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The Impact of the Endogenous Subtype on the Familial Aggregation of Unipolar Depression

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Summary. The endogenous/non-endogenous distinction of unipolar major depression is widely accepted, as is the family study approach to the validation of diagnostic distinctions. Rates of affective disorders were examined in 689 first-degree relatives of 184 patients with unipolar major depression and were compared with 312 first-degree relatives of 80 healthy controls. Only unipolar depression and alcoholism were more common in families of depressed probands compared with families of healthy controls. As a variety of diagnostic definitions of endogenous depression have been proposed, probands and relatives were diagnosed in a polydiagnostic manner. None of the five diagnostic definitions of endogenous depression was able to identify patients with an increased familial risk of unipolar depression.

Key words: Major depression – Unipolar depression – Endogenous depression – Polydiagnostic classification – Alcoholism

Introduction

The familial aggregation of psychiatric disorders, syndromes, and symptoms is a major clue to the aetiology of these conditions. Diagnostic discriminations propose the hypothesis that different diagnostic classes are different in their aetiological conditions. As a consequence, different diagnostic classes should be different in their familial pattern of occurrence. If this requirement is applied to subtypes of affective disorders, two hypotheses may be tested: (1) the subtype itself is more common in families of probands with that subtype as compared with probands with other subtypes of affective disorders; (2) a particular subtype is associated with an increased (or decreased) prevalence of depressive syndromes – not differentiated by subtypes – in families.

Among the affective disorders the distinction between unipolar and bipolar affective disorders has been found to fit both hypotheses, especially the first one. Most investigators have also found that relatives of bipolar probands are at a higher risk of major depression compared with relatives of unipolar probands (Gershon et al. 1982; Rice et al. 1987).

The familial pattern of occurrence of endogenous depression has received less attention and is less clear. Whereas early family studies found endogenous depression to be more common only in families of probands with this disorder (Stenstedt 1952, 1966) but not in families of probands with neurotic depression, recent family studies could not replicate this observation. With regard to the second hypothesis, some investigators have found patients with endogenous depression to have higher rates of depressive illness in their families than patients with non-endogenous depression (Perris et al. 1982; Leckman et al. 1985; McGuffin et al. 1987 for severe depression in relatives), at least for individual definitions of "endogenous depression". The most extensive study in this field did not find a difference between endogenous and non-endogenous depression with respect to familial loading (Andreasen et al. 1987). Furthermore, it was found that neurotic depression is associated with an increased rate of alcoholism in families compared with endogenous depression (Winokur 1985); this finding is at variance with more recent family studies (e.g. Andreasen et al. 1987).

These controversial findings justify a re-evaluation of the validity of the concept of endogenous depression using familial aggregation as the criterion. Families of 184 patients with unipolar depression and of 80 healthy controls were extracted from a recently conducted comprehensive family study and were tested for both of the two aforementioned hypotheses with regard to the endogenous/non-endogenous distinction.

Investigation of the impact of the endogenous/non-endogenous distinction on the familial aggregation is complicated by the fact that there is no agreement on an adequate criteria-based definition of endogenous depression. Therefore, a polydiagnostic approach (Berner and Katschnig 1985) combining the various approaches is most appropiate. As there have been proposed more than ten definitions of endogenous depression up to now, we selected for this family study five definitions in order to limit the scope of the interviews: endogenous type by

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Research Diagnostic Criteria (RDC; Spitzer et al. 1972), melancholia by DSM-III (APA 1980), autonomous depression as defined by the Yale Criteria (Leckman et al. 1984), endogenomorphic axial syndrome as defined by the Vienna Research Criteria (Berner et al. 1983), and endogenous versus neurotic depression defined by the Newcastle Scale (Carney et al. 1965). These five definitions represent very different concepts: the last mentioned definition combines longitudinal aspects such as premorbid personality, recurrency and duration, and symptoms revealed during the depressive episode.

The first four definitions exclusively refer to the symptomatology during an episode; diurnal variations are obligatory for the definition of endogenomorphic depression by the Vienna Research Criteria, whereas anhedonia and loss of reactivity are obligatory for the DSM-III diagnosis of melancholia; the Yale Criteria for autonomous depression allocate high weight to delusional depression. The two hypotheses mentioned will be tested for these five definitions of endogenous depression.

