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Panic disorder in women: a population-based twin study

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SYNOPSIS Previous studies based on probands from clinical samples suggest that panic disorder aggregates strongly in families and may be due to a highly penetrant single major locus. In this study we examine panic disorder as assessed at blind, structured psychiatric interview in 2163 women from a population-based twin registry. DSM-III-R diagnoses were assigned at a narrow and at a broad level both by clinician review and by computer algorithm. The familial aggregation of panic disorder in this sample was only modest. The relatively small number of affected individuals prevented a definitive resolution of competing genetic and non-genetic models of familial transmission. Although there was some inconsistency across diagnostic approaches, most results suggested that the familial aggregation of panic disorder was due largely to genetic factors. Using a multifactorial-threshold model, the best estimates of the heritability of liability ranged from 30 to 40%. From a familial perspective, panic disorder with phobic avoidance appears to represent a more severe form of the syndrome than panic disorder without avoidance. Our results, which suggest that in the general population panic disorder is only a moderately heritable condition, are at variance with results from several previous investigations based on clinically ascertained samples.

INTRODUCTION

DSM-III (American Psychiatric Association, 1980) introduced a major change in the nosology of the anxiety disorders when the diagnostic category of anxiety neurosis, as articulated in DSM-II (American Psychiatric Association, 1968), was subdivided into generalized anxiety disorder, characterized by periods of sustained 'free-floating' anxiety and panic disorder, distinguished by paroxysmal episodes of intense anxiety. Since the publication of DSM-III, panic disorder has been rapidly accepted as a valid psychiatric disorder in the United States (Breier *et al.* 1985) which has high reliability (Mannuzza *et al.* 1989) and probably a distinct pattern of response to treatment (Zitrin *et al.* 1981). Further strong evidence for the validity of panic disorder has come from psychiatric genetic investigations which have consistently suggested that panic disorder or panic-like syndromes strongly aggregate in families (Crowe *et al.* 1988; Crowe, 1990). A segregation analysis of 19 pedigrees, ascertained through a panic disorder proband, found that the best-fitting model suggested a highly penetrant autosomal dominant gene for panic disorder (Pauls *et al.* 1980). Based on these findings, linkage studies of this disorder have now been undertaken (Crowe *et al.* 1987, 1990; Mutchler *et al.* 1990).

These results appear to provide robust support for the validity of the diagnosis of panic disorder and suggest that it is strongly influenced by familial/genetic factors. However, only a single small sample twin study of panic disorder has been conducted (Torgersen, 1983). This included 29 co-twins of proband twins with panic disorder, and found probandwise concordances for panic disorder which were lower than would be predicted from the family study results and suggest, by contrast, that genetic factors play only a modest aetiological role in panic disorder.

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Furthermore, all major family and twin studies of panic disorder that have been carried out to date have begun with clinically ascertained probands. The proportion of individuals with panic disorder who seek mental health care is probably modest (Eaton *et al.* 1991) and the aetiological importance of familial/genetic factors may differ in treated and untreated cases. Diagnostic issues may be more problematical in the general population than in clinical samples as panic attacks, the core clinical phenomenon in panic disorder, may not be highly specific (Marks, 1987; Argyle & Roth, 1989), and are, in epidemiological samples, several times as common as narrowly defined panic disorder (Joyce *et al.* 1989; Klerman *et al.* 1991).

Patients with panic disorder differ widely in the degree to which they restrict their activities in response to panic attacks (Marks, 1987; Barlow, 1988). For example, in the Epidemiologic Catchment Area study, only about a third of individuals meeting criteria for panic disorder also had agoraphobia (Eaton *et al.* 1991). It is of considerable interest to clarify, from a familial/genetic perspective, why some individuals with panic disorder develop marked avoidance behaviours while others develop limited or no avoidance. One plausible hypothesis, which is partly supported by the only family study of which we are aware which has examined this question (Noyes *et al.* 1986), is that panic disorder with avoidance and/or agoraphobia represents a more severe variant of the condition than panic disorder without avoidance.

