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Familial Syndrome Patterns in Schizophrenia, Schizoaffective Disorder, Mania, and Depression

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Summary. A major problem with studies in the field of quantitative genetics is that of phenotypical heterogeneity. In particular, such heterogeneities show up in psychiatric investigations: index cases often tend to display more severe forms of disorders than the respective affected relatives. The principal goal of the present investigation was to test the phenotypical equivalence of the two populations of index cases and their affected relatives. Our analyses were based on 269 hospitalized patients with functional psychoses and 350 affected first degree relatives. As opposed to the majority of earlier investigations in which phenotypes were uniquely defined by diagnoses, phenotypes were represented in this study by a list of 22 psychiatric syndromes. Accordingly, multivariate statistical procedures were applied to analyze the intrinsic properties of the empirical lists. The results showed that typical syndrome patterns clearly appeared in both populations and that the phenotypical equivalence of the corresponding population sample sets lay between satisfactory and good. Furthermore, it was possible to select phenotypically homogeneous and reproducible subsets on the basis of the 22 syndromes. These subgroups can be used as basic material to study the genetic modes via current models from quantitative genetics. Nevertheless, our analyses revealed no clear breeding true of either affective disorders or schizophrenia.

Key words: Functional psychoses – Phenotypical equivalence – Multivariate

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Introduction

It is well-established that genetic determinants play an important role in the predisposition to psychiatric disorders. However, a genetic trait which does not fit simple Mendelian modes of inheritance raises serious methodical problems when testing a genetic hypothesis on the basis of large family studies. A major problem in such investigations is phenotypic heterogeneity: affected individuals within a family (as the unit of sampling) often differ not only in terms of severity or age of onset but also in terms of the form in which a disorder presents itself. Moreover, index cases (in most cases hospitalized patients) tend to have a more severe form of the disorder when compared whith their affected relatives. This is due to the selection of probands and because the information derived from relatives is less exhaustive than that of hospitalized patients. As a consequence, the presence or absence of phenotypic similarity cannot be accurately enough decided in a considerable number of secondary cases.

In the past decade, the field of quantitative genetics has focused on these problems. Current methods enable sophisticated analyses of family data to study the modes of transmission of complex traits, as well as the extent to which genetic effects operate or interact with the environment. Accordingly, the underlying models have been specifically designed to subtype affected individuals and to resolve possible heterogeneities. The basic idea of these models is that there exists a single continous variable termed disorder liability which represents all relevant genetic and

nongenetic sources of variation. Based on this assumption, the usual approach of quantitative genetics provides for modelling severity and sex effects, and for the genetic and environmental factors acting additively to determine liability. Models are parameterized in terms of correlations in liability between relatives and in terms of prevalences of males and females. Using Path Analysis, the distribution of liability can be partitioned into components in order to resolve the sources of family resemblence (Cloninger et al. 1978; Elandt-Johnson 1971; Elston and Yelverton 1975; Lalouel and Morton 1981; Rao et al. 1981; Reich et al. 1979, 1980; Rice et al. 1981; Rice and Reich 1983).

Although rapid advancement is currently being made in this field and the applied models have undoubtedly proved useful for testing genetic hypotheses, a weak point of these approaches cannot be overlooked. It originates from the fact that the criteria for diagnosis (diagnosis being used to define phenotypes) are not specific enough and the reliability of a diagnosis varies with the severity of illness and the information collected from the previous history. Consequently, the usefulness of this type of family data and, with that, the admissibility of most applied methods is in doubt. In view of these open questions concerning the validity of any genetic approach to the predisposition to psychiatric disorders, we investigated the structural properties of our family data in order to clear up this central problem.

Because of these methodical problems, we based our analyses of family data not on diagnoses but on a set of 22 syndromes provided by a syndrome check list, thus enabling the application of powerful multivariate procedures such as Multidimensional Scaling (MDS) and Cluster Analysis. The principal goal of the present investigation was to test the phenotypical equivalence of the index cases against their affected relatives. The goals also included (1) the detection of phenotypically homogeneous subgroups, (2) the investigation of their reproducibility, and (3) their impact on genetic hypotheses.

