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Familiality of Psychotic Disorders: A Polynosologic Study in Multiplex Families

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Introduction: **Phenotype definition of psychotic disorders has a strong impact on the degree of familial aggregation. Nevertheless, the extent to which distinct classification systems affect familial aggregation (ie, familiality) remains an open question. This study was aimed at examining the familiality associated with 4 nosologic systems of psychotic disorders (DSM-IV, ICD-10, Leonhard's classification and a data-driven approach) and their constituting diagnoses in a sample of multiplex families with psychotic disorders.** ***Methods:*** **Participants were probands with a psychotic disorder, their parents and at least one first-degree relative with a psychotic disorder. The sample was made of 441 families comprising 2703 individuals, of whom 1094 were affected and 1709 unaffected.** ***Results:*** **The Leonhard classification system had the highest familiality (h^2 = 0.64), followed by the empirical (h^2 = 0.55), DSM-IV (h^2 = 0.50), and ICD-10 (h^2 = 0.48). Familiality estimates for individual diagnoses varied considerably (h^2 = 0.25–0.79). Regarding schizophrenia diagnoses, Leonhard's systematic schizophrenia (h^2 = 0.78) had the highest familiality, followed by latent class core schizophrenia (h^2 = 0.74), DSM-IV schizophrenia (h^2 = 0.48), and ICD-10 schizophrenia (h^2 = 0.41). Psychotic mood disorders showed substantial familiality across nosologic systems (h^2 = 0.60–0.77). Domains of psychopathology other than reality-distortion symptoms showed moderate familiality irrespective of diagnosis (h^2 = 0.22–0.52) with the deficit syndrome of schizophrenia showing the highest familiality (h^2 = 0.66).** ***Conclusions:*** **While affective psychoses showed relatively high familiality estimates across classification schemes, those of nonaffective psychoses varied markedly as a function of the diagnostic scheme with a narrow schizophrenia phenotype maximizing its familial aggregation. Leonhard's classification of psychotic disorders may be better suited for molecular genetic studies than the official diagnostic systems.**

Key words: schizophrenia/affective psychoses/familial coaggregation/heritability/nosology/classification

Introduction

The nosologic structure of psychotic disorders has been subject of substantial interest and debate since Kraepelin[1] proposed his fundamental synthesis and dichotomy between dementia praecox and manic-depressive illness. Afterwards, several authors pointed out to the existence of a number of nonschizophrenic nonaffective psychoses (NSNAP) that could not easily be accommodated within this dichotomy,[2] and as a consequence several schemes for classifying psychotic disorders have been developed over time.[3–5] The debate about the best way to classify psychotic disorders continues and a recent review of the evidence using a range of validating criteria including familial-genetic risk factors concluded that "there is insufficient evidence of the etiology and pathophysiology to base group membership on causality".[6]

While there is a substantial genetic contribution to the aetiology of psychotic disorders,[7–11] and family-genetic factors have traditionally been regarded as a cornerstone of psychiatric nosology,[12,13] authors disagree about the phenotype(s) definition(s) best correlating with the familial-genetic underpinnings of psychotic disorders. As an example of this, polydiagnostic studies of schizophrenia have impressively demonstrated the variability in familial liability with differing diagnostic criteria.[14–16] A major research challenge is, therefore, to detect phenotypes that maximize the phenotype–genotype correlation as a first step in unravelling the molecular genetic underpinnings of psychotic disorders. A useful approach to this endeavour is to examine different classification schemes

and compare their predictive validity regarding familial aggregation. A number of previous studies have examined the familiality or heritability of specific diagnoses of psychotic disorders according to different diagnostic criteria,[5,8,16,17] but no one has comparatively examined the familiality/heritability estimates for whole nosologic systems and their constituting diagnoses, thus in the current study we address this question by using a polynosologic approach. In the same way that the polydiagnostic approach consists of applying different diagnostic criteria for a given disorder,[18,19] the polynosologic approach consists of applying different sets of nosological systems to the same group of subjects in order to compare their validity indicators.[4]