In this report, we examine panic disorder in a large sample of personally interviewed female twins, ascertained from the general population Virginia Twin Register. In particular, we examine the following questions.

(1) How important are familial factors in the aetiology of panic disorder in a general population sample and will their effects be similar in magnitude to that previously reported in clinical samples?

(2) To what extent is the familial aggregation of panic disorder due to genes *versus* shared familial environment?

(3) How consistent are the results obtained across several different diagnostic approaches to panic disorders?

(4) From a familial perspective, is the presence or absence of panic-associated avoidance behaviour an index of the severity of liability to panic disorder?

METHOD

As outlined in detail previously (Kendler *et al.* 1992; Walters *et al.* 1992), as part of a longitudinal study of the genetic and environmental risk factors for common psychiatric disorders in women, we personally interviewed 2163 female twins from the population-based Virginia Twin Register with a mean age ($\pm$S.D.) of $30{\cdot}1 \pm 7{\cdot}6$, including both members of 1033 pairs. Pairs were eligible to participate if both members returned previously mailed questionnaires. The refusal rate during the personal interview phase of this project was 8%. Eighty-nine per cent of the interviews were conducted face-to-face and 11% by telephone. All interviews were conducted by interviewers with Master's degrees in Social Work or at least two years clinical experience who were blind to the psychopathological status of the co-twin. Interviewers were trained for 80 h in the use of this instrument and their performance was regularly monitored. Interviewers were encouraged to comment on questionable areas in the interview and all provided a summary 'sketch' of the informant and the interview results. Zygosity was determined by an algorithm based on questionnaire responses, photographs and, where these sources were ambiguous, DNA polymorphisms (Spence *et al.* 1988) and yielded 590 monozygotic (MZ) pairs, 440 dizygotic (DZ) pairs and 3 pairs of unknown zygosity.

Panic disorder was assessed by an adapted version of the Structured Clinical Interview for DSM-III-R diagnosis (Spitzer *et al.* 1987). In this interview, if respondents admit to panic attacks but deny that they were either frequent (at least 4 in a 4-week-period) or resulted in a period of at least a month 'worrying a lot' about a recurrence, they are omitted from the section so that no further information about their panic attacks is obtained. Unfortunately, this procedure was followed in this study so that detailed information is not available on sub-clinical panic attacks.

Individuals who completed the panic disorder section were all asked 'Were there situations that you avoided because you were afraid you might have an attack? For example, going out

of the house alone, being in crowds, other public places, tunnels, bridges, buses or trains?' and rated as 'no significant phobic avoidance', 'limited phobic avoidance' and 'agoraphobia'. Because of the small numbers involved, for all analyses presented here, cases were subdivided into those without phobic avoidance and those with limited phobic avoidance *or* agoraphobia.

In this report we utilize two diagnostic approaches to panic disorder both using DSM-III-R criteria (American Psychiatric Association, 1987): a clinical diagnosis based on a blind review of the complete interview protocol by a senior diagnostically orientated psychiatrist (K.S.K.) and the application, by computer algorithm, of the DSM-III-R criteria.

On clinical review, diagnoses were made at three levels of certainty: definite, probable and possible (Kendler *et al.* 1991). This review took into account both the explicit information recorded in response to the structured questions, and the often extensive narrative material written by the interviewer. Definite diagnoses were assigned when all diagnostic criteria were clearly met. Probable cases were similar, but some modest uncertainty existed about one or more criteria, but the diagnosis still appeared to be appropriate. By contrast, a possible diagnosis was assigned to cases that clinically appeared to have a psychiatric disorder which most closely resembled, but did not meet, full criteria for panic disorder. In some cases, a possible diagnosis might be assigned to a twin who was omitted from the panic disorder section, but where the interviewer documented elsewhere the severity of symptoms associated with the panic attacks. For these analyses, definite and probable cases are combined into a category termed *clinician narrow* panic disorder. Adding possible cases to those with a definite or probable diagnosis created the category we termed *clinician broad* panic disorder.