Subjects and Methods

Probands

A total of 625 consecutively admitted inpatients of the university psychiatric hospital in Mainz with at least one living and available first-degree relative (aged between 20 and 70 years) was interviewed in a semi-structured manner (SADS-LA; Mannuzza et al. 1986); the SADS-LA provides diagnoses according to RDC (Spitzer et al. 1972) and DSM-III (APA 1980). We prefer to use RDC as the basic diagnostic system for defining unipolar major depression, as patients with mood-incongruent psychotic features and patients with hypomania or cyclothymia are not considered to suffer from a unipolar depression; according to the published family studies, both conditions are likely to identify groups of patients with a particular familial pattern of psychiatric disorders. Of the patients, 184 received the lifetime RDC diagnosis of unipolar major depression.

One hundred and nine subjects with at least one living and available first-degree relative (older than 17 years) were recruited in the general population with the assistance of a marketing company. This sample was matched to the patient sample for sex, age, educational status and area of residence. Recruitment was based on a random sampling procedure stratified by age, sex, educational status, and area of residence. These 109 subjects were interviewed by the SADS-LA for axis I and the SCID-II for personality disorders (Spitzer and Williams 1987). Twenty-nine subjects received a lifetime RDC diagnosis (including minor affective disorders and anxiety disorders) or a diagnosis of DSM-III personality disorders. The 80 subjects without any lifetime diagnosis were regarded as control probands.

Table 1. Sample of families of probands with unipolar major depression and of healthy probands

Proband type		
Unipolar major depression	Probands:	
	number	184
	sex ratio (m%)	41.2%
	age (mean)	49.6 years
	Relatives:	
	total number	689
	number living	609
	number interviewed	514
	sex ratio (m%)	48.3%
	age (mean)	44.9 years
Healthy controls	Probands:	
	number	80
	sex ratio (m%)	55.9%
	age (mean)	36.6 years
	Relatives:	
	total number	312
	number living	262
	number interviewed	221
	sex ratio (m%)	45.4%
	age (mean)	39.9 years

Relatives

All living first-degree relatives (older than 17 years) of both proband groups (as far as they could be located) were asked to participate personally in the family study; they were asked to come to the hospital for interview; if they were not able to come to the hospital, we offered to visit the relatives at their home. Travel expenses were covered by research funds of the hospital. In this way about 80% of the living first-degree relatives could be personally interviewed (Table 1).

The relatives were interviewed by administering the SADS-LA and the SCID-II blind to the diagnosis and the status of the proband. Furthermore, interviewed relatives were asked for the psychiatric history of other family members (excluding the proband) – especially those who were not available – by using the family history method (Mannuzza et al. 1985). This method provides RDC diagnoses for episodes of affective disorders (without subtyping by endogenous features), psychotic disorders, and alcoholism/drug abuse.

Psychopathological and Diagnostic Assessment

Diagnostic assessment was based on RDC. Diagnoses were achieved by application of the best estimate procedure as proposed by Leckman et al. (1982): the information provided by structured interviews, family history method, and, in the case of patients, medical records, was transformed into a final RDC diagnosis by two experienced psychiatrists. Probands and relatives were assessed independently of each other.

Further, unipolar major depression was subclassified by endogenous and non-endogenous depression in a polydiagnostic manner including the endogenous type (RDC), the melancholia subtype (DSM-III), the endogenous versus neurotic depression as defined by the Newcastle Scale (Carney et al. 1965), the Yale Criteria for autonomous depression (Leckman et al. 1984), and the endogenomorphic axial syndrome as defined by the Vienna Research Criteria (Berner et al. 1983). We selected these five diagnostic manuals mainly because they have been most frequently used in previous family studies (Andreasen et al. 1986; Leckman et al. 1984). As no structured interview for polydiagnostic lifetime diagnoses is currently available, the SADS-LA was extended by those criteria defined in the Newcastle Scale, The Yale Criteria, and in the Vienna Research Criteria for endogenomorphic depression, which are not included in the SADS-LA. The criteria for subtyping major depression by endogenous type as defined by RDC and by melancholia as defined by DSM-III are tapped by the original SADS-LA interview. All subtyping procedures refer to the most severe episode of major depression.

