Ernst Franzek
Helmut Beckmann

Psychoses of the Schizophrenic Spectrum in Twins

A Discussion on the Nature – Nurture Debate in the Etiology of "Endogenous" Psychoses

Springer-Verlag Wien GmbH

Priv. Doz. Dr. Ernst Franzek
Psychiatrische Klinik und Poliklinik, Universitäts-Nervenklinik,
Würzburg, Germany

Univ.-Prof. Dr. Dr. h.c. Helmut Beckmann
Psychiatrische Klinik und Poliklinik, Universitäts-Nervenklinik,
Würzburg, Germany

Translated by Susanne Bachmann-Lauer

Typesetting: Composition & Design Services, Minsk 220027, Belarus

Graphic design: Ecke Bonk

Printed on acid-free and chlorine-free bleached paper
SPIN: 10719091

With 2 Figures

Library of Congress Cataloging-in-Publication Data
Franzek, Ernst, 1953-
Psychoses of the schizophrenic spectrum in twins : a discussion of the nature-nurture debate in the etiology of "endogenous" psychoses / Ernst Franzek, Helmut Beckmann.
p. cm.
Includes bibliographical references and index.
ISBN 978-3-211-83298-1 ISBN 978-3-7091-6353-5 (eBook)
DOI 10.1007/978-3-7091-6353-5
1. Schizophrenia. 2. Diseases in twins. 3. Psychoses–Etiology.
I. Beckmann, H. (Helmut), Dr. II. Title.
RC514.F686 1999 99-25477
616.89'82–dc21 CIP

ISBN 978-3-211-83298-1

Foreword

Modern brain research has progressed tremendously in the last decades, largely due to the development of methods in neuro-imagery, biochemistry, pharmacology and histology. Despite this, it has not yet been possible to successfully apply these advances to a scientifically based, empirically verifiable psychiatry. This primarily concerns the endogenous psychoses, to use the words of the German psychiatrist Kurt Kolle from the "Delphian Oracle".

One of the reasons for the lack of progress in psychiatric research is the inconsistent and unreliable diagnostic methods which are currently carried out through expert consensus and which are then pronounced as setting a worldwide standard. The claim of reliability among various researchers is always emphasized, although often by sacrificing an adequate level of validity. These classification systems stand in contrast to the classification of endogenous psychoses based on a clinical-empirical approach and on highly differentiated descriptions of the illness, for example according to Leonhard. In contrast to operationalized diagnostics, a certain diagnosis can be provided here only when all, and especially when the characteristic symptoms of a clinical picture are clearly present. The endogenous psychoses with so-called "schizophrenic symptomatology" are subdivided according to the Leonhard classification into three large groups of illnesses, which in turn cover distinct clinical pictures: cycloid psychoses, unsystematic and systematic schizophrenia. A series of new research results point to the nosological autonomy of these groups of illnesses.

A finding which has not yet been acknowledged internationally has prompted us at this time to take on the challenge of conducting a systematic twin study, and the great effort associated with it, while taking the Leonhard classification into account. Leonhard reported that he had not seen a single monozygotic twin with systematic schizophrenia among the large number of endogenous psychotic twin test subjects that he had observed during his life-

time. Among the dizygotic twins, however, this disorder occurred in the frequency that was to be expected statistically. He posed the hypothesis that the close interpersonal contact generally experienced by monozygotic twins – if they grew up together – could possibly prevent these severe, irreversible illnesses; and that in contrast, a lack of communication in developmental stages which were sensitive with regard to the human psyche could predestine the occurrence of these illnesses. Let us say at this point that we were also unable to disprove Leonhard's findings, despite our systematic ascertainment of index-twins. We view this as a challenge in schizophrenia research and hope that dogmatic and ideological reservations about the classification of endogenous psychoses by Kleist and Leonhard will be dropped so that serious scientific discussion can begin. The spectrum of psychoses with schizophrenic and schizophrenia-like symptoms does not appear to be a continuum of disorders, but seems rather to consist of various subgroups with extremely different genetic, somatic and psychosocial origins. This twin study is further proof that innovative discoveries will be attainable in the area of endogenous psychoses only through a precise clinical-psychopathological differentiation of the psychiatric clinical pictures and specific scientific investigation.

