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Anxiety disorders and neuroticism: Are there genetic factors specific to panic?

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ABSTRACT – Data from 2,903 adult same-sex twin pairs were analysed to investigate whether the genetic determinants of symptoms of panic are different from those underlying the neuroticism personality trait. Our results suggest that much of the genetic variation influencing the physical symptoms associated with panic is of the nonadditive type, perhaps due to dominance or epistasis. In both sexes these nonadditive genetic effects on physical symptoms influence the reporting of "feelings of panic". In males they also account for as much as half the genetic variance in neuroticism. The remainder is additive and also accounts for the balance of genetic variation in "feelings of panic". In females genetic variance in neuroticism is entirely additive but is not an important source of covariation with either panic symptom. Thus, symptoms of panic seem to be shaped in part by unique genetic influences which do not affect other anxiety symptoms. That a substantial part of the genetic variance in neuroticism in males may be due to the nonadditive effects on physical symptoms of panic may help to explain the rather low correlation between the genetic influences found to affect neuroticism in males and their counterparts in females.

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Attacks of panic in safe circumstances that debilitate and recur are recognised as panic disorder. When sufferers avoid situations for fear of panic and so become disabled, the disorder is called agoraphobia, or panic disorder with extensive phobic avoidance. In such patients panic can be induced by infusions of sodium lactate (1) and suppressed by imipramine, an anti-depressant, but not by anxiolytic remedies (2). Pauls studied 19 kindreds of probands with panic disorder and concluded that "panic disorder is inherited as an autosomal dominant trait and that generalised anxiety disorder is a separate entity" (3, p. 643).

Is panic an endogenous anxiety syndrome that is determined by specific genetic factors, manifested as a biochemical abnormality and uniquely responsive to a limited range of drugs? The action of anti-depressant drugs in this condition has been supported (4), but the specificity has been disputed (5). The action of lactate, carbon dioxide and other chemical agents in provoking panic in patients with panic disorder but not in persons with other anxiety disorder or controls has been supported (6), but again the specificity has been questioned (7). This paper is focussed on part of this general hypothesis, that the genetic determinants of panic and agoraphobia are separate and different from the genetic factors that are causal in the other anxiety disorders.

In a recent study of 3,810 twin pairs, Kendler

et al. (8) looked at the role of genetic and environmental factors in seven symptoms of anxiety. For five symptoms of general anxiety they found that variation could be explained by the combination of the additive effects of genes and environmental experiences specific to the individual. However, for the two symptoms relating to panic there was evidence that non-additive genetic variance due to dominance or epistasis was also important. On this basis they therefore suggested that the genetic basis of panic may differ from that of general anxiety. However, the important issue is whether liability to panic is produced by specific genetic factors or by genetic factors influencing a trait associated with anxiety. Earlier, Jardine et al. (9) had found in the same data that genetic variation in total anxiety score (the sum of the seven symptom scores) is largely dependent on the same genes which determine variation in neuroticism, a personality trait known to be associated with vulnerability to anxiety, including panic disorder and agoraphobia (10). In a multivariate analysis of the symptom scores in the same data set, Kendler et al. (11) showed that a large part of the genetic variation in the two panic items was caused by genes which also influenced all the other anxiety and depression items. However, there was also evidence of a somatic anxiety factor and of smaller amounts of genetic variance specific to individual symptoms. The relationship of these genetic factors influencing individual symptoms to those influencing the neuroticism personality trait was not explored.

In this report, we clarify the role of specific and common genetic factors in the determination of liability to symptoms of panic by examining their relationship with neuroticism in the same large twin sample studied previously (8, 9, 11). In particular, our aim is to determine to what extent there are genetic factors specific to panic that are independent of genetic factors determining variation in neuroticism.

