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Genetics of Neurosis

The Effects of Sampling Variation Upon the Twin Concordance Ratio

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Summary: In a study of 229 neurotic same-sex adult twins admitted to all psychiatric in- and out-patient clinics and mental hospitals in Norway, a statistically significant, moderately higher concordance was found for MZ than for DZ twins. When the sample was subdivided, this higher concordance for MZ pairs was true only for male twins and for twins admitted to mental hospitals. The results are compared to those from earlier studies; different findings on the importance of genetic factors in the development of neuroses may be due to differences in sample selection.

Few will deny that environmental factors play an important part in the development of neurosis, but there is more disagreement about the role of genetic factors. Family studies show a higher proportion of neurosis in the first degree relatives of neurotic patients as compared to the relatives of controls (McInnes, 1937; Brown, 1942; Cohen, 1951; Alanen, 1966; Noyes *et al,* 1978). Interpretation of these results is very difficult. The correspondence with neurotic behaviour in relatives may be due to learning, as well as to the influence of genetic factors. The results from twin studies of neurosis are divergent. While Ihda (1960) found a similar concordance rate for neurosis in monozygotic (MZ) as in dizygotic (DZ) twin pairs (50 per cent against 40 per cent), Shields and Slater (1966) found a concordance rate which was almost three times higher in MZ than in DZ pairs (40 per cent against 15 per cent). Pollin *et al* (1969) state that there is little evidence for a genetic factor in neurosis, while Schepank (1973) maintains that genetic factors are involved. A problem with the earlier twin studies is that samples of neurotic twins are highly selected. Usually the samples are drawn from a single hospital or consist of twins who are detected haphazardly, and in an uncontrolled way. Experience from studies of schizophrenic twins shows the importance of using a complete nationwide population sample (Kringlen, 1967).

The purpose of this study is to investigate the influence of sampling variation upon the difference in concordance rates between MZ and DZ twin pairs; and hence, the conclusion as to the relative contributions of environmental and genetic factors in the development of neurosis. The data is analyzed separately for females, males, and twins admitted to mental hospitals, or in- and out-patient clinics. There is reason to believe that the difference in concordance rates between MZ and DZ twin pairs is also influenced by the composition in the sample of different types of neuroses. This issue is analyzed in forthcoming papers.

Methods

Sampling

The first step was to compile a register of patients with diagnoses of neurosis, borderline psychosis, pseudoneurotic schizophrenia, or variants of these diagnoses, including alcoholism, drug abuse and sociopathy. This broad spectrum of diagnoses was chosen to avoid missing wrongly diagnosed neurotic twins. All patients admitted to Norwegian mental hospitals and in- and out-patient clinics, and born between 1910 and 1955, were included. This register of 91,318 patients was checked against the twin register at the Institute of Behavioural Sciences in Medicine for patients born before 1946, and the twin register at the Institute of Medical Genetics for patients born in and after 1946. Because names sometimes change etc., all possible twins were included. Initially it appeared that 828 patients might be same-sex twins, and 487 female-male twins.

The next step was to examine the psychiatric records of the possible same-sex twins. When information about the birth place, the name of mothers and fathers etc., in the psychiatric records and twin registers were compared, some patients turned out not to be twins. Other patients were excluded from the sample because they had died, or were not neurotic or borderline psychotic. The addresses of the remaining patients were found in the Folk register, and a letter was sent to them asking for their cooperation and the name and

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TABLE I

Causes of reduction in the original number of possible twin pairs

Possible same-sex twin probands	828
Turned out not to be twins	136
Proband or co-twin dead	173
Proband neurological disease	29
Proband psychosis	33
Proband alcoholism	65
Proband drug abuse	10
Proband sociopathy	7
Proband or co-twin living outside Scandinavia	18
Address not found	3
Proband or co-twin too physically ill to be interviewed	4
Impossible to arrange an interview	3
Proband or co-twin refused to participate	29
Both twins probands	19
Total	529
Number of pairs interviewed	299

address of their co-twin. A few more turned out not to be twins, some of the co-twins were dead, some were living abroad and some refused to participate. Two hundred and ninety-nine twin pairs remained and were interviewed. Table I shows the reasons for exclusions from the original sample of same-sex twins.