Würzburg, 1999 *Ernst Franzek, Helmut Beckmann*

Table of contents

Introduction

The diagnostic dilemma in psychiatry

The history of psychiatry has been marked from the very beginning by the "conflict" between leading representatives of the field concerning diagnostic interpretations. For example, Heinroth (1773–1843) identified 48 different diagnoses of mental diseases, while Neumann (1814–1884) in his textbook of psychiatry wrote: "There is only one type of mental disease. We call it insanity." For a long time there was no agreement on a systematic classification of mental disorders. Using Kahlbaum's (1828–1899) fundamental idea of clinically oriented research methodology, Kraepelin (1856–1926) finally created a diagnostic-nosological classification system, in which he divided endogenous psychoses into two large groupings: manic-depressive disease and dementia praecox. This dichotomy is based primarily on the different prognoses of the two groups: favorable prognosis in the case of manic-depressive disease and unfavorable prognosis in the case of dementia praecox. Kraepelin defined the term "manic-depressive disease" rather broadly. He also did not see a disease entity in the actual sense, but rather "a group of disorders stemming from a common root, with gradual transitions between the individual types" (Kraepelin 1909). Kraepelin's paradigm of a dichotomy of endogenous psychoses dominated psychiatric research for decades. With the introduction of the term "schizophrenia" by Bleuler (1857–1939), however, the diagnostic-prognostic dichotomy was lost. Bleuler's "group of schizophrenia" included both favorable as well as unfavorable psychoses: "... it soon became apparent, however, that many disorders which cannot be distinguished in their psychopathological description from those psychoses which lead to 'dementia' have a good prognosis, similar to manic-depressive 'insanity'. A term had to be created which encompassed illnesses with similar symptomatol-

ogy, even when they result partly in recovery, partly in deficiency, and partly in 'dementia'" (Bleuler 1911). The resulting consequences for psychiatric research were summarized resignedly by Gruhle (1880–1958) in 1932: "It is somewhat discouraging to see that the controversies which took place between the years 1800 and 1850 were repeated almost identically from 1900 to 1930; the only difference being that these debates were no longer concerned with insanity as such, but rather with the three endogenous psychoses (idiopathic epilepsy, manic-depressive insanity, schizophrenia) and particularly its primary subject, schizophrenia".

In the last several years attempts have been made to solve this dilemma by means of atheoretical, operationalized diagnostics. Classifications are to be made exclusively on the basis of syndromes and without involving any kind of theoretical ideas about illness. This is also expressed by the fact that the term 'disease' was replaced for the most part by the term 'disorder' in the "Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) and Fourth Edition (DSM IV)" of the American Psychiatric Association, as well as in the "Tenth Revision of the International Classification of Diseases (ICD 10)" of the World Health Organization. The current state of schizophrenia research has been summarized pessimistically by Parnas (1990), similarly to Gruhle: "We have now at our disposal powerful genetic, biochemical, and brain-imaging technology. Nevertheless, there is an increased gap between these developments and the growth in our understanding of the etiology of schizophrenia.".

Independently from this development, Leonhard (1904–1988) led clinical-empirical research in a new direction. Starting from the physiological-psychological viewpoint set out by Wernicke (1848–1905) and the neuropathological-psychopathological viewpoint of Kleist (1879–1960), he integrated Kraepelin's etiological-prognostic concept and created an extremely differentiated nosology of endogenous psychoses (Leonhard 1956, 1995). While retaining Kraepelin's prognostic dichotomy, he divided both groups (manic-depressive disease and dementia praecox) into various distinct illnesses. Kraepelin's manic-depressive grouping was subdivided into monopolar phasic psychoses, bipolar phasic psychoses (manic-depressive disease in a narrower sense) and cycloid psychoses. Dementia praecox was divided into the nosologically independent unsystematic and systematic schizophrenias according to Kleist-Leonhard (Fig. 1). Psychiatry today has access to completely independent classification systems of mental illness; atheoretical operationalized systems based on "expert consensus" on the one

Favorable long-term prognosis		Unfavorable long-term prognosis	
Kraepelin: Manic-depressive disease		dementia praecox	
Favorable long-term prognosis		unfavorable long-term prognosis	
Leonhard: Affective psychoses	cycloid psychoses	unsystematic schizophrenia	systematic schizophrenia
Favorable long-term prognosis		unfavorable long-term prognosis	
Bleuler: Manic-depressive disease		group of schizophrenias	

Fig. 1. In his classification of endogenous psychoses, Leonhard retained Kraepelin's dichotomy of psychoses of long-term favorable and unfavorable prognoses. Bleuler's extension of the term "schizophrenia" – which also includes the cycloid psychoses according to Leonhard – makes prognostic diagnostics impossible

hand, and clinically-empirically founded nosology of the Wernicke-Kleist-Leonhard school on the other.

