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Using family studies to understand comorbidity

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Summary. Methods for investigating the nature of comorbidity of two psychiatric disorders, where each disorder is known to be familial, using family studies are described. The methods consist of using a study design which include relatives of four proband groups, namely probands with the pure form of each disorder, probands with the comorbid form of the disorders, and control probands who have neither of the disorders. Disorders in relatives were classified to parallel the disorder categories in probands. Patterns of transmission of these disorders between probands and relatives hypothesized under various models of comorbidity, and statistical methods for formally testing these hypothesis are described. These methods are illustrated, by applying them to data from a recent family study to investigate the relationship and the cause of comorbidity between panic disorder and major depressive disorder.

Key words: Comorbidity – Family studies – Familial transmission

Introduction

The term "comorbidity" is commonly used in the psychiatric literature to refer to patients with two or more co-occurring psychiatric disorders at some time in their life. With the extensive documentation in recent years of the existence of high comorbidity of psychiatric disorders in numerous studies (Caron and Rutter 1991; Maier and Merikangas 1992; Maser and Cloninger 1990), this phenomenon has emerged as a topic of major practical and theoretical significance, raising fundamental questions regarding the nature of these comorbid disorders. The most significant questions posed by the co-occurrence of two disorders in the context of genetic epidemiology are related to the number of discrete diseases involved. Specifically, as noted by Coryell et al. (1988), the frequent co-existence of two disorders raises the following questions: 1. Are they two separate disorders? 2. Is there only one primary disorder, in which symptoms suggesting the other disorder are only epiphenomena? 3. Is the comorbid form a distinct disorder unrelated to the component disorders? Or lastly, 4. Is there only one underlying disorder, with the various forms being different manifestations of this single disorder?

The most commonly employed methods used for investigating these issues are epidemiologic, longitudinal and family studies. Each of these designs has its unique strengths and weaknesses when used for this purpose [Klein and Riso (1993)]. The focus of this article will be on methods of using family studies to understand the phenomenon of comorbidity.

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The utility of family studies in investigating comorbidity

It is now widely recognized that to investigate the comorbidity of two disorders, which we shall designate A and B, we should ideally have four proband groups: probands with a pure form of disorder A (i.e. A without B), probands with a pure form of disorder B (i.e. B without A), probands with comorbidity between A and B, and control probands who have neither A nor B. In previous studies, the first-degree relatives were usually categorized by the presence or absence of disorder A (with or without disorder B), and the presence or absence of disorder of B (with or without disorder A). Patterns of familial transmission were assessed by comparing the rates of A, the rates of B, and the association between A and B in relatives of the several proband groups. More recently, however, it has been recognized by some investigators [Weissman et al. (in press); Klein and Riso (1993)] that this method of categorizing relatives disorders does not fully exploit the design of the study. These investigators have shown that categorizing the relative disorders to parallel the proband disorders, generally results in patterns of familial transmission being more clearly revealed. Additionally, categorizing relative dis-

Table 1. Patterns of risks in relatives, by proband diagnoses, under hypothesized models of comorbidity

Model	Diagnosis of relatives	Patterns of rates by proband group
1. Comorbidity due to A encompassing B	A	A = AB > B = C
	AB	A = AB > B = C
	B	B > AB = A = C
2. A and B are two separate disorders, (comorbid form is heterogenous)	A	A > AB > B = C
	AB	AB > A, B = C
	B	B > AB > A = C
3. Comorbid condition is a third independent disorder	A	A > AB = B = C
	AB	AB > A = B = C
	B	B > A = AB = C
4. The pure and comorbid condition are different phases or alternative expressions of the same disorder	A	A = AB = B > C
	AB	A = AB = B > C
	B	A = AB = B > C

orders in this manner enables us to use more rigorous statistical methods for testing competing hypotheses regarding the nature of the association between the two disorders.

Klein and Riso (1993) have given a detailed description of eight potential patterns of findings which can be generated using family studies, with four proband categories and the four parallel categories of relative disorders. Their discussion and the work of Weissman et al. (in press) show that the phenomenon of comorbidity is far more complex than had been initially perceived, and that previous approaches to the analysis of comorbidity have not addressed the full complexity of this phenomenon. Here, we will discuss only those patterns that are relevant to questions regarding the number of discrete diseases involved, which we consider to be of primary significance in the context of genetic epidemiology.