It may seem that the number of twin pairs out of 91,318 patients is low. However, early in the century many twins died because of the combination of premature birth, and poverty. For instance, in Denmark, in more than 65 per cent of twin pairs one or both twins died before the age of six (Hauge *et al,* 1968). It is also possible that the twin register is incomplete. Still, this sample is far more representative of the total in the country than any previous estimate.

Interview

All twins were personally interviewed by the author. The interview probed for information about childhood, the twin relationship, relation to parents, socio-economic conditions in childhood, school, youth, marriage, work and current life circumstances. Information was sought about any situation which possibly led to emotional disturbance. The psychiatric symptoms were asked for using a semistructured interview, the Present State Examination (PSE) (Wing *et al,* 1974). This interview was constructed for use in international studies of severe psychiatric disorders, but it has also been used for samples of in- and outpatients with less severe disorders, and in population studies (Wing *et al,* 1978). The PSE was used for lifetime symptoms, not just symptoms in the previous month. Information was also available from psychiatric records.

Zygosity determination

The procedure for determination of the twins' zygosity is described elsewhere (Torgersen, 1979a). Briefly, all the twins filled out a postal questionnaire dealing with similarity of childhood appearance, and how often, and by whom, the twins' identities were mixed up. Blood typing analysis was obtained from both twin partners in three-quarters of the twin pairs: 10 genetic markers were analyzed, namely, ABO, MNS, Rh (C,D,E,c,e), Kell, haptoglobin, group specific component, phosphoglucomutase, C3 complement component, acid phosphatase, and glutamate-pyruvate transaminase. Not all tests could be performed for all twins. In 95 per cent of the twin pairs the questionnaire and the blood typing analysis gave the same result. In half of the cases where these methods disagreed, the genetic markers were the same in both twins, though they were clearly dissimilar in appearance. Consequently, they were classified as dizygotic. Since there was 95 per cent agreement between the questionnaire and blood typing methods of zygosity determination, in the cases where bloodtyping was not available, the questionnaire was used, with the assumption of a 5 per cent error.

Concordance methods

The two commonest methods of calculating concordance are the proband-wise and the pair-wise method. The difference arises when both twins in a pair are probands, for instance if both twins are admitted to the hospital where the study is performed. If the proband-wise method is used such pairs are counted twice. If the pair-wise method is used the pairs are counted once. As almost all studies of neurotic twins have used the proband-wise method, this method is used here.

Diagnostic procedure

Information from the interview and the psychiatric records, if any, was gathered in a 1–4 page case-summary for proband and co-twin separately. The personal history, psychiatric symptoms, if any, and emotional and social functioning were carefully described. All information which could disclose the twins' zygosity, who was co-twin to whom, and the diagnoses from psychiatric institutions, was excluded from the case-summary. The case-summaries were distributed to two psychiatrists and to the author more than a year after the case-summary was written. It was impossible by then for the author to remember who was whose co-twin, or anything about the twins' zygosity. The results of the analysis of zygosity was not yet known. The three judges made diagnoses accord-

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ing to the 9th edition of WHO's International Classification of Diseases, supplemented with the diagnosis of borderline psychosis. A twin was regarded as a case if his symptoms, emotional problems and social dysfunction were as pronounced as those in a patient who might be treated in an in- or out-patient psychiatric institution. The diagnoses were compared, and the twin was given the diagnosis proposed by a majority of the judges. If all three disagreed the diagnosis was made after discussion.

When the subdivisions of neurosis and psychosis are disregarded, and the twins are given a diagnosis of either psychosis, borderline psychosis, neurosis, alcoholism, drug abuse, sociopathy, or normal, the agreement among the judges amounted to a generalized kappa (Fleiss, 1971) of 0.69. This is similar to that reported in the reliability studies of DSM-III (Spitzer *et al*, 1979; American Psychiatric Association, 1980). As the high reliability of DSM-III is emphasized, the reliability of our diagnostic procedure must be regarded as good.