The nature – nurture controversy

The significance of heredity and environment with regard to the origin of mental illness was recognized from the very beginnings of psychiatry. One of the pioneers of psychiatry, Philippe Pinel (1745–1826), included heredity in addition to upbringing, irregularities in lifestyle and passions among the causes of mental illness (Ackerknecht 1985). Whether heredity or environmental factors would become more central to scientific interest was often determined by the given *zeitgeist*. Experience has shown, however, that the exclusive emphasis on only one of the two factors always leads to a dead end. Under the rubric "Wege und Irrwege der Genetik in der Psychiatrie" ("Right and Wrong Paths of Genetics in Psychiatry"), Propping once again demonstrated impressively how a too one-sided scientific viewpoint can lead to the depths of an ideologically motivated inhumanity (Propping 1989). Finally, the statement by Zerbin-Rüdin that it is not a question of "body or soul" and "nature or nurture" in the origin of mental disorders, but rather "body and soul" and "nature and nurture" (Zerbin-Rüdin 1974) is not a new development, but rather a return to the original position. It is pointless and "quite artificial and not biological" (Propping 1989) to attempt to determine the exact percentage attributable to heredity or the environment. In addition, the phenotype, or physical manifestation, is too far removed from the human genotype.

Outwardly visible human characteristics have usually developed over a number of reactions and intermediate stages, from the genetic make-up to the final phenomenological state. The level of the visible phenotype is preceded by the level of the gene products (proteins), which is preceded by the chromosomal level and finally the gene level (DNA level) (Propping 1984). In addition, some hereditary characteristics are very resistant to environmental influences (such as height) while others are very susceptible (such as body weight).

On the other hand, to achieve an exact etiology and treatment for mental illness it is absolutely necessary to determine the relative importance of heredity and/or environmental factors: whether, for example, a hereditary disposition only occurs in certain environmental constellations or, on the other hand, if certain environmental constellations can possibly prevent the clinical manifestation of a hereditary disposition.

Methods of clinical genetics in psychiatry

Clinical genetics investigate genetic variability at the level of the phenotype, i.e. distinct illnesses must first be clinically recognized as such and described and defined by their pattern of symptoms. Only when this step has been completed is it advisable to carry out further research on the gene product, chromosome and/or gene. Clinical genetics in psychiatry are based essentially on research with families, adopted children and twins. The occurrence of certain illnesses within a family points to heredity, even though it does not provide absolute proof. The disorder could possibly also be the result of a pathogenic environment which has affected all members of a family equally. On the other hand, the sporadic occurrence of an illness in a family does not necessarily exclude heredity. A small number or no siblings, or a rare recessive gene, for example, could be the reason (Zerbin-Rüdin 1974).

Adoption studies present a suitable means of separating the influence of the family environment and that of heredity with regard to the occurrence of mental illness. There are essentially three strategies which can be followed:

1. Children of mentally ill parents are examined who have grown up with healthy adoptive parents. Adopted children with healthy biological parents are used as controls.
2. The frequency of biological parents becoming ill is compared with adoptive parents in the case of persons who were adopted at an early stage and are now mentally ill.

3. Children of healthy biological parents are examined who have grown up with mentally ill adoptive parents. Adopted children of healthy biological parents whose adoptive parents are also healthy are used as controls.

An essential objection against the adoption method is that neither parents who give up their children for adoption nor parents who adopt children represent a group that is comparable to that of the normal population. As a result, the influence of genetic factors tends to be underestimated in adoption studies, since a higher rate of mental irregularities is expected even within the control groups (Propping 1989).

Twin research is the subject of this investigation, and will be explained in detail in the following chapters.