The main goal of the present study was to examine the degree of familial aggregation, also known as familiality/transmissibility[20] or multifactorial/generalized heritability,[21] of 4 nosologic systems and their constituting diagnoses in multiply affected families with psychotic disorders. The nosologic systems examined were the DSM-IV,[22] the International Classification of Diseases, tenth edition (ICD-10),[23] the Leonhard classification of "endogenous" psychoses,[24] and an empirically driven classification. The Leonhard classification holds a unique position in psychiatric nosology by comprising 5 main categories of psychotic disorders defined on the basis of different patterns of symptoms, long-term course and outcome: unipolar psychoses, bipolar psychoses, cycloid psychoses, unsystematic schizophrenias, and systematic schizophrenias (see supplementary material for a brief account of this nosologic system). This classification has shown good reliability[25] and important clinical-genetic validity.[26–28] Lastly, we used latent class analysis (LCA) to empirically test for the existence of discrete patients groups in our study population, because this approach has yielded promising results for identifying genotype–phenotype correlations in psychotic disorders.[29–31] Two secondary aims of the study were to examine the familiality relationships of specific psychotic disorders to the reference categories of schizophrenia and bipolar disorder, and to explore the familiality of psychopathology domains irrespective of diagnostic categories. With these goals in mind we sought to determine the nosological system, specific diagnoses and domains of psychopathology that could maximize the phenotype–genotype correlation.

Methods

Ascertainment

Probands were identified through the psychiatric case register of Navarra (Spain)[29] as patients who had attended the psychiatric facilities, either as inpatients or outpatients, from a defined catchment area of 350,000 inhabitants between 1990 and 2014. They were recruited through systematic screening, those with a lifetime diagnosis of a functional psychotic disorder and a first-degree relative with the same diagnosis being eligible for inclusion in the study. Between 2008 and 2014 the eligible probands were contacted and invited to participate in the study.

Proband's inclusion criteria were: age >15 years, residing in Navarra, meeting a lifetime DSM-IV criteria for a functional psychotic disorder (DSM-IV schizophrenia criterion A symptoms), having at least one first-degree relative with a DSM-IV functional psychosis and willing to participate, as well as both biological parents being willing and able to participate. The latter criterion was required to delineate the relationships between the affected members of each family.[32] Of the eligible probands, 10% were unavailable or refused to participate such as 13% of their affected and 17% of their unaffected first-degree-relatives. All families were Caucasian and of European ancestry. The project was approved by the ethics committee of the Regional Health Service of Navarra and written informed consent was obtained from all study participants or their legal representatives.

Subjects

The present study is based on a total of 441 families comprising 2703 individuals, of whom 1094 were affected and 1709 unaffected (table 1). The average of subjects per family was 6.98 (SD = 2.56, range 3–17) and the average of affected subjects per family was 2.80 (SD = 1.18; range 2–8). Of the 441 families described thus far, 312 (70.7%) had 2 members affected, 75 (17.0%) had 3 members affected, 37 (8.4%) had 4 members affected, and 18 (5.9%) had 5 or more members affected. The proportion of 2- and 3-generation families was 92.4% and 7.6%,

Table 1. Sample Description (N = 2703)

	Probands	Mothers	Fathers	Siblings	Sons
No.	441	441	441	1175	205
Age, mean (SD), years	38.1 (12.7)	61.9 (10.8)	63.7 (10.3)	39.0 (11.1)	26.8 (8.4)
Education, mean (SD), years	10.3 (3.5)	8.6 (2.8)	9.1 (3.1)	10.4 (3.2)	11.0 (3.9)
Male, %	54.9	0	100	50.3	52.2
Affected, %	100	39.7	21.5	28.0	26.3
Onset of illness, mean (SD), years	24.5 (9.5)	25.6 (12.8)	24.9 (13.6)	24.7 (10.7)	20.1 (7.4)
Time from onset, mean (SD), years	13.6 (9.6)	25.4 (12.6)	24.7 (13.9)	14.2 (11.4)	10.3 (9.4)

respectively. In the case of 3-generation families the index proband was selected from the intermediate generation in order to connect subjects from the other 2 generations according to their first-degree relatedness with the index proband.

Probands and affected relatives did not significantly differ in their DSM-IV diagnoses excepting for delusional disorder (probands = 2.3%, relatives = 7.4%, $P < 0.001$) (supplementary table S1). Of the 1094 affected subjects, 216 (19.7%) had never been hospitalized and 65 (6%) had never been in psychiatric care, all the latter being relatives.

