ELSEVIER

Seymour S. Kety and the Genetics of Schizophrenia

Philip S. Holzman, Ph.D.

For those who never had the opportunity to know him, I can attest that Seymour Kety was an approachable person with a droll sense of humor. My colleague Steven Matthysse tells the story of his first contact with Seymour, a story that has no relation to the issue of Seymour's work on the genetics of schizophrenia. The story began in 1961, when Steve was a graduate student in theoretical physics at Yale. Seymour had been the scientific director of the NIH's Mental Health Institute and was now the chief of its Laboratory of Clinical Science. He had already published his influential critiques of the biological studies of schizophrenia, and followed them with a paper called *A Biologist Examines the Mind and Behavior*, which was published in 1960 in *Science*. In that paper Seymour discussed aspects of the problem of consciousness, and Steve wrote to him about his gloss on some of Seymour's arguments. He received no reply at the time, but nine years later when Steve was working for Seymour at the Massachusetts General Hospital, to his delight, he received this letter: "Thank you for your recent letter. Although I regret the delay in this reply (I have been away from my desk too frequently), I usually make it a firm policy to answer my correspondence within a week or at the latest within a decade . . . . Sometime when you are in the neighborhood, I would be delighted to have a visit from you to learn more about your very worthwhile suggestion . . . ."

From the Laboratory of Psychology, Mailman Research Center, McLean Hospital Belmont Massachusetts, and Harvard Medical School, Cambridge, Massachusetts and Department of Psychology, Harvard University, Cambridge, Massachusetts.

Address correspondence to: Philip S. Holzman, Psychology Research Laboratory, Mailman Research Center, McLean Hospital, 115 Mill Street, Belmont, MA 02178.

Received November 16, 2000; accepted February 10, 2001.

From the time that schizophrenia was first described in the 19th century, there was much evidence that schizophrenia ran in families. But in the mid-20th century, most influential researchers believed that schizophrenia was something one acquired by a kind of social contagion from one's parents, and the prescribed treatment, therefore, was educational, psychological, and sociological manipulation. Family prevalence, although compatible with genetic factors, did not prove that they were present, since measles, pellagra, kuru, money, and silverware also run in families, as Seymour was fond of telling audiences. And none of them is genetically transmitted.

The atmosphere in American psychiatry and psychology in the mid-20th century was churlishly biased against recognizing genetic factors in the development of schizophrenia. Consider R.D. Laing's *The Politics of Experience*, in which the author stated magisterially, "It seems to us that *without exception* the experience and behavior that gets labeled schizophrenic is a *special strategy that a person invents in order to live in an unlivable situation*" (Laing 1967, p. 115). " . . . There is no such 'condition' as 'schizophrenia,' " he continued a bit later in the book, "but the label is a social fact and the social fact is a *political event*" (Laing 1967, p. 121) (italics in the original). A few years later, Theodore Lidz, of Yale University, confidently wrote, "It seems unlikely . . . that the cognitive disorder can be transmitted genetically . . . rather than experientially. . . . I am specifically trying to convey that the nature and origins of schizophrenic disorders are comprehensible without any unknown X-factor if we . . . examine the nature of the aberrant settings in which the patients grew up" (Lidz 1973, p. 12).

In 1961 Seymour began to wrestle with the issue of the genetics of schizophrenia. He employed the same scientific strategy he had always used of looking for the simplest solution to the puzzle. That schizophrenia had

NEUROPSYCHOPHARMACOLOGY 2001–VOL. 25, NO. 3

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/01/$–see front matter
PII S0893-133X(01)00276-7

