Eur Arch Psychiatr Neurol Sci (1989) 239:43–48

European Archives of Psychiatry and Neurological Sciences

The Use of Eye Movement Dysfunctions in Exploring the Genetic Transmission of Schizophrenia

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Summary. Eye movement dysfunctions have been found in a large number of schizophrenic patients and in about half of their first-degree relatives. The distribution of these traits within the families of schizophrenic patients suggests a model of genetic transmission that fits an autosomal dominant model, which we have called the "genetic latent trait model." The model, with seven parameters, was fitted to a U.S. population and the model was cross-validated on an independent Norwegian sample. Although the model does not invalidate other, more conventional solutions to the puzzle of schizophrenic transmission, such as multifactorial transmission, the latent trait model does more easily permit linkage studies and therefore will allow refutation or support from the use of molecular genetics techniques.

Key words: Schizophrenia – Eye movements – Genetics – Twins – Latent trait

Introduction

The use of eye movement dysfunctions as an aid in studying the genetics of schizophrenia is explored in this paper. Our strategy of testing the unaffected family members of psychotic patients permitted us to discover a familial pattern in eye movement dysfunctions. This familial pattern has assumed a prominence equal to that of searching for the neurophysiological significance of eye movement dysfunctions in schizophrenia. The data on familial patterns of eye movement dysfunctions have made it possible to formulate a theoretical model, which we call a "genetic latent structure model," that has the power to map the genetic transmission of schizophrenic disorders. The description and testing of that model are the purpose of this paper. The formulation of the latent trait model emerged from collaboration with my colleague Steven Matthysse.

The pertinent basic findings with respect to schizophrenia and eye movement dysfunctions are reviewed together with the data that led to the formulation of the genetic latent structure model.

This article was presented in part at the Symposium on Eye Movements and Psychopathology, Berlin, 23–24 June 1988

Eye Movement Dysfunctions

In 1908 Diefendorf and Dodge reported that schizophrenic patients showed impaired pursuit eye movements. That study, which used a motion picture camera to record eye movements, showed that the impairment was found only in schizophrenic and not in manic-depressive patients. Further, Diefendorf and Dodge noted that it was only the pursuit movements that were implicated, and not the saccadic or refixation movements. In 1973, while then unaware of the Diefendorf and Dodge (1908) study, we reported that a large number of schizophrenic patients showed smooth pursuit eye movement dysfunctions (Holzman et al. 1973), and we followed that report with a replication study on a much larger sample that included a number of first-degree relatives (Holzman et al. 1974), 40% of whom also showed pursuit abnormalities. The principal finding of the high prevalence of eye movement dysfunction in schizophrenics has received confirmation from several independent studies (for example, Shagass et al. 1974; Klein et al. 1976; Kuechenmeister et al. 1977; Salzman et al. 1978; Brezinova and Kendell 1977; Pass et al. 1978; Cegalis and Sweeney 1979; May 1979; Mialet and Pichot 1981; Iacono et al. 1981). About 60% of schizophrenic patients show eye movement dysfunctions, compared with about 8% of the normal population. In a recent study from Vienna, Saletu et al.

(1986) report frequencies almost identical to those we reported (55% of schizophrenics; 10% of normal controls).

Investigations of eye movement dysfunctions were at first confined to smooth pursuit eye movements, those made when following a moving object. Later it became apparent that the eye movement dysfunctions were detectable even when the target was stationary, and saccadic movements, under certain conditions, may also be implicated (Schmid-Burgk et al. 1982, 1983).

Eye Movement Dysfunctions and Schizophrenia

In any study of schizophrenic patients, the role of artifacts must be carefully considered. Therapeutic drugs, inattention, motivational drift, and generalized deficit are the usual variables that contaminate almost all studies of performance by schizophrenic patients. In the case of eye movement dysfunctions, however, these artifacts appear to play no decisive role.