We also developed a computer algorithm precisely operationalizing the DSM-III-R criteria as recorded by the interviewer, and this algorithm defined what we term *computer narrow* panic disorder. In addition, we also created a category which we term *computer broad* panic disorder, which added to the computer narrow category cases that met 2 or 3 (rather than 4 or more) of the individual panic symptoms in criterion C and/or stated that their symptoms reached peak intensity more gradually than required by criterion D (within 10 min).

Inter-rater reliability was measured among 53 randomly chosen cases assessed at the same interview by two interviewers. For clinician-broad and computer-broad diagnoses of panic disorder, the chance corrected agreement (κ) (Cohen, 1960) was, respectively, $0{\cdot}85 \pm 0{\cdot}03$ and $0{\cdot}66 \pm 0{\cdot}05$.

The presentation of results from twin studies

Almost all previous twin studies of medical and psychiatric illness ascertained affected twins through treatment facilities so that twin pairs were divisible into three categories: discordant for affection (proband affected and co-twin unaffected), concordant for affection in which one twin is a proband and concordant for affection in which both twins are probands. In these studies, probandwise concordance is an appropriate and efficient statistic.

In this report twins are ascertained from the general population so that pairs are divisible into three different categories: concordant for non-affection, discordant for affection and concordant for affection. Probandwise concordance, which includes information only from the latter two categories, can be applied to such a study but, since it ignores twins concordant for non-affection, is very inefficient.

In the interest of historical continuity, we present probandwise concordance rates in this report. However, our analyses emphasize a more appropriate and efficient statistic which uses all available information: the tetrachoric correlation, or, as it is sometimes termed, the 'correlation of liability' (Pearson, 1901; Falconer, 1965). This statistic assumes that underlying the observed dichotomous distribution of affection status there exists a continuous, normally distributed latent liability. The tetrachoric correlation represents the correlation between these underlying liability distributions rather than the observed dichotomous variables. The tetrachoric correlation assumes that liability to illness can be approximated by a normal distribution. Although this has often been interpreted to require large numbers of factors of small effect, in reality, a normal distribution can be closely approximated by a small number of factors of moderate size (Kendler & Kidd, 1986).

A tetrachoric correlation fit to a 2 × 2 table is a 'perfect fit' and provides no test of the liability-threshold model. However, in testing whether our narrow *versus* broad definitions of panic disorder or the distinction between panic disorder with and without avoidance behaviours represent different levels of 'severity' on the same liability continuum (Reich *et al.* 1972), a polychoric correlation is calculated from a 3 × 3 table, cross-classifying each member of the twin pair into unaffected, broad but not narrow panic disorder and only narrow panic disorder or unaffected, panic disorder without avoidance and panic disorder with avoidance. A χ^2 goodness-of-fit test is available for testing this multiple threshold model.

Statistical analysis

The impact of the age at interview, type of interview (phone *v.* face to face), and zygosity on the risk for panic disorder was analysed by logistic regression (SAS Institute, 1990). In addition, the relationship between probability of cooperation and affection status for panic disorder was assessed by determining whether the disorder is more prevalent in twins without *v.* with an interviewed co-twin. To test the 'equal environmental assumption' (i.e. that MZ and DZ twins are equally correlated for their exposure to aetiologically significant environmental variables) we assessed the degree of environmental similarity of the twins in childhood (Loehlin & Nichols, 1976) and their frequency of contact in adulthood (Kendler *et al.* 1986). We then regressed a dummy variable coded 0 if the twin pairs were concordant for affection or non-affection for panic disorder and 1 if they were discordant onto these indices of environmental similarity by logistic regression. Controlling for zygosity, these analyses test whether similarity of environmental experiences of the twin pair predicts twin similarity for panic disorder. All of these potential biases were tested using the broad diagnostic approaches because the larger sample size maximized power of detection. However, similar trends were seen when these were applied to the narrow diagnoses.