Subjects and questionnaires

A questionnaire, including the Delusions-Symptoms-Stated Inventory (DSSI) (12) and the Eysenck Personality Questionnaire (EPQ) (13), was mailed to 5,967 twin pairs aged 18 years and over from the Australian NH and MRC Twin Registry. Completed questionnaires were returned by both members of 3,810 twin pairs; 1,233 monozygotic (MZ) females, 567 MZ males, 751 dizygotic (DZ) females, 352 DZ males, 907 DZ opposite-sex. The data and the sample have been described in detail elsewhere, and been shown to be representative of the general Australian population with respect to anxiety and neuroticism scores (8, 9, 14). To simplify the analyses, only data for the 2,903 same-sex pairs will be analysed here.

In this report, we concentrate on the twins' responses to the two items from the DSSI concerned with symptoms of panic and with the neuroticism (N) scale of the EPQ. The two panic items are: 1. Recently I have been breathless or had a pounding of my heart; 2) Recently, for no good reason, I have had feelings of panic. Each panic item was scored 0, 1, 2 or 3 according to the degree of distress claimed i.e. "none", "a little", "a lot" or "unbearably". The N scale consists of 23 items of the Yes/No type which are scored 0 or 1 so total N scores can range from 0–23 in the direction of increasing neuroticism.

Analysis

Ordinary factor analysis takes the correlation matrix of a series of variables measured on a sample of unrelated individuals and attempts to ascribe the covariation between variables to a number of latent factors. The factor is a theoretical construct but may find ready interpretation in terms of biology. For example, correlations between most body measuresments can largely be explained by two factors which may be called a "length" factor and a "breadth" factor. If a variable is influenced by a factor it is said to load on the factor. Variation not explained by factors is termed specific to the variable.

To a geneticist, and indeed to anyone interested in biology, the frustrating aspect of phenotypic factor analysis is that it does not seem to get us much closer to the underlying genetic and environmental causes of covariation and specific variation. This cannot be accomplished, even in

principle, unless measurements are made on constellations of related individuals. One of the most appealing genetic designs is the classical twin study of MZ and DZ twins reared as unbroken pairs. These are easy to ascertain; within each pair there is a perfect matching for age and home background; provided MZ and DZ pairs can be shown to be sampled from the same population, one provides a perfect control for the other in the separation of genetic and environmental variation. The fundamental assumption of the classical twin method is that environmental variation within MZ pairs is the same as that found within DZ pairs. This assumption has been hotly debated and has been the subject of much empirical research. The arguments and evidence are summarised by Kendler (15) who concludes, at least in the psychiatric context, that the assumption of equal environments seems to stand up well to empirical testing.

The method of multivariate genetic analysis adopted in this paper is a generalisation of factor analysis. It capitalises on the information provided by MZ and DZ twins to estimate common factor and specific variation separately for both genetic and environmental sources of covariation (11, 16). We are thus no longer restricted to estimating phenotypic factors but can now assess the degree to which separate genetic and environmental factors are responsible for correlations between variables. For example, we can determine the extent to which the genetic and environmental factors responsible for variation in neuroticism (9, 14) are the same as, or different from, those responsible for variation in liability to panic (8). We can also ask whether variation not determined by a general factor but specific to, say, panic is environmental or genetic. Caution is needed in interpreting the presence of a genetic common factor. It is safe to infer that a gene, or set of genes, is influencing several characters at the same time and this is known as pleiotropy, but the number and magnitude of individual gene effects cannot be inferred (17). A similar caveat applies to the interpretation of common environmental factors. It must also be remembered that measurement error will be estimated as environmental variation and will often account for most of what is estimated as environmental specific variance. The techniques employed in this paper are new in their application to psychiatric data and conceptually difficult to those unfamiliar with multivariate analysis and quantitative genetics. Nevertheless, we argue that the insights provided by these techniques are novel, biologically illuminating and repay study. Carey (18) has provided an excellent commentary to an earlier paper (11) which introduces psychiatrists to these methods.