Phenotyping

All participants underwent face-to-face psychiatric assessments using the Comprehensive Symptoms and History Schedule (CASH).[33] The CASH is a semi-structured interview designed to provide a comprehensive information base concerning clinical features psychotic and mood disorders. Because the information base is broad, the schedule is not wedded to a specific diagnostic system thus permitting clinicians and researchers to make diagnoses using a wide range of systems, including the DSM-IV and ICD-10 classifications. Diagnoses from the Leonhard classification were made using both the clinical information gathered through the CASH and the operational diagnostic criteria developed by Leonhard himself.[34] Demographics, premorbid adjustment, age at illness onset, mode of onset, duration of illness, number of months spent in hospital, course and the global assessment of functioning were all assessed with the history section from the CASH. Occupational and social functioning over the past year was assessed with the Disability Assessment Schedule.[35] Subjects meeting DSM-IV criteria for schizophrenia were also rated for deficit features using the Schedule for the deficit syndrome.[36]

Interviews were conducted by experienced psychiatrists or clinical psychologists with established reliability (>0.80) for CASH global symptom ratings and diagnoses.[37] Full blind assessment within families was not possible, since not all family members could be assessed by different raters. Information for rating symptoms and diagnoses was derived from all available sources of information, including direct diagnostic interviews, family history reports and medical records. Two senior researchers (VP, MJC) through a best estimate procedure using all the available records arrived at independent diagnoses, reached a consensus and determined the final diagnoses. Such final diagnoses were blind performed to subject identity and group status (proband, relative) in about 75% of the pedigrees.

Statistical Methods

The latent class typology was derived from 14 CASH ratings of affected subjects using the Latent Gold software.[38] Severity scores were dichotomized by a median split before inclusion in the analysis and latent cluster models specifying from 1 to 10 classes were fitted after adjustment for the non-independence of data expected in our sample. The best fitting model was selected on the basis of the Bayesian Information Criterion (BIC),[39] clinical interpretability and resemblance with other LCA solutions using a similar methodology.

After defining the phenotype in accordance with the 4 classification systems, concordances among classification schemes and among specific diagnoses were examined using the lambda and kappa statistic, respectively.

To clinically characterize the 4 nosologic systems, and more specifically to further validate the LCA solution, the distribution of relevant demographic and clinical variables across classification systems was examined. For continuous measures, a 1-way analysis of the variance was used followed by multiple comparisons with the Bonferroni test. For categorical variables, we used χ^2 2×4–6 analyses that, if significant, were followed by a series of 2×2 χ^2 analyses.

Lastly, familiality was examined by means of generalized linear mixed models.[40] Familiality of the phenotypes defined by nosologic systems was examined using mixed-effects multinomial logistic regression, and familiality of specific diagnoses and domains of psychopathology was examined using mixed-effects binary logistic regression. All models included age and gender as fixed effects, and family membership as a random effect. A robust sandwich estimator was used to account for the non-normality of the data. Two models were run for each variable: a null model incorporating only the fixed effects ($h^2 = 0$), and a general model with the addition of family membership as a random effect. Log likelihoods for each model were compared using the Wald chi-squared statistic with 1 *df*. For clustered data, the mixed-effects model assumes that data within clusters (ie, families) are dependent. The degree of dependence is jointly estimated along with the regression coefficients of the fixed effects. The degree of dependence attributable to families is characterized by the between-families variance, which is estimated in the mixed model. In a design such as ours, an estimate of familiality (h^2) indicates the portion of phenotypic variance accounted for by family membership. This estimated variance represents the population variance of family effects, and therefore our results pertain to the population of families of which this sample is representative.

As variance components are nonnegative by definition, a 1-tailed *P*-value was applied as is typical for this test,[41] and adjusted Wald confidence intervals were calculated.[42] *P*-values of familiality analyses were corrected for multiple comparisons using the family-wise Bonferroni method.[43] Apart from LCA, all other statistical analyses were performed using IBM SPSS Statistics 20.[44,45]

Due to the low prevalence rate of DSM-IV and ICD-10 diagnoses other than schizophrenia and affective psychoses, they were merged into a single group of NSNAP

within each nosologic system. Using the DSM-IV system, and to examine whether specific disorders belonged to the schizophrenia or bipolar spectrum, we examined the effect on familiality estimates of adding specific disorders to the reference categories of schizophrenia and bipolar disorder.

Results

Latent Class Analyses

Using the criteria of statistical fit (BIC parameter), clinical interpretability and resemblance with previous studies,[29,30] the 6-class solution was considered as the best fitting one (supplementary table S2).