The subtyping of depressive episodes by endogenous depression was limited to directly interviewed patients, for the information that can be obtained by the family history method was not precise enough to subclassify depressive episodes in patients who were not directly interviewed.

Table 2. Lifetime morbid risk (%, age corrected) for unipolar depression in families by proband type

Proband type		Morbid risks in first-degree relatives for:			
		Minor or major depression (unipolar)	Major depression, unipolar (2 weeks' duration)	Major depression, unipolar (4 weeks' duration)	Major depression, unipolar (recurrent)
Unipolar major depression (all subtypes)		30.7	21.6	14.9	10.3
RDC	Major depression				
	endogenous type	33.0	23.4	15.6	11.3
	without endogenous type	28.4	20.1	14.1	9.0
DSM-III	Major depression				
	with melancholia	32.9	21.8	16.3	11.6
	without melancholia	28.8	21.4	13.6	9.3
Newcastle Scale	Endogenous depression	32.6	23.9	17.4	8.9
	Neurotic depression	28.8	19.9	12.1	11.1
Yale	Autonomous depression	33.7	24.0	15.3	13.9
	Non-autonomous depression	29.0	20.3	14.2	8.5
Vienna Research Criteria	Endogenous depression	29.9	23.7	14.9	8.9
	Non-endogenous depression	31.9	19.4	14.8	11.3
Healthy controls		15.7	9.8	4.9	3.8

Data Analysis

Lifetime morbid risks in relatives reported in this paper were corrected for age by the Strömgren-Weinberg method; the age at onset distribution was modelled by a log normal distribution as proposed by Gershon et al. (1982).

Comparisons between subtypes were performed by survival analysis (Cox multivariate proportional hazard model); simultaneous models were used (Lee 1980). This model was used to identify those subtypes of major depression that predicted an increased risk of major depression in the relatives controlled for age, sex, and interview status. The dependent variable was time to illness in relatives (age at onset of the disorder for affected relatives and age as a censored variable in non-affected relatives). The method of subtyping to be tested for its predictive power was introduced as an independent variable. Covariates were age and sex in probands and relatives; if relatives who were not personally interviewed were included in the analysis, the interview status (interviewed versus family history only) was introduced as a further covariate. The proportional hazard ratios might be considered as relative risks.

Results

Morbid Risks of Unipolar Depression in Families

The age-corrected lifetime prevalence of unipolar major depression was 21.6% in first-degree relatives of probands with the same disorder and 9.8% in relatives of healthy controls and 11.2% in relatives of unscreened controls (Table 2). Subdividing the relatives by sex and interview status reveals the following figures: the age-corrected lifetime prevalences of unipolar major depression were 14.6% in directly interviewed male relatives of probands with unipolar major depression and 7.5% in the analogue group of relatives of healthy controls; 28.9% in directly interviewed female relatives of probands with unipolar major depression and 14.2% in the analogue group of relatives of healthy controls; 12.7% in not directly interviewed male relatives of probands with unipolar major depression and 6.8% in the analogue group of relatives of healthy controls; 26.0% in not directly interviewed female relatives of probands with unipolar major depression and 11.1% in the analogue group of relatives of healthy controls.

The ratio of hazards (relative risk) for major depression among first-degree relatives of depressed probands compared with relatives of healthy controls was 2.0; the relative risk was 1.9 if relatives of unscreened controls were the comparison group; these ratios are controlled for the effects of age and sex of relatives and probands and the relatives' interview status. Both rates indicate a significantly increased risk of unipolar depression in the families of the patient group ($P \leq 0.01$, one-sided).

The lifetime prevalences of broader and more stringent definitions of unipolar depression are also presented in Table 2. The relative risks (hazard ratios controlled for the effects of relatives' and probands' age and sex and the relatives' interview status) of first-degree relatives of depressed probands compared with relatives of healthy controls for these various diagnoses were: 1.8 for all types of unipolar depression (major, minor, intermittent depression) and 2.7 for recurrent major depression; both ratios of hazards indicate increased risks for relatives of patients as compared with relatives of controls ($P \leq 0.01$, one-sided).