For this analysis we compute matrices containing correlations of the two discontinuous panic items and the continuous measure of neuroticism measured on first and second twins. There are three variables and two twins so each matrix is 6×6. A separate matrix is computed for male and female MZ and DZ twins and these four matrices are shown in Table 1. Because each matrix is symmetrical about the diagonal, only one triangle of each matrix is shown.

It is a reasonable biological assumption that characters as complex as response to a questionnaire item on panic will be determined by many different factors, some environmental and some, perhaps, genetic. Given multifactorial determination then the Central Limit Theorem of theoretical statistics suggests that the liability, or trait which underlies response to this item will be approximately normally distributed. Correlations are computed under this assumption, viz. that underlying each categorical panic item on which response is measured on a four point scale there is a continuously distributed scale of liability, and that the joint distribution of this scale with liability scales underlying other items, and with continuous measures, is bivariate normal (19). Thus the matrices in Table 1 contain three types of correlations: 1) polychoric correlations for the two discontinuous panic items, obtained by the method of maximum likelihood (20). A polychoric correlation is calculated between continuous normally distributed latent traits assumed to be underlying two discrete items; 2) product-moment correlations between neuroticism in twin 1 and twin 2; and 3) correlations between the discrete panic items and the continuous neuroticism measure calculated as an approximation to the polyserial correlation (21). A polyserial correlation is calculated between a normally dis-

Table 1
Correlations[a] between neuroticism and two symptoms of panic for twins 1 and 2 (females upper triangles, males lower triangles)

MZ (1233 female, 567 male pairs)			*Females*					
			1	2	3	4	5	6
1. Neuroticism	- twin 1			0.37	0.56	0.52	0.13	0.30
2. Heart pounding	- twin 1	m	0.44		0.45	0.23	0.33	0.27
3. Feelings of panic	- twin 1	a	0.64	0.49		0.33	0.21	0.44
4. Neuroticism	- twin 2	1	0.46	0.24	0.51		0.36	0.58
5. Heart pounding	- twin 2	e	0.27	0.34	0.30	0.33		0.49
6. Feelings of panic	- twin 2	s	0.41	0.35	0.55	0.65	0.46	
DZ (751 female, 352 male pairs)			*Females*					
			1	2	3	4	5	6
1. Neuroticism	- twin 1			0.28	0.55	0.25	0.07	0.19
2. Heart pounding	- twin 1	m	0.40		0.39	0.14	0.11	0.12
3. Feelings of panic	- twin 1	a	0.43	0.34		0.15	0.08	0.04
4. Neuroticism	- twin 2	1	0.17	0.10	0.17		0.42	0.59
5. Heart pounding	- twin 2	e	0.15	-0.01	-0.05	0.38		0.44
6. Feelings of panic	- twin 2	s	0.27	-0.13	0.31	0.64	0.42	

[a]Product-moment correlation between neuroticism in twin 1 and twin 2; polyserial correlations between neuroticism and panic items; intercorrelations of panic items are polychoric.

tributed latent trait underlying a discrete item and a continuously distributed variable. Provided the assumption of bivariate normality of liability scales is true, it can be shown under a wide variety of conditions that the polychoric and polyserial correlations are the least biased estimators of correlations involving categorical variables (22). It is therefore desirable to use these rather than the corresponding product-moment correlations.

However, since such matrices are not necessarily positive definite it is not possible to use maximum likelihood, so we had to fit models by a least squares procedure in which the MZ and DZ matrices were weighted by their degrees of freedom (23, 24). Standard errors were not available for the approximate polyserial correlations, so it was not possible to weight further the individual correlations within matrices. However, we have found (Heath, unpublished) that the estimates of factor loadings are robust to variations in the method used for weighting, and that unweighted solutions give estimates close to those of the appropriate weighted solution. On the other hand, the validity of goodness of fit tests depends critically upon the correct weighting of statistics and although approximate tests can be used (23, 24) we place less reliance on these than on the parameter estimates themselves. Therefore, we do not attempt to compare the fits of alternative models in this paper. Rather, it is in the nature of a confirmatory factor analysis in which we draw together intriguing features from the results of our three previous analyses of the data (8, 9, 11), to fit a single model which we believe describes the causes of covariation between the two DSSI panic symptoms and neuroticism.