The Zurich Family Study

In 1970, a family study under Scharfetter was started which aimed at the formulation and testing of nosological hypotheses with regard to functional psychoses, including schizophrenia and affective disorders (Scharfetter and Nuesperli 1980). Within the scope of this study, 269 index cases were collected, all of them hospitalized in the psychiatric university hospital of Zurich between 1970 and 1976. Index cases and 350

Table 1. Distribution of ICD8 diagnoses within the samples of index cases and relatives

	Diagnosis (ICD 8)								
	295.0	295.1	295.2	295.3	295.4	295.5	295.6	295.7	295.9
Index cases	0	33	38	69	0	0	0	40	0
Relatives	5	30	71	49	3	4	5	19	7
	Diagnosis (ICD 8)								
	296.0	296.1	296.2	296.3	296.4	296.8	296.9		
Index cases	24	3	35	26	1	0	0		
Relatives	29	5	48	22	0	2	8		
	Diagnosis (ICD 8)								
	297.1	297.9	298.0	298.9	299.0				
Index cases	0	0	0	0	0				
Relatives	2	2	4	1	34				

Legend:
295.0 Simple schizophrenia
295.1 Hebephrenic schizophrenia
295.2 Catatonic schizophrenia
295.3 Paranoid schizophrenia
295.4 Acute schizophrenic episode
295.5 Latent schizophrenia
295.6 Residual schizophrenia
295.7 Schizoaffective disorder
295.9 Unspecified type of schizophrenia
296.0 Involutional melancholia
296.1 Manic-depressive psychosis, manic type
296.2 Manic-depressive psychosis, depressed type
296.3 Manic-depressive psychosis, circular type
296.4 Mania, circular type
296.8 Atypical forms of affective psychoses
296.9 Unspecified type of affective psychoses
297.1 Involutional paraphrenia
297.9 Unspecified paranoid syndromes
298.0 Reactive depressive psychosis
298.9 Reactive psychosis unspecified
299.0 Unspecified psychosis

affected first degree relatives (ascertained from 1747 first degree relatives under risk) were assessed independently by means of a syndrome check list, standardized for clinical records.

Relations Between Features

Family studies are well-known to reveal likely evidence that index cases have a more severe form of a psychiatric disorder when compared with their affected relatives: the relative frequencies of the 22 syndromes derived from the index cases of the present study tended to be considerably above the corresponding frequencies based on their affected relatives. Table 2 reflects this phenomenon impressively.

However, genetic studies ascertaining individuals by the proband method usually select index cases from a hospital population. Thus, the likely evidence shown in Table 2, namely, that psychiatric disorders are more severe in index cases than in their relatives, is actually misleading. The difference between probands and relatives is probably just the result of differing ascertainment. It remains questionable whether index cases and relatives are phenotypically equivalent with regard to psychiatric disorders. Accordingly, any attempt to determine modes of inheritance must take this problem into account. As opposed to earlier approaches in the literature in which phenotypes are uniquely defined by diagnosis, phenotypes were parameterized here in terms of feature vectors[1] comprising 22 items. The question of phenotypical equivalence between the above two populations was reduced to the question of similarity in structure between the respective sets of feature vectors. The method of MDS is a very efficient way of gaining insight into the structural properties of empirical data. Accordingly, the two sets of feature vectors were analyzed separately using this procedure.

In Fig. 1 the resulting two configurations of image points (index cases and relatives) have been plotted onto the plane defined by the three centers of gravity, one for each group of items, (a), (b), and (c). Such a plot reflects the relationships between items in terms of distances; two items are close to each other if they appear together in the same subset of individuals, whereas items which are mutually exclusive are plotted far apart from one another. Accordingly, the relative positions of these items groups to each other give information about combined occurrences: groups (1) and (2) and groups (2) and (3) are more likely to appear together than groups (1) and (3). Although the similarity between both configurations has not been determined analytically, the coincidence between the corresponding plots can easily be detected visually.