General remarks on twin origination

The introduction of the twin method in clinical genetics is most often traced back to Galton (1876). According to Vogel and Motulsky, however, Galton did not correctly recognize the essential aspect of the method – namely the existence of two different twin types. Dareste, however, had already reported on the distinction between monozygotic and dizygotic twins in 1874 to the Société d'Antropologie (Vogel and Motulsky 1986).

Biology of twin origination

Monozygotic and dizygotic twins

Dizygotic twins are conceived when two ova are ovulated in the woman's same cycle and are fertilized by two different sperms. Due to their common genetic background, dizygotic twins have about 50 per cent of their genes in common, like ordinary siblings. Each of the dizygotic twins always has his own chorion and his own amnionic cavity with surrounding membrane. Depending on the distance in which the two embryos are implanted in the uterus, the placenta can be separated or joined. If the placenta is joined, the separating membranes consist of amnion-chorion-chorion-amnion.

Monozygotic twins originate when a fertilized ovum in an early embryonic stage divides into two genetically identical daughter cells – a kind of asexual reproduction. This can occur up to about two weeks after fertilization. If the fertilized egg-cell up to the morula stage has already divided before the differentiation of the trophoblast (day five after fertilization), the twins will each have a separate chorion and amnion and the separating membrane will consist of amnion-chorion-chorion-amnion. These monozygotic twins have the same intrauterine conditions as dizygotic twins and cannot be distinguished from them at the embryonic stage. If

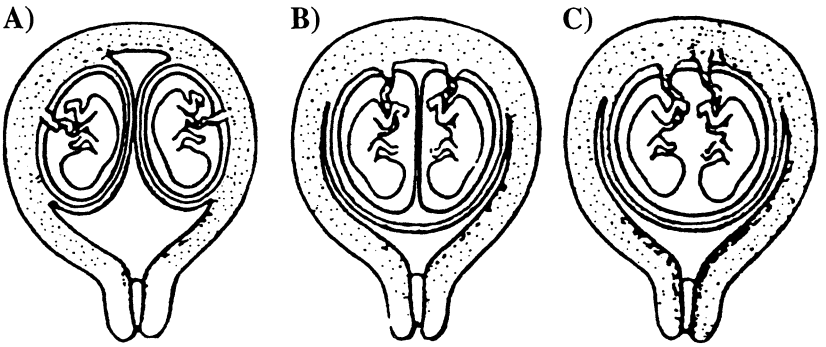

Fig. 2. (modified by Langman 1977). (A) Monozygotic twins with separate chorion and amnion. The division of the fertilized egg-cell has taken place before differentiation of the trophoblast (up to day five after fertilization). (B) Monozygotic twins with common chorion but separate amnion. The division of the inner embryonic cell mass takes place after the morula stage but before differentiation of the amnion (about day five – ten after fertilization). (C) Monozygotic twins with common chorion and amnion. Division takes place only after differentiation of the amnion (after day ten after fertilization)

the egg-cell divides after the morula stage, but before the differentiation of the amnions (between approximately days five and ten after fertilization), the twins will share a common chorion but have their own amnion. This separating membrane now consists of amnion-amnion. If division takes place only after the differentiation of the amnion (after day 10 after fertilization) the twins will have a common chorion and a common amnion, i.e. there is no separating membrane between the individuals (Fig.2). Twins with a separate chorion and amnion can therefore be dizygotic or monozygotic. Approximately one-third of monozygotic twins belong to this category. Twins with a common chorion, however, are always monozygotic. They generally have a separate amnion. Only a small number of monochorionic twins (ca. 4%) possess a common amnion (Bulmer 1970).

The effect of differences in intrauterine environment

An extremely important question for the subsequent discussion is whether monozygotic and dizygotic twins have different intrauterine environmental conditions. In a retrospective evaluation of ultrasound measurements carried out during the second trimester, Gilmore et al. (1996) found considerable differences in the brain development and body size of monozygotic twins. It has been known for a long time that twins have a significantly higher rate of birth defects than ordinary children (Benirschke and Kim 1973, Kohl and Casey 1975, Little and Bryan 1986), and that monozy-