In our models, the expected correlations between MZ and DZ twins can be expressed as a function of four sources of covariation, two genetic and two environmental.

Expected genetic correlations are based on the assumptions of polygenic inheritance, viz. that genetic varition in the trait is determined by a large number of genes acting independently and of small and equal effect. In fact, the expectations are not greatly altered if there is a smaller number of genes, they are of different effect, and there is some non-independence between loci (epistasis). In human studies, the best one can do is estimate all the various types of genetic variation with two unknown parameters; VA, the additive genetic variace, results primarily from the additive effects of alleles at each locus; VD, the dominance variance, results from the non-additive effects of two alleles at a locus. In twin studies, VD also estimates certain types of epistasis, or interactions between dif-

Table 2
Inferences about sources of variation from different patterns of MZ and DZ correlations

Observed	Inference
$r_{mz} = r_{dz} = 0$	ES
$r_{mz} = r_{dz} > 0$	ES + EC
$r_{mz} = 2r_{dz} > 0$	ES + VA
$r_{mz} < 2r_{dz} > 0$	ES + VA + EC[a]
$r_{mz} > 2r_{dz} > 0$	ES + VA + VD

[a] If there is correlation between spouses then the estimate of EC may be inflated by extra additive variance due to assortative mating.

ES = specific environmental variance; EC = common or familial environmental variance; VA = additive genetic variance; VD = dominance variance.

ferent loci. By the terms "additive" and "non-additive" we mean the following. Suppose variation in a trait is entirely governed by a pair of alleles at a single locus. Then if these alleles act additively, the mean value of offspring from a given pair of individuals should always be the mean of the two parental values. If there is dominance, however, the mean value of offspring will depend upon the particular combination of parental genotypes. Environmental effects are divided into two categories; ES, specific environmental variance, is the result of environmental experiences that are unique to the individual and shared with no-one else, not even the co-twin or members of the same family; EC, common or familial environmental variance, results from environmental experiences shared by both members of a twin pair.

Three of these parameters (VA, VD and EC) contribute to the phenotypic similarity between relatives, but since there are only two correlations only two of them can be estimated. ES, by definition, is equal to $1 - r_{mz}$. The inferences about sources of variation from various patterns of MZ and DZ correlations are shown in Table 2. Basically, EC increases the DZ correlation above half the MZ correlation and dominance decreases it below this value. Thus EC and VD are negatively confounded, and if both are present, the value of the third parameter estimated additional to ES and VA will depend on the precise relative importance of shared environment and dominance variance. The role of statistical methods is to distinguish between the various inequalities shown in Table 2, so refining the inferences which can be made from twin correlations.

Results

We know from previous analyses of these data that shared familial environment (EC) appears to play no part in determining individual differences in neuroticism and the two symptoms of panic. But individual environmental experiences (ES) and additive gene effects (VA) are important causes of variation in both sexes (8, 9). For the two symptoms of panic there is evidence that dominance gene action (VD) (or epistasis) may also be important (8), and there is slight evidence that dominance may play a part in male variation in neuroticism (14). We now investigate the extent to which these three sources of variation, ES, VA and VD, are responsible for the covariation of neuroticism and symptoms of panic. Each source may influence the two panic symptoms and neuroticism through a set of common factor loadings. This is illustrated by the path diagram in Fig. 1. In addition, there may be ES, VA and VD variance specific to each character and paths representing these contributions are also indicated in the figure.