Following the notation of Klein and Riso (1993) these patterns are outlined in Table 1. The first column lists the hypothesized relationship between the two disorders. The second column lists which dependent variable (i.e. the condition in the relative) is being considered. Column three presents the predicted relationship among the independent variables, i.e. the expected ordering of the proband group under the hypothesized model, with respect to the rates of disorder in relatives. For example, Model 1 hypothesizes that there is only one primary disorder A and when A and B occur together B is an epiphenomenon of A. The patterns of rates of the pure form of A, the comorbid form of A and B, and the pure form of B obtained under this model for the different proband groups are shown in the third column. That is, the rates of the pure form of A will be higher in relatives of groups with the pure form of A and the comorbid form AB when compared to relatives of the control group, while relatives of probands with the pure form of B will have rates similar to that of control probands. Similarly, the rates of the comorbid form AB will be higher in relatives of proband groups with the pure form of A, and the comorbid form AB when compared to the control proband group; rates in relatives of probands, with the pure form of B will be similar to relatives of the control probands. The rates of the pure form of B will be higher in relatives of probands with the pure form of B when compared to relatives of control probands; rates in relatives of comorbid probands and probands with the pure form of A, will however have rates similar to control probands.

Model 2 hypothesizes that A and B are two separate disorders. However, since it has already been established that A and B together occur in proportions greater than that due to chance alone, it is hypothesized that the comorbid form is a heterogenous mixture which comprises both "atpyical" forms of both disorders A and B as well as some cases where the two disorders occur together by chance. Under this hypothesis (contrary to that which is stated in Klein and Risso) it is expected that rates of comorbidity in relatives of comorbid probands will be higher than rates in relatives of probands with the pure form of A and probands with the pure form of B. In addition, rates of comorbidity in relatives of the latter two proband groups should be higher than rates of comorbidity in relatives of control probands. Patterns of rates in relatives of the pure forms of A and B by proband group are as shown in column three and are self-explanatory.

In Model 3 it is hypothesized that the comorbid condition is a third, independent condition. Implicit in this hypothesis is the assumption that the pure forms of A and B are also independent disorders. Thus, we expect to find rates of the pure form of A in relatives of probands with the pure form of A to be higher than rates of the pure form of A in relatives of proband groups AB, B and control probands. Similarly, we would expect to find rates of the pure form of B in relatives of probands with the pure form of B to be higher than rates in relatives of probands with AB, A and control probands. Finally, we would expect to find rates of AB in relatives of probands with AB to be higher than rates in relatives of probands with the pure form of A, with the pure form of B and the control probands.

Model 4 hypothesizes that the pure and comorbid forms of A and B are different phases or alternative expressions of the same underlying disorder. Under this hypothesis it is expected that the rates of the pure form of A, the pure form of B and the comorbid form AB in relatives will be similar among the probands with the pure and comorbid forms of the disorders, and will be greater than the respective rates in the relatives of comorbid probands.

Statistical methods of testing hypotheses

Multinomial logit models (Agresti, 1990) are particularly well suited to performing formal statistical analyses of the patterns of transmission discussed in the preceding section. These models unlike the usual logistic regression models, or the proportional hazards model, allow the outcome variable to have more than two levels, thus allowing us to simulataneously study the association between multiple relative disorder categories and multiple proband disorder categories, while at the same time controlling for other potential confounding variables such as age and sex of relatives and age and sex of probands.

In order to use multinomial logit models, the relatives in each of the four proband groups are first categorized into the following four mutually exclusive groups: 1. relatives with the pure form of A, 2. relatives with the comorbid form AB, 3. relatives with the pure form of B, and lastly, 4. relatives who have neither A nor B. To understand the relationship between the response variables in this model and the response variables discussed in the previous section, we first form the following ratios for each of the four proband categories:

$$\frac{\text{Proportion of relatives with the pure form of disorder A}}{\text{Proportion of relatives with neither A nor B}} = \frac{p_A}{p_{\overline{AB}}}$$

$$\frac{\text{Proportion of relatives with the pure form of disorder B}}{\text{Proportion of relatives with neither A nor B}} = \frac{p_B}{p_{\overline{AB}}}$$

$$\frac{\text{Proportion of relatives with the comorbid form AB}}{\text{Proportion of relatives with neither A nor B}} = \frac{p_{AB}}{p_{\overline{AB}}}$$

(Note that when A and B are low-prevalence disorders these quantities will be approximately equal to the rates of disorder A, B and AB respectively in relatives).

