JAE, Lin TY (1992) Smooth-pursuit eye tracking in first-episode psychotic patients and their relatives. J Abnorm Psychol 101:104–116

Kendler KS (1988) The genetics of schizophrenia: an overview. In: Nasrallah HA, Tsuang MT, Simpson JC (eds) Handbook of schizophrenia: Nosology, epidemiology, and genetics, vol 3. Elsevier, Amsterdam, 437–462

Kendler KS (1991) The Structured Interview of Schizotypy: version 1.6 (German translation by V. Arolt and M. Pinnow)

Kendler KS, Diehl SR (1993) The genetics of schizophrenia. Schizophr Bull 2:261–285

Levy D, Holzman PS, Matthysse S, Mendell NR (1993) Eye tracking dysfunction and schizophrenia: a critical perspective. Schizophr Bull 19:461–536

Matthysse S, Holzman PS, Lange K (1986) The genetic transmission of schizophrenia: application of Mendelian latent structure analysis to eye tracking dysfunctions in schizophrenia and affective disorders. J Psychiatr Res 20:57–76

Moises HW, Yang I, Kristbjarnarson H, Wiese C et al. (1995) An international two-stage genome-wide search for genetic susceptibility genes (letter). Nature Genet 11:321–324

Moser A, Kömpf D, Arolt V, Resch T (1990) Quantitative analysis of eye movements in schizophrenia. Neuro-ophthalmology 10:73–80

Myles-Worsley M, Dale P, Polloi A, Levy A, Freedman R, Byerley W (1992) Eye-tracking abnormalities in two Micronesian families with schizophrenia. Psychiatr Genet 2:209–212

O'Donovan MC, Owen MJ (1992) Advances and retreats in the molecular genetics of major mental illness. Ann Med 24:171–177

Radant AD, Hommer DW (1992) A quantiative analysis of saccades and smooth pursuit during visual pursuit tracking: a comparison of schizophrenics with normals and substance abusing controls. Schizophr Res 6:225–235

Reulen JPH, Marcus JT, Koops D, Vries RF de, Tiesinga G, Boshuizen K, Bos JE (1988) Precise recording of eye movement: the IRIS technique, part 1. Med Biol Eng Comput 26:20–26

Rutter M (1994) Psychiatric genetics: research challenges and pathways forward. Am J Med Genet 54:185–198

Sherrington R, Brynjolfsson B, Petursson H, Potter M, Dudleston K, Barraclough B, Wasmut J, Doobs M, Gurling H (1988) Localisation of a susceptability locus for schizophrenia on chromosome 5. Nature 336:164–167

Spitzer RL, Williams J (1985) Structured Clinical Interview for DSM-III Personality Disorders (SCID-II). New York State Psychiatric Institute, Biometrics Research Department, New York

Straub RE, McLean CJ, O'Neill FE, Burke J et al. (1995) A potential susceptibility locus for schizophrenia on chromosome 6p24–22: evidence for genetic heterogeneity. Nature Genet 11:287–293

Sweeney JA, Haas GL, Li S (1992) Neuropsychological and eye movement abnormalities in first episode and chronic schizophrenia. Schizophr Bull 18:283–293

Wang S, Sun C, Walczak CA, Ziegle JS et al. (1995) Evidence for a susceptibility locus for schizophrenia on chromosome 6pter-p22. Nature Genet 11:41–46

Whicker L, Abel LA, Dell'Osso LF (1985) Smooth pursuit eye movements in the parents of schizophrenics. Neuro-ophthalmology 5:1–8

Yee R, Baloh R, Marder S, Levy DL, Sakala SM, Honrubia V (1987) Eye movements in schizophrenia. Invest Ophthalmol Visual Sci 28:366–374