The number of unique statistics in each correlation matrix is $6 \times 5/2$, and there are two matrices for MZ and DZ twins of the same sex so there is a total of 30 statistics and these are shown in Table 1. Eighteen parameters are estimated corresponding to the eighteen paths shown in Fig. 1: a factor loading and a specific component for each of the three sources on each of the three variables. In fact, the ES specific components (En, Eh, Ep) are not independently estimated but are obtained by difference.

The variance accounted for in the two panic symptoms and in neuroticism from factor and specific sources is shown in Table 3, separately for females and males. For example, for heart pounding in female twins 53% of the variance is due to specific environmental influences, and this will include measurement error - how ever we may interpret that in this context. A common environmental factor, which also influences feelings of panic and Neuroticism, accounts for a further 14% of variance. Environmental influences unique to the individual and not shared

Table 3
Proportions of variance accounted for by additive genetic, dominance and individual environmental sources which are either general to all three measurements or specific to only one of them. Symbols corresponding to paths in Fig. 1 are shown in brackets

	Environment		Additive genes		Dominant genes	
	Factor (E_g)	Specific (E_n, E_h, E_p)	Factor (A_g)	Specific (A_n, A_h, A_p)	Factor (D_g)	Specific (D_n, D_h, D_p)
Females						
Neuroticism	0.21	0.27	0.51	0.00	0.01	0.00
Heart pounding	0.14	0.53	0.05	0.06	0.09	0.13
Feelings of panic	0.31	0.27	0.13	0.00	0.29	0.00
Males						
Neuroticism	0.11	0.43	0.20	0.00	0.20	0.06
Heart pounding	0.14	0.51	0.00	0.00	0.34	0.00
Feelings of panic	0.16	0.26	0.32	0.02	0.24	0.00

with the co-twin thus account for 67% of variance. The heritability, or proportion of total variance due to genetic differences is thus 0.33. One third of this (11% of the total) is additive genetic variation and the remainder (9 + 13 = 22%) is dominance or other nonadditive genetic variation. About one half of both additive and nonadditive variation is due to genes which also influence the other symptom and Neuroticism – 14% of the total (5% + 9%). The remainder (6% + 13%) is due to genes which specifically influence heart pounding but not the other two characters.

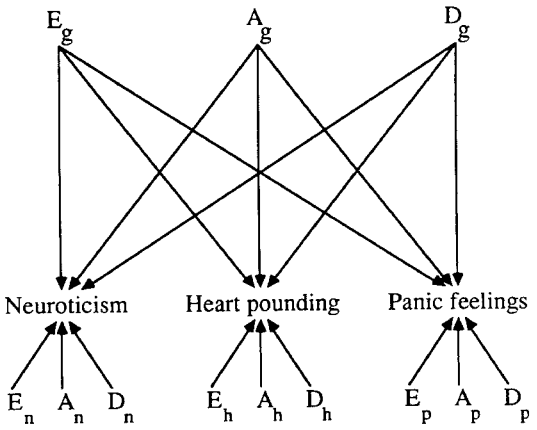

Fig. 1. Model for covariation of panic symptoms and neuroticism. Covariation results from general factors of individual environmental experiences (Eg), additive genes (Ag) and dominant genetic effects (Dg) which potentially influence all three behaviours. Variance specific to each behaviour may also be environmental, additive genetic, or dominant genetic in origin but will be specific to Neuroticism (En, An, Dn), breathlessness/heart pounding (Eh, Ah, Dh) or feelings of panic (Ep, Ap, Dp). This model was fitted to the correlations shown in Table 1. Proportions of variance due to each source (squares of estimated path coefficients) are in Table 3.

Discussion

Genetic factors are important in individual differences in the two symptoms of panic and in the neuroticism personality trait, as has been previously established in these data (8, 9). However, these factors appear to be mainly nonadditive (dominance or epistasis) for the panic symptoms, and this has also been noticed (8). Previously unremarked is that about half the genetic variance for neuroticism also appears to be nonadditive in males (26% dominance vs. 20% additive), although in females (where numbers are larger and there is more power to discriminate between models) virtually all the genetic variance is additive (51% additive, 1% dominance). We shall return to this point below.