a higher concordance in monozygotic twins than in dizygotic twins was compatible with genetic factors, but Seymour rejected the twin method because he knew that there were alternative explanations for these concordance rates. He chose the adoption strategy, which had earlier been used by psychologists in studies of the genetic aspects of intelligence. The design, he believed, should be a nationwide study, in which one did not make the mistake of going to mental hospitals to find schizophrenic patients and seeking whether any among them had been adopted, because this approach already biased the study in favor of hospitalized schizophrenics. A better approach would be to gather a national sample of all adopted individuals and find the people with schizophrenia among them. He teamed up with the psychologist David Rosenthal at the NIMH and with the psychiatrist Paul Wender, then at St. Elizabeth's. If Lidz and Laing were correct, the rate of schizophrenia in the adoptive parents of schizophrenics should be just as high as the rate of schizophrenia in the biological parents of schizophrenics. They were able to interest a group of Danish scientists, headed by Fini Schulzinger, to join the study. With assiduous efforts to keep the study blind, they conducted a series of investigations, over the course of three decades, which disentangled environmental from genetic factors, and showed that genetic factors play a definitive role in the etiology of schizophrenia. Two crucial conclusions from these studies remain incontrovertible. First, children born to a schizophrenic mother and reared in an adoptive family become schizophrenic at the same rate as those reared by the biological mother, who is schizophrenic. Second, biological relatives of an adopted schizophrenic have significantly elevated rates of chronic schizophrenia in their families but the adoptive family members of a schizophrenic have a rate of chronic schizophrenia that is no higher than that in families with an adoptive child who is not schizophrenic. These studies thus demonstrated that schizophrenia was confined almost exclusively to the biological families of the schizophrenic adoptees and that the adoptive relatives of the schizophrenic adoptees as well as the relatives of normal adoptees show the low general population lifetime incidence of schizophrenia (Kety et al. 1976, 1978). As a result of these studies we no longer hear shrill voices proclaiming that schizophrenia arises from toxic interpersonal family environments.

Of great interest was the finding that, in addition to chronic schizophrenia in the biological family of schizophrenic adoptees, there appeared conditions that now are termed *schizotypal personality disorder*, and which Bleuler and Kety called "latent schizophrenia." These conditions also did not appear at an increased rate in the adoptive family members. They have many of the symptoms of schizophrenia except that they are neither as handicapping nor as obvious. "In nuce" (that is, "in a nutshell"), wrote Bleuler, "this is a milder form of schizophrenia" [Bleuler 1950, p. 239 (first published in 1911)]. Kety, like Bleuler, found this condition in relatives, and gave it a genetic basis because of the adoption strategy. He thus confirmed that there is another syndrome like schizophrenia that is genetically related to schizophrenia.

There was a complication, however. Kety also found latent schizophrenia in the relatives of individuals with affective disorders. Whereas he did not find an overrepresentation of affective disorders in the biological relatives of schizophrenics, there was a perceptibly but not significantly higher incidence of schizophrenia in the affective disorder adoptees than in the control population. Therefore, his studies raised the question of whether we are dealing with two separate disorders. This finding introduced the idea of the "schizophrenia spectrum," which presumes that there are a number of conditions that, although not recognizable as a schizophrenic psychosis, nevertheless seem related to the psychotic condition. Seymour thought of schizophrenia as Bleuler and Kraepelin did, as a syndrome, a collection of symptoms that seem to hang together and that permit one to recognize its varying manifestations (Kety 1980).

Since the time of Seymour's demonstration of a clear genetic basis for schizophrenia, and in spite of spectacular developments in molecular genetics, there has been relatively little progress in finding chromosomal linkage with schizophrenia, let alone in finding the actual gene or genes implicated in schizophrenia. True, many reports of linkage with schizophrenia have appeared, but the literature is also rife with failures to replicate those claims. One reason for these failures to replicate is that researchers typically have been using schizophrenia alone as the pertinent phenotype; but schizophrenia alone recurs at too low a rate within families to give linkage efforts enough statistical power to detect linkage. Seymour's concept of the schizophrenia spectrum broadens the target phenotype, and thus laid the foundation for recognizing non-clinical pleiotropic expressions of schizophrenia, which are able to provide enough statistical power to detect linkage, if indeed it is present.