Of major significance here is the finding, first reported from our laboratory (Holzman et al. 1974), that eye movement dysfunctions run in the families of schizophrenic patients. Clarification of the trait and specificity status of eye tracking dysfunctions in schizophrenia came with more family prevalence data. An earlier study (Holzman et al. 1974) reported that 40% of the first degree relatives of schizophrenics showed eye tracking dysfunctions that were indistinguishable from those shown by the schizophrenic patients. In contrast, only about 10% of the relatives of nonschizophrenic psychiatric patients showed similar dysfunctions. A recent, more systematic study, in which contemporary diagnostic criteria were used, reported that 34% of the parents (or 55% of parental pairs) of schizophrenic patients compared with 10% of the parents (or 17% of parental pairs) of manic depressive patients had eye movement dysfunctions (Holzman et al. 1984). Parental eye movement dysfunctions were significantly related to the diagnosis of the patient, that is, whether or not the patient was schizophrenic, but not to the patient's eye tracking performance, that is, whether or not the patient showed good or disrupted eye tracking. Almost identical family data have been reported by Siegel et al. (1984). Levy et al. (1983), too, showed that of 47 first-degree relatives of 21 patients with bipolar affective illness, only 13% showed abnormal purusit, a figure that did not differ significantly from the normal population prevalence of 8%. Moreover, when they excluded those relatives who themselves had been hospitalized and treated for an affective disorder or were currently receiving lithium, only 2% of the sample showed impaired pursuit. These studies strongly supported the conclusion that eye tracking dysfunctions, while accompanying many disparate diseases, occurs in the families of schizophrenics and not in the families of patients with bipolar affective disorder.

Eye Movement Dysfunctions as a Genetic Indicator

The determination of the genetic contribution to the appearance of eye tracking dysfunctions in first-degree family members of schizophrenics emerged from two studies of twins discordant for schizophrenia. The first study examined sets of Norwegian monozygotic (MZ) and dizygotic (DZ) twins who were clinically discordant for schizophrenia. These twins had been previously identified and studied by Kringlen (1967), who had determined that the clinical concordance of schizophrenia was 25%–38% for monozygotic twins and about 9% for dizygotic twins, depending upon whether a set of narrow or broad criteria for schizophrenia was employed. This pool of Norwegian twins, then, provided the sets of MZ and DZ twins discordant for schizophrenia. A finding that eye tracking dysfunctions were twice as concordant among clinically discordant MZ as among the discordant DZ twins would provide encouraging, although not conclusive, evidence of a trait marker for schizophrenia that is genetically transmitted.

The first twin study (Holzman et al. 1977) showed results that were quite consistent with the genetic transmission of the eye tracking dysfunction as a trait. But the numbers of subjects (11 sets of MZ and 15 sets of DZ twins) were too low for statistically significant differences to emerge. In addition, the subjects were, on average, about 55 years old, and it is known that eye tracking integrity tends to degrade with age. Therefore a second study with younger discordant twins was undertaken. The results of the second study were almost identical with those of the first (Holzman et al. 1980). These studies suggest that there is a significant genetic contribution to eye tracking efficiency. The studies, however, did not unequivocally rule out nongenetic mechanisms that may be responsible for both psychosis and eye tracking dysfunctions, such as viral, toxic, and perinatal influences. Nor did those studies address the relation of eye tracking dysfunctions to schizophrenia, since the investigators did not employ comparison groups consisting of twins with other psychoses. The family studies (Holzman et al. 1984; Levy et al. 1983) did, however, support the view that eye tracking dysfunctions are associated with schizophrenia and tend to

occur within families in which there is a member with clinical schizophrenia.

In the two twin studies (Holzman et al. 1977, 1980) there was a perplexing incongruity. There were five sets of DZ twins in which the schizophrenic twin had good eye tracking but the unaffected twin had impaired eye tracking. In the family prevalence study (Holzman et al. 1984) there was a similar discordant finding: a number of schizophrenic patients with unimpaired pursuit movements had parents with eye tracking abnormalities. If eye tracking abnormalities represent a graded marker of vulnerability, they should be present in almost all schizophrenics. But about 40% of schizophrenics show normal pursuit. If, however, schizophrenia causes eye tracking dysfunctions, why should the healthy relatives show tracking abnormalities? If eye tracking dysfunctions are inherited, as suggested by the appearance of impaired tracking in the healthy relatives, why should the schizophrenic relatives of the normal relatives have good tracking?

Matthysse et al. (1986) suggested a model to account for these apparent incongruities. The model postulates a latent trait that is transmitted in a modified Mendelian fashion, that is, although the presence of the latent trait is determined by a single major locus, the latent trait can occur without the allele that is responsible for it (as a phenocopy), and the allele can be present without the trait (as in partial penetrance). The model further proposes that the central nervous system disease process that is the outcome of the latent trait produces clinical schizophrenia or bad eye tracking or both, because it can invade one or another region of the brain independently or together. The symptoms that arise reflect the brain regions invaded. Neurofibromatosis reflects a similar model of genetic transmission. The gene for neurofibromatosis is an autosomal dominant, but with varying expressivity, or pleiotropy. Thus, the full syndrome occurs more rarely than one or two indicators of it. Tumors of peripheral and cranial nerves, subnormal intelligence, café-au-lait spots, areas of depigmentation, as well as skeletal abnormalities are among the numerous manifestations of the disease. As in schizophrenia, it is not unusual for a family history of neurofibromatosis to be well hidden or unnoticed when the proband has the full syndrome. Furthermore, family members with the disease may be overlooked because they manifest only the mildest of symptoms.