The tetrachoric and polychoric correlations and their standard errors were calculated separately for MZ and DZ twins by the beta test version of PRELIS II (Jöreskog & Sörbom, 1988). Models were fitted to these correlations by the computer program LISREL using asymptotic weighted least squares (Heath *et al.* 1989; Jöreskog & Sörbom, 1989; Neale *et al.* 1989). In the full model used in this report, resemblance in twins is assumed to result potentially from two sets of latent factors: (i) additive genes (A), which cause the correlation in MZ twins to be twice that of DZ twins (because MZ twins share all their genes identical by descent, while DZ twins, like non-twin siblings, share on average only half their genes); and (ii) family or 'common' environment (C), which causes the correlation in MZ and DZ twins to be the same. In addition to 'common' environment (those environmental factors, such as social class of rearing or parental behaviour, which make members of a twin pair similar for liability to panic disorder), the model also contains individual specific environment (E), which, in addition to measurement error, reflects those environmental experiences (such as traumatic life events experienced by only one twin) that may make members of a twin pair different for liability to panic disorder. Models which included dominance genetic variance were fit to the data on panic disorder, but in no case did these models fit better than models without dominance (results available on request).

Our formal analysis of the twin correlations begins with fitting an ACE model, which, as its name implies, includes additive genes (A), common environmental (C) and individual-specific environment (E). The fit of this model is assessed by a goodness-of-fit χ^2 test. We then fit two simpler models which postulate different causes for any observed familial aggregation of panic disorder. The AE model (which contains only additive genes (A) and individual-specific environment (E)) assumes that all familial aggregation results from additive genetic effects, while the CE model (which contains only common environment (C) and individual-specific environment (E)) assumes that all observed familial aggregation is the result of shared environmental influences.

The goal of model-fitting is to explain the observed data as well as possible with as few parameters as possible. We operationalize this goal with the use of Akaike's information criterion (Akaike, 1987), which equals the χ^2 value minus twice the degrees of freedom. In seeking to minimize the value of Akaike's

Table 1. *Population prevalence, probandwise concordance and tetrachoric correlations in MZ and DZ twins for four definitions of panic disorder*

Diagnosis	Population prevalence		Probandwise concordance		Tetrachoric correlation	
	MZ	DZ	MZ	DZ	MZ	DZ
Clinician						
Narrow	5·7	6·3	23·9	10·9	+0·47±0·12	+0·17±0·17
Broad	9·5	13·1	23·2	15·7	+0·35±0·10	+0·07±0·12
Computer						
Narrow	4·7	4·7	14·5	14·6	+0·32±0·15	+0·32±0·17
Broad	7·4	7·8	20·7	14·5	+0·36±0·11	+0·20±0·14

information criterion, we seek the model which best reflects the balance of both goodness-of-fit and parsimony. In addition, it is possible to compare directly the CE or AE model with the ACE model by a χ^2 difference test with one degree of freedom, with that found for the ACE model. Further details of the application of biometrical genetic models to twin data are outlined by us elsewhere (Eaves *et al.* 1989; Heath *et al.* 1989; Neale *et al.* 1989).

The final step of twin analysis was to estimate, based on the best fitting model, the proportion of variance in liability to panic disorder due to individual specific environment (e^2) and, depending upon the results of model-fitting, additive gene action (a^2) or common environment (c^2). The proportion of variance in liability due to additive genetic effects in the multifactorial-threshold model is often termed 'heritability'. In addition, we estimate, from the population risk and the probandwise concordance rates in MZ and DZ twins (Suarez *et al.* 1977), the broad heritability of panic disorder assuming that it is the result of an incompletely penetrant two-allele single major locus.

RESULTS

Lifetime prevalences and agreements of two diagnostic approaches

Of the 2163 interviewed twins, 126 or 5·8% were judged on clinical blind review to meet lifetime criteria for narrowly defined panic disorder while another 110 or 5·1% were added for the broadly clinically defined disorder. Applying DSM-III-R diagnostic criteria by computer algorithm yielded a diagnosis of narrow panic disorder in 99 twins or 4·6% of the sample. Eliminating the requirement of paroxysmal onset and reducing the minimum number of required symptoms from 4 to 2 added another 65 cases or 3·0% of the sample. The chance corrected agreement between the narrow clinician and computer-derived diagnoses of panic disorder was very high ($\kappa = 0{\cdot}96 \pm 0{\cdot}03$) and substantially higher than that found between the broad clinician and computer diagnoses ($\kappa = 0{\cdot}70 \pm 0{\cdot}03$).