gotic twins have considerably more than dizygotic twins (Heady and Heasman 1959, Barr and Stevenson 1961, Stevenson et al. 1966). Birth defects are frequently found in only one of the monozygotic twins (Morison 1949, Fogel et al. 1965). A specific birth defect syndrome has not yet been identified. The risk of birth defects is increased, for example, for congenital heart defects, anencephaly, and cleft lip and/or palate (Vogel and Motulsky 1986, Spellacy 1988). It is also known that the perinatal mortality of monochorionic twins is approximately twice as high as that of dichorial twins (Heady and Heasman 1959, Bulmer 1970). Monochorionic twins are always monozygotic. In approximately 90% of the monochorionic placentas there are links in the blood circulation of the twins. In the case of arterial-venal shunts, which are not compensated for by other vascular links, one twin will bleed slowly into the other and will cause the so-called "twin transfusion syndrome". This occurs to some degree in 15–30% of monochorionic twins (Rausen et al. 1965, Campion and Tucker 1973). In the case of dichorial twins, placental vascular links between the two twins occur extremely rarely (Nicholas et al. 1957). The "transfusion syndrome" can lead to a chronic deficiency of oxygen and other important nutrients. One twin will be small and pale, with remarkably reduced levels of hemoglobin and serum proteins, and often suffers from hypoxia. The other twin is large and plethoric and often develops cardiac insufficiency with hydrops and polyhydramnios. Weight differences of up to 1000 grams can occur. The "transfusion syndrome" is generally viewed as the main cause of increased pre- and perinatal mortality and the increased rate of birth defects in monochorionic twins (Rausen et al. 1965, Campion and Tucker 1973, Vogel and Motulsky 1986, Spellacy 1988). In addition, in the case of monochorionic twins with only one amnion, the high prenatal mortality rate is also attributed to umbilical cord twisting (Bulmer 1970).

Frequency of twin births

According to Propping (1989), almost one in every 100 births in central Europe is a twin birth, making approximately every 50th person in the general population a twin. About 40% of twins are monozygotic, while the remaining 60% are dizygotic. Dizygotic twins are about equally the same or different sex. According to Weinberg (1902, 1909), the frequency of monozygotic and dizygotic twin rates is estimated according to the following formulas:

$$m = \frac{(G - U)}{N}$$

$$m = \frac{2U}{N}$$

m Monozygotic (identical) twin rate
d Dizygotic (fraternal) twin rate
G Number of same-sex twins
U Number of different-sex twins
N Number of all twin pregnancies

The formulas are based on the assumption that the sex ratio is 1:1, which is not quite correct, as a slightly higher number of boys are born than girls. Same-sex dizygotic twins also appear to be somewhat more frequent than different-sex twins, although the resulting difference is viewed as negligible (Bulmer 1970, Vogel and Motulsky 1986). The twin rates which can be calculated from these formulas are based entirely on the number of all twin pregnancies and not on the number of twin births. They therefore include both stillbirths and live births.

Frequency of monozygotic twins

Monozygotic twins occur at approximately the same frequency in all ethnic groups (approximately 3.5 for every 1000 births). Propping assumes that the rate of asexual division in early embryonic stages could be a universal constant (Propping 1989). According to Bulmer (1970) experiments with animals show that this phenomenon could arise as the result of a developmental inhibitor (e.g. lack of oxygen) in a very early embryonic stage. Nevertheless, the cause of the origin of monozygotic twins still remains unclear (LaBuda, et al. 1993).

Frequency of dizygotic twins

While the probability of having monozygotic twins is approximately the same for all women, the probability of having dizygotic twins is different for each woman. The relative frequency of dizygotic twins increases with the age of the mother, with a maximum between the ages of 35 and 39. After the age of 39, the frequency decreases (McArthur 1953, Bulmer 1970, Krüger and Propping 1976). One possible cause currently under discussion is the increased level of gonadotropin FSH in older women, which increases the frequency of multiple pregnancies. The frequent multiple pregnancies of women treated with hormones supports this

hypothesis. The reduced twin rate in the last phase of the woman's reproductive years is attributed to the decline in polyovulation, despite a higher FSH level (Vogel and Motulsky 1986). Regardless of the woman's age the relative number of dizygotic twins also increases with the number of previous births (Bulmer 1970). A hereditary disposition is also assumed as dizygotic twin births occur more frequently in some families (Weinberg 1909, Bulmer 1970). This familial pattern is found exclusively on the maternal side. Male dizygotic twins or fathers of dizygotic twins do not have an increased probability of fathering twins. The differing frequency of dizygotic twins in different ethnic groups is also interpreted genetically. For example, the twin rate in the Caucasian population is approximately 8 per 1000 births, while the rate in the African population is almost twice as high, and the rate in the Asiatic population is barely half as much (Bulmer 1970, Propping and Krüger 1976, Vogel and Motulsky 1986).