The response variables in the model are the logarithms of the above quantities. The independent variables in the model will denote the disorder status of the probands. By exponentiating the regression coefficients associated with the independent variables corresponding to the response variable log $(p_A/p_{\overline{AB}})$ we can obtain the odds ratios, comparing the odds of a relative in a specified proband category having the pure form of disorder A with the odds of a relative in the control proband group having disorder A. Similarly, exponentiating the regression coefficients associated with the response variables $\log(p_{AB}/p_{\overline{AB}})$ and $\log(p_B/p_{\overline{AB}})$ respectively will enable us to compare the odds of a relative having AB, or a relative having B in a specific proband disorder category with that of the control probands.

Computer software for multinomial logit models is readily available using the SAS computer software package. Despite its many advantages in approaching these issues, one of the drawbacks of the multinomial logit model (which is also shared by the usual logistic regression model) is that it does not allow the risk of developing the disorder to vary with age, i.e. implicit in this model is the assumption that the risk of developing the disorder remains constant over a relative's lifetime. When there is only one disorder of interest the problem can be easily overcome by using survival analysis techniques developed for univariate response variables, such as the well-known proportional hazards regression model, instead of the logistic regression model to estimate association between proband disorder and relative disorder. Unfortunately, however, survival analysis models capable of handling multivariate response variables in a manner analogous to multinomial logit models do not (to the best of our knowledge) exist.

If the age distribution of relatives is approximately the same in all of the proband groups, the fact that the multinomial logit model does not allow the risk of disorder to vary with age will not affect the validity of using the regression coefficients to estimate the association between relative disorders and proband disorders. On the other hand, if the age distribution of relatives among these probands is significantly different, then it would also be advisable to examine the association between relative disorder category, by computing lifetime rates adjusted for age using survival analytic techniques (Cox and Oakes 1984), for the mutually exclusive categories. We could also apply a series of proportional hazards models (Kalbfleisch and Prentice 1980), considering each of the pure forms and the comorbid forms of the disorder in turn as the univariate response variable and the proband disorder categories as the independent variables. If the results of the different approaches discussed in this section converge, the we would feel confident that the estimated patterns of transmission were valid.

Application of models

The high comorbidity of panic disorder and major depression (MDD) in individuals has been well documented in epidemiologic (Angst et al. 1990; Boyd et al. 1984), clinical (Barlow et al. 1986), longitudinal and cross-sectional studies (Maser et al. 1990; Biederman et al. 1991; Strauss et al. 1988; Weissman 1990) of adults and children. However, it is unclear if panic disorder and MDD are distinct disorders, the same disorder, whether one disorder leads to the other (although both may have different pathophysiologies) or whether occurrence of both MDD and panic together in individuals represents a distinct syndrome that is different from either disorder alone (Dube et al. 1986). Since both panic disorder and MDD have been shown to be familial disorders, family studies are an especially useful method for investigating the relationship between these disorders.

To date, results from family studies relevant to these questions have been limited and contradictory (Crowe et al. 1983; Leckman et al. 1983; Pauls and DiBendetto 1987; Coryell et al. 1988). One of the reasons that these studies have failed to clarify the situation is that none of them have had the full range of proband groups necessary to investigate these relationships. In this section, we present the results of applying the models discussed in the previous section to data from a new family study designed to include the necessary diagnostically mutually exclusive proband groups and their relatives that are needed to study the familial relationship between panic and depression and attempt to understand the high occurrence of comorbidity between these two disorders (Weissman et al., in press).

Study methodology

Proband ascertainment

The study methodology has been described in detail by Weissman et al. (in press). In brief, potential probands were ascertained consecutively from speciality treatment clinics for depression or anxiety disorders affiliated with Yale University and from the New Haven site of the Epidemiologic Catchment Area study (ECA). By design about 66% of the ill probands were selected from treatment clinics and 34% from the ECA. Probands were selected to be white and 18–70 years of age, in addition to meeting the diagnostic criteria for one of the four groups of interest, i.e. panic without MDD, panic with MDD, early onset MDD, and never mentally ill controls. Consecutive subjects from the clinics and the ECA, who initially met the inclusion criteria, were sampled and, after giving informed consent, reinterviewed blindly by a member of the research team using the Schedule for Affective Disorder and Schizophrenia-Lifetime Version (SADS-LA) (Mannuzza et al. 1986). All subjects meeting the diagnostic and demographic inclusion criteria and agreeing to participate were accepted in the study. Acceptance was blind to the subject's willingness to have family members interviewed as well as to family size and diagnoses among relatives.