Characterization of Classification Systems

The level of diagnostic concordance among classification schemes varied substantially. The highest concordance was observed between DSM-IV and ICD-10 ($\lambda = 0.86$), the Leonhard's system had moderate concordance levels with the other systems (λ between 0.40 and 0.56), and the empirical system had moderate concordance levels with the other systems (λ between 0.55 and 0.59). Specific concordance values for the 3 diagnoses represented in the 4 nosologies are presented in supplementary table S4. The demographic and clinical characteristics of the subjects across nosologic systems and specific diagnoses are presented in supplementary tables S5–S8.

Familiality Estimates

All 4 nosologic systems showed significant familial aggregation (table 2). The highest familiality estimate was obtained with Leonhard's classification ($h^2 = 0.64$) followed by the empirical ($h^2 = 0.60$), DSM-IV ($h^2 = 0.50$), and ICD-10 ($h^2 = 0.48$) systems. Non-overlapping confidence intervals indicated that Leonhard's classification showed significantly more familiality than the DSM-IV and ICD-10 classifications and that the empirical classification showed significantly more familiality than the ICD-10 classification.

Table 2. Familiality Estimates for 4 Nosologic Systems of Psychotic Disorders

Nosologic System	h^2	95% CI	SE	Z	P
DSM-IV	0.50	0.46–0.55	0.04	12.53	<0.001
ICD-10	0.48	0.44–0.52	0.04	12.02	<0.001
Leonhard	0.64	0.60–0.69	0.04	16.83	<0.001
Latent class analysis	0.60	0.55–0.66	0.04	15.71	<0.001

Note: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; ICD-10, International Classification of Diseases, tenth edition.

Except for the ICD-10 NSNAP, all other diagnoses from the different nosologies showed significant evidence of familial aggregation, although their magnitude varied considerably across specific diagnoses (table 3). Regarding schizophrenia phenotypes, the most familial one was Leonhard's systematic schizophrenia ($h^2 = 0.78$) followed by latent class core schizophrenia ($h^2 = 0.74$), DSM-IV schizophrenia ($h^2 = 0.48$), and ICD-10 schizophrenia ($h^2 = 0.41$). Both Leonhard's systematic schizophrenia and latent class core schizophrenia showed significantly more familial aggregation than schizophrenia defined according to official classifications.

Affective psychoses showed substantial familiality across nosologic systems: h^2 between 0.64 and 0.77 for psychotic bipolar disorder and between 0.60 and 0.71 for psychotic depression. As a rule, within each nosologic system the intermediate group(s) of psychoses showed lower familiality estimates than the extreme groups of schizophrenia and affective psychoses.

We repeated the analyses including pedigrees' size, age structure, and number of affected members as covariates in addition to age and gender, and the results were very similar (supplementary table S9).

Combining diagnoses of DSM-IV schizophrenia or bipolar disorder with other DSM-IV specific diagnoses showed that only delusional disorder increased the familiality of schizophrenia and just marginally (table 4). Familiality estimates for diagnostic-free symptoms and syndromes showed that whereas delusions and hallucinations had no significant evidence of familiality ($h^2 = 0.05$ and 0.16, respectively), bizarre behavior, inappropriate affect, negative symptoms and mania showed substantial familiality (h^2 between 0.41 and 0.52). Noteworthy, the deficit syndrome of schizophrenia displayed the highest familiality among domains ($h^2 = 0.66$) (table 5).

Discussion

Main Findings

This study examined for the first time the familial aggregation of alternative nosologic systems and their constituting diagnoses in a broad sample of multiple affected families with psychotic disorders. In this article, we assume that familiality—phenotypic resemblance among first-degree relatives—is a useful standard that can guide the selection of phenotypes that will be most effective in defining genetically homogeneous forms of psychotic disorders.[46] Furthermore, the primary advantage of our approach is that we have estimated the familiality of specific disorders in the context of the boundary disorders, the whole nosologic system and across nosologic systems.