Table II shows the distribution of diagnoses of the probands. In 19 twin pairs, both twins were probands. The number of probands is 318, the number of pairs 299. This paper deals only with pairs whose probands are given a diagnosis of neurosis. The number of such probands is 229 and the number of pairs is 219 as both of the twins in 10 pairs are probands. The age range is 18 to 66, with a mean of 44 years. The number of monozygotic female probands is 69, dizygotic females 91, monozygotic males 23 and dizygotic males 46.

TABLE II

The distribution of research diagnoses in probands

Diagnoses	Number of probands
Psychosis	14
Borderline psychosis	53
Neurosis	229
Alcoholism	5
Drug abuse	1
Sociopathy	2
Normal	14
Total	318

Results

Table III shows the concordance rates for MZ and DZ pairs, females and males are analyzed separately, and together. For females, the MZ/DZ ratio is 1.2 both for neurosis and for all psychiatric diagnosis in co-twins, and is not statistically significant. For males, however, the MZ/DZ ratio is 2.3 for neurosis and 2.2 for all psychiatric diagnoses, and is statistically significant. When both sexes are combined the MZ/ DZ ratio is 1.5 for neurosis and 1.4 for all psychiatric diagnoses in co-twins, and is statistically significant.

Table IV shows the consequences of taking the twin sample from different kinds of psychiatric institutions. Probands that have been admitted to more than one kind of institution are classified according to the most severe institution in the following order: out-patient clinic (and day-hospital), in-patient clinic, and mental hospital. If probands have only been admitted to psychiatric out-patient clinics and day-hospitals we find a low MZ/DZ ratio, 1.2 both for neurosis and for all psychiatric diagnoses of co-twins. The MZ/DZ ratio is somewhat higher when the probands have been admitted to psychiatric in-patient clinics, 1.4 for neurosis and for all psychiatric diagnoses of co-twins. When the twin proband sample comes from mental hospitals, the MZ/DZ ratio is as high as 2.1 for neurosis and 2.3 for all psychiatric diagnoses. The higher MZ/DZ ratio for twin samples from mental hospitals holds for both females and males. Conversely, males have a higher MZ/DZ ratio irrespective of what kind of institution the probands have been treated in. Also,

TABLE III

Diagnoses of the MZ and DZ co-twins of neurotic probands, females, males and both sexes

		Neurosis			All psychiatric diagnoses			Total	
Sex		Number	%	MZ/DZ ratio	Number	%	MZ/DZ ratio	Number	%
Female	MZ	31	44.9	1.2	35	50.7	1.2	69	100.0
	DZ	33	36.3		38	41.8		91	„
Male	MZ	8	34.8	2.3*	13	56.5	2.2***	23	„
	DZ	7	15.2		12	26.1		46	„
Both sexes	MZ	39	42.4	1.5**	48	52.2	1.4***	92	„
	DZ	40	29.2		50	36.5		137	„

*P <0.05
**P <0.02
***P <0.01

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TABLE IV

Diagnoses of the MZ and DZ co-twins of neurotic probands, admitted to psychiatric out-patient clinics (and day hospitals), in-patient clinics, and to mental hospitals

		Neurosis			All psychiatric diagnoses			Total	
Facility		Number	%	MZ/DZ ratio	Number	%	MZ/DZ ratio	Number	%
Out-patient clinic	MZ	10	37.0	1.2	13	48.1	1.2	27	100.0
	DZ	8	32.0		10	40.0		25	"
In-patient clinic	MZ	23	39.7	1.4	27	46.6	1.4	58	"
	DZ	25	27.5		31	34.1		91	"
Mental hospital	MZ	5	71.4	2.1*	7	100.0	2.3**	7	"
	DZ	7	33.3		9	42.9		21	"

*P <0.05
**P <0.005

the effect of the kind of psychiatric institution, and sex, shows the same tendency for different subtypes of neuroses.