Diagnostic criteria for probands

Exclusionary diagnoses for all groups were schizophrenia, mania, Briquet's disease, antisocial personality disorder, and anorexia. Drug and alcohol abuse were not exclusionary, due to the small number of potential probands without these conditions. However, these disorders had to be chronologically secondary to the primary diagnosis, chronologically primary but mild, or followed by substantial periods of recovery before the onset of the inclusion diagnosis. The specific inclusion criteria for each proband group will now be described.

Panic disorder with or without MDD. Probands were required to meet DSM-III panic disorder criteria based on the SADS-LA. For MDD, the Research Diagnostic Criteria (RDC), modified to require an illness of at least 4 weeks and impairment of functioning in the major social role, were adopted. Probands in the panic disorder without MDD group could have no evidence of MDD by any diagnostic criteria at any level of certainity at any time.

Early onset MDD. Probands were required to have a history of MDD according to the modified RDC as described above, with the first episode occurring before age 30 years. Probands in this group could have no evidence of any panic disorder or panic attacks by any diagnostic criteria at any level of certainity. The cutoff onset age of 30 years was used as the criterion because of our previous work indicating that this form of MDD was the most familial (Weissman et al. 1984b).

Never mentally ill controls. These probands received no lifetime psychiatric diagnosis during any of the three waves of the ECA interviews based on the Diagnostic Interview Schedule (DIS), nor at blind reinterview with the SADS-LA.

Assessment of relatives

All first-degree relatives were enumerated systematically from the proband using the Pedigree Collection Form (Thompson et al. 1980); permission for contact with relatives was obtained from the proband. Direct interviews using the SADS-LA, either in person or by telephone, were carried out with all consenting relatives. In addition, family history information on first-degree relatives was obtained from all probands and interviewed relatives using a modified family history method for RDC (FH-RDC) initially developed by Andreasen et al. (1977). An earlier version of this modification was used in previous family studies by Weissman et al. (1984a), and a further revision has been made by Mannuzza et al. (1985). All assessments were performed by clinically trained interviewers blind to proband diagnoses.

Best-estimate diagnosis

Best-estimate diagnoses, based on all information available concerning each proband and relative, were made by a psychiatrist or clinical psychologist blind to proband diagnosis, unaware of whether the subject was a proband or a relative, and not involved in the data collection. Diagnoses were made according to RDC (Spitzer et al. 1978), DSM-III, and DSM-III-R (American Psychiatric Association 1987) criteria, and assiged one of three levels of certainity: possible, probable, or definite (Leckman et al. 1982). Age at onset and severity of impairment due to each disorder were also estimated. Probands whose best-estimate diagnoses were not consistent with the original diagnostic category assigned were either formally reassigned or excluded without knowledge of the data on relatives.

Final sample of probands and relatives

In the results reported here, we have used the original probands diagnostic system described above and we present DSM-III diagnoses in relatives. The final sample consists of 193 probands. Thirty of the probands had panic disorder with no MDD, 77 had panic disorder plus MDD, 41 had early onset MDD without panic, and 45 were normal controls. A total of 1,047 adult (age 17.5 years and older) first-degree relatives were assessed, of whom 435 were directly interviewed. Family history information from two or more informants was available for 77% of all relatives.

Demographic and clinical characteristics of probands

The demographic and clinical characteristics of the probands and relatives have already been described in detail (Weissman et al., in press). To summarize, there were no differences among the proband groups in age, marital status, number of times married, social class, education or religion. Significant gender differences were found

Table 2. Rates/100 in interviewed and uninterviewed relatives ($n = 1047$) by proband group

Lifetime rate/100 in first-degree relatives	Proband diagnoses			
	Panic, no MDD	Panic + MDD	MDD (onset <30 years, no panic)	Never mentally ill
Panic, no MDD	7.8	3.2	1.0	0.4
Panic + MDD	6.4	4.8	2.9	0.4
MDD (onset <30 years, no panic)	7.1	9.7	21.0	5.5
MDD (onset >30 years, no panic)	7.1	5.9	8.6	6.7

Table 3. Ratio of proportion of relatives having a specified disorder to proportion of relatives having neither panic nor depression (odds) by proband group

Odds for disorders categories of first degree relatives	Proband diagnoses			
	Panic, no MDD	Panic + MDD	Early onset MDD	Never mentally ill
Panic, no MDD	0.10	0.041	0.014	0.0045
Panic + MDD	0.064	0.062	0.043	0.0045
Early onset MDD (<30 years, no panic)	0.099	0.097	0.317	0.063
Late onset MDD (>30 years, no panic)	0.099	0.059	0.129	0.077

among the proband groups. Specifically, there were significantly more female probands in the panic plus MDD, and early onset MDD groups.