[1] A feature vector is the mathematical representation of a list of features (here: syndromes)

Table 2. Relative frequencies of syndromes derived from index cases compared with that derived from their affected relatives. (MC: mood congruent; MIC: mood incongruent)

	Percent frequencies	
	Patients	Relatives
1. Schizophrenic thought disorder	61	40
2. Hypochondriasis	25	11
3. Compulsion/phobia	8	2
4. Delusions/unsystematic (MC)	29	17
5. Delusions/unsystematic (MIC)	62	37
6. Delusions/systematic (MC)	1	0
7. Delusions/systematic (MIC)	1	0
8. Hallucinations/acoustic (MC)	13	5
9. Hallucinations/acoustic (MIC)	44	25
10. Hallucinations/optical (MC)	8	2
11. Hallucinations/optical (MIC)	19	6
12. Hallucinations/other (MC)	8	2
13. Hallucinations/other (MIC)	28	10
14. Disorder of eog consciousness	53	15
15. Depressive syndrome	82	58
16. Manic-like syndrome	37	13
17. Schizophrenic incongruent affect	65	36
18. Inhibited-stuporous	70	30
19. Agitated-excited	85	55
20. Attempted suicide	37	21
21. Amnestic psychosyndrome	5	5
22. Other symptoms	27	11

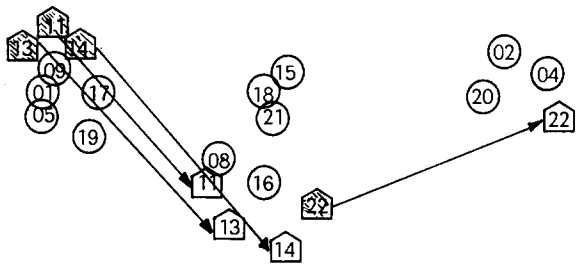

Fig. 1. Distances between items represent mutual relationships with regard to their appearance in individuals (image points are numbered according to Table 2). There are differences between index cases and relatives for items 11/13/14/22 which are plotted twice

Three clearly distinguishable groups of items in both index cases and relatives separately exist:

(a) – (01) schizophrenic thought disorder
  – (05) unsystematic delusions (mood incongruent, MIC)
  – (09) acoustic hallucinations (MIC)
  – (17) schizophrenic incongruent affect
  – (19) agitated excited

(b) – (08) acoustic hallucinations (mood congruent, MC)
– (15) depressive syndrome
– (16) manic-like syndrome
– (18) inhibited-stuporous
– (21) amnestic psychosyndrome
(c) – (02) hypochondriasis
– (04) unsystematic delusions (MC)
– (20) attempted suicide

The items of each group are closely related to each other and appear in the same subsets of individuals in both populations. However, some discrepancies between the two configurations caused by the following 4 items also exist:

– (11) optical hallucinations (MIC)
– (13) other (e.g., haptic, olfactory, gustatory) hallucinations (MIC)
– (14) disorder of ego-consciousness
– (22) other symptoms

Within the population of index cases, items 11, 13, and 14 were more frequently rated in the subgroup of individuals with a dominating schizophrenic symptomatology, whereas, in the relatives, these items appeared together with the affective symptomatology. This findings cannot be explained by the different empirical frequencies of the respective items. On the contrary, the shift of the item other symptoms was mainly due to the fact that it had been rated in only 11% of the relatives as oppposed to 27% within the index cases. In summary, the similarity in structure between the two sets of feature vectors derived from index cases and relatives, respectively, was sufficiently high thus making investigations aiming at phenotypically subgroups within both populations very promising.

Phenotypically Homogeneous Subgroups

Our interest will now focus on the analysis of relations between subjects represented by corresponding feature vectors of syndromes. In this analysis, the dimension of the similarity matrices was identical to the total number of individuals studied. The analysis itself was based on approved multivariate procedures and follows a conception comprising 5 different, interdependent steps:

– computation of similarity matrices by systematic comparisons of individual syndrome patterns by means of a set-theoretical similarity measure. In our case this step resulted in a (269×269) matrix derived from index cases, and a (350×350) matrix derived from affected 1st degree relatives,
– nonmetric multidimensional scaling which yielded a metric representation of the relational data,
– cluster analysis to gain insight into the structural properties of the empirical data. These were described by means of intrinsic groupings,
– definition of prototypes which allowed interpretation of results in terms of psychiatric concepts,
– comparison of prototypes independently derived from the samples of index cases and the samples of affected 1st degree relatives, respectively, in order to test the reproducibility of results.