Familial Risks of Unipolar Depression by Proband Subtype

Table 2 also presents the lifetime prevalences of various types of unipolar depression by endogenous and non-endogenous subtypes of probands defined by various sets

Table 3. Lifetime morbid risk (%, age corrected) for bipolar disorders and alcoholism in families by proband type

Proband groups		Morbid risks in first-degree relatives for:		
		Bipolar II disorder (major depression with hypomania)	Bipolar I disorder (mania)	Alcoholism
Unipolar major depression (all subtypes)		1.5	1.0	10.6
RDC	Major depression			
	endogenous type	2.0	1.0	10.6
	without endogenous type	0.7	1.0	10.5
DSM-III	Major depression			
	with melancholia	1.7	1.2	10.5
	without melancholia	1.1	0.8	10.6
Newcastle Scale	Endogenous depression	2.0	1.2	10.7
	Neurotic depression	1.2	0.8	10.4
Yale	Autonomous depression	1.6	1.4	12.0
	Non-autonomous depression	1.3	0.4	9.7
Vienna Research Criteria	Endogenous depression	2.0	2.1	6.5
	Non-endogenous depression	0.9	0.0	12.9
Healthy controls		1.0	0.6	7.8

of criteria. Among the 184 probands with unipolar major depression, 123 were diagnosed as endogenous type by RDC, 71 as melancholia by DSM-III, 80 as endogenous depression by the Newcastle Scale, 59 as autonomous depression by the Yale Criteria, and 98 as endogenomorphic axial syndrome by the Vienna Research Criteria. The hypothesis that particular subtypes of probands are characterized by an increased familial risk of unipolar depression is examined next.

Whatever diagnostic definition for subtyping probands was used, endogenous as well as non-endogenous depression showed a significantly increased familial risk of all types of unipolar depression: all relative familial risks of patient subgroups compared with healthy controls (ratios of hazards controlled for sex and age in relatives and probands and for the interview status in relatives) were significantly different from 1.0 (indicating balanced risk) for all definitions of unipolar depression in relatives. Endogenous and non-endogenous types of probands were not substantially different in their degree of familial loading, no matter which definition of endogenous depression was used: the relative risks of unipolar major depression in first-degree relatives of probands with endogenous depression compared with relatives of probands with non-endogenous depression varied between 1.4 (Newcastle Scale) and 1.0 (Vienna Research Criteria), neither of which is significantly ($P \leq 0.05$, one sided) different from 1.0 (balanced risk). Also, no significant deviation from the balanced risk was found if the relative risks of other types of unipolar depression were examined, no matter which definition of endogenous depression was used.

Morbid Risks of Bipolar and Non-Affective Disorders in Families

Schizophrenic and schizoaffective disorders were not found to be more common in relatives of probands with unipolar major depression as compared with relatives of healthy controls: 0.8% of the relatives of probands with unipolar depression were diagnosed as having schizophrenia or a schizoaffective disorder and the same percentage of relatives of healthy controls received one of these two diagnoses. As the rates for schizophrenia and schizoaffective disorders are rather low in the sample under study, they have not been broken down by the endogenous/non-endogenous distinction.

Bipolar disorders were slightly more common in families of probands with unipolar depression (1.0% bipolar I disorder and 1.5% bipolar II disorder in relatives of patients with unipolar major depression and 0.7% bipolar I disorder and 1.0% bipolar II disorder in relatives of healthy controls). The relative risks (ratios of hazards controlled for sex and age of probands and relatives and for the relatives' interview status) of relatives of probands with unipolar depression compared with relatives of healthy probands were calculated for various definitions of bipolar disorders: for bipolar I disorder 1.6 and for bipolar II disorder 1.4; none of these ratios indicates a significant deviation from the balanced risk (1.0).

Table 3 indicates that alcoholism and/or drug abuse were more common in relatives of probands with unipolar major depression (age-corrected lifetime risk 10.6%) compared with relatives of healthy controls (7.8%) or

with relatives of unscreened controls (8.2%). The rate of alcoholism was threefold higher in male than in female relatives; this ratio was valid in both comparison groups. Controlling for probands' and relatives' age and sex and the interview status in relatives, a trend toward an increased risk of alcoholism and/or drug abuse was observed in families of depressive probands compared with families of controls (ratio of hazards 1.6 compared with families of healthy controls, $P = 0.05$, and 1.5 compared with families of unscreened controls, $P = 0.06$). However, the increased familial risk of alcoholism/drug abuse in depressive probands was mainly due to the comorbidity of alcoholism/drug abuse and unipolar major depression in probands: the age-corrected lifetime risk of alcoholism/drug abuse was 15.0% in families of probands with both disorders and 8.3% in families of probands with unipolar major depression and without a history of alcoholism/drug abuse.