Demographic characteristics of relatives

Only information on age and sex were available on both interviewed as well as uninterviewed relatives. Relatives in the four proband groups did not differ significantly by gender. Differences in age among these proband groups were found to be statistically significant; however, since the average age of relatives in these different proband groups ranged from 48 to 52 years, it is unlikely that these differences are clinically significant.

Investigation of patterns of familial transmission of panic and depression between probands and relatives

In order to investigate patterns of transmission of the pure forms of panic and depression and their comorbid form, we first examined the lifetime rates of panic disorder without depression, panic disorder with depression, early onset (<=30 years) MDD (without panic), and late onset (>30 years) MDD (without panic), in relatives of the four proband groups. These lifetime rates in relatives by proband diagnostic categories are shown in Table 2.

A comparison of the patterns in this table with the patterns generated by the hypothesized models in Table 1 indicate that the patterns shown in Table 2 are very similar to the patterns obtained under Model 2, if we define panic as disorder A and early onset (<=30 years) MDD as disorder B. [The only difference being that we have a fourth category of disorder, namely late onset (>30 years) MDD].

The ratio of the proportion of relatives having the specified disorder to the proportion of relatives having neither panic nor depression (known as the odds) are presented in Table 3. These quantities form the basis for fitting the multinomial logit models described in the preceding section. Response variables in the multinomial logit model are logarithms of these quantities. When the disorders have low prevalence, these quantities should be approximately equal to the quantities presented in Table 2 (divided by 100).

If each of the quantities in the first three columns of each row is divided by the last column (i.e. the odds for the never mentally ill probands), we obtain the odds ratios corresponding to the respective disorders. For example, if we divide the quantity in the first row and first column in Table 3 by the quantity in the first row and fourth column, we obtain the ratio of the odds of a relative of a proband with panic (no MDD), having panic (no MDD), compared with the odds of a relative of a never mentally ill proband having panic (no MDD). These quantities will be approximately equal to the relative risks of developing the specified disorders, which, in turn, should be equal to the ratio of the rates shown in Table 2. Therefore, the magnitude and the statistical significance of the estimated odds ratios will indicate which of the patterns shown in Table 1 and, hence, which of the hypothesized models fit the data.

Table 4 presents these odds ratios (and significance levels obtained from the multinomial logit model). An odds ratio which is significantly greater than one, implies that the odds of a relative in one of the ill proband groups having a specified disorder is greater than the odds of a relative of a never mentally ill proband having that same disorder.

Table 5 presents these odds ratios adjusted for the potential confounding effects of age, sex and interview status of relatives. In general, the pattern of odds ratios across proband groups should be similar to the pattern of relative risks across proband groups, providing the link

Table 4. Crude odds ratios comparing rates to NMI relatives (N = 1047) by proband group

Lifetime rate/100 in first-degree relatives	Proband diagnoses		
	Panic, no MDD	Panic + MDD	MDD (onset <30 years, no panic)
Panic, no MDD	24.17**	9.19**	3.19
Panic + MDD	19.78*	13.79*	9.50*
MDD (onset <30 years, no panic)	1.57	2.01*	5.01***
MDD (onset >30 years, no panic	1.29	1.00	1.69

* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$

Table 5. Adjusted odds ratios comparing rates to NMI relatives (N = 1047) by proband group

Lifetime rate/100 in first-degree relatives	Proband diagnoses		
	Panic, no MDD	Panic + MDD	MDD (onset <30 years, no panic)
Panic, no MDD	20.81**	9.44**	3.36
Panic + MDD	17.38*	14.08*	9.88*
MDD (onset <30 years, no panic)	1.41	2.02*	5.29***
MDD (onset >30 years, no panic)	1.26	1.09	1.77

* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$

between the patterns of odds ratios seen in Table 5 and patterns under hypothesized models shown in Table 1. For example, results presented in Table 5 show that panic disorder (no MDD) is approximately 24 times more likely to occur in relatives of probands with panic disorder (no MDD) than in relatives of never mentally ill probands; it is approximately 9 times more likely to occur in relatives of probands with panic disorder and MDD, than in relatives of never mentally ill probands, and is no more likely to occur in relatives of early onset (<30 years) MDD (no panic) than in relatives of never mentally ill probands (Note that even though this last odds ratio is 3.19, it is not statistically significantly different from 1). Comparing results in Table 5 with the hypothesized patterns in Table 1, we see that the pattern of odds ratios in the first row of Table 5 is similar to the pattern which would be obtained if we divided the rates of disorder A in relatives of each of the proband groups A, AB and B, by rates of disorder A in relatives of the control probands, where the patterns of rates of disorder A in relatives by proband group, as shown in Table 1, correspond to Model 2. The odds ratios associated with panic plus MDD in relatives, presented in Table 5, show that panic with MDD is approximately 17 times more likely to occur in relatives of probands with panic only than in relatives of never mentally ill probands; it is approximately 14 times more likely to occur in relatives of probands who also have panic with MDD than relatives of never mentally ill probands; and it is approximately ten times as likely to occur among relatives of probands with early onset (< = 30 years) MDD than in relatives of never mentally ill probands. A comparison of this pattern of odds ratios to the pattern which would be obtained if we divided rates of the disorder AB in relatives of each of the proband groups A, AB, B by the rates of disorder AB in relatives of control probands, where the pattern of rates of disorder AB, as shown in Table 1, correspond to Model 2, shows that the patterns are virtually identical. From Table 5, it will also be seen that early onset (< = 30 years) MDD is approximately five times more likely to occur in relatives of probands with early onset MDD than in relatives of never mentally ill probands; it is approximately twice as likely to occur in relatives of probands with panic plus MDD than in relatives of never mentally ill probands; however, relatives of probands with panic disorder (no MDD) are no more likely to have early onset MDD than relatives of never mentally ill probands. When this pattern of odds ratios is compared to the pattern of rates among proband groups associated with Model 2 in Table 1, it will be seen that the patterns are virtually identical. Results presented in the last row of Table 5 show that none of the odds ratios are significantly different from one – indicating that relatives of the ill proband groups are no more likely to have late onset (>30 years) MDD than relatives of never mentally ill probands. Taken together, the results presented in Table 5 are most consistent with the patterns of transmission generated by hypothesizing that the relationship between panic and depression is that described by Model 2.

Patterns of familial transmission of age-adjusted lifetime rates

As the risk of developing panic and/or MDD varies with age, we also computed age-adjusted lifetime rates using survival analytic techniques (Cox and Oakes 1984) for specific disorders in relatives, for each of the proband groups. When computing age-adjusted lifetime rates for panic plus MDD, we defined the age of onset of the comorbid form as the maximum of the age at first onset of either panic or MDD (When computing age-adjusted rates for panic without MDD, or MDD without panic, we defined the age at first onset of panic with MDD which is now considered "censored" in survival analysis terminology as the minimum of the age at first onset of either panic or MDD). The age-adjusted lifetime rates (together with their associated standard errors) and a test of group differences (i.e. whether age-adjusted rates for a specified disorder are significantly different across proband groups) using these techniques are presented in Table 6.

A comparison of the unadjusted lifetime rates presented in Table 2 with these age-adjusted rates show that, with the exception of late onset MDD (onset >30

Table 6. Age-adjusted lifetime rates/100 for all adult first-degree relatives ($N = 1047$) by proband group

Age-adjusted lifetime rates/100 in first degree relatives	Proband diagnoses			
	Panic, no MDD	Panic + MDD	MDD (onset <30 years, no panic)	Never mentally ill
Panic, no MDD**	10.6 (3.1)	4.7 (1.3)	1.1 (0.74)	0.7 (0.74)
Panic + MDD*	8.1 (2.7)	6.7 (1.5)	3.0 (1.4)	0.4 (0.42)
MDD (onset <30 years, no panic)**	7.7 (2.3)	10.9 (1.6)	21.4 (2.9)	5.5 (1.4)
MDD (onset >30 years, no panic)	20.2 (5.8)	14.4 (2,3)	16.3 (2,6)	10.1 (1.6)

** P value for test of group differences < 0.001
* P value for test of group differences < 0.05

Table 7. Adjusted relative risks comparing rates of panic disorder and major depressive (nonmutually exclusive groups) in relatives of ill to relatives of never mentally ill probands