Decline of dizygotic twin births in civilized countries

A decline in dizygotic twin births has been observed in all civilized countries since the mid 1950s. The current average younger age of the mothers is viewed only as a partial explanation. According to Propping and Krüger (1976), it seems more plausible to seek an explanation in the fact that a maternal disposition to increased fertility plays a much less important role than before in this era of birth control. Recent research in Italy and the USA has shown that the birth rate of dizygotic twins has stabilized again since the early 1980s (Allen and Parisi 1990).

The twins method in research

Characteristics of the twin constellation

Twins represent a distinctive social group (Schepank 1974, 1993). They are apparently less dependent on communication with the rest of their environment, since – if they grow up together – they always have a partner of the same age. The attachment to each another is much more intense with monozygotic twins than with dizygotic twins. While monozygotic twins often strive to attain similarity and identification with each other, dizygotic twins tend to show more competitive behavior and a wish to distinguish themselves from their partner (Bischoff 1959, Bracken 1969, Schepank 1993). Generally, the identification with the partner appears to be stronger in female monozygotic twins than in male pairs (Vogel and Motulsky 1986). However, there are a significant number of dizygotic twins who also exhibit a strong degree of attachment and a pronounced aspiration for similarity. Conversely, it is possible for monozygotic twins to be less attached to each other and show a strong wish to distinguish themselves from each other (Schmidt 1986). It is even possible for an extreme animosity to develop between the twins. Attempts to attain similarity and/or difference are also influenced by the environment. In the past, it was more often the case that the identical nature of monozygotic twins was additionally emphasized by clothing, etc., while currently many educators place more value on emphasizing their individuality (Friedrich and Kabat vel Job 1986).

Specific role assignments often occur with twins. One twin is often the speaker and/or the more dominant of the two, while the other twin is more subordinate and less independent. Shields (1962) examined 44 pairs of monozygotic twins who grew up separated and compared them to a control group of 44 pairs of monozygotic twins who grew up together. He discovered that the dominant/subordinate axis was the most distinctive characteristic of monozygotic twins. Interestingly, Shields found a significant rela-

tionship between a higher birth weight and the leadership role in the pair (Shields 1962).

Von Verschuer was able to show that the so-called "twin fate", which means that an illness or death of a monozygotic twin automatically results in the same fate for the other, occurs only very rarely. "Individual destiny remains unpredictable" and "the constant photographic similarity of twin fates is a myth" (Zerbin-Rüdin 1974).

The methodological basis of twin research

Classical twin research

Classical twin research is based methodologically on the comparison of monozygotic and dizygotic twins and assumes the same environmental factors for both twin types. According to Galton's law, heredity is indicated when the correspondence of a certain trait is greater between monozygotic twins than between dizygotic twins. In the case of non-heredity, monozygotic and dizygotic pairs do not differ considerably in their correspondence (concordance) or lack of correspondence (discordance) for the trait. All phenomenological differences between monozygotic twins are attributed to the influence of the environment (Zerbin-Rüdin 1980). Galton's law should, however, be applied with certain restrictions. In the case of monozygotic twins, unfavorable prenatal conditions could lead to increased concordance as well as increased discordance for hereditary and non-hereditary illnesses (see pages 7, 8). Therefore, birth weight and complications during pregnancy and birth should always be taken into consideration in twin studies (Campion and Tucker 1973). Also the fact that some monozygotic twins are concordant for an illness while others are discordant can be accounted for by various explanations: 1. the manifestation of a hereditary illness is influenced considerably by non-genetic factors, or 2. there is both a hereditary form as well as a non-hereditary form of the illness. In order to be able to make this distinction it is necessary to compare the empirical familial pattern of an illness of concordant and discordant pairs. If there is no genetic type of an illness, the morbidity risk of close relatives of discordant pairs is not greater than in the normal population. If non-genetic factors must be present in order for the illness to become manifest, the morbidity risk of relatives in both concordant and discordant twins is approximately equal (Vogel and Motulsky 1986).