In females then, there are good grounds for supposing that the genetic effects on panic are largely distinct from those affecting neuroticism – the genetic common factor that accounts for 51% of the total variance in neuroticism only accounts for 5% in heart pounding and 13% in feelings of panic. We also note that cognitive panic (feelings

of panic) is considerably affected by dominant gene action (29% of the total), but this has only trivial pleiotropic effects on neuroticism (1% of the total). [When a single gene affects more than one phenotype this is described as pleiotropy]. However, these dominance effects do account for 9% of the variance in physical symptoms of panic (breathless or heart pounding). But even more of the genetic variance in physical panic is specific to that symptom and two thirds of it is due to dominant rather than additive gene effects (13% vs. 6% of total variance).

Some of these features also hold in males, but there are also some interesting sex differences in genetic architecture. There is evidence of a large degree of dominance variance for both cognitive (24% of total) and physical panic (34%), but now there are pleiotropic effects on neuroticism accounting for fully 20% of male variance. There are also dominance effects specific to neuroticism and accounting for 6% of male variance. This factor accounts for all male genetic variance in physical symptoms. The general additive genetic factor accounts for 20% of variance in male neuroticism and 32% of variance in cognitive panic. Genetic variation for feelings of panic in males then, is simply the sum of dominant gene effects which produce physical symptoms of breathlessness and pounding heart, and additive gene effects for neuroticism.

It may seem surprising that nonadditive genetic variance for neuroticism in males is detected here when it has gone unnoticed in previous analyses of the same data (9, 14) and of the same trait in other large twin series (25). It is well known that the classical twin study provides only very low power to detect dominance, even when it is a major source of variance (26). However, it seems that this power is increased if the dominance is a source of covariation between related traits, and these contributions are estimated simultaneously in a genetical analysis of covariance structure, as has been performed here. A similar result was found in the analysis of covariation between finger ridge counts (27). We also note that Eaves & Young found some evidence of genetical non-additivity in their analysis of twin data on neuroticism subscales (25, pp. 157–162).

The newcomer to the field may also be surprised at the apparently large disparities between men and women in the causes of individual differences in panic symptoms and personality. In fact, such sex heterogeneity is the rule rather than the exception for both physical and mental traits (14, 28, 29). In our previous analysis of these data we estimated a correlation of only 0.58 between the genetic effects acting on neuroticism in males and in females (14, p. 33). This may reflect the substantive role of dominance variation in males which is not evident in females. We also replicated an earlier finding that genetic variance for neuroticism appears to increase with age in females, but not in males (14, p. 27). These facts point to different evolutionary pressures having shaped the causes of variation in men and women in the aspects of behaviour measured here. This should be no more surprising than sex differences in the evolution of chest girth.

It could be objected that the item we are interpreting as physical symptoms of panic, "Recently I have been breathless or had a pounding of my heart", is actually eliciting symptoms of respiratory illness or tachycardia which have nothing to do with panic or anxiety disorder. To this we may respond: 1) the item appeared in a section of the questionnaire entitled "Feelings", 2) about 80% of the sample was aged less than 40 and therefore these medical conditions are unlikely to have made much impact on our results; and 3) all of the genetic variance for this symptom in males, and about one half that in females, covaried with the cognitive panic symptom and neuroticism.

The notion that persons who panic are very quick to react to the physical symptoms of breathlessness or palpitations would be consistent with the position on lactate infusion adopted by Magraf et al. (7), with the evidence on provocation with hyperventilation and carbon dioxide by Holt & Andrews (30), and with the observation that both imipramine and behavior therapy are of benefit to people who panic (5).