Proband group	Relative diagnosis	
	Panic disorder	MDD
Panic disorder, no MDD	16.5** (3.86, 70.67)	1.45 (0.88, 2.40)
Panic disorder, with MDD	9.83** (2.36, 40.88)	1.63* (1.09, 2.44)
MDD (onset <30 years, no panic)	3.93 (0.81, 18.78)	2.68** (4.09, 1.76)

Adjusted for age, sex and interview status
* $P < 0.05$
** $P < 0.01$

years) without panic, the age-adjusted rates differ very little in magnitude when compared to the unadjusted lifetime rates. The large difference in magnitude between adjusted and unadjusted lifetime rates of late onset depression are due to the fact that a number of relatives are younger than 30 years and hence not at risk for late onset depression. Consequently, these individuals are excluded from the denominator when computing age-adjusted lifetime rates causing these rates to be far larger in magnitude than the unadjusted rates. However, it is reassuring to note that, in spite of the difference in magnitudes, the patterns and statistically significant differences between the rates in relatives by proband group, for the specific disorders, were identical to those obtained using the multinomial logit model, and consistent with the patterns of transmission generated under the relationship between panic and depression hypothesized in Model 2 described in Table 1.

Results using standard methods

The standard approaches to exploring the familial transmissions of comorbid disorders by studying the association between the proband disorder status and panic disorder (with or without depression) in relatives, and proband disorder status and MDD (with or without panic) in relatives was also performed, using proportional hazard analysis. Results obtained from this set of analyses are presented in Table 7.

These results show that relatives of probands with panic disorder without MDD have a 16-fold increase in risk of developing panic disorder compared to relatives of never mentally ill probands. Relatives of probands who have panic with MDD were found to have a ten-fold increase in risk of developing panic disorder when compared to relatives of never mentally ill control probands. Relatives of early onset MDD probands did not have a significantly higher risk of developing panic disorder than relatives of control probands. When MDD is relatives is considered, we find that relatives of probands with panic disorder without MDD do not have a significantly higher risk of developing MDD than relatives of never mentally ill probands; relatives of probands who had panic disorder with MDD and relatives of probands with early onset MDD without panic had a significantly higher risk of developing MDD than relatives of never mentally ill probands.

Comparison of methods of analysis

It will be noted that the results reported in Table 7 support the findings reported in the previous section, i.e. that panic and MDD are two distinct and separate disorders, since probands who have panic without MDD do not seem to transmit MDD (with or without panic disorder) to their relatives and probands with early onset MDD do not seem to transmit panic disorder (with or without MDD) to their relatives. However, results using this method of analysis alone do not shed any light on the nature of the comorbid form of the disorders. Furthermore, when individuals with the comorbid form of the disorder constitute a sizeable proportion of the total number of individuals with the disorder, as is the case with panic disorder, the association found between probands with MDD without panic disorder and relatives with panic disorder (with or without MDD), could be solely due to the association between these probands and relatives with panic comorbid with depression. This

could result in misleading conclusions regarding the relationship between these disorders. Although this association was not found in the data presented here, it could well be the reason for probands with MDD without panic seeming to have relatives with an elevated risk of panic disorder reported in other studies.

Summary and discussion

Application of the methods described above reveal that the model that was most consistent with the data was that panic and MDD are two distinct disorders and that the comorbid form is a heterogenous collection of "atypical" forms of panic disorder, "atypical" forms of MDD and possibly some cases where panic with MDD is a different subtype.

Further study is needed to clarify the different components of the heterogenous comorbid forms. In terms of genetic linkage studies of panic disorder, based on our findings, we would recommend that separate analysis be performed with phenotypic assignment; first with panic disorder alone, then with panic disorder and comorbid MDD, but that MDD alone not be considered part of the panic spectrum.

A comparison of these methods of analysis where relative disorders are classified to parallel proband disorder categories with standard methods show that, in general, the methods introduced here give more detailed information regarding patterns of transmission than the standard methods, resulting in greater insight into the possible mechanisms that lead to comorbidity. In addition, the new methods provide more rigorous statistical tests of hypotheses regarding the nature of the relationship between the two comorbid disorders. Lastly, application of the methods introduced here suggest that the phenomenon of comorbidity is (at least in the case of panic plus MDD) far more complex than was previously recognized.

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