We found that the way in which psychotic disorders are classified has a strong impact on familiality, because estimates varied greatly across both nosologic schemes and specific diagnoses. The nosologic system best capturing familial effects was Leonhard's classification followed

Table 3. Familiality Estimates for 4 Nosologic Systems and Specific Diagnoses of Psychotic Disorders

Nosologic System	Specific Diagnosis	h^2	95% CI	SE	Z	P
DSM-IV	Schizophrenia (n = 395)	0.48	0.42–0.56	0.10	4.73	<0.001
	Nonschizophrenic nonaffective psychoses (n = 294)	0.29	0.23–0.37	0.10	2.91	0.004
	Psychotic bipolar disorder (n = 239)	0.64	0.56–0.74	0.14	4.68	<0.001
	Psychotic depression (n = 166)	0.60	0.50–0.72	0.16	3.74	<0.001
ICD-10	Schizophrenia (n = 419)	0.41	0.35–0.48	0.09	4.34	<0.001
	Nonschizophrenic nonaffective psychoses (n = 270)	0.23	0.18–0.31	0.10	2.38	0.017[a]
	Psychotic bipolar disorder (n = 232)	0.65	0.56–0.76	0.14	4.58	<0.001
	Psychotic depression (n = 161)	0.65	0.55–0.77	0.16	4.03	<0.001
Leonhard	Systematic schizophrenia (n = 283)	0.78	0.69–0.88	0.14	5.48	<0.001
	Unsystematic schizophrenia (n = 234)	0.39	0.31–0.49	0.13	3.02	0.002
	Cycloid psychosis (n = 230)	0.60	0.51–0.72	0.15	3.94	<0.001
	Psychotic bipolar disorder (187)	0.77	0.67–0.89	0.16	4.68	<0.001
	Psychotic depression (n = 160)	0.67	0.57–0.79	0.16	4.07	<0.001
Latent class analysis	Core schizophrenia (n = 224)	0.74	0.64–0.84	0.15	4.77	<0.001
	Non-core schizophrenia (n = 203)	0.38	0.30–0.48	0.14	2.75	0.006
	Nonschizophrenic nonaffective psychosis (n = 141)	0.55	0.43–0.69	0.19	2.81	0.005
	Schizoaffective disorder (n = 155)	0.57	0.47–0.69	0.17	3.32	0.001
	Psychotic bipolar disorder (n = 208)	0.71	0.61–0.82	0.16	4.59	<0.001
	Psychotic depression (n = 163)	0.71	0.61–0.83	0.17	4.32	<0.001

Note: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; ICD-10, International Classification of Diseases, tenth edition.
[a]No longer significant after Bonferroni correction ($P > 0.012$).

Table 4. Effects on Familiality Estimates of Adding DSM-IV Categories of Psychotic Disorders to the Reference Diagnoses of Schizophrenia and Bipolar Disorder[a]

		h^2	95% CI	SE	Z	P
Schizophrenia spectrum[b]	Schizophrenia + schizophreniform disorder	0.48	0.42–0.55	0.10	4.84	<0.001
	Schizophrenia + delusional disorder	0.49	0.43–0.56	0.10	5.00	<0.001
	Schizophrenia + brief psychotic disorder	0.39	0.34–0.46	0.09	4.33	<0.001
	Schizophrenia + schizoaffective disorder	0.39	0.34–0.45	0.09	4.44	<0.001
	Schizophrenia + psychosis NOS	0.43	0.38–0.50	0.09	4.77	<0.001
	Schizophrenia + psychotic bipolar disorder	0.05	0.03–0.10	0.05	1.12	0.262
	Schizophrenia + psychotic depression	0.20	0.16–0.25	0.06	3.19	0.001
Psychotic bipolar spectrum[c]	Psychotic bipolar disorder + schizophreniform disorder	0.51	0.43–0.59	0.12	4.08	<0.001
	Psychotic bipolar disorder + delusional disorder	0.37	0.30–0.45	0.11	3.36	0.001
	Psychotic bipolar disorder + brief psychotic disorder	0.53	0.46–0.62	0.12	4.29	<0.001
	Psychotic bipolar disorder + schizoaffective disorder	0.58	0.50–0.66	0.12	4.76	<0.001
	Psychotic bipolar disorder + psychosis NOS	0.51	0.45–0.58	0.10	5.09	<0.001
	Psychotic bipolar disorder + psychotic depression	0.42	0.35–0.50	0.11	3.91	<0.001

[a]It was assumed that the added diagnosis pertained to the corresponding diagnosis spectrum if familiality estimate of the combined diagnoses increased that of the reference category.
[b]Reference category schizophrenia, $h^2 = 0.48$ (95% CI = 0.42–0.56).
[c]Reference category psychotic bipolar disorder, $h^2 = 0.64$ (95% CI = 0.56–0.74).