His widening of the concept of schizophrenia calls to mind the distinction between exophenotypes and endophenotypes, introduced by John and Lewis (1966). Exophenotypes are the external symptoms of a disorder that clinicians detect during an examination. An endophenotype, on the other hand, is a characteristic that requires special tools, tests, or instruments for detection. For the most part, the presence of an endophenotype is less prone to subjective judgment than is the assessment of symptom typicality. Further, as Gottesman and Shields (1972) noted, refutation of a polygenic theory of schizophrenia, which has been advanced by many people, would require the identification of an endophenotype that segregates as a single gene does. This distinction influenced the direction in which we steered

our laboratory. My colleagues Steven Matthysse and Deborah Levy and I set about investigating associated endophenotypes of schizophrenia. We believed that, when physiologically dissected, they could lead to a more precise delineation of schizophrenia. Consequently, we have been studying several of these endophenotypes, such as eye tracking dysfunctions, thought disorder, spatial working memory, and craniofacial dysmorphic features. With respect to eye tracking dysfunction and thought disorder, these endophenotypes are distributed in a way that is consistent with a single dominant gene (Holzman et al. 1988). Unlike symptoms, however, they permit a parsing of their intrinsic processes so that not only their genetic distribution but also their pathophysiology can be discerned.

Consider eye movement dysfunctions. Here, the shortened story is as follows. A large number of schizophrenia patients have difficulty following a moving target with their eyes (Holzman et al. 1973, 1974). If asked to follow a moving spot of light, they do it with irregular eye movements, rather than the smooth eye movements that are typical of normal pursuit. And, anywhere from about 25% to 40% of these patients' first-degree relatives show the same dysfunction. Only about 5% of the normal population shows the same pattern. Figure 1 illustrates the usual tracing of a patient with schizophrenia and that of a normal control. Careful study of this pattern, which is typical of most patients with schizophrenia, revealed that the impaired smooth pursuit occurs only when higher cortical centers are recruited, as in following a moving car, but not when the eyes are moved by lower centers, such as the oculo-cephalic reflex, full-field optokinetic nystagmus, or vestibular nystagmus (Latham et al. 1981; Levy et al. 1978; Lipton et al. 1980). Further, other kinds of eye movements are normal, such as saccadic and vergence eye movements (e.g., Iacono et al. 1981; Levin et al. 1981, 1982).

A further dissection showed that in schizophrenia patients, the eyes do not move as fast as they should to keep up with the target's speed, as measured by a low ratio of eye speed to target speed, a measure called "steady state gain." That is, those with abnormal smooth pursuit eye movements lag behind the moving target, and compensatory refoveating saccadic eye movements become necessary to keep the target in central view (Levin et al. 1988). But why was this low gain smooth pursuit occurring? Could it be that these people judge speeds poorly? We set about to test this possibility, using the methods of psychophysics. Simultaneously, we set about using the trait of abnormal pursuit tracking as a genetic indicator, in the way Kety had implied in his narrow expansion of what ought to be included as schizophrenia (Holzman et al. 1988; Matthysse et al. 1986).

Because the eye tracking abnormality occurs about seven times more frequently in the families of schizophrenia patients than does schizophrenia itself, we have been using this endophenotype—in addition to schizophrenia itself—in our search for chromosomal linkage. Thus far, there is one report of linkage (Arolt et al. 1996) with a lod score of 3.7 for eye tracking abnormality on chromosome 6p (D6S271). In a large study of Danish families, we have found support for this finding with a lod score of 2.34 in approximately this same area (D6S1017).

Physiological studies of this phenomenon continue as well. Smooth pursuit eye movements are complex oculomotor activities. They consist of processes that initiate pursuit and other processes that maintain pursuit.