The definition of similarity between two realizations of a feature vector is undoubtedly the central question of any approach delaing with psychiatric data. This is because one has to define the meaning of coincidence in rare features, coincidence in unspecific/frequent features, and coincidence in features not present.

Obviously, additional information about the structure of the empirical data should be used to design a problem-oriented similarity measure. There is recent evidence that set-theoretical similarity measures can provide powerful solutions to this problem (Levandowski and Winter 1971; Tversky 1977; Stassen 1985). In 1983 we introduced a generalized Jaccard coefficient which is particularly suitable for processing psychopathological data. Moreover, it was especially designed to process features with nonlinear graduations if the certainty of information is better when deciding on the presence of a feature rather than on its graduation (Angst et al. 1983). For our purposes we adapted the simplest version of this set-theoretical approach which is based on rectangular regions. Such a region depends on the graduation of the feature involved and on its specificity (weight). We chose a nonlinear characteristic of the graduation and associated feature not present with a region of unity size times weight. Weights were chosen reciprocal to the empirical frequencies of features, with appropriate modifications at the bounds. Accordingly, the coincidence of patterns in rare features was more highly rated than in frequent and unspecific features.

The ensemble of regions formed a pattern, and two individuals were termed similar with respect to the underlying syndromes if their patterns were well-matched. The formalization of the approach yielded

an elementary similarity function, based on set-theoretical operations:

$$s_{ij}^{(\nu)} = \frac{R_i^{(\nu)} \cap R_j^{(\nu)}}{R_i^{(\nu)} \cup R_j^{(\nu)}} \quad s(m_i, m_j) = \frac{\sum_{\nu} \{R_i^{(\nu)} \cap R_j^{(\nu)}\}}{\sum_{\nu} \{R_i^{(\nu)} \cup R_j^{(\nu)}\}}$$

The term $s_{ij}^{(\nu)}$ denoted the similarity of the ν-th syndrome between two vectors m_i, m_j and $R_k^{(\nu)}$ was a region of the described form (proportional to the graduation and the specificity of the ν-th syndrome). A possible modification of the final similarity measure provided for the inclusion of the significance of complete feature groups as important a priori information by introducing additional weights for appropriately organized feature groups: e.g., the 13 social items of a questionnaire might be half as important as the 10 somatic items. It should be noticed that, because of the set-theoretical nature of the similarity measure, the relation

$$[s(n,m) + s(m,p)] * s(n,p) \geq s(n,m) * s(m,p)$$

did not hold for arbitrary patterns n, m, and p. Therefore, $s(n,m)$ was a so-called nonmetric similarity measure not satisfying the requirements of standard clustering procedures or of graphic space diagrams.

The method of Nonmetric Multidimensional Scaling (NMDS) provides not only for a reduction of redundancy and dimensionality but also for the recovery of metric information from the nonmetric similarity matrices. For the NMDS, the numerical values of the interindividual similarities are not as important as their rank order, and the algorithm searches for a configuration of N image points for which the rank order of the corresponding $N(N-1)/2$ distances is the same as the rank order of the original similarities. Such a configuration is derived by minimizing an appropriate criterion function under constraints (stress). As opposed to the method of Principal Component Analysis or Factor Analysis, where samples are simply projected onto the subspace associated with the N largest eigenvalues, the separation between intrinsic classes is preserved when applying NMDS (Kruskal 1964, 1977; Lingoes 1979).

The principal goal of Cluster Analysis is to discover natural groupings that possess strong intrinsic similarities within empirical data. In recent years, many new ideas have been contributed to this field and a considerable number of different algorithms are available designed to cover various problems. However, according to practical experience as well as to innumerable investigations, feature vectors derived from psychiatric patients are characterized by a distinct individuality on the one hand, and a variety of interindividual similarities on the other. For a cluster analytic approach, this fact implies serious cohesion problems because of the presence of rare observations, of sparse subgroups or outliers within the empirical data, or because of the presence of groupings which merge into one another. In such cases, when clusters do not form essentially compact clouds of nearly equal size that are rather well separated from one another, clustering procedures which create minimum variance partitions by minimizing or maximizing an appropriate criterion function do not yield reasonable results. Indeed, such procedures may impose structure on data rather than finding structure in it.