by the empirical, DSM-IV, and ICD-10 classifications. The superiority of Leonhard's and empirical classifications over the official systems appears to be due to the fact that they take into account the course of the disorders. Within each system, schizophrenia and affective psychoses had the highest familiality levels. Furthermore, whereas familiality estimates for affective psychoses were substantial and fairly similar across nosologies, those for nonaffective psychotic disorders varied considerably, and more specifically, a narrow schizophrenia phenotype maximized the familial aggregation of the disorder. This pattern of findings highlights the influence of phenotype definition on familiality estimates of psychotic disorders and raises some doubts about the familial-genetic validity of nonaffective psychotic disorders as defined in the official classification systems.

Combining DSM-IV categories of psychotic disorders produced mainly negative findings regarding the adscription of specific NSNAP to the schizophrenia or bipolar spectrum in that only delusional disorder appeared to

Table 5. Familiality Estimates for Diagnostic-Free Lifetime CASH Symptom and Syndromes and the Deficit Syndrome in DSM-IV Schizophrenia Subjects

	h^2	95% CI	SE	Z	P
Delusions (n = 925)[a]	0.05	0.03–0.07	0.03	1.74	0.082
Hallucinations (n = 526)[a]	0.16	0.12–0.21	0.07	2.35	0.018[b]
Positive formal thought disorder (n = 488)[a]	0.22	0.18–0.28	0.07	3.07	0.002
Bizarre behavior (n = 378)[a]	0.43	0.36–0.50	0.11	4.08	<0.001
Inappropriate affect (283)[a]	0.45	0.38–0.54	0.12	3.73	<0.001
Catatonic behavior (n = 363)[a]	0.33	0.27–0.40	0.10	3.32	0.001
Negative syndrome (n = 257)[c]	0.52	0.44–0.61	0.13	3.98	<0.001
Manic syndrome (n = 327)[d]	0.41	0.34–0.49	0.11	3.84	<0.001
Major depressive syndrome (n = 553)[d]	0.31	0.26–0.36	0.07	4.19	<0.001
Deficit syndrome (n = 85)[e]	0.66	0.53–0.81	0.20	3.22	0.001

Note: CASH, comprehensive assessment of symptoms and history; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition.
[a]Defined as feature present at the level of mild or higher.
[b]No longer significant after Bonferroni correction ($P > 0.005$).
[c]Defined as all 4 CASH negative symptom global ratings present at the level of mild or higher.
[d]Defined as fulfilling the DSM-IV criteria for mania or major depression.
[e]Assessed only in DSM-IV schizophrenia subjects.

pertain to the schizophrenia spectrum. Diagnostic-free symptoms and syndromes showed low familiality levels for typical psychotic symptoms such as delusions, hallucinations and positive formal thought disorders, and moderate to substantial familiality levels for bizarre behavior, inappropriate affect, catatonia, mania, and the negative syndrome, which suggests that these psychopathological domains appear to retain important familial-genetic information irrespective of diagnostic categories. Of particular interest, and in line with previous findings in high-density families,[47] was the substantial familial aggregation of the deficit syndrome, which was even higher than that of consensus schizophrenia definitions.

Given that this is the first study comparing levels of familial aggregation across different nosologies of psychotic disorders, our results are not readily comparable with any in the literature. However, and considering that our familiality estimates measure the maximal effect of genes,[21] some aspects of our results merit comments in relation to previous findings. Overall, our familiality estimates for DSM-IV or ICD-10 schizophrenia and bipolar disorder are more consistent with family studies reporting heritabilities of ~60%,[10,11] than twin studies reporting heritabilities of ~80%.[8,9,48] Our familiality estimates for psychotic depression were somewhat higher than those reported for major depression,[49] which could be explained by the higher heritability of psychotic depression relative to the nonpsychotic form.[50] In contrast to twin studies showing a substantial correlated liability between bipolar disorder and major depression,[48,51] and in line with family studies showing a lack of cross-transmission,[52] we found that merging these diagnoses into a single category of affective psychosis resulted in decreasing familial aggregation regarding individual disorders, although this finding does not necessarily contradict a common liability for both types of psychotic mood disorders.