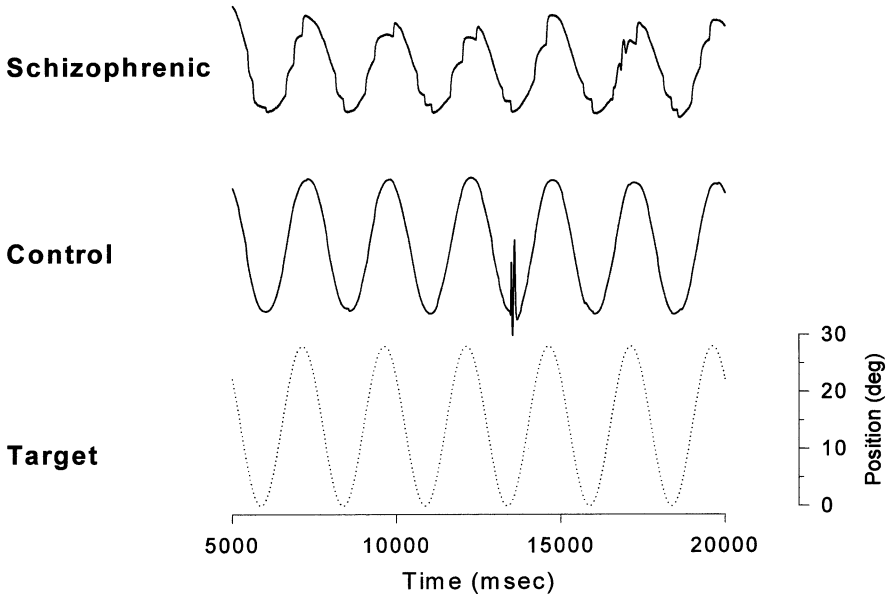

Figure 1. Smooth pursuit eye movement tracings from a schizophrenia patient (top panel) and from a normal control (middle panel). The participants were asked to follow a target (a small circle) that moved sinusoidally at a frequency of 0.4 Hz (bottom panel). Recording was by infrared reflectometry. The tracing made by the schizophrenia patient is significantly more irregular than that produced by the control participant, suggesting low gain pursuit with frequent catch-up saccadic eye movements.