Test for biases and the equal environment assumption

Using the broadly defined clinician or computer diagnoses, the probability of lifetime illness was unrelated to age at interview ($\chi^2 = 0{\cdot}13$ and 1·60, respectively, both df = 1, NS), zygosity ($\chi^2 = 2{\cdot}04$ and 0·07, both df = 1, NS) or cooperation status of the cotwin ($\chi^2 = 0{\cdot}26$ and 0·07, both df = 1, NS). Twins interviewed in person were more likely to receive a diagnosis of panic disorder using the clinician broad diagnosis of panic disorder than twins interviewed by phone ($\chi^2 = 4{\cdot}76$, df = 1, $P = 0{\cdot}03$). However, no such effect was seen with the broad ($\chi^2 = 2{\cdot}36$, df = 1, NS) or narrow ($\chi^2 = 0{\cdot}18$, df = 1, NS) computer diagnoses nor the clinician narrow diagnosis ($\chi^2 = 0{\cdot}90$, df = 1, NS).

The similarity of childhood environment was unrelated to similarity for panic disorder using either the clinician broad ($\chi^2 = 1{\cdot}21$, df = 1, NS) or the computer broad diagnosis ($\chi^2 = 0{\cdot}11$, df = 1, NS). Frequency of contact as adults was also unrelated to similarity with respect to panic disorder using either diagnostic approach ($\chi^2 = 0{\cdot}34$ and $\chi^2 = 2{\cdot}85$, respectively, both df = 1, NS).

Table 2. *The fit of twin models and the parameter estimates of the best-fitting model for four definitions of panic disorder*

Criteria	Fit in χ^2 units			Parameter estimates*		
	ACE	CE	AE	a^2	c^2	e^2
Clinician						
Narrow	0·16	2·30	0·16†	0·46	—	0·54
Broad	0·65	3·22	0·65†	0·32	—	0·68
Multiple-Threshold	0·51	3·50	0·51†	0·35	—	0·65
Computer						
Narrow	0·00	0·00†	0·78	—	0·32	0·68
Broad	0·00	0·74	0·02†	0·37	—	0·63
Multiple-Threshold	0·00	0·63	0·07†	0·37	—	0·63

* Of best fitting model.
† Best fit model by Akaike's Information Criterion (Akaike, 1987).

Probandwise concordances and tetrachoric correlations

Although modest in overall magnitude, probandwise concordance for lifetime panic disorder was substantially higher in MZ than in DZ twins both for the clinician narrow (23·9 *v.* 10·9%) and the clinician broad diagnosis of panic disorder (23·2 *v.* 5·7%) (Table 1). However, for the computer narrow diagnosis, the concordance rate in the two twin types was indistinguishable (14·5 *v.* 14·6%, respectively). For the computer broad definition, the concordance rate in MZ twins was somewhat greater than that found in DZ twins (20·7 *v.* 14·5%).

As expected, for three of the four definitions, the tetrachoric correlation in MZ twins (ranging from +0·35 to +0·47) was substantially greater than that found in DZ twins (ranging from +0·07 to +0·20). Given the relatively large standard errors of these correlations, none of these estimates differ significantly from one another. However, for the computer narrow diagnosis, the correlation in MZ twins was lower than that found for any other definition (+0·32) and the DZ twin correlation was higher (+0·32).