Familial Risks of Bipolar and Non-Affective Disorders by Proband Subtype

Subtypes of depressed probands defined by the endogenous/non-endogenous distinction were compared with regard to the rate of bipolar disorders and alcoholism/drug abuse in their families (Table 3). The hypotheses tested are that (a) endogenous depression is associated with an increased risk of bipolar disorders in families; (b) non-endogenous depression is associated with an increased risk of alcoholism/drug abuse in families.

With regard to the familial risk of bipolar disorders it is obvious from Table 3 that the Vienna Research Criteria fit hypothesis (a): no bipolar I disorder was found among relatives of probands with the endogenomorphic depressive axial syndrome. However, owing to the low base-rate of bipolar disorder none of the relative risks of relatives of endogenous depressive probands compared with relatives of non-endogenous depressive probands was found to be significantly ($P \leq 0.05$, one-sided) different from 1.0 for any type of bipolar disorder.

Alcoholism/drug abuse was less common among the relatives of patients with endogenomorphic depression as defined by the Vienna Research Criteria when compared with relatives of depressive patients who do not match these criteria (ratio of hazards: 0.5, $P \leq 0.05$, one-sided); after controlling for the comorbidity with alcoholism/drug abuse in the probands, the relative risk approaches the balanced risk (ratio of hazards 0.9, $P > 0.10$). The other four definitions of endogenous depression were not able to discriminate groups of patients with different familial rates of alcoholism/drug abuse (relative risks varying between 0.9 and 1.1).

Subtype Diagnosis Among Depressed Relatives

Major depression in directly interviewed relatives was subclassified by the various definitions of endogenous depression; not directly interviewed relatives were excluded from this analysis. The hypothesis was tested that "endogenous depression" is aggregating in families.

Table 4. Lifetime morbid risk (%, age corrected) of subtype diagnoses in interviewed relatives by proband subtype

RDC

Diagnosis in probands:	Diagnosis in relatives: MDD endogenous type	MDD without endogenous type
MDD endogenous type	9.1	14.6
MDD without endogenous type	6.9	13.3

DSM-III

Diagnosis in probands:	Diagnosis in relatives: MDD with melancholia	MDD without melancholia
MDD with melancholia	5.1	16.9
MDD without melancholia	4.2	17.3

Newcastle Scale

Diagnosis in probands:	Diagnosis in relatives: endogenous depression	neurotic depression
endogenous depression	9.8	14.4
neurotic depression	8.9	11.2

Yale Criteria

Diagnosis in probands:	Diagnosis in relatives: autonomous depression	non-autonomous depression
autonomous depression	4.9	19.8
non-autonomous depression	3.0	17.8

Vienna Research Criteria

Diagnosis in probands:	Diagnosis in relatives: endogenous depression	non-endogenous depression
endogenous depression	12.8	11.0
non-endogenous depression	8.6	10.6

MDD, Major depressive disorder

Table 4 refers to those relatives of probands with unipolar depression who also suffered from unipolar major depression and presents the extent to which the subtypes diagnosed in depressed probands and depressed relatives were concordant. Neither of the diagnostic definitions of endogenous depression revealed a trend for a subtype-specific familial aggregation; all chi-square tests for association provided non-significant results (chi-square $P \leq 0.05$, two-sided).