We studied the criterion for grouping feature vectors derived from psychiatric patients both analytically and experimentally, and found a modified algorithm which aims at clustering around iteratively optimized centers (Meisel 1973). This algorithm provides a powerful solution to the problems described. During optimization, new clusters are created to accommodate samples far from the existing ones, and old clusters are destroyed when their members have been taken over by new constellations. Accordingly, a sample may be assigned to more than one cluster, where the assignment is determined by controlling thresholds rather than by minimization.

So-called prototypes are used to describe the characteristics of clusters in terms of the initial data. In our case the definition of prototypes resulted in typical profiles of the basic 22 syndromes. These syndrome patterns were compared by means of the set-theoretical similarity measure in order to determine the relative position of an element within a cluster as well as the relative positions of clusters to each other (for most analyses the mere membership to an abstract cluster is insufficient information). Moreover, complete cluster solutions were compared by simply comparing the corresponding sets of prototypes.

Results

Because of the nonmetric nature of the set-theoretical similarity measure, we applied MDS to get a metric representation of our nonmetric similarity matrices. The NMDS solution of our data, which will now be discussed, was based on a 10-dimensional image space and was determined with the aid of the diagram "loss function versus dimension". The goodness-of-fit achieved was considered to be good, and increasing the dimension of the image space yielded no substantial improvements. The final configurations of image points derived independently from the two sample sets suggested a partitioning into 6 and 7 natural groupings, respectively, which, however, did not form well-separated, compact clouds. Due to rare observations, sparse subgroups or outliers within the

Table 3. Natural groupings derived independently from index cases and relatives respectively

	Elements		Cluster characterization
	Probands	Relatives	
(1)	14	93	Nonpsychotic depressive syndrome
(2)	—	22	MC-psychotic nonsuicidal depressive syndrome
	35	38	MC-psychotic suicidal depressive syndrome
(3)	9	27	Bipolar nonpsychotic manic-depressive syndrome
(4)	24	28	Bipolar psychotic manic-depressive syndrome, MC-delusions, hallucinations, nonsuicidal
	9	—	Bipolar MC-psychotic manic-depressive syndrome, suicidal
(5)	21	9	Schizobipolar (manic-depressive) MC- and MIC-psychotic syndrome, suicidal
(6)	136	116	Schizophrenic syndrome, thought disorder, MIC-affect, delusions, hallucinations

Retarded and agitated features are present in all clusters

Table 4. Distribution of ICD8 diagnoses within cluster solutions derived independently from index cases and relatives

	Index cases				Relatives			
	295+297	295.7	296+298	298.9+299	295+297	295.7	296+298	298.9+299
(1)	—	—	14	—	16	1	46	30
(2)	—	—	—	—	12	1	8	1
	1	2	32	—	10	—	27	1
(3)	—	1	8	—	2	3	22	—
(4)	2	7	15	—	12	3	11	2
	—	—	9	—	—	—	—	—
(5)	12	8	1	—	2	7	—	—
(6)	116	20	—	—	112	4	—	—

empirical data, 15% of the samples were not part of these groupings and formed a few smaller clusters (<9 elements) whose relevance remains undecided, as well as a number of other isolated elements.

A large but not very compact grouping formed the center of each solution. It comprised about 50% of index cases (33% within the sample of affected relatives) and was identified without difficulty as the schizophrenic group. Though the coincidence of forms dominated within this group, there were a variety of individual variants which could be seen directly from the corresponding interpoint distances within the multidimensional image space. In both solutions the additional groupings (with at least 9 elements) were arranged around these centers.