Multiple threshold model for narrow *v.* broad diagnoses

In this analysis, we tested, using the multiple threshold model, whether the narrow and broad diagnosis of panic disorder could be considered as different levels of 'severity' on the same continuum of liability (Reich *et al.* 1972). For both the clinician and computer based diagnoses, the multiple threshold models (all df = 3) fit well in both MZ ($\chi^2 = 6{\cdot}82$, $P = 0{\cdot}08$ and $\chi^2 = 2{\cdot}22$, $P = 0{\cdot}53$, respectively) and DZ twins ($\chi^2 = 1{\cdot}33$, $P = 0{\cdot}72$ and $\chi^2 = 2{\cdot}91$, $P = 0{\cdot}41$, respectively), suggesting that the categories of narrow and 'broad but not narrow' panic disorder differ quantitatively and not qualitatively, reflecting increasingly severe levels of liability to panic disorder. The estimated polychoric correlations for panic disorder from the multiple threshold model applied to the clinician diagnoses were $+0{\cdot}37 \pm 0{\cdot}10$ and $+0{\cdot}10 \pm 0{\cdot}11$, in MZ and DZ twins, respectively. The parallel estimates applied to the computer diagnoses were $+0{\cdot}36 \pm 0{\cdot}11$ and $+0{\cdot}22 \pm 0{\cdot}14$.

Results of twin models

In both the multiple threshold models, and in three of the four definitions of panic disorder, the best fitting model by Akaike's information criterion (Akaike, 1987) was the AE model, which suggested that variance in liability to panic was due only to additive genes and individual-specific environment (Table 2). In each of these cases the AE model fits as well or nearly as well as the full ACE model, but was preferable because of its greater parsimony. The estimates of heritability from these models were modest, ranging from 0·32 to 0·46. Of note, the estimates of heritability from the two multiple threshold models were very similar (clinician 0·35 and computer 0·37). However, in none of these models could the CE model, which suggests that variance in liability to panic is due only to familial and to individual specific environment, be rejected by the rigorous χ^2 difference test against the full ACE model. The definitions with which the CE model came closest to exclusion were the clinician-broad ($\chi^2 = 2{\cdot}57$, $P = 0{\cdot}11$) and the clinician multiple threshold ($\chi^2 = 2{\cdot}99$, df = 1, $P = 0{\cdot}08$).

By contrast, with the computer narrow diagnosis, the best fitting model by Akaike's information criterion (Akaike, 1987) was the CE model, estimating that 32% of the variance in liability to panic disorder was due to shared familial factors. However, in this model the AE model was not even close to being excluded against the full model ($\chi^2 = 0{\cdot}78$, $P = 0{\cdot}38$).

Table 3. *Polychoric correlations, the fit of twin models and the parameter estimates for the best-fitting model for panic disorder stratified as a function of the presence or absence of avoidance behaviour*

Diagnostic approach	Polychoric correlations ± S.E.		Fit in χ^2 units			Parameter estimates*	
	MZ	DZ	ACE	CE	AE	a^2	e^2
Clinician	+0·37 ± 0·10	+0·10 ± 0·11	0·51	3·49	0·51†	0·34	0·66
Computer	+0·41 ± 0·10	+0·18 ± 0·14	0·02	1·60	0·09†	0·40	0·60

* Of best fitting model.
† Best fit model by Akaike's Information Criterion (Akaike, 1987).

Multiple threshold model for panic disorder with or without avoidance

In these analyses, we tested, using the multiple threshold model, whether panic disorder with and without avoidance behaviour could be considered as different levels of 'severity' on the same liability continuum (Reich *et al.* 1972). Using the clinician-broad and the computer-broad diagnoses of panic disorder, 38·5 and 43·9% respectively, of cases with lifetime panic disorder also reported associated phobic avoidance and/or agoraphobia. With the clinician-broad diagnosis, the multiple threshold model fit marginally in MZ twins ($\chi^2 = 7{\cdot}77$, df = 3, $P = 0{\cdot}05$) and well in DZ twins ($\chi^2 = 1{\cdot}05$, df = 3, $P = 0{\cdot}79$). With the computer-broad diagnoses, the threshold model fits well in both zygosity groups (MZ: $\chi^2 = 5{\cdot}95$, df = 3, $P = 0{\cdot}11$; DZ: $\chi^2 = 4{\cdot}15$, df = 3, $P = 0{\cdot}25$). The polychoric correlations obtained from these multiple threshold models and the results of twin model fitting are seen in Table 3. For both the clinician- and computer-based diagnoses, the AE model fits best for panic disorder stratified as a function of the presence or absence of avoidance behaviour. Heritability estimates (0·34 for clinician-based and 0·40 for computer-based diagnoses) are similar to those obtained above.