Discussion

Rates of Affective Disorders in Families Compared with Other Family Studies

The lifetime prevalence rate of affective disorders observed in this family study is grossly comparable with the figures obtained by other recent family studies using similar methods of recruitment and case identification: 21.6% for unipolar major depression (minimum duration 2 weeks); 14.9% if the minimum duration is 4 weeks; 1.0% for bipolar I disorder and 1.5% for bipolar II disorder were found in this study. The corresponding figures in the NIMH Collaborative Study (Andreasen et al. 1987) were 28.8% for unipolar depression (minimum duration 2 weeks), 0.6% for bipolar I disorder and 2.9% for bipolar II disorder; the corresponding figures in the Yale Family Study (probands with severe major depression) were: 17.5% for unipolar depression (minimum duration 4 weeks), 2.1% for bipolar disorder; the corresponding figures in Gershon's et al. study (1982) were: 16.6% for unipolar major depression (minimum duration 4 weeks) and 2.9% for bipolar disorder. The rates in the relatives of healthy controls were 9.8% (unipolar major depression) and 1.4% (bipolar disorder) in our study compared with 5.6% (unipolar disorder) and 1.8% (bipolar disorder) in the Yale Family Study and with 5.8% (unipolar depression) and 0.5% (bipolar disorder) in Gershon's family study. These figures are different from other studies. A recent family study by McGuffin et al. (1988) used the PSE and the CATEGO classification, and nearly 40% of the relatives of probands with unipolar depression received the same diagnosis. More recent family studies mainly conducted in Europe before the era of structured clinical interviews and criteria-based and broadly accepted diagnostic schedules obtained substantially lower risks of affective disorders in relatives of probands with unipolar depression. These discrepancies can be explained by different methods of collecting the information on the relatives and of case identification in patient and non-patient samples.

The lifetime prevalences of alcoholism and/or drug abuse are also grossly comparable with the rates reported by recent family studies in the United States using similar approaches to recruitment and diagnoses. We found 7.8% lifetime rate in relatives of healthy controls, the Yale family study reported 9.0% (Merikangas et al. 1985) and Gershon et al. (1982) reported 4.2% for alcoholism and 2.6% for drug abuse. In families of probands with unipolar depression 10.6% were diagnosed as alcoholism/drug abuse (lifetime) in our study; the corresponding percentage in the Yale Family Study was 14.4%; in the study of Gershon et al. it was 6.6% for alcoholism and 0.6% for drug abuse; and in the NIMH Collaborative Study it was 15.0% for alcoholism and 5.8% for drug abuse. Furthermore, our results are in agreement with those of Merikangas et al. (1985) in that the increased risk of alcoholism in families of probands with unipolar depression can be explained by the co-occurrence of alcoholism and depression in probands and the familial aggregation of alcoholism.

The Impact of the Endogenous Subtype on Familial Loading

Endogenous depression did not have a significantly higher morbid risk of unipolar depression in first-degree relatives, no matter which definition was used for defining endogenous depression and no matter which definition was used for identifying unipolar depression in relatives. This conclusion is in agreement with a series of results reported in other recent studies, which also relied on criteria-based diagnoses. These studies (Yale Family Study, Leckman et al. 1984; NIMH Collaborative Study, Andreasen et al. 1986; a study using the family history method without direct interviews of relatives, Zimmerman et al. 1986) generally reported negative findings with regard to the impact of the endogenous/non-endogenous distinction on the risk of unipolar depression in families.

Andreasen et al. (1986) used four ways of subtyping probands with unipolar major depression by the endogenous versus non-endogenous distinction: the RDC, the DSM-III, the Newcastle and the Yale criteria; they failed to find any significant difference between the endogenous and the non-endogenous proband type with regard to the morbid risks of directly interviewed relatives. However, Andreasen et al. (1986) found that the Newcastle endogenous depressive probands have a tendency to show an increased familial risk of recurrent unipolar depression. Based on this finding they speculated that longitudinal factors that are included as criteria in the Newcastle Scale predict longitudinal factors in first-degree relatives. Our family study was not able to confirm this hypothesis: neither the original finding of Andreasen et al. (1986) could be replicated nor could the Newcastle endogenous depression be observed to show any tendency to "breed true".

Leckman et al. (1984) used the same set of criteria as Andreasen et al. with the exception of the Newcastle Scale. The endogenous/non-endogenous distinction as defined by the RDC – and the DSM-III – criteria could not be supported by different risk figures of unipolar depression in families. However, the Yale criteria for autonomous depression were able to identify a proband group with an increased risk of unipolar depression compared with probands with non-autonomous depression. In agreement with Andreasen et al. (1986) we were not able to confirm this finding of the Yale Family Study. However, we found recurrent depression to be more frequent among relatives of patients with autonomous depression compared with relatives of probands with non-autonomous depression. Although this difference failed to achieve significance, it is noteworthy as Andreasen et al. (1986) reported a similar trend.