From a clinical point of view, probands and relatives were essentially partitioned into 6 groupings of special interest. They consisted of (1) classical nonpsychotic depression, (2) MC psychotic suicidal and nonsuicidal depression, (3) bipolar nonpsychotic syndrome, (4) bipolar MC psychotic syndrome, and (5) schizobipolar MC and MIC psychotic syndrome with suicidal symptoms. Finally, there was the (6) classical, clearly schizophrenic cluster. Two affective clusters differed only in the presence or absence of suicidal activity, being present either only in probands or only in relatives. Consequently, it seemed reasonable to include them within the corresponding suicidal or nonsuicidal affective groupings.

Apart from their clinical interpretation, the resolved clusters also differed in terms of cohesion and compactness: samples of the peripheral clusters showed a greater scatter than those which belonged to the center of each of the two solutions. Therefore, samples associated with affective disorders were subdivided into a variety of types whereas the different forms of schizophrenia were not resolved. In prespecifying appropriate initial variances as a priori information, this lack of resolution was eliminated. However, for purposes of defining phenotypically homogeneous subgroups, a further subdivision of samples was not of central interest, rather, the elimination of isolated elements and of sparse subgroups. The distribution of ICD8 diagnoses with respect to the cluster solutions confirmed the clinical interpretation, on the one hand, and reflected the selective mechanism of the method of approach, on the other (Table 4).

The systematic comparison of appropriately arranged prototypes showed a remarkable coincidence between the two independently derived solutions: besides the schizophrenic group (whose correspond-

INDEX CASES (N=269) **CLUSTER: 2. N=136**

	ITEM	MISS	ABS	REL	10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
1	SCHIZOPHRENIC THOUGHT DISORDER	0	125	91.9%	%%
2	HYPOCHONDRIASIS	0	28	20.6%	%%%%%%%%%%
3	COMPULSION AND PHOBIA	0	10	7.4%	%%%%
4	DELUSIONS: UNSYSTEMATIC (MC)	0	18	13.2%	%%%%%%%
5	DELUSIONS: UNSYSTEMATIC (MIC)	0	132	97.1%	%%%
6	DELUSIONS: SYSTEMATIC (MC	0	0	0.0%	
7	DELUSIONS: SYSTEMATIC (MIC)	0	2	1.5%	%
8	HALLUCINATIONS: ACOUSTIC (MC)	0	5	3.7%	%%
9	HALLUCINATIONS: ACOUSTIC (MIC)	0	104	76.5%	%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
10	HALLUCINATIONS: OPTICAL (MC)	0	12	8.8%	%%%%
11	HALLUCINATIONS: OPTICAL (MIC)	0	44	32.4%	%%%%%%%%%%%%%%%%
12	HALLUCINATIONS: OTHER (MC)	0	6	4.4%	%%
13	HALLUCINATIONS: OTHER (MIC)	0	64	47.1%	%%%%%%%%%%%%%%%%%%%%%%%%
14	DISORDER OF EGO-CONSCIOUSNESS	0	110	80.9%	%%
15	DEPRESSIVE SYNDROME	0	102	75.0%	%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
16	MANIC-LIKE SYNDROME	0	49	36.0%	%%%%%%%%%%%%%%%%%%
17	SCHIZOPHRENIC INCONGRUENT AFFECT	0	134	98.5%	%%%
18	INHIBITED-STUPOROUS	0	84	61.8%	%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
19	AGITATED-EXCITED	0	128	94.1%	%%%
20	ATTEMPTED SUICIDE	0	38	27.9%	%%%%%%%%%%%%%%
21	AMNESTIC PSYCHOSYNDROME	0	0	0.0%	
22	OTHER SYMPTOMS	0	29	21.3%	%%%%%%%%%%%