We note two potential limitations of this data set. First, the symptoms are all self-reported, and second, symptoms rather than diagnoses were examined, so the results cannot necessarily be extrapolated to clinical cases. Nevertheless, our results bear some similarity to those of Pauls et al. (3) who found evidence of dominance in panic disorder in a patient study. To overcome

the limitations inherent in a questionnaire study of a population sample, we have a study in progress on the etiology of clinically diagnosed panic disorder in a large sample of twins.

A further note of caution must be sounded about the robustness of our results. It is in the nature of the twin design that estimates of additive and dominant genetic variance are highly negatively correlated (26). It is in the nature of covariance structure analysis that estimates of common factor and specific variance are also negatively correlated. Thus, the results quoted in Table 3 may be unstable to sampling fluctuations. Ideally, extensive bootstrap analyses (e.g. 31) are required to investigate the stability of our results. However, these are beyond the scope of our computing resources. That certain essential features of our findings are replicated in males and females lends credence to our argument. Further support can only come from new studies, and these are underway in Virginia and in a follow-up study in Australia.

The existence of genetic dominance (or epistasis) for physical symptoms of panic would suggest that this response has been subject to intense natural selection during the course of human evolution (32). Certainly, one would expect that rapid mobilisation of the flight or fight response has been adaptive, but perhaps hypersensitivity of this response in the modern world causes anxiety disorder of which panic disorder is one manifestation. In this case, one might predict that polymorphisms underlying variation in this behaviour are currently subjected to stabilising selection away from the extremes of apathy and panic towards an optimum alertness. It is tempting to draw an analogy with the immune response which when vigilant against pathogens undoubtedly confers a selective advantage, but when hyperactive impedes the organism with hayfever, eczema and more severe autoimmune diseases.

Conclusions

Previously we showed that that total anxiety and total depression scores in these data covary with neuroticism, mainly because they are influenced by the same genes (9). Later we analysed the individual anxiety symptoms and found that each was genetically influenced but that the two panic items in the anxiety scale manifested some genetic nonadditivity, due either to genetic dominance or epistasis and specific to each item (8). In a multivariate analysis of the seven anxiety and six depression items we subsequently showed (11) that a single genetic factor accounted for most of the genetic covariance between all 13 items. Anxiety symptoms were differentiated from depression symptoms by environmental influences. They also detected a minor "somatic anxiety" genetic factor which loaded on the "breathless/heart pounding" item and also on the "pain or tension in head" item.

Here we have taken the two items from the DSSI/sAD which seem to measure symptoms of panic, and have explored the extent and causes of covariation of these with the neuroticism personality trait.

In essence, our results confirm that much of the genetic variation influencing the physical symptoms associated with panic is nonadditive, perhaps due to dominance or epistasis. In both sexes these nonadditive genetic effects influence the reporting of "feelings of panic". In males they also influence the neuroticism personality trait and may account for as much as half the genetic variance for neuroticism in men. The remainder is additive and also accounts for the balance of genetic variation in "feelings of panic". In females genetic variance in neuroticism is entirely additive but is not an important source of covariation with either panic symptoms.

Our results are important in two respects. Firstly they reinforce the view that symptoms of panic are shaped in part by certain genetic influences which are unique and do not affect other anxiety symptoms. Secondly, that a substantial part of the genetic variance in neuroticism in males may be due to the nonadditive effects on physical symptoms of panic. This may help explain the rather low correlation between the genetic influences found to affect neuroticism in males and those acting in females.

Why the genetic liability to neuroticism/anxiety takes clinically distinct forms in different individuals, even in MZ twins who are genetically identical, is not known. Our data suggest very strongly that systematic aspects of the family

environment which are shared by co-twins cannot explain the heterogeneity of symptoms manifested by twins. Rather, they imply that idiosyncratic environmental experiences, perhaps at critical stages of development, determine the very different manifestations of anxiety disorder. Thus, it is worth noting that over half the variance in physical symptoms and over one quarter of that in feelings of panic is individual environmental variance specific to the symptom.

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