Zimmerman et al. (1986) tested four definitions of endogenous depression (among them RDC, DSM-III, Newcastle Scale) for their ability to identify a proband group with an increased risk of unipolar major depression (as compared with the proband group with non-endogenous major depression). This authors could not confirm this hypothesis for any of the definitions of endogenous depression; moreover, they reported the un-

expected finding that the familial risk of unipolar depression was significantly higher in probands with non-endogenous depression compared with those with endogenous depression when using the Newcastle Scale. Although we agree with Zimmerman et al. (1986) that endogenous depression is not associated with a significantly increased risk of unipolar depression in families, we were not able to find the reverse relationship reported by Zimmerman et al. (1986). The comparability of this study with our family study is limited by differences in collecting diagnostic information on relatives: Zimmerman et al. were only using the family history method and did not directly interview the majority of living relatives.

Winokur (1984) and subsequently Zimmerman et al. (1986) found alcoholism and drug abuse to be more frequent among relatives of patients with neurotic depression compared with relatives of patients with endogenous depression. We could not replicate Zimmerman's finding when defining neurotic depression by the Newcastle Scale. Other definitions – mainly the Vienna Research Criteria – were more successful in discriminating patients with from those without a family history of alcoholism; alcoholism was less common in families of patients with endogenous depression. However, this finding is merely due to the comorbidity between alcoholism and non-endogenous depression; as alcoholism is familial, the risk of alcoholism is increased in families of patients with the additional diagnosis of alcoholism. Therefore, the criterion of "family history of alcoholism" has only a low degree of validity.

With the exception of Leckman et al. (1980) this is the first study intending to subclassify not only probands, but also affected relatives for endogenous depression in a polydiagnostic manner. There is agreement between these studies that neither the RDC nor the DSM-III nor the Newcastle definition of endogenous depression nor the Yale Criteria for autonomous depression identify a breeding true condition (i.e. a subtype is significantly more common among affected relatives of probands with this subtype compared with affected relatives of affected probands without this subtype).

Limitations

For the interpretation of these findings one has to be aware of the general limitations of family studies; the interview data were collected in a retrospective manner. This limitation might be especially relevant for subtype designations that are based on the most severe episode, which may have occurred long ago. The possibility cannot be excluded that the observed low degree to which "endogenous depression" bred true is due to the low sensitivity of the retrospective method. Furthermore, owing to the same limitation the number of symptoms or the duration of impairment reported for a remote episode of illness might be underestimated and, as a consequence, the minimum number of symptoms required for matching the diagnosis of major depression might be missed. However, this point is less likely to be critical, as differences among subtypes could also not be obtained when using a broader concept of unipolar depression, which requires only a minimum of two depressive symptoms and a 1-week duration for case identification in relatives.

Conclusion

In general, the familial rates of affective disorders observed in the family study are in agreement with family studies recently conducted in the United States using similar methods of recruitment, psychopathological and diagnostic assessment; apparently, the impact of the differences between American and central European populations on the prevalences and the familial aggregation of affective disorders is of limited importance.

The familial patterns of affective disorders observed in this study are heterogeneous: both highly loaded families and sporadic depression are frequent. The endogenous/non-endogenous distinction of unipolar depression was not able to discriminate probands who differ by their familial laoding. No matter which of the five definitions of endogenous depression under study is chosen, endogenous and non-endogenous depression cannot be descriminated by different patterns of familial aggregation, at least if the comorbidity with non-affective disorders in probands is taken into account. Furthermore, there was no evidence for endogenous depression to breed true in families. Combining these findings with those reported by Leckman et al. (1984) and Andreasen et al. (1986) it is unlikely that the cross-sectional pattern considered to be characteristic of endogenous depression has any validity if familial aggregation is the criterion. Features related to previous course and personality are only included in the Newcastle Scale and might lose their validity if they are combined with less valid signs included in this scale. Therefore, course-related features need to be further investigated in order to identify subtypes associated with a distinct pattern of familial aggregation.

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