AFFECTED FIRST DEGREE RELATIVES (N=350) **CLUSTER: 1. N=116**

	ITEM	MISS	ABS	REL	10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
1	SCHIZOPHRENIC THOUGHT DISORDER	0	107	92.2%	%%
2	HYPOCHONDRIASIS	0	5	4.3%	%%
3	COMPULSION AND PHOBIA	0	4	3.4%	%%
4	DELUSIONS: UNSYSTEMATIC (MC)	0	3	2.6%	%
5	DELUSIONS: UNSYSTEMATIC (MIC)	0	104	89.7%	%%%
6	DELUSIONS: SYSTEMATIC (MC	0	0	0.0%	
7	DELUSIONS: SYSTEMATIC (MIC)	0	1	0.9%	%
8	HALLUCINATIONS: ACOUSTIC (MC)	0	4	3.4%	%%
9	HALLUCINATIONS: ACOUSTIC (MIC)	0	75	64.7%	%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
10	HALLUCINATIONS: OPTICAL (MC)	0	5	4.3%	%%
11	HALLUCINATIONS: OPTICAL (MIC)	0	17	14.7%	%%%%%%%
12	HALLUCINATIONS: OTHER (MC)	0	3	2.6%	%
13	HALLUCINATIONS: OTHER (MIC)	0	29	25.0%	%%%%%%%%%%%%%
14	DISORDER OF EGO-CONSCIOUSNESS	0	39	33.6%	%%%%%%%%%%%%%%%%%
15	DEPRESSIVE SYNDROME	0	34	29.3%	%%%%%%%%%%%%%%%
16	MANIC-LIKE SYNDROME	0	13	11.2%	%%%%%%
17	SCHIZOPHRENIC INCONGRUENT AFFECT	0	98	84.5%	%%
18	INHIBITED-STUPOROUS	0	49	42.2%	%%%%%%%%%%%%%%%%%%%%%
19	AGITATED-EXCITED	0	99	85.1%	%%%
20	ATTEMPTED SUICIDE	0	13	11.2%	%%%%%%
21	AMNESTIC PSYCHOSYNDROME	0	2	1.7%	%
22	OTHER SYMPTOMS	0	11	9.5%	%%%%%

Fig. 2. Prototypes of the schizophrenic clusters derived independently from index cases *(top)* and affected relatives *(bottom)* (here prototypes are defined by the empirical frequency profiles of items as determined from a cluster analysis)

ing prototypes were identical), 3 other groupings existed with good coincidence, whereas the remaining 2 groupings were still characterized by a satisfactory coincidence (Fig. 2). In other words, despite the different quality of data derived from index cases and relatives, the structural properties of the two sample sets were in good accordance. Typical syndromal patterns appeared sufficiently clear in both populations and suggested a partitioning of cases into groups of phenotypes. Moreover, the overall coincidence of structural properties of the two sample sets implied sufficient phenotypical equivalence of the corresponding populations of index cases and affected relatives.

In order to study the implications of our findings on genetic questions, we cross-tabulated, as a first approach, phenotypes derived independently from index cases and their affected relatives under the constraint of given relations (Table 5). Several findings were impressive. In all proband groups many cases with depressive and schizophrenic syndromes were found. Among relatives of depressives and bipolars one-fourth of secondary cases were classified as schizophrenics. In schizoaffectives, this figure rose to 38%, and in schizophrenic probands to 48%. The load of relatives with depression and bipolar disorder was even greater. A high percentage of affective disorders among relatives was found in all 4 proband groups. The highest frequency was 73% of depressive secondary cases among relatives of depressive probands. The high occurrence of both psychoses independent of the diagnostic grouping of the probands

Table 5. Cross-tabulation of index cases versus relatives according to the cluster solutions derived independently from the corresponding sample sets. Full table kappa test yields $k = 0.131/P < 0.01$; kappa test restricted to depression and schizophrenia yields $k = 0.248/P < 0.01$

n	Probands	Relatives				
		Depressive *n* (%)	Bipolar *n* (%)	Schizobipolar *n* (%)	Schizophrenic *n* (%)	*n*:*n* ratio
49	Depressive	62 (73)	15 (17)	2 (2)	20 (24)	85:26
42	Bipolar	26 (46)	9 (16)	2 (4)	13 (23)	56:37
21	Schizobipolar	18 (49)	4 (11)	—	14 (38)	37:63
136	Schizophrenic	71 (43)	24 (15)	4 (2)	79 (48)	165:83

Ratio: schizophrenic/# depressive + bipolar (relatives)
(%): may exceed 100 because clusters are not mutually exclusive

raises the hypothesis of a great overlap on the syndromal level between the two major psychoses schizophrenia and affective disorder. There was no clear breeding true, even if there was some homotypical preponderance (73%) of depression among relatives of depressive probands and, of schizophrenic syndromes (48%) among relatives of schizophrenic probands.