The concordance rates are uninfluenced by the age of the twins when interviewed. Hence, it is not necessary to make a correction for age. Also, if the twin pairs are excluded when the zygosity determination by the two methods disagrees, the results are the same. Finally, socio-economic status of parents, and the rural or urban birthplace are not related to the ratio between the concordance rates for MZ and DZ pairs.

Discussion

The purpose of the study was to get as complete a sample as possible of neurotic twins who were treated in psychiatric institutions in Norway. To obtain this, we started with a broad concept of neurosis, and included all probands who could be a twin, according to information in the twin register. Thus we did not lose many neurotic twins in the initial phase. Yet, we found fewer twins than might be expected. The reason for this seems to be the high mortality of twins. This fact might influence our results. However, it is not easy to know whether a high mortality of twins in a population will increase or reduce the MZ/DZ ratio. And this is a problem in all twin research. Another reduction in our sample was due to twins living outside Scandinavia, others who had no address, and some were too physically ill to be interviewed, or it was impossible for other reasons to arrange an interview. This group, however, did not amount to more than 8 per cent of the total number of twin pairs. Eight per cent refused to participate. There is little reason to believe that cases lost in this way could influence our results greatly. In any case, the sample in this study is more of a complete national sample than in any earlier twin study.

The interviewer was blind to the zygosity of the twins. Perhaps he could guess, but when a structured interview such as the PSE is used, it is less easy to be influenced by suspicions about zygosity. A zygosity bias might have led to a greater difference between the concordance rates for MZ and DZ twins; but we found a very small difference, compared to earlier studies. The use of two other judges improves the diagnostic procedure. But the criteria employed for a diagnosis of neurosis may be loose. It is, however, not easy to use, for example, Research Diagnostic Criteria with retrospective material. Agreement between three judges may be more practical. Furthermore. it was not the aim of the study to investigate different neuroses separately. Anyhow, it is difficult to explain our main result as to the different MZ/DZ ratios in different subsamples as a consequence of shortcomings in the methodology. The results showed that there was a statistically significant moderately higher concordance for neurosis in MZ than in DZ twin pairs. The result was similar when all the psychiatric diagnoses of co-twins were the basis for the concordance rates.

When the sample was split up into subsamples it was found that the higher concordance in MZ pairs only held for male pairs and pairs that had a proband who had been admitted to a mental hospital. The reason for the low MZ/DZ ratio in female pairs may be that female twins, who are more attached to their co-twins, are more affected by the breakdown of their co-twin, irrespective of whether the twin pair is MZ or DZ. Another possibility is that females are more prone to report and exaggerate minor neurotic symptoms, and thus it may be that a number of the female co-twins have not experienced a definite psychiatric reaction. However, the fact that the frequency of all psychiatric diagnoses was higher for male than for female MZ co-twins (56.5 per cent against 50.7 per cent) weakens this interpretation.

If we accept that females develop neurotic reactions

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that are less influenced by genetic factors, there are two explanations. A cultural explanation is that females are more exposed to enviromental pressure because of sex-role stereotypes. This may also explain why neurosis is much more common among females than among males (Dohrenwend and Dohrenwend, 1976). A genetic explanation based upon multifactorial threshold models may say that neurosis is more frequent in females, but has a higher genetic loading in males. Both explanations explain our results, which show a higher hereditary component in males than in females in the determination of neurosis, and are supported by other studies. Coppen and co-workers (1965) found that neuroticism seemed to have a stronger familial tendency in males than in females. Also, in another study by the author, phobic fears seem to be more strongly determined by hereditary factors in males than in females; although this sex difference is not mentioned in the paper (Torgersen, 1979b).