The Latent Trait Hypothesis

The latent trait model assumes that in the case of the schizophrenic disorder, the smooth pursuit system is invaded with higher probability than the system that is involved in schizophrenic psychosis – whatever that system is. The model also assumes that this disease process is at least partially genetically determined. Schizophrenia with good tracking occurs when the disease invades the less probable area and spares the more probable one. First-degree relatives will also be at risk for having the same disease process, and that process will cause eye movement dysfunctions with high probability, and schizophrenia with low probability.

The disease process is, of course, a hypothetical one and therefore it is called a latent trait. Unlike schizophrenia and eye tracking dysfunctions, the trait is not observed, although, in principle, it is capable of being observed. When the necessary tools for observing it become available, we presume it will be found. Matthysse et al. (1986) chose a single gene model because it is the simplest one, and they constructed an equation for testing its fit to the data. The equation includes the following variables: (1) the probability of the occurrence of phenocopies; (2) the penetrance of the latent trait in heterozygotes; (3) the penetrance of the latent trait in homozygotes; (4) the probability of the latent trait giving rise to schizophrenia; (5) the probability of the latent trait giving rise to eye tracking dysfunctions; (6) the probability of schizophrenia arising without the latent trait; and (7) the probability of eye tracking dysfunctions occurring without the latent trait.

The equation was then employed to search, within a large sample of patients and their family members tested in Chicago and Boston, for the probability of any family member having the latent trait. If an individual has the latent trait, the likelihood that he/she has schizophrenia, eye movement dysfunctions or both can be computed. The mathematics are those of maximum likelihood estimates. The equation permits one to test whether the eye movement dysfunctions in schizophrenia, in manic-depressive illness. or in any other disease, are an independent expression of the latent disease process or an epiphenomenon, that is, an outcome of having the disease itself.

The results of the mathematical test for the Chicago-Boston sample are that in schizophrenia the data fit the latent trait model, but in manic-depressive illness the data are more easily explained as an epiphenomenon (Matthysse et al. 1986), that is, in manic-depressive illness, poor eye tracking is an outcome of the disease; in schizophrenia it is an outcome of family transmission.

It should be noted that in the aforementioned report (Matthysse et al. 1986) an equation has merely been fit to the available data. The results do not represent a test of the model. Such a test was conducted

Table 1. The prevalence in the Norwegian sample of clinical schizophrenia and of eye movement dysfunctions in the offspring of monozygotic (MZ) and dizygotic (DZ) twins with schizophrenia, manic depression , or reactive psychosis, and in the offspring of the unaffected cotwins. See Matthysse et al. (1986) for explanation of the derivation of the predictions

Offspring of	*N*	Families	Schizophrenia		Pursuit dysfunctions	
			Predicted	Observed	Predicted	Observed
SZ MZ proband	24	10	1.18	2	7.20	8
SZ MZ cotwin	33	17	1.62	1	10.23	10
SZ DZ proband	20	9	0.99	0	6.25	4
SZ DZ cotwin	43	11	1.13	0	8.10	9
MD/RP MZ proband	25	10		0	2.08	3
MD/RP MZ cotwin	16	7		0	1.28	1

using a unique sample: the offspring of MZ and DZ twins discordant for schizophrenia. With the collaboration once again of Einar Kringlen of the University of Oslo, a complete national sample of twins in Norway was checked for those who had ever been hospitalized for a psychosis. After further screening, twins were selected if one and only one twin met the criteria for schizophrenia, bipolar affective disorder, or reactive psychosis.

In this design of testing the offspring of discordant twins, the offspring of the MZ twins provide a special kind of control over environment: although they are actually nieces and nephews of the affected twin, genetically they are first-degree relatives of the schizophrenic twin. Thus the study has features of an adoption study as well as of a twin study: offspring are reared from birth in an environment that is different from that of their genetic first-degree relatives, who are legally their aunts or uncles.

In the study of offspring of discordant Norwegian twins, the clinical diagnoses of the twins' conditions were obtained from clinical examinations performed by Professor Kringlen over a priod of 5 years in the 1960s. His diagnostic protocol was supplemented by hospital records. The diagnoses followed the Scandinavian conventions of strict criteria for schizophrenia, manic-depressive illness, and reactive psychosis, and it seems probable that the diagnostic criteria used do not differ significantly from current DSM-III criteria. A total of 213 subjects were tested, of whom 170 were offspring of the twins, 29 were grandchildren, and 14 were spouses, some probands, and some "dummy" subjects who bore no relationship to the study, but were entered in order to protect the blind.