The finding that there was no breeding true of schizobipolar illness was also impressive. There was not a single secondary case classified as schizobipolar again, 49% were depressive, 11% bipolar, and another 38% schizophrenic. In terms of morbidity for schizophrenia among relatives, the schizobipolar families were in an intermediate position between the two major functional psychoses. This finding is in line with other studies. In the last column of Table 5 we computed the ratio of the number of secondary cases among relatives for schizophrenia versus the total number of those with affective disorder. The ratio showed a systematic trend getting higher and higher from depression via bipolar and schizobipolar illness to schizophrenia. If one uses familial concordance as a validator, the fact that the higher ratio was for schizophrenia suggested that the schizophrenia cluster was the most specific, thus placing schizophrenia on the top of any hierarchy that might be used for the functional psychoses. This finding confirms the trend found in an analysis based on ICD diagnostic groups and morbid risk figures of the same sample (Angst and Scharfetter 1985).

At first glance, the lack of a clear breeding true was disappointing, but really reflected an unbiassed assessment of the data present in clinical records of probands and relatives. However, a substantial loss of information may blur the picture, and it is certainly true that the probands selected by psychiatric hospitalization were on the average sicker than their affected relatives. Therefore, the latter should have a milder and less distinct psychopathological picture. The fact remains, however, that in the two clearest diagnoses, depression and schizophrenia, there was good evidence of breeding true.

Conclusions

As opposed to the majority of earlier investigations in which phenotypes were uniquely defined by diagnoses, we analyzed our family data on the basis of a set of 22 syndromes. According to this approach, phenotypes were represented by different combinations of the 22 features. Within the scope of our investigation, we aimed at a central problem of quantitative genetics: are the two populations of hospitalized index cases and affected relatives phenotypically equivalent in regard to psychiatric disorders? This problem is of particular interest because all subsequent investigations into intrafamilial phenotypical ressemblence essentially depend on an answer to this question.

Although the relative frequencies of the 22 syndromes derived from the index cases were considerably above the corresponding frequencies of their affected relatives, the structural analysis of the relations between features revealed clear evidence that the syndromal patterns within the two sample sets were indeed comparable. Thus, a detailed analysis of the mutual relations between individuals in order to determine phenotypically homogeneous subgroups was indicated. This latter analysis was performed independently for the two populations of index cases and affected relatives, so that the reproducibility of resulting groupings could be tested. In consequence of this reproducibility, all major subgroups of the two sample sets were mutually correspondent, and the two structures as a whole were in good accordance. With regard to genetic questions these results implied:

(1) Despite the different qualities of information derived from hospitalized index cases and affected relatives, typical syndromal patterns

appeared sufficiently clear in both populations.

(2) The phenotypical equivalence of the two populations of index cases and their affected relatives was found to be satisfactory to good. Thus, genetic approaches to the predisposition of psychiatric disorders are correct and useful.

(3) It is possible to select phenotypically homogeneous and reproducible subgroups on the basis of appropriate sets of psychiatric features by means of the above methods.

(4) A first analysis by simply cross-tabulating index cases versus relatives according to the correspondent phenotypes revealed no clear breeding true of affective disorders on the one hand and of schizophrenia on the other, but there was more overlap between the two major psychoses (on a purely descriptive level) than generally stressed. Adding course variables to the cross-tabulations, e.g., chronic versus episodic may result in better separation and more breeding true. This would be a useful next step.

(5) The resulting subgroups can be used as a basic material in order to study the modes of genetic effects by means of current models from quantitative genetics.

In conclusion, the major point made in this paper is that as far as genetic questions are concerned, typical syndromal patterns appear sufficiently clear in both populations of index cases and their affected relatives and the phenotypical equivalence of the two populations is satisfactory to good. Accordingly, the effects of different data qualities which usually arise in connection with large family studies on psychiatric disorders, will not bias genetic studies, provided phenotypes are appropriately defined. However, this investigation, while providing a basis for the analysis of genetic determinants in the predisposition to psychiatric disorders, still requires extension on the problem of intrafamilial resemblance.

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