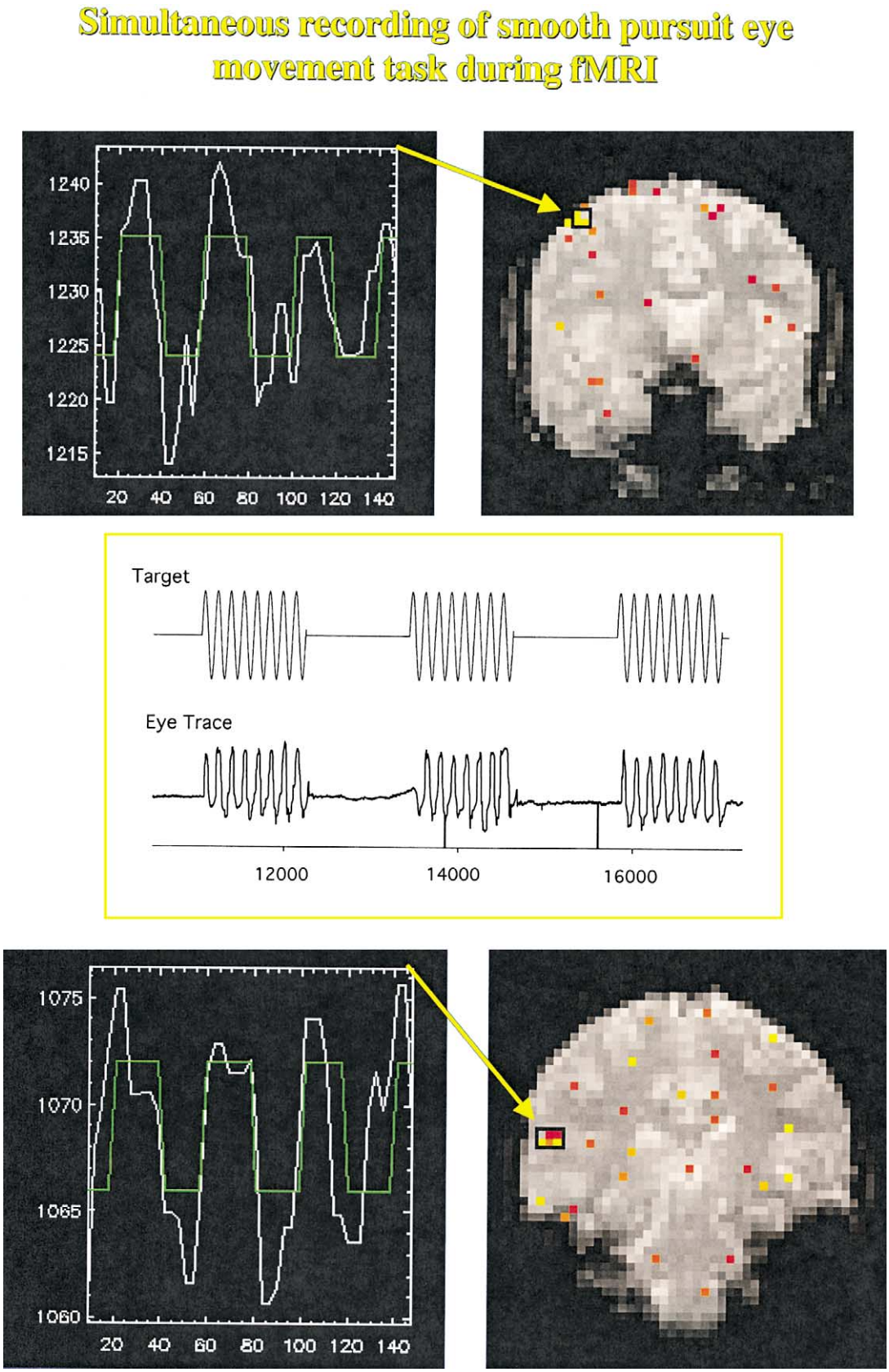

Figure 2. Simultaneous eye movement recording and fMRI of a participant while following a sine wave target oscillating at 0.4 Hz for 20 sec, alternating with 20 sec of visual fixation (central panel). Arrows point to significant activation in the frontal eye fields (top panel) and the inferior parietal area, which is close to area MT/MST, the motion-sensitive areas of the extrastriate cortex (bottom panel).

Both processes depend upon the presence of motion signals from a stimulus, intact pathways in the brain for processing the motion signals, and an intact motor apparatus for executing eye movements. When any of these component processes is compromised, smooth pursuit becomes abnormal. Where in the brain does the abnormality in schizophrenia occur? The motor apparatus functions normally in schizophrenia, as evidenced by the unimpaired eye movements other than smooth pursuit. Of the more than 20 areas of the extra-striate cortex, two are specifically recruited for motion processing: the middle temporal and the medial superior temporal areas (MT/MST). Elegant studies have shown that lesions to these areas impair motion detection and produce the same kind of eye tracking abnormalities that we see in schizophrenia (e.g., Newsome et al. 1985). Our psychophysical experiments confirmed that schizophrenic patients and a portion of their relatives do have difficulty in accurately detecting the speed of moving objects, although their other visual capacities, such as detection of color, contrast, or position, are normal (Chen et al. 1999b, 1999c). Indeed, our studies have shown that they tend to substitute position and contrast cues for velocity cues in order to adapt to the moving environment around them (Chen et al. 1999a). We have also looked at the relation of these raised velocity sensitivity thresholds to eye tracking abnormalities. We found that raised velocity thresholds were highly related both to a sluggish onset and maintenance of smooth pursuit.

We have used the concept of spectrum raised by Seymour's genetic studies of schizophrenia and the powerful tool of brain imaging to identify physiological characteristics that are not picked up by symptom identification. At the present time, in collaboration with Drs. Perry Renshaw and Deborah Yurgelun-Todd of the McLean Imaging Center, we are employing functional magnetic resonance to visualize the activation of these small brain areas when motion detection is and is not required of the observer (Figure 2). In this way, we continue Seymour's conceptual and empirical leap of recording the brain's ongoing activities.

Seymour's scientific style was easy, unpretentious, and direct as he sought the simplest solution to a difficult problem. The simplicity of his approach to science is illustrated in his use of chelation with citrate for lead poisoning and in his solution to the problem of measuring cerebral blood flow and metabolism. Equally direct and simple was his approach to the role of genetics in schizophrenia.

Seymour was a giant among us. Like many great athletes and musicians, he made difficult and formidable tasks look easy. He continued to honor us with his presence in our laboratory, offering advice, commentary, and jokes. His tread was soft, yet gracefully and unobtrusively dazzling. We owe much to him. This symposium is but one way we can say to him, "Thank you, Seymour. We are privileged to have been touched by your brilliance and friendship."

ACKNOWLEDGMENTS

Supported by NIMH grants MH 31154, 31340, MH 44876, 49487, 01021, and from the Roy Hunt Foundation.