DISCUSSION

The familial aggregation of panic disorder

A major goal of this investigation was to determine the magnitude of familial aggregation found for panic disorder in a general population sample of women. Co-twins of affected twins were at increased risk for panic disorder compared to the general twin population, but the magnitude of this increased risk was modest. On average across the various definitions of panic disorder the relative risk for panic disorder in co-twins of affected twins *versus* the entire twin sample was only around 1·5- to 2-fold in DZ co-twins and 3-fold in MZ co-twins. In reviewing earlier studies of panic disorder and panic-like syndromes seen in clinical settings, Crowe (1990) concludes that the average relative risk for panic disorder in first-degree relatives of affected probands is around 7-fold.

However, our results are not entirely outside the range found in previous family studies. While in one study by Crowe *et al.* (1983), the risk for panic disorder in sisters of affected probands was over 13 times greater than that found in female relatives of controls, in another sample from the same research group, the relative risk in sisters of panic disorder *v.* control probands was only 2-fold (Noyes *et al.* 1986). A recent large sample family history study estimated that first-degree relatives of clinically ascertained panic disorder probands had a five-fold increased risk of illness (Hopper *et al.* 1987). While differences in clinical instruments and diagnostic procedures could explain the differences between our results and those of most previous family studies of clinically ascertained samples, our results are consistent with the hypothesis that panic disorder as diagnosed in a general population sample is less familial than panic disorder seen in clinical settings. Since we did not record treatment-seeking for panic disorder in our sample, we are unfortunately unable to evaluate this hypothesis directly.

Genetic and environmental risk factors in the aetiology of panic disorder

The second major goal of this investigation was to determine the extent to which any observed familial aggregation of panic disorder was the result of genetic *versus* shared environmental factors. Prior to these analyses we tested for a variety of potential biases in our sample and, in particular, found no evidence that our results are biased by violations of the equal environment assumption. Unfortunately, our ability to discriminate definitively between genetic and environmental transmission of panic disorder in families was limited because of low statistical power. The rigorous evaluation of competing hypotheses in population-based twin studies can require very large sample sizes when examining relatively rare disorders the liability to which are only moderately correlated in twin pairs (Martin *et al.* 1978). Although our sample size of affected twins (i.e. 166 twin pairs of known zygosity with one or more member with a clinician-broad diagnosis of panic disorder) was much larger than the one previous twin investigation of panic disorder (29 pairs) (Torgersen, 1983), we were unable to discriminate, with a high degree of confidence, between genetic and familial-environmental transmission. Interestingly, our results are relatively similar to those found by Torgersen (1983), at least in MZ twin pairs. Of the 13 MZ co-twins of panic disorder proband twins in his sample, two had panic disorder (probandwise concordance for 'narrow' panic disorder = 15·4%) and two had panic attacks (concordance for 'broadly' defined panic disorder = 31%).

The results of 7 of the 8 diagnostic-statistical models tested favoured the hypothesis that the familial aggregation of panic disorder was due largely or entirely to genetic factors. However, using computer operationalized strict DSM-III-R criteria, the best fit model indicated that familial transmission of panic disorder was entirely environmental. These results are in contrast to our findings for major depression in this sample, in which 9 different diagnostic approaches to the disorder all yielded the same best fitting twin model (Kendler *et al.* 1992). While it is possible that the differences obtained between our different diagnostic approaches to panic disorder are meaningful, two arguments suggest that they may be the result of stochastic variation in the small number of concordant MZ and DZ pairs. First, the high agreement between the narrow clinician and computer diagnoses of panic disorder makes it improbable that the computer algorithm was truly identifying an aetiologically distinct subgroup of cases. Secondly, in the computer diagnoses, the multiple threshold model fits well and yet suggests that familial transmission of the liability to panic disorder is largely genetic. While our power to discriminate definitively competing hypotheses is low, our results suggest that panic disorder is probably transmitted within families largely for genetic reasons. It may also be argued that the clinician diagnoses, which used written information from the interview that was inaccessible to the computer, may be more valid than the diagnoses derived by computer algorithm.