Pursuit eye movements were recorded without knowledge of the parental diagnosis and twin status of the proband. Recording was by infrared reflected light into a portable computer for later scoring and evaluation.

The eye movement records were examined and scored after the American team returned from Norway, still without knowledge of the subjects' clinical status, the clinical status of the proband to whom the subject was related, and of the relationship of the subject to the proband.

The results of the Norwegian twin offspring study have been reported in another publication (Holzman et al. 1988). Table 1 shows the predicted and observed frequencies of eye movement dysfunctions and of clinical schizophrenia for the Norwegian sample of offspring (but not of the children of those offspring). The predictions were based on the latent trait model which was generated from the Chicago-Boston sample (Matthysse et al. 1986). It is noteworthy that 3 of 77 offspring of all schizophrenic probands and of their MZ cotwins displayed overt clinical schizophrenia. This prevalence of 3.9% is very close to the 4.9% predicted by the latent trait model and to the 3.7% obtained by Tsuang et al. (1980).

The comparison of predicted and obtained eye movement dysfunctions shows conspicuous congruence. A chi-square of 2.43 with 5 degrees of freedom indicates a nonsignificant difference between the obtained and predicted prevalence. Likewise, within each group there is no significant chi-square between the predicted and obtained frequencies of eye movement dysfunctions, that is, the percentage of eye movement dysfunctions among the offspring of the affected MZ and DZ twins (12 of 44, or 27.3%) does not differ from that found among the offspring of the unaffected MZ cotwins (10 of 33, or 30.3%).

Table 2 shows the maximum likelihood estimates for the eight parameters that were obtained for the Chicago-Boston sample and for the Norwegian replication sample. The estimates are extremely close in both samples except for the estimation of the percentage of homozygotes. When one applies the estimates of the Chicago-Boston sample to the Norwegian

Table 2. Maximum likelihood estimates for the Chicago-Boston sample and the Norwegian offspring sample and theoretical estimates for a pure dominant solution

Parameter	Chicago-Boston sample	Norwegian sample	Pure dominant
Gene frequency (% of population)	2.23	3.85	3.56
Occurrence (%) of phenocopies (those without the gene who have the latent trait)	0.004	0.0001	0.0001
Probability a heterozygote has the latent trait	99.88	82.58	84.03
Probability a homozygote has the latent trait	99.90	99.99	89.21
Probability a person with the latent trait has eye movement dysfunctions	65.45	62.62	63.71
Probability a person with the latent trait has schizophrenia	11.38	8.55	8.92
Probability a person without the latent trait has eye movement dysfunctions	5.34	4.82	5.01
Probability a person without the latent trait has schizophrenia	0.10	0.06	0.07

data, there is no significant difference between their likelihood and the maximum likelihood (chi-square = 0.65, NS).

When one equates the number of heterozygotes with the number of homozygotes, as required in a strict dominant model, the parameters fit the Norwegian sample with no significant chi-square. Holzman et al. (1988) reported the estimates for the maximum likelihood dominant solution, and these are contained in Table 2. No recessive model fits the data well, and if one excludes genetic transmission, the fit is extremely poor.

From these data, then, one can conclude that a single dominant gene can account for the transmission of a latent trait whose manifestations are either schizophrenia, eye movement dysfunctions, or both. It is quite apparent that the eye movement dysfunctions studied by our laboratory and by others can become very useful as a tool for genetic research, particularly at a time when the new techniques of molecular genetics are becoming available for linkage studies. We do not claim that other models may not account for the data, or indeed, that a polygenic background of the single major locus or even a pure polygenic model may not prove to be valid. We merely point to the finding that two very different samples are equally hospitable to the parameters of the Mendelian latent trait model.

The assumption of a single locus for the latent trait has a heuristic purpose. It transcends the unsatisfactory classificatory schemes based on phenotypic description of the psychoses, and it offers a model that can be used to select individuals with a high probability of possessing the latent trait, a process that will permit molecular genetic studies to be pursued with more favorable prospects of success.

Acknowledgements. Many of the studies referred to in this paper were supported by Public Health Service grants MH 31340 and MH 31154 and a grant from the Benevolent Foundation of the Scottish Rite, Northern Masonic Jurisdiction.

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Received October 17, 1988