REFERENCES

Arolt V, Lencer R, Nolte A, Müller-Myhsok B, Purmann S, Schürmann M, Leutelt J, Pinnow M, Schwinger E (1996): Eye tracking dysfunction is a putative phenotypic susceptibility marker of schizophrenia and maps to a locus on chromosome 6p in families with multiple occurrence of the disease. Am J Med Genet (Neuropsychiatric Genetics) 67:564–579

Bleuler E (1950): (first published in 1911) Dementia Praecox or the Group of Schizophrenias (H Zinkin, trans.). New York, International Universities Press

Chen Y, Nakayama K, Levy DL, Matthysse S, Holzman PS (1999b): Psychophysical isolation of motion processing deficits in schizophrenics and their relatives and its relation to eye tracking deficits. Proc Natl Acad Sci USA 96:4724–4729

Chen Y, Palafox G, Nakayama K, Levy D, Matthysse S, Holzman P (1999c): Motion perception in schizophrenia. Arch Gen Psychiatry 56:149–154

Chen Y, Palafox G, Nakayama K, Levy DL, Matthysse SW, Holzman PS (1999a): Dependence of impaired eye tracking on deficient velocity discrimination in schizophrenia. Arch Gen Psychiatry 56:153–161

Gottesman II, Shields J (1972): Schizophrenia and Genetics. A Twin Study Vantage Point. New York, Academic Press

Holzman PS, Kringlen E, Matthysse SW, Flanagan S, 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 discordant twins. Arch Gen Psychiatry 45:641–647

Holzman PS, Proctor LR, Hughes DW (1973): Eye tracking patterns in schizophrenia. Science 181:179–181

Holzman PS, Proctor LR, Levy DL, Yasillo NJ, Meltzer HY, Hurt SW (1974): Eye tracking dysfunctions in schizophrenic patients and their relatives. Arch Gen Psychiatry 31:143–151

Iacono WG, Tuason VB, Johnson RA (1981): Dissociation of smooth pursuit and saccadic eye tracking in remitted schizophrenics: an ocular reaction time task that schizophrenics perform well. Arch Gen Psychiatry 38:991–996

John B, Lewis KR (1966): Chromosome variability and geographic distribution in insects. Science 132:711–721

Kety S (1980): The syndrome of schizophrenia: unresolved questions and opportunities for research. Br J Psychiatry 136:421–436

Kety SS, Rosenthal D, Wender P (1978): Genetic relationships within the schizophrenia spectrum: evidence from

adoption studies. In Spitzer RL, Klein DF, (eds), Critical Issues in Psychiatric Diagnosis. New York, Raven Press, pp 213–223

Kety SS, Rosenthal D, Wender PH, Schulsinger F (1976): Studies based on a total sample of adopted individuals and their relatives: why they were necessary, what they demonstrated and failed to demonstrate. Schizophr Bull 2:413–428

Laing RD (1967): The Politics of Experience. New York, Ballentine Books, Inc.

Latham C, Holzman PS, Manschrek T, Tole J (1981): Optokinetic nystagmus and pursuit eye movements in schizophrenia. Arch Gen Psychiatry 38:997–1003

Levin S, Holzman PS, Rothenberg SJ, Lipton RB (1981): Saccadic eye movements in psychotic patients. Psychiatry Res 5:47–58

Levin S, Jones A, Stark L, Merrin EL, Holzman PS (1982): Saccadic eye movements of schizophrenic patients measured by reflected light technique. Biol Psychiatry 17:1277–1287

Levin S, Luebke A, Zee D, Hain T, Robinson DR, Holzman PS (1988): Smooth pursuit eye movements in schizophrenics: quantitative measurements with the search-coil technique. J Psychiatric Res 22:195–206

Levy DL, Holzman PS, Proctor LR (1978): Vestibular responses in schizophrenia. Arch Gen Psychiatry 35:972–981

Lidz T (1973): The Origin and Treatment of Schizophrenic Disorders. New York, Basic Books, Inc.

Lipton RB, Levin S, Holzman PS (1980): Horizontal and vertical pursuit movements, the oculocephalic reflex, and the functional psychoses. Psychiatry Res 3:193–203

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 disorder. J Psychiatric Res 20:57–65

Newsome WT, Wurtz RH, Dursteler MR, Mikami A (1985): Deficits in visual motion processing following ibotenic acid lesions of the middle temporal visual area of the Macaque monkey. J Neuroscience 5:825–840