The reason for the higher concordance in MZ than in DZ twin pairs when the probands had been admitted to a mental hospital may be that severe neurotic reactions, which necessitate treatment in in-patient clinics and mental hospitals, are more influenced by genetic factors. Another possibility is that a dramatic admission to an in-patient service influences the co-twin, especially the MZ co-twin, and makes him susceptible to a neurotic breakdown. It may also be that some of the probands admitted to mental hospitals are wrongly diagnosed, and are psychotic. Table V compares the results of this study with results from earlier studies of neurotic twins. It shows that the concordance for MZ as well as DZ pairs is different in different studies. The MZ/DZ ratios in two of the earliest studies are almost the same as in this study, while the MZ/DZ ratios in three other studies are somewhat higher. When the earlier studies are summed up, the MZ/DZ ratio is higher in earlier studies than here.

This study shows that the MZ/DZ ratio was different for different subsamples. Therefore it could be that the different results between the studies are due to differences in the samples. First, let us consider the Maudsley twin study (Shields and Slater, 1966). The sample consisted of twins admitted to in- and out-patient psychiatric services of the Maudsley and the Bethlem Royal Joint Hospital in an eleven-year period, and to Belmont Hospital in a three-year period; all with hospital diagnoses other than epilepsy, brain tumor and psychosis. We are told nothing about how many were admitted to the in- or out-patient services. It may be that a number of these patients would be hospitalized in a mental hospital in Norway. More important, compared to our study, is the sex distribution in the Maudsley twin series. The Maudsley twins consisted of almost the same number of female and male twins. In the present study 30 per cent of probands are males. This is important because our study showed a striking difference between the MZ/DZ ratio in females and males. In fact, the Maudsley twin study showed much the same, if all psychiatric diagnoses of co-twins are included they found a MZ/

TABLE V

The results of studies of neurotic twins after the second world war

	MZ Neurotic co-twins			DZ Neurotic co-twins			MZ/DZ-ratio
Investigation	Number of pairs	Number	%	Number of pairs	Number	%	
Slater (1953)*	8	2	25.0	43	8	18.6	1.3
Ihda (1960)**	20	10	50.0	5	2	40.0	1.3
Braconi (1963)	20	18	90.0	30	13	43.3	2.1
Parker (1964)	10	7	70.0	11	4	36.4	1.9
Shields and Slater (1966)***	62	25	40.3	84	13	15.5	2.6
Total	120	62	51.7	173	40	23.1	2.2
This study	92	39	42.4	137	40	29.2	1.5

*Pairwise concordance method.

**Originally presented in Japanese (Ihda, 1960). Later also presented in German (Ihda, 1965).

***Originally presented in French (Shields and Slater, 1966). The paper was later published in English (Shields and Slater, 1969). The data about neuroses in co-twins are presented in Slater and Shields (1969) and Shields (1973).

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DZ ratio of 1.5 for females and 2.0 for males (nothing is said about the MZ/DZ ratio if only neurosis in co-twins are included). These ratios are little different from ours (1.2 for females and 2.3 for males).

Parker's sample (1964) is a two-year continuation of Shields and Slater's sample of consecutive admissions to Maudsley and Belmont hospitals; and in his small group there are almost as many males as females. Braconi's study (1961) differs from all other studies in that almost all the MZ pairs are concordant. It is, however, difficult to compare the Braconi twin study with the others. For, 66 per cent of the twins were under 15 years of age, and only 12 per cent were over 20. And Rutter (1972) maintains tthat there is no continuity between childhood neurosis and neurosis in adulthood. Many individuals with neurotic problems in childhood are normal in adulthood, others develop schizophrenic reactions later on. Nevertheless if we consider only pairs older than 17 in Braconi's study, we find that three out of five MZ and four out of six DZ pairs are concordant. Among the twin pairs over 17 there is no clear difference in concordance between MZ and DZ pairs. The concordance is negligibly higher for DZ pairs.

Conclusion

This study has shown that any conclusion from twin studies, as to the relative contribution of heredity and environment in the development of neurosis, will depend upon sampling. If the sample consists of predominantly females from out-patient clinics, the conclusions would be that hereditary factors are of no importance. Conversely, if most of the twins are males from mental hospitals, the results would show that neurosis is genetically determined. Consequently, any statement about the relative importance of genetic and environmental factors in the development of neurosis has to be qualified by sex, and the severity, and perhaps also, subtype of neurosis.

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