Polydiagnostic studies of familial aggregation in psychotic disorders have mainly focused on schizophrenia and provided mixed results. Whereas some studies concluded that broadly defined schizophrenia is more familial/heritable,[53,54] others favor a restrictive phenotype,[54,55] and yet others support a "middle-of-the-road" phenotype.[14–58] Though these differences may be due to a number of methodological factors, our findings clearly support the higher familial validity of narrow schizophrenia definitions, which is in line with recent studies that using the polygenic risk score have found higher molecular validity for the more severe schizophrenia forms.[59,60]

Implications

The most obvious implication of our study would be to implement the Leonhard's nosology in studies addressing the familial/genetic underpinnings of psychotic disorders. This, however, is not a realistic option mainly due to the complexity of Leonhard's classification scheme. Given that the main differences among classifications involved nonaffective psychotic disorders, and particularly schizophrenia, a pragmatic option would be to define within DSM schizophrenia a subgroup of subjects characterized by enduring symptoms, which would be very close to Leonhard's concept of systematic schizophrenia. While DSM-IV and ICD-10 NSNAP groups appeared to show poor familial aggregation, Leonhard's cycloid psychoses and the broad latent class of schizoaffective disorder showed substantial familiality, which suggests that these diagnoses may be adequate phenotype candidates for genetic research. On the other side, our findings support the "domains of psychopathology"

approach[61] as an alternative and complementary strategy to diagnostic categories, in that some domains—particularly those consisting of disorganization and negative symptoms—appear to convey relevant familial/genetic information.[32,62] Given the substantial familiality of negative symptoms across diagnostic classes, and particularly deficit symptoms within schizophrenia, they appear to be chiefly useful phenotypic targets for genetic research.

In further refining the phenotypes that maximize their correlation with the genotype, polygenic risk scores will probably become an important tool in the near future. Polygenic scores, which aggregate the effects of thousands of DNA variants from genome-wide association studies, have the potential of providing individual-specific estimates of genetic liability.[63] In this regard, a recent study revealed that a considerable proportion (~50%) of the association with familial aggregation of schizophrenia/psychosis was mediated through polygenic risk scores.[64] Thus, polygenic scores appears to be a promising instrument to examine the genetic validity of a great number of phenotypes including behavioral traits, domains of psychopathology, and diagnoses.[65] Anyway, a phenome-wide scanning approach[66] to the psychoses phenotype using fine-grained rating of symptoms and signs, domains of psychopathology, clinical features including course of the disorder, and refined clinical diagnoses will be necessary to determine those phenotypes conveying familial/genetic information. More specifically, the domain of psychopathology model for enduring negative symptoms of schizophrenia could also be applied to other psychopathological manifestations such as reality-distortion, disorganization, catatonia, and cognitive symptoms.

Limitations

Several limitations need to be considered when interpreting our findings. First, our familiality estimates quantify the strength of familial resemblance and represents the percentage of variance, ie, due to all familial effects including additive genetic and those of the familial environment, thus we could not distinguish between genetic and environmental contributions to familial aggregation. However, while everything familial is not genetic, variables that are not familial are unlikely to be genetically informative. Further, most of the familial resemblance of psychotic disorders is due to genetic factors,[8,10] although heritability, as an index of genetic influence, may be of limited explanatory power unless viewed in the context of interaction with environmental factors.[67,68] Second, our ascertainment strategy may result in cohort effects due to the selection of family members willing to participate, which may have limited recruitment of more severely disturbed or socially isolated patients. Nevertheless, any such effect should be relatively weak because the Health Service of Navarra is public and highly accessible as most people with psychoses have contact with psychiatric services.[69] Third, because the selection of families with high familial/genetic loading, extrapolation of our results to more general populations of psychotic disorders should be done cautiously and the family estimates need to be interpreted as pertaining to our population of psychotic patients from multiplex families. This limitation, however, does not necessarily invalidate the comparison among familiality estimates within this sample, because our primary goal was examining these estimates across nosologies and diagnoses rather than estimating the familial risk in the general population. Four, inclusion of patients was based on DSM-IV criteria, which prioritizes the different diagnostic systems. Lastly, total blindness to proband's diagnosis was not possible and this could be an important factor influencing diagnosis. Because these limitations, our results should remain tentative until they can be replicated in other high-density families and preferably in a population-based sample of psychotic disorders.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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