The heritability of panic disorder

Even if, as the evidence favours, the familial transmission of panic disorder in this general population sample is the result largely of genetic factors, the maximum proportion of variance in liability to panic disorder accounted for by genetic factors in our sample is modest. The estimated heritability of liability to panic disorder (30–40%) contrasts sharply with estimates of over 65% for schizophrenia (Kendler, 1983) and manic depressive illness (McGuffin & Katz, 1989).

Our results are not consistent with previous evidence from complex segregation analysis that panic disorder is due to a highly penetrant autosomal dominant single major locus (Pauls *et al.* 1980) which would predict much higher twin concordance rates than observed in the present study. Our findings are somewhat less discrepant with model fitting to morbid risk results from family study data (Crowe *et al.* 1983) which predict, using either a single major locus or multifactorial models, moderately higher concordance rates than we obtain. Forms of panic disorder may exist that are the result of a highly penetrant single major locus that can be detected by linkage analysis. However, our findings suggest that if they exist, such cases constitute a modest proportion of the individuals in the general population who meet, on personal interview, the criteria for lifetime panic disorder.

Because of previous interest in single major locus models for panic disorder, we also obtained estimates for broad heritability under this model of transmission (James, 1971; Suarez *et al.* 1977). These estimates ranged, for the different diagnostic definitions of panic disorder, between 14 and 19%. In general, heritability estimates of a dichotomous disease state using a single major locus model are lower, and often substantially so, than estimates of 'heritability of liability' obtained from the same data using the multifactorial threshold model.

Panic disorder with and without phobic avoidance

The final goal of this paper was to evaluate the hypothesis that phobic avoidance is an index of the severity of liability to the panic disorder syndrome. Our results are generally consistent with this hypothesis, although the fit of one of the multiple threshold models (MZ twins given clinician diagnosis) was marginal. These findings suggest that, from a familial perspective, panic disorder with significant phobic avoidance or agoraphobia probably represents a more severe form of the disorder than does panic disorder unaccompanied by avoidance. These results should be interpreted with caution, however, because of the limited power to reject multiple threshold models given the small number of twins in this sample falling into the affected liability classes.

Limitations

The results of this investigation apply only to females and given the substantial differences in prevalence of panic disorder across genders (Eaton *et al.* 1991) and results of model fitting to family study data (Crowe *et al.* 1983), there may be important sex differences in the role of genetic and environmental factors in panic disorder.

Our ability to explore other diagnostic approaches to panic disorder was markedly limited by our use of the 'skip-out' in the panic disorder section of our diagnostic instrument. We collected no systematic information about individuals who reported a history of panic attacks but denied that they ever had 4 in a 4-week-period or at least a month's resultant anticipatory anxiety. Therefore, we are unable to examine rigorously the category of 'panic attacks without panic disorder', and its relationship to more classically syndromal panic disorder. This limitation may be a substantial one, as respondents may not recall with high accuracy the maximum frequency with which panic attacks occurred (Robins, 1989).

Finally, we were impressed with the difficulties involved in assessing panic disorder in the general population. In particular, it was often difficult to distinguish clearly between situational and spontaneous panic attacks. Furthermore, in people with unambiguous spontaneous panic attacks, it was not always clear whether they met other criteria for panic disorder (Robins, 1989). In twin models based on a single assessment, unreliability of measurement, if uncorrelated in twin pairs, is indistinguishable from the effects of individual specific environment. If our twin models were applied to the results of multiple assessments, or had we systematically enquired about panic attacks of less frequent occurrence and included such cases in our modelling, the estimated heritability of liability to panic disorders could be considerably higher than that reported here.

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